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Extended Interval Gentamicin Dosing in Preterm Neonates

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ABSTRACT

This study aimed to characterize the pharmacokinetic parameters of gentamicin achieved after the implementation of an extended interval gentamicin dosing protocol of 5 mg/kg every 48 hours in neonates < 35 weeks corrected gestational age (CGA). Fifty-four treatment courses were used to calculate the pharmacokinetic parameters of gentamicin clearance, half-life, volume of distribution, and serum levels which were examined for correlations with birth weight, gender, CGA, and post-natal age (PNA). Mean gentamicin clearance was lower in neonates < 14 days PNA. The mean peak gentamicin level was 8.3 mg/L. Neonates < 14 days PNA had higher mean gentamicin levels at 24 h post-dose (1.7 mg/L vs. 1.1 mg/L) and 48 h post-dose (0.3 mg/L vs. 0.2 mg/L). Extended interval gentamicin 5 mg/kg every 48 hours resulted in serum peak levels of 6 – 12 mg/L in 98% of cases compared to a predicted 2% of cases with once-daily doses of 2.5 or 3 mg/kg. Increased clearance with advanced PNA suggests the need for more frequent dosing in premature neonates >14 days of age.

MESH Terms: gentamicin, neonatology, pharmacokinetics and drug metabolism, aminoglycosides, drug monitoring

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic frequently used for empiric treatment of sepsis, meningitis, necrotizing enterocolitis, and urinary tract infections in the neonatal intensive care unit. The most common organisms responsible for neonatal sepsis include Staphylococcus epidermidis, Group B Streptococcus, Escherichia coli, Klebsiella pneumoniae, and Enterobacter species.[1,2] Although resistance rates vary, gentamicin is effective in treating the most common Gram-negative pathogens isolated in Canada. [3,4]

Traditional doses of gentamicin in neonates less than 35 weeks corrected gestational age (CGA) range from 2.5 to 5 mg/kg/dose given every 8 to 24 hours depending on the patient's gestational age and/or birth weight. At our institutions, gentamicin dosing has been traditionally based on CGA: 2.5 mg/kg once-daily in neonates less than 30 weeks CGA and 3 mg/kg once-daily in neonates between 30 and 34 weeks CGA.

Since most infants receive gentamicin for only 48 hours while sepsis is ruled out, a longer dosing interval would lead to fewer children being exposed to a second dose. Numerous studies examining the pharmacokinetics of extended interval gentamicin doses in premature neonates have reported acceptable gentamicin therapeutic levels with doses ranging from 3.5 to 5 mg/kg every 36 to 48 hours.[5 -12] As 36-hour dosing intervals have greater potential for increased medication errors involving missed doses or incorrect administration times, our institutions adopted a change in gentamicin dosing practice from every 24 hours to every 48 hours. A dose of 5 mg/kg had been previously reported as well tolerated in premature infants.[5]

The primary aim of this pharmacokinetic analysis was to confirm the simplified dosing protocol resulted in gentamicin serum levels within accepted institutional target ranges.

METHODS

Retrospective application to the University of Manitoba Health Research Ethics Board and the St Boniface Hospital Research Review Committee was sought and granted after a clinical change in gentamicin dosing was implemented at our institutions; this change was based on previously published work and therapeutic drug monitoring was undertaken for quality assurance. Subsequently, a research project was developed, and ethics approval sought to conduct a pharmacokinetic analysis of the levels obtained during clinical care. Written consent was not obtained from the patient's parent or guardian as this was an evaluation of a previously implemented quality improvement project already in place within the patient care areas.

"As 36-hour dosing intervals have greater potential for increased medication errors involving missed doses or incorrect administration times."

All neonates admitted to the neonatal intensive and intermediate care units of the Health Sciences Centre and St Boniface General Hospital in Winnipeg, Canada between March 10 and June 10, 2014, who were less than 35 weeks CGA and required gentamicin, received a dose of 5 mg/kg every 48 hours. Gentamicin was always initiated empirically in combination with either vancomycin or a β lactam antibiotic. All patients had at least one blood culture drawn, and gentamicin was discontinued if the preliminary blood culture(s) were negative at 36 to 48 hours.

Patients were excluded if no gentamicin serum level was collected with the sampling time documented; if they had congenital renal anomalies, moderate to severe hydronephrosis, or hypoxic ischemic encephalopathy (HIE); or if the first dose of gentamicin was not administered at our facilities.

For newborns, the initial dose of gentamicin was prepared and administered by a nurse in the delivery room. All other doses were supplied to the nursing units from the pharmacy in unit dose syringes. All doses were administered via direct intravenous infusion over 3 to 5 minutes, which has been shown to be as safe as more prolonged infusions of gentamicin. [13].

Serum gentamicin levels were collected by nursing staff via heel stick or an indwelling arterial catheter; whenever possible, serum levels were drawn with other scheduled blood-work. Acceptable gentamicin trough levels were between 0.5 – 2 mg/L and peak levels were between 6 – 12 mg/L. Serum gentamicin concentrations were measured by the facility laboratory using the Roche Cobas c501/Cedia Gentamicin II assay package.

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As part of the protocol, a pharmacist reviewed each serum level and recommended a frequency change to ensure acceptable targets based on the calculated time at which concentrations would drop below 0.5 mg/L. Dosing frequency was adjusted to q24h if the serum level was expected to drop below 0.5 mg/L within 36 hours of the dose.

Data were analyzed using a population pharmacokinetic nonparametric adaptive grid program, Pmetrics, version 1.2.9, 2009-14 Rstudio, Inc. [14] In modeling, each concentration was weighted to the inverse of the assay error variance. Akaike's Information Criterion assisted in identifying the optimal pharmacokinetic model. We examined for a 1 and 2-compartment pharmacokinetic model with gentamicin in this neonatal population. A two-compartment pharmacokinetic open model with zero-order drug infusion and first-order elimination was chosen based on lowest-log likelihood values using Akaike's information criterion.

"The percentage of extended interval and once-daily serum levels outside target ranges were compared using the Z-test for two population proportions."

Serum levels at 1, 24, and 48 hours post-dose were calculated from actual serum levels using a one-compartment model based on each patient's elimination rate constant (k_e) and the equation: $C0=C1e\text{-}k_e\tau$ where C equals serum concentration, and τ is the time between C0 and C1. Mean peak and trough gentamicin levels, and the parametrically distributed pharmacokinetic parameters of clearance (CL) and volume of distribution (Vd) were compared using a Student's t-test. Mann-Whitney U-test statistic was used to compare the nonparametric pharmacokinetic parameter of half-life (t1/2). The number of gentamicin courses requiring pharmacist intervention for dose adjustment was compared for patients less than or greater than 14 days post-natal age (PNA) using the two-tailed Fisher's exact test. The percentage of extended interval and once-daily serum levels outside target ranges were compared using the Z-test for two population proportions.

RESULTS

A total of 47 neonates were eligible for inclusion in the analysis between March 10 and June 10, 2014. Of these, five patients were initiated on gentamicin on more than one occasion resulting in a total of 56 possible treatment courses. One patient was excluded for receiving an inappropriate initial dose of 2.5 mg/kg, and one patient was excluded for receiving the initial dose at an external facility leaving 54 courses for analysis (Table 1). No patients were found during the study period with HIE, congenital renal impairment, or hydronephrosis. An average of 12 days (range 4 to 21) washout period elapsed between gentamicin courses in any patient receiving more than one treatment course. One patient died from complications of necrotizing enterocolitis, and one patient died from complications of prematurity not related to sepsis during the review period; both were included in the analysis.

Pharmacokinetic analysis was performed on 54 gentamicin courses with mean CL and Vd of 43 mL/kg/h (95% Confidence Interval (CI) 39-46), and 0.58 L/kg (95% CI 0.56-0.60), respectively while median t1/2 was 9.8 h (Interquartile Range (IQR) 9.3-10.6). A one-compartment model best represented the data according to Akaike Information Criterion. Covariate analysis was assessed for birth weight, gender, CGA, and PNA. Clearance was approximately 34% lower in neonates with PNA less than 14 days (mean 39 mL/kg/h (95% CI 37-40) vs. 59 mL/kg/h (95% CI 47-71) p=0.008). Neonates less than 30 weeks CGA had slightly lower mean CL than older neonates (43 mL/kg/h (95% CI 39-46) vs. 45 mL/kg/h (95% CI 41-50) p=0.04). The median gentamicin t1/2 at 24 hours post-dose was about 29% higher in neonates less than 14 days PNA compared to older neonates: 9.8 h (IQR 9.4-

Table 1: Patient demographic and pharmacokinetic characteristics.

		CGA (wk)*	Birth Weight (g)*	PNA (d)*	CL (mL/kg/h)£	$t_{1/2}$ (h)*	Vd (L/kg)£
All Courses (n=54)		32.0 (28.7-33.1)	1653 (1093-2113)	0 (0-9)	43 (39-46)	9.8 (9.3-10.6)	0.58 (0.56-0.60)
PNA	<14 d (n=43)	31.9 (28.3-33.1)	1720 (1215-2140)	0 (0-0)	39 (37-40)	9.8 (9.4-10.6)	0.57 (0.54-0.59)
	≥14 d (n=11)	32.0 (29.5-33.2)^{NS}	1200 (995-1470)^	21 (15-30)#	59 (47-71)¥	7.6 (5.7-10.7)^	0.62 (0.58-0.66)^
CGA	<30 wk (n=18)	27.5 (26.9-28.5)	945 (848-1160)	1 (0-10)	43 (39-46)	10.6 (9.4-12.6)	0.55 (0.54-0.57)
	≥30 wk (n=36)	33.0 (32.0-33.6)#	1865 (1618-2188)#	0 (0-4)^{NS}	45 (41-50)^	9.8 (9.3-10.2)^{NS}	0.59 (0.56-0.62)^{NS}
Gender	Male (n=23)	30.0 (28.5-33.0)	1520 (1120-1970)	0 (0-6)	40 (37-44)	9.8 (9.6-10.7)	0.58 (0.55-0.60)
	Female (n=31)	32.1 (29.3-33.3)^{NS}	1669 (1095-2130)^{NS}	0 (0-9)^{NS}	45 (40-50)^{NS}	9.7 (9.3-10.6)^{NS}	0.58 (0.55-0.61)^{NS}
Birth Weight	<1500 g (n=23)	28.0 (27.0-30.0)	1010 (900-1200)	6 (0-15)	44 (38-51)	10.0 (8.4-11.6)	0.58 (0.55-0.60)
	≥1500 g (n=31)	33.0 (32.0-33.6)#	2015 (1700-2275)#	0 (0-0)¥	42 (39-45)^{NS}	9.8 (9.3-10.2)^{NS}	0.58 (0.55-0.61)^{NS}

CGA = Corrected Gestational Age; PNA = Post-Natal Age; CL = Clearance; $t_{1/2}$ = Half-Life; Vd = Volume of Distribution
** Median (Interquartile Range) £ Mean (95% Confidence Interval) ^{NS} p >0.05 ^ p <0.05 ¥ p <0.01 # p <0.001*

10.6) vs. 7.6 h (IQR 5.7-10.7) p=0.012. Volume of distribution was lower in neonates less than 14 days PNA: 0.57 L/kg (95% CI 0.54-0.59) vs. 0.62 L/kg (95% CI 0.58-0.66) p=0.04. Neither CL nor t1/2 nor Vd was significantly impacted by birth weight or gender (Table 1).

A total of fifty peak levels (drawn at 0.7 to 5.7 h post-dose, mean 1.7 ± 0.6 h), forty-six 24 hour post-dose levels (drawn at 11.5 to 24.3 h post-dose, mean 22.1 ± 2.0 h), and fifteen trough levels (drawn at 39.0 to 52.3 h post-dose, mean 47.1 ± 2.7 h) were documented among all treatment courses. Post-dose levels were drawn in all courses at least 40 minutes after the dose was administered to ensure the alpha-distribution phase was completed and would not influence pharmacokinetic calculations. Serum sampling occurred over a wide range of times post-dose as these sampling variations were accounted for in the pharmacokinetic modeling used to calculate each pharmacokinetic parameter.

Table 2: Gentamicin serum levels corrected to 1, 24, and 48 hours after patients received the first dose of extended interval gentamicin 5 mg/kg.

		Calculated Gentamicin Levels (mg/L) (Mean (95% Confidence Interval))		
		1 h post dose	24 h post dose	48 h post dose
PNA	<14 d (n=43)	8.5 (8.1-8.8)	1.8 (1.7-1.9)	0.4 (0.3-0.4)
	≥14 d (n=11)	7.4 (6.9-8.0)[¥]	1.1 (0.7-1.5)[#]	0.2 (0.1-0.3)[¥]
CGA	<30 wk (n=19)	8.5 (8.0-8.9)	1.8 (1.6-2.1)	0.4 (0.3-0.5)
	≥30 wk (n=35)	8.2 (7.8-8.6)[NS]	1.5 (1.4-1.7)[^]	0.3 (0.2-0.3)[^]
Gender	Male (n=23)	8.2 (7.8-8.6)	1.7 (1.5-1.9)	0.4 (0.3-0.4)
	Female (n=31)	8.3 (7.9-8.8)[NS]	1.6 (1.4-1.8)[NS]	0.3 (0.2-0.4)[NS]
Birth Weight	<1500 g (n=23)	8.2 (7.8-8.7)	1.6 (1.3-1.9)	0.3 (0.3-0.4)
	≥1500 g (n=31)	8.3 (7.9-8.7)[NS]	1.6 (1.5-1.8)[NS]	0.3 (0.3-0.4)[NS]

PNA = Post-Natal Age; CGA = Corrected Gestational Age
[NS] = not significant (p>0.05) [^] = p <0.05 [¥] = p <0.01 [#] = p <0.001

The actual serum levels were used to calculate expected concentrations at exactly 1, 24, and 48 hours post-dose (Table 2). The mean peak for all patients was 8.3 mg/L (95% CI 8.0-8.6). Serum gentamicin levels were not significantly influenced by either gender or birth weight. However neonates less than 14 days PNA had significantly higher calculated average gentamicin levels at 1 hour post-dose (8.5 mg/L (95% CI 8.1-8.8) vs. 7.4 mg/L (95% CI 6.9-8.0) p=0.007), at 24 hours post-dose (1.7 mg/L (95% CI 1.6-1.8) vs. 1.1 mg/L (95% CI 0.7-1.6) p=0.002), and at 48 hours post-dose (0.3 mg/L (95% CI 0.3-0.4) vs. 0.2 mg/L (95% CI 0.1-0.3) p=0.03). CGA did not influence peak levels, but patients less than 30 weeks CGA showed a trend towards higher 24 and 48-hour post dose levels (Table 2). Although the effect of PNA and CGA differences in serum levels were statistically significant, the clinical significance of these differences is unknown.

For patients greater than 14 days PNA, two of nine calculated 24-hour post-dose levels were greater than 2 mg/L (2.2 mg/L in both instances). Both of these levels occurred in the same patient during different antibiotic courses and periods of acute renal decompensation secondary to the use of inotropes and suspected ileus. All other courses in patients greater than 14 days PNA resulted in 24-hour post-dose levels less than 2 mg/L.

Table 3: Comparison of serum levels between extended interval (5 mg/kg q48h) and traditional dosing regimens (2.5 mg/kg <30 weeks or 3 mg/kg ≥ 30 weeks CGA q24h)

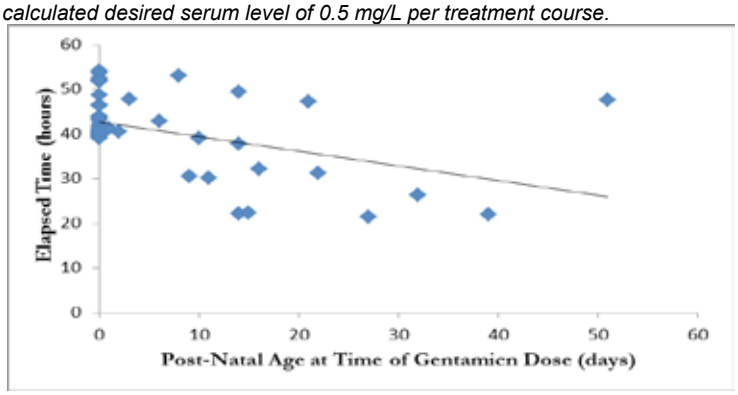
	Serum level 1 hour post-dose (mg/L) (mean (95% CI))		Serum level 24 hour post-dose (mg/L) (mean (95% CI))	
	Once-daily	Extended Interval	Once-daily	Extended Interval
< 14 days PNA (n=43)	4.7 (4.5-4.9)	8.5 (8.1-8.8)[#]	1.0 (0.9-1.0)	1.8 (1.7-1.9)[#]
≥ 14 days PNA (n=11)	4.2 (3.8-4.5)	7.4 (6.9-8.0)[#]	0.6 (0.4-0.8)	1.1 (0.7-1.5)[NS]
All patients (n=54)	4.6 (4.4-4.8)	8.3 (8.0-8.6)[#]	0.9 (0.8-1.0)	1.6 (1.5-1.8)[#]

PNA = Post-Natal Age; CI = Confidence Interval
[NS] p >0.05 [#] p <0.001

"Although our pharmacokinetic analysis revealed a one-compartment model, we hypothesized that possible two compartment distribution of gentamicin into the relatively large percentage of body water found in neonates may explain the observed shorter t1/2 within the first 24 hours"

The serum t1/2 for each extended interval gentamicin course was used to extrapolate peak and trough serum levels expected with traditional once-daily dosing regimens of 2.5 mg/kg q24h or 3 mg/kg q24h in neonates less than 30 weeks or 30 to 35 weeks CGA, respectively (Table 3). Extended interval gentamicin doses of 5 mg/kg resulted in significantly more peak levels within the target therapeutic range of 6 – 12 mg/L when compared to once-daily dosing (98% vs. 2%, p=0). Significantly more trough levels were below the minimum range of 0.5 mg/L for extended interval compared to once-daily dosing (85% vs. 11%, p=0). In neonates less than 14 days PNA, extended interval trough levels were below 0.5 mg/L in 81% (35/43) of courses as compared to 2% (1/43) with once-daily gentamicin.

Figure 1: Time elapsed from first dose of extended interval gentamicin to the calculated desired serum level of 0.5 mg/L per treatment course.



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The average time from initial extended interval dose to a projected desired low serum level of 0.5 mg/L was longer in neonates less than 14 days PNA: 43 h (95% CI 41-44) versus 33 h (95% CI 26-39) p=0.002 (Figure 1). As PNA increased, the elapsed time decreased. Although the impact of post-antibiotic effect with aminoglycosides has been called into question,[15] we still anticipate antibacterial effects at levels of 0.5 mg/L with gentamicin, as CANWARD data have demonstrated an MIC50% for E.coli (for example) of < 0.5 mg/L.[4]

"No adverse events from gentamicin including urine output less than 1 mL/kg/hr were identified during the review period."

Pharmacists intervened for six treatment courses during which the expected serum level at 36 hours post-dose was calculated to fall less than 0.5 mg/L. A duration of 36 hours was deemed acceptable since laboratory reporting time to positivity of definitive Gram-negative cultures is less than 36 hours incubation.[16-18] There was no difference between groups in the number of interventions required based on CGA, gender, or birth weight. There was a trend towards pharmacist intervention being required in 27% (3/11) of courses in neonates greater or equal to 14 days PNA and 7% (3/43) of those less than 14 days PNA (p=0.06). During the data analysis it was determined that four additional courses were sub-therapeutic before 36 hours post-dose and may have warranted dosage adjustments; however, gentamicin had been discontinued shortly after the first dose at the discretion of the physician. Based on the calculated level at 36 hours post-dose, an intervention should have been required for serum level less than 0.5 mg/L in 64% (7/11) of courses in patients greater than or equal to 14 days PNA versus 5% (2/43) of courses in patients less than 14 days PNA (p< 0.001).

No positive blood or cerebrospinal fluid cultures were documented during the review period. One patient died from complications of necrotizing enterocolitis after receiving one dose of gentamicin but had been switched to cefotaxime within 12 hours of birth. No adverse events from gentamicin including urine output less than 1 mL/kg/hr were identified during the review period.

DISCUSSION

Most studies in the literature have reported dosing recommendations based on pharmacokinetic analysis performed within the first few days after birth. However, our patients ranged from 0 to 51 days PNA, and subsequent covariate analysis revealed that increasing PNA correlates with decreased gentamicin t1/2 and trough serum levels. This may be attributed to renal maturation which occurs over the first few weeks of life in premature neonates.[19,20] Renal maturation occurs slowly during fetal development with the kidneys reaching maturity at approximately 36 weeks gestational age.[21] As a result, most infants born at less than 35 weeks have impaired renal function as evidenced by reduced glomerular filtration rate (GFR) when compared to older neonates.[20,21] However, renal maturation in premature neonates improves during the first weeks of life.[19]

Most evidence for extended interval gentamicin dosing in premature neonates has been limited to patients less than two weeks of age which may not accurately reflect the interval required to achieve appropriate serum levels in older premature neonates. Avent et al. reported that neonates older than seven days with weight greater than 1200 g and neonates older than 30 days but weight less than 1200 g required dosing of gentamicin 5 mg/kg every 24 hours versus every 48 hours to achieve optimal serum levels.[22] Recent publications have shown that dosage individualization tables and a 22-hour post-initial dose level can be used to determine an appropriate dosing interval in older neonates.[11,12] However with our dosing protocol, there is no need to perform any serum gentamicin monitoring in neonates being treated empirically pending preliminary culture results which will result in less blood-work requirements in most neonates.

The calculation of gentamicin t1/2 and subsequent calculation of serum levels at 1, 24, and 48 hours post-dose relied on the assumption that t1/2 remains constant throughout the treatment period. Glomerular maturation and fluid shifts from intracellular to extracellular compartments during the first few days to weeks of life may impact gentamicin clearance and its drug distribution.[20,23] As a result of these glomerular filtration rate and volume changes, we anticipated a decrease in t1/2 from 24 to 48 hours of age as renal function improved. Thirteen gentamicin courses had 1, 24, & 48-hour levels documented which we used to calculate independent half-lives for the first 24 hour period (t1/224h) and the second 24 hour period (t1/248h) post-dose. The ratio of t1/224h/ t1/248h was calculated to quantify the t1/2 change. Unexpectedly, the calculated gentamicin t1/2 was larger on day two than on day one post-dose; this effect occurred in patients of all PNA groups. Although our pharmacokinetic analysis revealed a one-compartment model, we hypothesized that possible two compartment distribution of gentamicin into the relatively large percentage of body water found in neonates may explain the observed shorter t1/2 within the first 24 hours.[8,24] In order to ensure this discrepancy in t1/2 did not alter the calculated serum levels, calculations were performed using both t1/224h and t1/248h in all 13 patients with three available serum levels. There was no significant difference found between serum levels calculated using either t1/224h or t1/248h.

Pharmacokinetic modeling of our critically ill neonatal patients using population modeling programs like either the nonparametric adaptive grid program PMetrics, or nonlinear mixed-effects modeling (NONMEM) has allowed for sparse blood sampling to provide relatively accurate parameter estimates of central

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tendency, their variance, and covariance.[14] We have recommended to regulatory agencies to consider PMetrics as the population modeler of choice for initial pharmacokinetic data exploration as it is not constrained by the shape of the population parameter distribution as it is for NONMEM.[25] Thus in our critically ill setting the great advantage with PMetrics is that it can identify diversity in parameter values without making any assumptions about normality. Such diversity could include fast or slow eliminators of gentamicin or a population of neonates with uniquely different distribution spaces from the population average.

Extended-interval dosing resulted in target peak serum levels of 6 – 12 mg/L in 98% of courses. At our institutions, the MIC's to gentamicin in 2013 for 90% or more of our isolates of E coli, K pneumonia, and Enterobacter cloacae were ≤ 1 mg/L, and the MIC's for S epidermidis in 60% of isolates was ≤ 1 mg/L. Since the antibacterial efficacy of gentamicin is maximized when the peak:MIC ratio is 8 to 12,[26] the achievement of peak serum levels greater than 6 mg/L was the primary target of the new dosing regimen. As we did not look directly at antimicrobial cure rates, it can only be inferred that the achievement of higher peak levels will result in improved antibiotic efficacy.

"Gentamicin doses of 5 mg/kg every 48 hours in neonates less than 35 weeks CGA were more effective than once-daily dose protocols in achieving peak serum levels between 6 – 12 mg/L after the first dose in almost all patients."

We did not examine the effect of plasma creatinine levels as it is not an accurate marker of renal function during the early neonatal period as a result of maternal creatinine transfer.[27,28] Also, creatinine levels have not been shown in neonates to correlate with gentamicin serum levels.[27] As the majority of our gentamicin doses were administered at birth, the patients had no baseline plasma creatinine level measured. We, therefore, were unable to assess the impact of gentamicin on neonatal renal function. We did, however, review all plasma creatinine levels sampled within 72 hours post-dose in 35 patients with documented plasma creatinine; 91% of courses coincided with a decrease in plasma creatinine from 24 to 72 hours post-dose. Only 9% of patients had an initial post-dose plasma creatinine level greater than the normal maximum value of 1 mg/dL.

Extending gentamicin intervals have been shown to minimize gentamicin renal toxicity which may be secondary to lower gentamicin trough levels.[29,30] With more effective attainment of peak serum concentration targets from this regimen, it may afford to decrease the duration of prolonged gentamicin exposure and thereby theoretically decrease the risk of vestibular damage.[31,32] Interestingly, there is no association between elevated peak concentrations and auditory toxicity with the aminoglycosides. [31]

Other limitations include relatively small sample size, particularly in the patient subgroup greater than 14 days PNA. Five patients were included in the analysis after receiving gentamicin on more than one occasion during their hospitalization which may lead to a perception of selection bias. However, the pharmacokinetic influences in the neonatal period are changing rapidly and the first parameter dataset was not used to influence the fitting of the second data set analysis. Each treatment course was treated separately and as two distinct assessments.

CONCLUSIONS

Gentamicin doses of 5 mg/kg every 48 hours in neonates less than 35 weeks CGA were more effective than once-daily dose protocols in achieving peak serum levels between 6 – 12 mg/L after the first dose in almost all patients. Increased clearance in neonates greater than 14 days PNA warrants more frequent dosing intervals to ensure adequate treatment. PNA rather than CGA, gender, or birth weight may be a more reliable determinant for predicting gentamicin levels associated with extended interval gentamicin dosing in premature neonates.

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Reference: 1. Frese SA et al. *mSphere.* 2017;2(6):e00501-17.

Case Report: Schinzel Giedion Syndrome

W. Kyaw, DO, G. Noh, MD, H. Truong, MD

Newborn infants with multiple congenital anomalies are not uncommon in the NICU setting. In the absence of a recognizable syndrome, array comparative genomic hybridization is often the first test ordered in the genetic work up. Herein we present a case of a rare, but distinctive malformation syndrome, identified by characteristic dysmorphic features which prompted single gene testing, rather than array CGH. Early diagnosis of this case allowed for appropriate clinical management given the poor prognostic implications derived from genetic test results.

Case

A 4-day old infant born to a 26-year-old G2P2 mother at 38 and 1/7 weeks via Cesarean section for fetal distress. Antenatal ultrasonography revealed a sacral teratoma. Otherwise, pregnancy was uneventful. Patient's two-year-old brother from same non-consanguineous parents was reported to be phenotypically normal. The patient's birthweight was 3515 grams, Apgars were 8 and eight at 1 minute and 5 minutes. In addition to 11 cm x 11 cm sacrococcygeal teratoma noted antenatally, the patient was noted to have multiple congenital abnormalities at birth: large posterior fontanel, penoscrotal hypospadias, and bilateral cryptorchidism. MRI of the brain showed under gyration of the frontal lobes, small posterior fossa and dysmorphic appearing brainstem as well as right perisylvian polymicrogyria. Renal ultrasound showed moderate to severe bilateral hydronephrosis.

The following facial dysmorphic features were appreciated: ocular hypertelorism with shallow orbits, bulge between the eyebrows, short with a widened nasal bridge, anteverted nares, posteriorly rotated low set ears and protruding tongue. The infant was also hirsute and had long fingers with camptodactyly of distal interphalangeal joints, long toes with hypoplastic nails, left fifth toe with wide nailbed suggestive of postaxial polydactyly and overriding right fifth toe.

Picture 1: Lateral facial view.

Picture 2: Front Facial View

Picture 3: The foot in its dorsal aspect

Picture 4: The foot in its lateral aspect

The patient's hospital course was complicated by seizures on day 14 of life and inconsistent gag along with poor feeding. He eventually required a gastrostomy tube. He underwent resection of sacrococcygeal teratoma with final pathology consistent with immature teratoma.

Given above congenital abnormalities and marked dysmorphic features, Schinzel-Giedion syndrome (SGS) was suspected and confirmed via direct sequencing of the SETBP1 gene which revealed a disease-causing heterozygous guanine-to-adenine mutation at position 2602 causing D868 amino acid substitution.

On follow up examination at three months of age, the patient had severe growth retardation with microcephaly and continued intractable seizures. Two soft masses suspicious of teratoma later developed on his left lower extremity. Surgical resection was not pursued for this or his urogenital anomalies due to the poor prognosis associated with SGS. He passed away at age six months from respiratory complications secondary to pneumonia.

DISCUSSION

Schinzel-Giedion syndrome (SGS) is a rare autosomal dominant disorder with approximately 50 reported cases worldwide. SGS was first described in two siblings by Schinzel and Giedion in 1978 which initially suggested recessive inheritance [1]. However, in 2010, Hoischen et al. identified heterozygous de novo SETBP1 mutations in 12 patients, confirming dominant inheritance [2]. Acuna-Hidalgo, R. et al. (2017) later reported de novo SETBP1 mutations in additional 26 cases [3]. The exact function of the SETBP1 gene remains largely unknown to date. Classic SGS is caused by a gain of function mutations.

SGS is characterized by multiple malformations including brain, renal, skeletal and cardiac defects. Brian malformation includes corpus callosum hypoplasia, cortical atrophy, ventricle anomalies, abnormal gyration, delayed myelination, and choroid plexus cysts. Neurological manifestations such as profound cognitive disability, refractory seizures, difficulty in breathing and swallowing have been reported. Various renal abnormalities are commonly seen in SGS and include hydronephrosis, megacalyces, hydroureter, pyeloureteral junction stenosis, and vesicoureteral reflux. Craniofacial malformations seen in this case are classic: widely patent fontanels, shallow orbits, ocular hypertelorism, short nose with low nasal bridge and anteverted nares. Although not seen in our patient, skeletal abnormalities such as sclerotic skull base, multiple wormian bones, hypoplastic first ribs, broad ribs, hypoplasia of distal phalanges, tibial bowing, broad cortex and increased density of long bones have been described. Hypertrichosis is also another common finding seen with SGS. In addition, increased risk of malignancy is an associated feature.

Most affected individuals do not survive past childhood. Individuals with the D868 mutation have the shortest lifespan associated with SGS with an average of 18 months [3]. The most common cause of death is pneumonia secondary to impaired CNS function affecting swallowing and breathing. Other causes of death have also been reported including metastatic tumors, congenital cardiac defects, lung hypoplasia, and sudden cardiac arrest.

In our case, clinical recognition of the syndrome prompted appropriate targeted gene testing which in turn helped provide an early diagnosis. Given poor prognosis based on the current understanding of the genotype-phenotype relationship in SGS, the family was counseled against further invasive interventions, and palliative care measures were pursued to lessen undue suffering for our patient.

We are grateful to our patient's family for their generosity in allowing us to share his case.

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FROM THE NATIONAL PERINATAL INFORMATION CENTER
Perinatal Readmission Trends

Sandra Boyle, BS, Tara Wilcox, BA and Janet H. Muri, MBA

The National Perinatal Information Center (NPIC) is driven by data, collaboration and research to strengthen, connect and empower our shared purpose of improving patient care.

For over 30 years, NPIC has worked with hospitals, patient safety organizations, insurers, and researchers to collect and interpret the data that drives better outcomes for mothers and newborns.

In FY 2012, the Centers for Medicare and Medicaid Services (CMS) introduced the Hospital Readmissions Reduction Program (HRRP) aimed at reducing readmissions in the Medicare population in three patient groups: Acute Myocardial Infarction (AMI), Heart Failure (HF) and Pneumonia (PN). CMS tied this initiative to a reduction in Medicare reimbursement if the hospital's readmission rate in the patient group was greater than expected in comparison to the average performance of all hospitals. Subsequent CMMS FY Final Rules have expanded the HRRP to include patients admitted for Chronic Obstructive Pulmonary Disease (COPD), elective total hip arthroplasty (THA), total knee arthroplasty (TKA) and coronary artery bypass graft (CABG). In FY 2019, the reimbursement reduction is capped at 3% and hospitals are stratified into five peer groups and hospital performance is assessed relative to the performance of hospitals within the same peer group.

As with many changes in reimbursement and/or quality initiatives, CMS is a prime mover. The focus on maternal and neonatal readmission has escalated since the introduction of CMS HRRP even though perinatal readmission rates are much lower (~ 1-2%) than those seen in the CMS patient categories which are often greater than 10-15%. Regardless, birth hospitals have been scrutinizing their readmission rates more closely knowing potential payment reductions by Medicaid or private payers could follow the CMS lead.

For perinatal readmissions, the questions are: What is a reasonable rate? What percent of readmissions are unavoidable and reflect good care? Are there unintended consequences to not readmitting a mother or infant?

Clapp, et al recently documented a retrospective cohort study using State Inpatient Data Bases from California, Florida and New York: "The relative effects of patient and hospital factors on postpartum

readmissions". They found that patient factors such as race and insurance status along with co-morbidities such as obesity, diabetes, hypertension and tobacco use were associated with higher readmission rates which, for the most part, are outside the control of the hospital. Using hospital readmission rates as a hospital quality indicator tied to reimbursement may unfairly penalize a hospital for factors beyond their control.

Birth hospitals strive to limit readmissions knowing the impact they have on the mother, infant and entire family. Interruption in breastfeeding, bonding and overall family disruption, especially if there are other children at home and/or travel is involved, can be especially challenging.

NPIC has been reporting on maternal and inborn readmissions for well over 10 years. Our recent report displaying data for the period 4/1/2017-3/31/2018 shows the overall NPIC Perinatal Center Data Base for maternal readmissions to be 1.0% of delivered women discharged to home and readmitted within 30 days (the CMS cutoff) and 1.1% within 42 days, the usually defined postpartum period. An analysis of the coded reasons driving these readmissions shows 42.3% for hypertension, 18.7% for major puerperal infection, 14.4% for delivery complications including surgical, and 8.1% for selected infections with the balance made up of cardio/pulmonary, obstetric thrombosis/pulmonary embolism and other conditions including pre-existing conditions. The NPIC Trend Data Base, made up of all the hospitals that have been participating in the data base for the analytic period CY 2013- Q1, 2018 shows a significant upward trend in postpartum readmissions from 1.0% in CY 2013 to 1.1% in Q1, 2018.

We know that these obstetric readmission rates are slightly understated since some mothers, especially those delivered at a subspecialty hospital, may seek care at a local facility and their readmission may not be captured by the delivery hospital. We suspect this number is no more than .1-.2% given other analyses we have performed on closed systems that capture all maternal readmissions to any hospital within the system.

The NPIC Perinatal Data Base newborn readmission rate for the same period was also 1.1%. This rate includes newborns born in the hospital that were discharged to home and readmitted within 28 days. More than half of the newborn readmissions were for jaundice and related conditions (55.8%), 7.5% for feeding problems, 6.8% for temperature regulation, 6.0% for respiratory problems, 4.1% for infections and, a notable 19.9%, for a wide range of "other" coded problems.

In a 2013-2017 trend analysis of newborns discharged to home and readmitted within 7 days, we found the readmission rate fell from .8% to .7%, more than a 10% decline.

NPIC is planning to conduct a special analysis mirroring the Clapp article and looks forward to sharing those results in a future Neonatology Today article.

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4. *ICD 10 codes within each category can be obtained by contacting mservices@npic.org.*

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Reference: 1. Data on file. Hampton, NJ: Mallinckrodt Pharmaceuticals.

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INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

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INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

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Wean from INOmax. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

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 US-1800236 August 2018

NICU Transition Planning with Military Families

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The National Perinatal Association (NPA)is an interdisciplinary organization that strives to be a leading voice for perinatal care in the United States. Our diverse membership is comprised of healthcare providers, parents & caregivers, educators, and service providers, all driven by their desire to give voice to and support babies and families at risk across the country.

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Much attention has focused on the stress of NICU admission and the trauma experienced by families when their newborn is admitted to the neonatal intensive care unit (NICU). Much less attention has been paid to the stress of hospital discharge. However, the transition from the NICU to home, once again, changes a NICU family's entire world. How the discharge process occurs is vital to ensuring the competence and confidence of primary caregivers and a safe transition from NICU to home for infants and their families. When the family is part of the military, there are additional factors and special circumstances to keep in mind during transition planning. Since the United States has approximately 1.3 million active-duty troops, 865,000 individuals in reserve, and approximately 200,000 active troops deployed in more than 170 countries, NICU transition planning affects a large number of military families and deserves special attention.

There are two related concepts involved in this transition process for every family: 1) the discharge readiness of NICU families and 2) the discharge preparation program used by the NICU. NICU discharge readiness implies that the primary caregivers have attained technical skills and knowledge, have developed confidence with infant care and are experiencing emotional comfort with the discharge plans. NICU discharge preparation is the process of facilitating discharge readiness to successfully make the transition from the NICU to home. Discharge readiness is the desired outcome for families, and discharge preparation is the process used by the NICU to achieve that goal.

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We have discussed NICU discharge readiness and preparation in more detail in the October and November 2015 issues of Neonatology today (respectively). Briefly, every family needs the following:

- NICU discharge preparation to begin shortly after admission and continue until families are prepared to take their infant(s) home
- Inclusion of the family as full partners in the discharge planning process following the tenets of family-centered care
- A NICU discharge preparation program that includes all of the following: 1) well-defined discharge teaching philosophy, 2) structured education program tailored to the family's specific needs and circumstances, 3) defined curriculum, 4) family assessment of discharge readiness; and 5) process for the transition of care to a medical home

After a NICU family has completed the structured education program with its well-defined curriculum is a potentially optimal time to have a family assessment (a key component of a successful discharge process). The goal of a family assessment would be to better understand the family's specific needs and circumstances. A family assessment could include some of the following questions: what is is the family structure, what are the social support systems, what does the family think of its social support systems, are they adequate, what potential barriers to learning does the family have, what is their home environment like, are there financial considerations to take into account, are there transportation challenges, how much previous experience does the family have, what are their coping habits and styles, and how equipped are they to handle their infant at home? Determining if a family has a military connection is part of the family assessment.

Discharge transition planning for military families

In addition to the common issues, military families often have deployment, relocation, and support considerations that affect their discharge transition planning. With this in mind, when holding discharge planning meetings or teaching sessions with military families, allow for more lead time and be flexible with the timing to allow parents to be able to participate. If one of the parents is either deployed or at an away-training, the medical team could offer remote discharge teaching using video or video chat (e.g. Skype, FaceTime, ZOOM, etc.) to allow the inclusion of both parents. Relocation issues frequently arise for military families. It is important to assess where the family is currently and where they are going to be after transition from the NICU to ensure they are connected with proper resources. A discharge family assessment would ascertain if the family is anticipating a move to a new duty location within the next 6 months. This information will help to better plan for coordinated ser-

vices.

Military families can receive medical care in both military and civilian settings. The military has an electronic medical record that can follow the family regardless of which military facility they receive medical care. When military families are cared for in civilian facilities, their records are not automatically transferred to the military medical record. Therefore, it is important to provide military families with copies of their pertinent medical records from civilian medical settings that they may take with them to military medical system or to other civilian medical settings. Discharge summaries should contain information on how to obtain a copy of medical records if needed.

In addition to the traditional support programs, military families have support programs specifically designed for them. For example, the Military OneSource (Military family support) provides information and referrals to services and resources available wherever the family is located nationally and internationally. They can also provide information on obtaining needed financial support, medical supplies, and baby care equipment if family will be getting relocated and the baby will have ongoing medical needs after discharge. Military OneSource can be contacted at 800-342-9647 or www.militaryonesource.mil. Non-medical supportive counseling is also available in-person or on-line for any member of the family should there be a need.

The Exceptional Family Member Program (EFMP) is a mandatory enrollment program that works with either military and civilian agencies to provide comprehensive and coordinated community support, housing, educational, medical, and personnel services to families that have a member with special needs. The EFMP can help ensure a family does not get moved to an area that doesn't have the needed services.

The Red Cross is a resource for military families when the medical team feels there is a life and death emergency for the infant or parent and the active duty parent needs to be returned from deployment or training. In these situations, the hospital or community Red Cross office can be contacted to initiate the process of getting the command's permission to bring the military member home.

Discharge readiness should not be assumed at the time of discharge, but rather, should be actively planned for and assessed. Each NICU should make every effort to make sure that parents are prepared for discharge to prevent untoward events after discharge and to support this important transition for NICU graduates and their families. Each NICU should also conduct regular evaluations of their discharge preparation program to allow improvement over time. With an active process that included discharge planning begun shortly after admission, structured education, and attention to the family's needs, circumstances and resources, the transition to home can be smooth, even in the most complex cases.

TAKE HOME POINTS

1. When planning for discharge of a NICU baby, it is important for the medical team to be aware if the family is involved in the military to ensure a reasonable discharge teaching timeline and to ensure appropriate resource allocation.
2. Military families often receive care in both military and civilian medical settings. In fact, most families have a hybrid, so it is important that their civilian medical records be provided to them to help ensure appropriate continuity of care.
3. A NICU discharge preparation program should include all of the following: 1) well-defined discharge teaching philosophy, 2) structured education program, 3) defined curriculum, 4) family assessment of discharge readiness, and 5) process for the transition of care to a medical home.
4. There are special support programs designed to help with the unique needs of military families. Clinicians should be aware of how to direct military families to access this information.

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State of the Art: Bowel Ostruction in the Neonate

Theodore V. De Beritto, MD, Mario Zaritzky, MD, Joseph R. Hageman, MD

IIntroduction

Bowel obstructions are one of the most common surgical emergencies in the newborn period. The etiology is often related to four main factors: environmental exposures, genetic predisposition, vascular events, or developmental prematurity. The incidence of such events is about 1 in every 2000 live births [Juang 2012]. The most successful management comes with the timely recognition of initial symptoms, appropriate diagnosis, and selection of the necessary intervention.

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- Environmental Exposures: can include both intrauterine and extrauterine events that are associated with maternal nutrition, maternal disease (such as small left colon syndrome from maternal diabetes), intrauterine hypoxia, or factor dysregulation (such as Insulin Like Growth Factor).
- Genetic Predisposition: includes syndromes like VACTERL (vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal anomalies, renal or radial anomalies, and limb abnormalities) that are associated with conditions that can result in a possible obstruction.
- Vascular Events: most often thromboembolic. In utero, thrombosis of the superior mesenteric artery can lead to conditions such as small bowel atresia (depending on the timing of the insult). Extrauterine embolic events can lead to bowel necrosis.
- Developmental Immaturity or Prematurity: predisposes a newborn to possible underdeveloped anatomy, inadequate peristalsis, possible abnormal intestinal microbiome, and increased risk of perforation.

Key Signs

Bowel obstruction in the newborn period can present differently, it is important to obtain a thorough birth and maternal history as well as perform frequent assessments for evolution of symptoms in each patient [Juang 2012].

Four concerning signs of bowel obstruction include:

- Polyhydramnios on prenatal ultrasound or magnetic resonance imaging
- Emesis: either non-bilious or bilious
- Failure to pass meconium in the first day after birth
- Abdominal distension (depending on level of obstruction)

Types of Obstruction

Different types of bowel obstruction include intrinsic, extrinsic, and intraluminal obstructions. Each obstruction is characterized by the location of obstruction, timing of when the obstruction occurred, and the anatomy affected [de Silva 2006].

- Intrinsic Obstruction: the bowel is obstructed by an indwelling structure or error of embryogenesis that most often affects the patient's anatomy. Examples of such obstructions can be either continuous, as with an esophageal web (the bowel is not interrupted), or interrupted as with duodenal atresia (there is a segmented gap in the mesentery).
- Extrinsic Obstruction: obstruction most commonly caused by compression of the bowel by an overlying anatomical defect (vascular ring or band), twisting of the bowel (volvulus or malrotation), or incarceration (inguinal hernia or duplication cyst).
- Intraluminal Obstruction: caused by a substance, most often meconium (as in the case of meconium ileus or meconium cyst), that is blocking the pathway within the lumen of the bowel [Ladd 194].

Presentation and Anatomy

Foregut: consists of the esophagus, stomach, and duodenum. This section of the gastrointestinal system is vascularized by several different vessels including the inferior thyroid artery, thoracic aorta, intercostal arteries, celiac artery, and superior mesenteric artery. In the newborn period, some of the most common obstructions and abnormalities include:

- Esophageal Atresia with or without Tracheoesophageal Fistula (TEF): This congenital malformation occurs during the 4th week of embryological development and is present in about 1 in every 2,000-4,000 live births. Neonates with this condition may initially present with choking, coughing, and/or cyanosis with the onset of feeding. Milder cases may only present with increased production of secretions. Management after initial resuscitation is primarily surgical. Morbidity and mortality of these patients is directly dependent on the

TEF being an isolated condition (with a better outcome), or as part of a syndrome such as VACTERL [Smith 2014].

- Esophageal Webs and Vascular Rings: Infants with these conditions typically present with feeding difficulties, particularly dysphasia and reflux. The narrowing of the esophagus is caused by 2-3mm thick concentric extensions of the normal esophageal or vascular tissue that can be located anywhere along the esophagus. These findings occur in about 1 in every 25,000-50,000 live births. The management of these malformations is typically medical, but based on the severity of the symptoms can often include surgery to release the strictures [Miller 1968].

- Pyloric Stenosis: This condition is the most common cause of intestinal obstruction in infancy [Pandya 2012]. Infants typically present with non-bloody, non-bilious emesis that can occur intermittently or with every feed. These patients often also have poor weight gain and may develop jaundice. The incidence of this condition is 2 in every 1,000 live births and presents at about 2-6 weeks of postnatal life, predominantly in males. Diagnosis is made by an abdominal ultrasound and the mainstay of treatment is with a surgical pyloromyotomy, which involves the division of the muscles of the

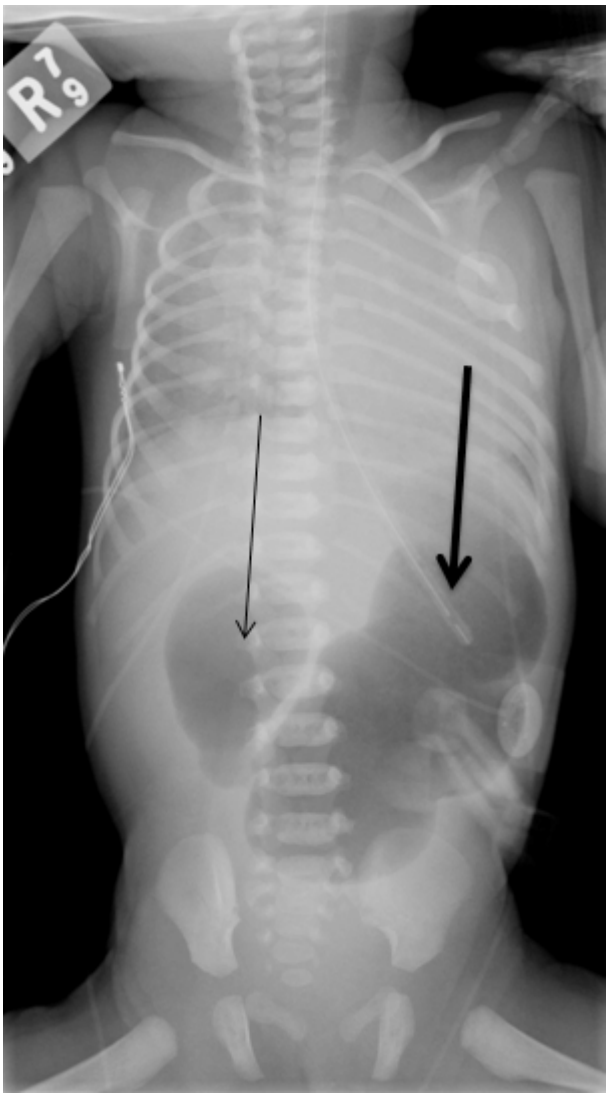

Figure 1. Abdominal radiograph demonstrating the classic "double bubble" sign associated with duodenal atresia (thick black arrow indicates the stomach, thin black arrow indicates the duodenum)

pylorus to promote opening of the gastric outlet.

- Duodenal Atresia: Occurring in about 1 in every 2,500-5,000 live births, this condition is one of the most common surgically treated procedures and is associated with Trisomy 21 in up to 40% of cases. Neonates with this condition present with predominantly bilious vomiting and abdominal distension. After placement of an orogastric tube for decompression and diagnosis with an abdominal radiograph demonstrating the classic "double bubble" sign (Figure 1), the surgical procedure performed is a duodenoduodenostomy, which involves anastomosing two portions of the duodenum in an effort to bypass an obstruction. Long term survival after the procedure is excellent at about 86-90%.

Midgut: consists of the jejunum, ileum, ascending colon and proximal transverse colon. This section of bowel is primarily vascularized by the superior mesenteric artery. The most common obstructions in this portion of the GI system include:

- Jejunoileal Atresia: This particular condition can be defined as a stenosis (with a patent intestinal lumen) or atresia (discontinuous bowel, see Figure 2) and occurs during embryologic development. The neonate often presents with bowel obstruction and symptoms of bilious vomiting and abdominal distension. With a similar incidence to duodenal atresia, the patient is also managed medically and treated surgically [Piper 2008].

"Malrotation, particularly with a volvulus, presents with abdominal pain, distension, and emesis. As bowel can actively necrose, this condition is often emergent and requires surgical intervention."

- Malrotation: This condition can occur at the foregut, midgut, or hindgut during embryologic development, but commonly presents as a midgut volvulus. During normal abdominal development, the GI tract migrates out of the abdominal cavity and rotates 270 degrees around the superior mesenteric vessels before returning back to the peritoneum. This condition emerges when there is an incomplete or non-rotation of the intestines. Malrotation, particularly with a volvulus, presents with abdominal pain, distension, and emesis. As bowel can actively necrose, this condition is often emergent and requires surgical intervention. Intestinal malrotation occurs as often as 1 in every 200-500 live births, but is symptomatic in only 1 in every 6,000 live births. Mortality in this condition can range from 0-14%, with the more acute surgical cases carrying the worst outcomes [Lee 2012].

- Meconium Ileus: Neonates that have not passed meconium within the first 24-48 hours after birth warrant further investigation. Meconium related issues include several different conditions: meconium plug syndrome (functional colonic obstruction by a solid meconium mass, see Figure 3), meconium ileus-equivalent syndrome (first presentation of conditions like cystic fibrosis), and meconium peritonitis (perforation of the bowel related to meconium accumulation). In each of these conditions, patients present with abdominal distension and bilious emesis. The hallmark of diagnosis is with radiography. Further testing may be indicated, such as in the situation where cystic fibrosis is suspected, and therefore, sweat chloride testing should be undertaken. Treatment can include both medical (water soluble contrast enema) and surgical intervention and varies with the acuity of the patient and the treatment of the underlying disease [Takacs 2014].

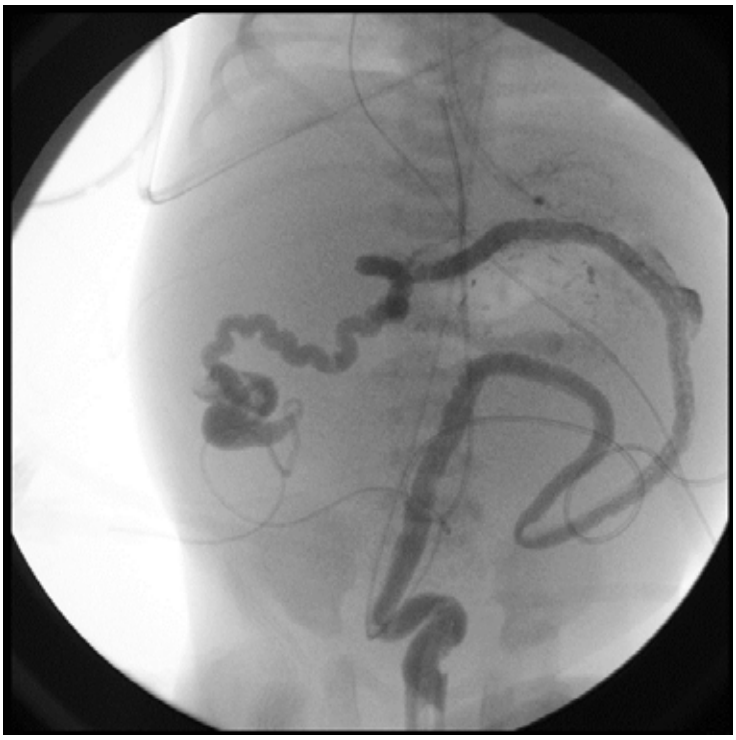

Figure 2. Barium enema demonstrating jejunoileal atresia with microcolon

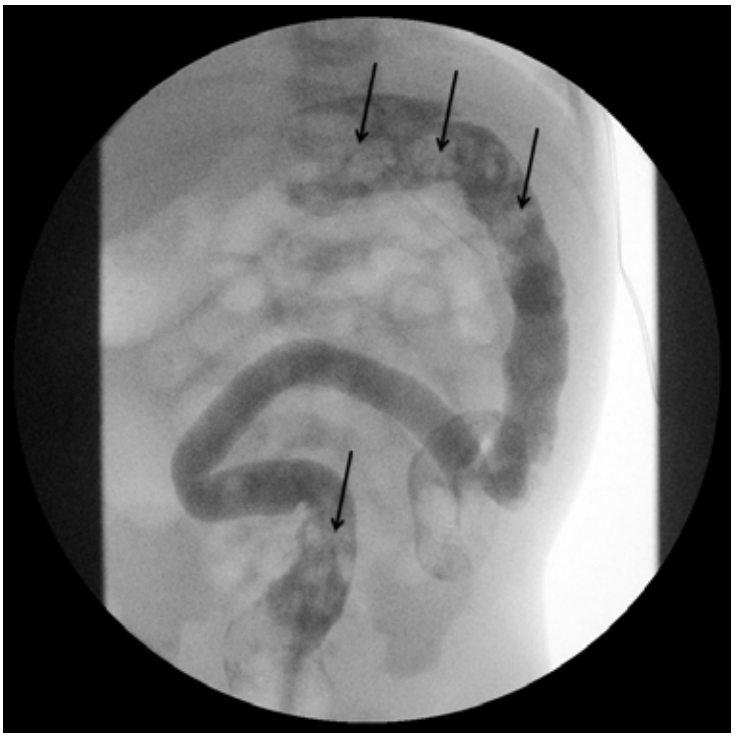

Figure 3. Contrast enema demonstrating meconium plug syndrome (black arrows indicate meconium pellets)

Hindgut: consists of the distal transverse colon, descending colon, sigmoid colon, and the rectum. The blood supply to the proximal portion is supplied by the inferior mesenteric artery and the rectum is supplied by the internal iliac vessels. Obstructions affecting this portion of bowel include:

- Hirschsprung's Disease: This condition should be considered when a newborn has not passed meconium within the first 24-48 hours after birth or in a child who has had chronic constipation since birth. Other symptoms include bilious vomiting, poor feeding, and abdominal distension. Approximately 1 in every 5,400-7,200 live births are affected, with a 4:1 predilection toward males. Initial abdominal radiograph will demonstrate bowel distension or obstruction and possibly an empty rectum. A barium enema may demonstrate a "transition zone" between the normally-innervated proximal bowel which becomes dilated, to the aganglionic distal portion of the bowel which will appear more narrow in caliber (see Figure 4). A suction or full thickness biopsy of the rectum is necessary for diagnosis. The tissue obtained will demonstrate poorly innervated submucosal (Meissner) plexus and myenteric (Auerbach) plexus as a result of disrupted neuronal migration in utero. Treatment is surgical with removal of the poorly innervated tissue and re-anastomosis of viable bowel [Butler 2013].

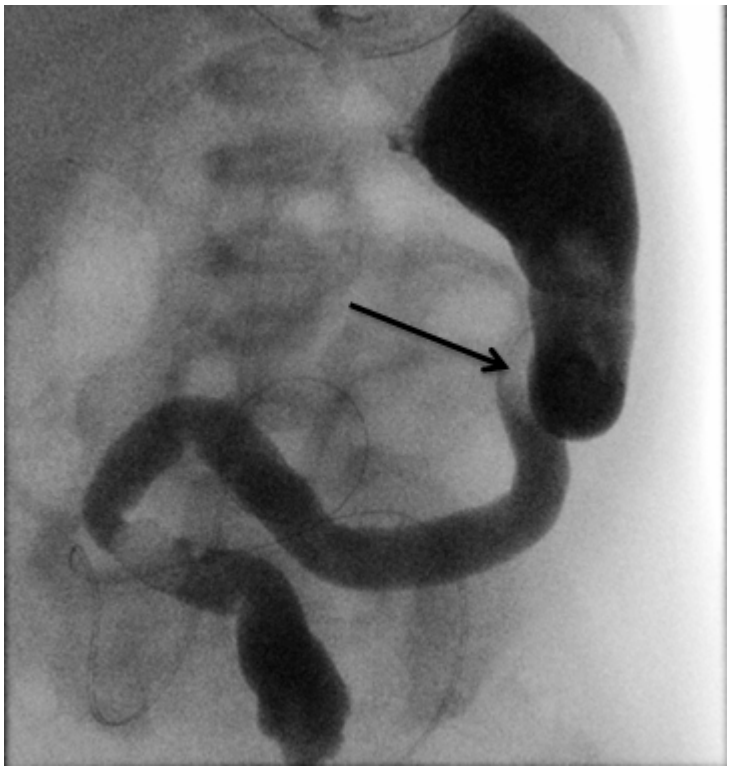

Figure 4. Contrast enema demonstrating the "transition zone" (black arrow) between the normally-innervated but dilated proximal bowel to the narrow, aganglionic distal bowel which can be seen in Hirschprung Disease

- Small Left Colon Syndrome: This condition is defined by the change in luminal caliber of the left colon at or near the splenic flexure. It is theorized that this condition is neural or drug-induced in nature. In about half of the cases, there will be a history of maternal gestational diabetes mellitus. Neonates will often present with abdominal distension and signs of distal obstruction, most prominently, a failure of meconium passage within the first 24-48 hours after birth. Treatment after initial resuscitation is a contrast enema that is both diagnostic and therapeutic in nature.
- Imperforate Anus: Though most commonly associated with a syndrome such as VACTERL or Trisomy 21, this condition can also occur as an isolated finding. As the structures of the anus are malformed, the muscles, nerves, and vessels that supply this portion of the GI system can also have a similar degree of malformation. The most severe cases can include the spine and urogenital region as well. These infants are first diagnosed during initial physical examination or when the patient has failed to pass meconium. These anorectal malformations occur in about 1 in every 5,000 live births. Management is surgical with the creation of an anal opening and pulling viable bowel through to create functional anorectal anatomy [Pena 1995]. Anorectal malformations may also be associated with an entero-vaginal fistula in female newborns.

The section above includes conditions listed under the locations at which they are most commonly found, although many of these conditions can be found in other portions of the bowel. For example, atresias, webs, and vascular rings can be found throughout the bowel.

Diagnostic Evaluation

With neonatal bowel obstruction and other abdominal pathology, the basis of diagnosis lies with imaging. Once the neonate presents with signs of obstruction (such as emesis, abdominal distension or delay in meconium passage) it is paramount to begin an immediate work-up. Depending on the level of obstruction relative to the Ampulla of Vater, the emesis may be bilious. Obstructions distal to the Ampulla will likely produce bilious emesis that is dark green in color. Furthermore, the level of obstruction is also correlated with abdominal distension. The more distal the obstruction, the more likely the neonate is to have abdominal distention. These physical exam findings are vital in determining which imaging modality to select, see Figure 5 for a diagnostic flowsheet.

Beginning with abdominal radiography and ultrasonography (in cases of pyloric stenosis), valuable information can be obtained. In consultation with a radiologist, the imaging modalities below can often be key in choosing the next steps of intervention and can be curative in some conditions.

- Abdominal Radiography (See Figure 6)
- Upper GI with Contrast
- Contrast Enema
- Abdominal Ultrasound (if Pyloric Stenosis is Suspected)

Treatment

Non-Operative Management

With proximal bowel obstruction, the patient may begin to exhibit signs of fluid loss and electrolyte imbalance from excess vomiting. With distal obstructions, the patient may also exhibit abdominal distension and sequestration of fluid within the bowel lumen. To reduce morbidity and mortality, it is important to manage these symptoms as they occur.

- Fluid Resuscitation: to correct fluid loss and electrolyte imbalance. This can be accomplished mainly through administration of intravenous fluids. If the neonate is demonstrating significant bleeding or coagulopathy in combination with hypovolemia, administration of packed red blood cells or fresh frozen plasma may be necessary. The amount of fluids should be titrated to changing lab values and frequent as-

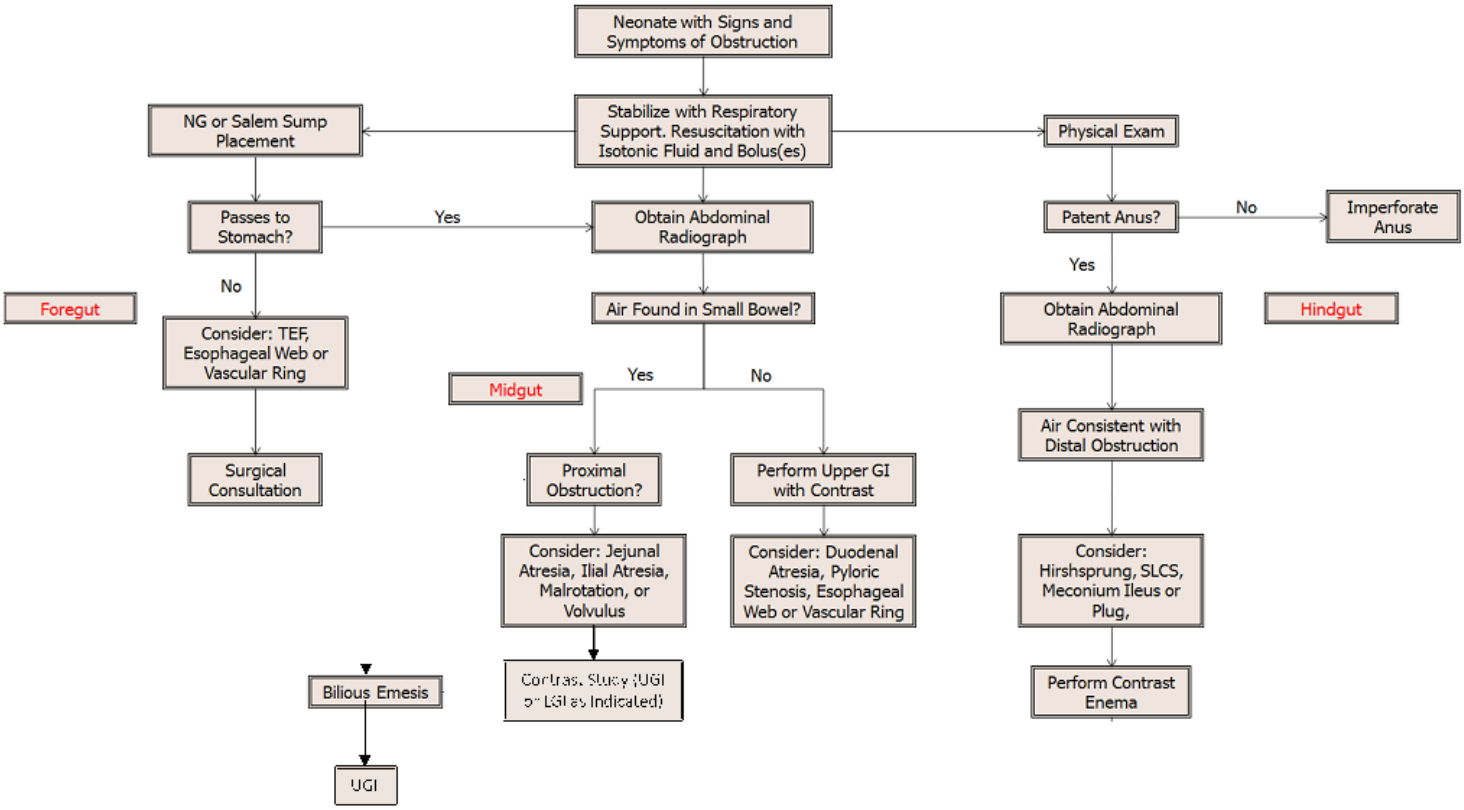

Figure 5. Pathway for diagnosis of a newborn bowel obstruction. TEF (Tracheoesophageal Fistula), SLCS (Small Left Colon Syndrome), UGI (Upper Gastrointestinal Tract Radiography), LGI (Lower Gastrointestinal Tract Radiography) [Adapted from De Beritto 2016]

sessment of vital signs, nasogastric tube and urine output, total intake and output, and perfusion status.

- Gastric Decompression: usually performed via dual lumen nasogastric tube which can be placed to suction. This helps to remove excess air and fluid from the GI tract (via continuous or intermittent suction) as well as provide bowel rest.

- Respiratory and Cardiovascular Support: this may be necessary and accomplished through endotracheal intubation for respiratory support and/or use of volume resuscitation and vasopressor medications, as needed, to ensure hemodynamic stability.
- Bowel Rest: Enteral feedings should be discontinued and the babies made nil per os (NPO) to provide bowel rest.

- Antibiotics: In the case of suspected infection, empiric antibiotics may be started. However, the routine use of "broadened" antibiotic coverage of anaerobic organisms is not recommended, unless there is concern for bowel perforation. Patients with significant bowel distension or inflammation are at increased risk for bacterial translocation for which IV antibiotics should be considered. Blood cultures should always be sent prior to the initiation of antibiotics.

Operative Management

With consultation from a pediatric surgeon, some bowel obstructions will need to be managed operatively. Once stable from a hemodynamic and electrolyte standpoint, the patient can be taken for surgery. The basis of surgical management involves the removal of necrotic tissue, decompression of any ring or vascular abnormality, and/or correction of any anatomical defect.

Post-Operative Management

In the immediate post-operative period, derangements in electrolytes, hemodynamics, respiratory status, and fluid balance can occur. This is usually managed through vital sign monitoring, assessing for peripheral perfusion, observing urine output, and providing adequate respiratory support. Further management includes:

- Bowel Rest and Gastric Decompression: as in the preoperative period, NPO status and the use of a dual lumen nasogastric tube are necessary to rest the bowel during the healing period.

- Total Parenteral Nutrition (TPN): IV nutrition is necessary to meet the patient's nutritional goals prior to the establishment of enteral feeding. In the immediate post-operative period, the intestinal mucosa may need time to heal and regenerate. As the recovery process continues, slow initiation of enteral feeds can be accomplished beginning with trophic feeds and advancing as tolerated by the patient.

- Antibiotic Therapy: in the immediate post-operative period, patients are often placed on broad spectrum antibiotic coverage. The duration of the course is dependent on the patient's condition and if there was any bowel perforation at the time of surgery.

Complications

Complications in the post-operative period are most commonly strictures and adhesions. In the newborn with a bowel obstruction, about 10% will have a stricture at the operative site, while 5% of patients will have a stricture or adhesion at another site along the GI tract depending on the etiology of the obstruction [de la Hunt 2006]. Other complications include: impaired gut motility or prolonged ileus (from decreased bowel use), malabsorption or short-gut syndrome (related to remaining gut length, removal of the ileocecal valve or amount of bowel ischemia at time of diag-

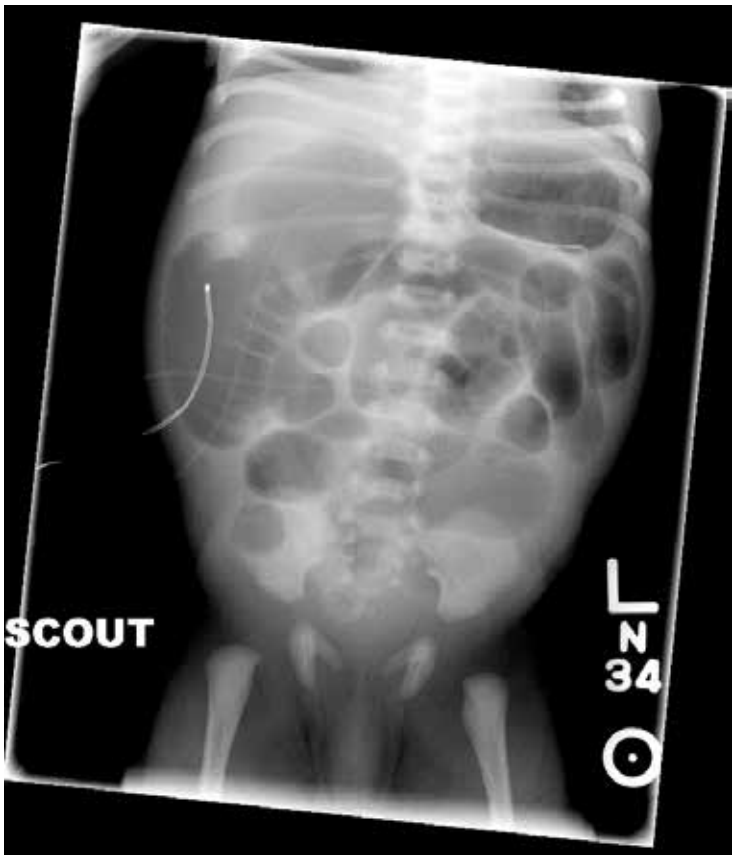

Figure 6. Abdominal radiograph demonstrating bowel obstruction with abdominal distension and no distal air

nosis), and local or systemic infection (related to catheter use or intraoperative infection).

Prognosis

Morbidity and mortality of newborn bowel obstruction varies with the condition and the time to diagnosis. For conditions like meconium ileus and small left colon syndrome, prognosis is good and often curative after initial intervention. For surgical cases, the morbidity and mortality are often related to the amount of bowel resected. In cases with extensive bowel necrosis, the mortality can be as high as 65-75% [de la Hunt 2006]. It is important to recognize that any delay in time to intervention may lead to an increase in morbidity and mortality.

Infants can be considered for discharge home once they have demonstrated adequate caloric intake and weight gain on enteral feeds, and are otherwise stable. Rarely, infants with severely compromised gut lengths may require TPN at the time of discharge. Furthermore, they should have no signs of further obstruction, laboratory values that have returned to normal, and if surgical intervention was necessary, they should have recovered and regained GI function appropriately. Follow-up for these patients is usually with a primary care physician, GI specialist, and with the surgical service (as needed).

Other Considerations

Though most cases of newborn bowel obstruction are sporadic events, it is important to consider other factors that may have contributed. It is necessary to obtain a thorough maternal history as some maternal conditions can contribute to newborn findings. If the patient exhibits abnormal features after complete physical examination, it may also be necessary to consult Genetics for further consideration of a possible syndrome [De Beritto 2016].

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June 13, 2019
The California Endowment
Downtown Los Angeles

"Infants and Kids Win - Graduate Medical Education Law Completed for Next Five Years"

Darby O'Donnell, JD

The Alliance for Patient Access (allianceforpatientaccess.org), founded in 2006, is a national network of physicians dedicated to ensuring patient access to approved therapies and appropriate clinical care. AfPA accomplishes this mission by recruiting, training and mobilizing policy-minded physicians to be effective advocates for patient access.

This past month, Members of Congress and pediatric patient advocates were enthused when President Trump signed H.R. 5385, the Dr. Benjy Frances Brooks Children's Hospital Graduate Medical Education Support Reauthorization Act of 2018 (CHGME).

While this is a widely supported program, CHGME requires reauthorization, i.e. renewal, by Congress every few years to remain viable as a program and to maintain the programmatic funding provided within the program.

This reauthorization will ensure funding is available for five more years, through 2023.

"The program provides funding for medical training in children's hospitals for pediatric medical residents, with a $25 million increase over the current funding level, for a total of $325 million per year."

The legislation, like the program, has garnered broad, bipartisan support since it was first created in 1999 as a response to the lack of available funding to train pediatric specialists. The program provides funding for medical training in children's hospitals for pediatric medical residents, with a $25 million increase over the current funding level, for a total of $325 million per year.

One of the bill's sponsors, the current ranking member on the House Energy and Commerce Committee's Health Subcommittee, Rep. Gene Green (D-Texas) provided that: "Hospitals that receive the funding represent less than one percent of all hospitals but train half the country's pediatricians and pediatric specialists."

Rep. Green also noted that freestanding children's hospitals do not receive "much Medicare reimbursement because their patient population is primarily under 18."

A primary purpose of the program is to encourage the development of a stronger pediatric workforce. Since its inception, CHGME has steadily increased the number of pediatric specialists and has strengthened those specialties. It has also helped to "enhance pediatric research capabilities, and care for vulnerable and underserved children" in children's hospitals, as noted by the House Republican Policy Committee.

Importantly, the majority of pediatric subspecialists trained at children's hospitals are direct beneficiaries of CHGME. "In some fields — such as pediatric rehabilitation medicine — virtually all physicians receive their training at CHGME hospitals," according to the Children's Hospital Association (CHA). Other pediatric specialists, such as pediatric anesthesiologists, otolaryngologists, geneticists, and pathologists also benefit from the program.

Finally, CHA notes that eligible facilities training these providers, including 58 children's hospitals that receive CHGME funding, train approximately half of the nation's pediatricians - more than 7,000 annually. Eligible hospitals supported by CHGME have "collectively increased their residency training by 113 percent."

"Eligible hospitals supported by CHGME have "collectively increased their residency training by 113 percent."

Enactment of this vital legislation helps to continue the increase in specialists and subsequently counteract shortages in certain pediatric specialist populations, a win for infants and children who benefit directly from access to these highly trained professionals and who require unique care specific to their growing bodies.

NT

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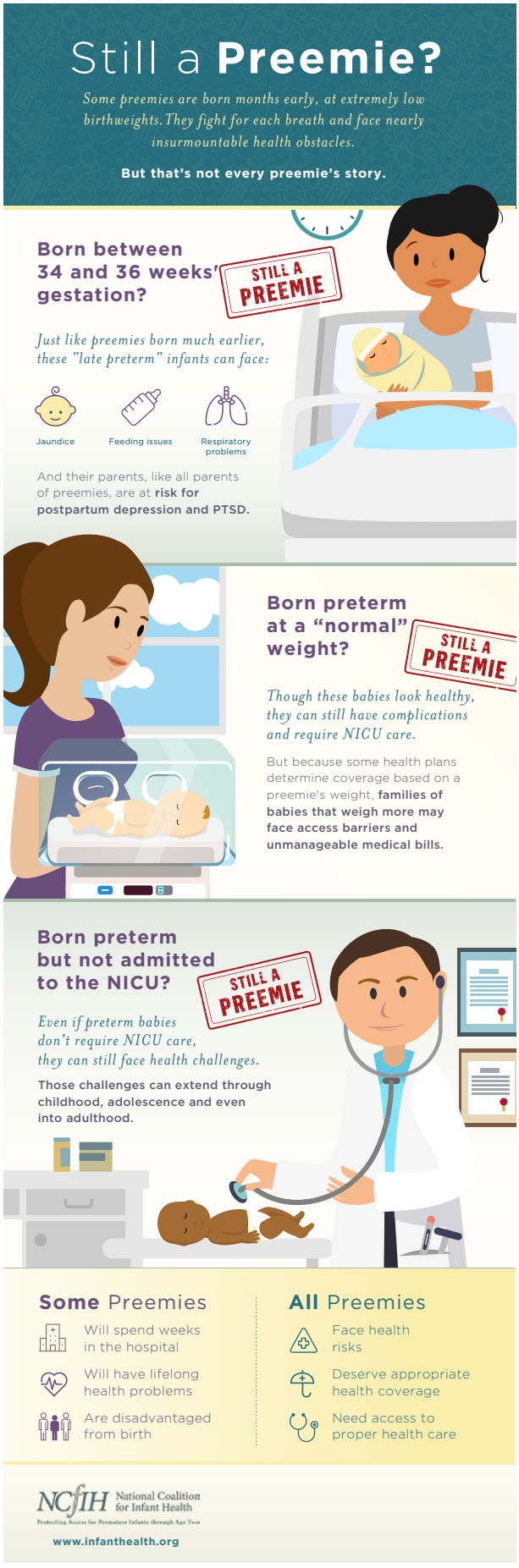

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Compiled and Reviewed by Mitchell Goldstein, MD Editor in Chief

Study: Ways to Maximize Nutrition and Growth for the Smallest Preemies

Automated tool is needed to rapidly calculate nutritional intake for very low birth weight infants during transition from IV nutrition to feeds through the gut.

Released: 30-Aug-2018 11:05 AM EDT

Source Newsroom: Ann and Robert H. Lurie Children's Hospital of Chicago

Newswise — The tiniest of premature infants – weighing just over two pounds at birth on average – start out receiving nutrition intravenously. Over the next several days or weeks, they are transitioned to enteral (or through the gut) feeds, often delivered through feeding tubes if the baby still cannot suck or swallow. During this transition, preemies are fed through a mixture of methods, but the total protein intake tends to drop, which interferes with growth. To help clinicians maximize nutrition and growth in these infants, researchers quantified the gains and losses of different nutrition delivery practices during the transition to enteral feeds. Their results were published in The Journal of Pediatrics.

"Growth and nutrition are essential for premature babies, since as they get bigger they generally require less intervention," says lead author Gustave Falciglia, MD, MSc, neonatologist at Ann & Robert H. Lurie Children's Hospital of Chicago and Assistant Professor of Neonatal-Perinatal Medicine at Northwestern University Feinberg School of Medicine. "Our study provides important information to help neonatologists assess the total nutritional effects of their combined orders as they gradually decrease intravenous nutrition and increase enteral feeds."

Currently, the electronic health record does not calculate the total nutrition babies receive from various nutritional delivery practices during the transition to full enteral feeds. Managing optimal nutrition during the transition is a complex process and the study suggests that an automated system is needed to help clinicians weigh the tradeoffs in calorie and protein intake with different nutrition delivery practice decisions.

"Ultimately, we would like to develop an automated tool to provide immediate feedback on the calories and protein the baby is getting through multiple vehicles used to deliver nutrition during the transitional stages," says Dr. Falciglia. "This would substantially help clinicians optimize nutrition and growth in very low birth weight infants."

The study was a retrospective analysis of detailed nutritional and fluid data received by 115 very low birth weight infants over 4,643 days at Lurie Children's regional neonatal intensive care unit (NICU). The median gestational age was 28 weeks and median birth weight was 1,060 grams. Infants admitted within the first week of life and discharged after the first month of life were included. The study excluded infants with chromosomal abnormalities or congenital anomalies because of the uncertain influence these conditions may have had on metabolism and growth.

Changes in calories and protein intake were estimated during five transition phases from full intravenous nutrition to full enteral nutrition. In each phase, researchers determined the effects of nutrition delivery practices including intravenous nutrition, intravenous lipids, central line, feeding fortification, fluid restriction and excess non-nutritive fluid intake. Based on their findings, the authors recommend specific approaches to maximize calorie and protein intake during various transition phases.

Research at Ann & Robert H. Lurie Children's Hospital of Chicago is conducted through the Stanley Manne Children's Research Institute. The Manne Research Institute is focused on improving child health, transforming pediatric medicine and ensuring healthier futures through the relentless pursuit of knowledge. Lurie Children's is ranked as one of the nation's top children's hospitals in the U.S.News & World Report. It is the pediatric training ground for Northwestern University Feinberg School of Medicine. Last year, the hospital served more than 208,000 children from 50 states and 58 countries.

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NT

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Current URL: www.cme.hsc.usf.edu Click on *course calendar*, then sort by month (March 2019)
Future URL: www.thegravensconference.com

Questions? Email the meeting planner at brose@health.usf.edu

Highlights include: Two receptions, dinner cruise, and presentation of Gravens Award

American Academy of Pediatrics, Section on Advances in Therapeutics and Technology Membership Drive (Originally posted in NT June, 2018)

American Academy of Pediatrics (AAP), Section on Advances in Therapeutics and Technology (SOATT) announces a membership drive

The American Academy of Pediatrics' Section on Advances in Therapeutics and Technology (SOATT) invites you to join our ranks! SOATT creates a unique community of pediatric professionals who share a passion for optimizing the discovery, development and approval of high quality, evidence-based medical and surgical breakthroughs that will improve the health of children. You will receive many important benefits:

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- Network with other pediatricians, pharmacists, and other health care providers to be stronger advocates for children.
- Invitation for special programming by the Section at the AAP's National Conference.
- Access to and ability to submit research abstracts related to advancing child health through innovations in pediatric drugs, devices, research, clinical trials and information technology; abstracts are published in Pediatrics.

AAP members can join SOATT for free. To activate your SOATT membership as an AAP member, please complete a short application at http://membership.aap.org/Application/AddSectionChapterCouncil.

The Section also accepts affiliate members (those holding masters or doctoral degrees or the equivalent in pharmacy or other health science concentrations that contribute toward the discovery and advancement of pediatrics and who do not otherwise qualify for membership in the AAP). Membership application for affiliates: http://shop.aap.org/aap-membership/ then click on "Other Allied Health Providers" at the bottom of the page.

Thank you for all that you do on behalf of children. If you have any questions, please feel free to contact:

Mitchell Goldstein, MD, FAAP, Section Chairperson, MGoldstein@llu.edu and

Christopher Rizzo, MD, FAAP, Membership Chairperson, crizzo624@gmail.com

NT

Masimo Announces FDA Clearance of the rainbow Acoustic Monitoring® RAS-45 Sensor for Infant and Neonatal Patients

An acoustic sensor for monitoring neonatal patients.

Irvine, California – September 10, 2018 – Masimo (NASDAQ: MASI) announced today FDA clearance of RAS-45, an acoustic respiration sensor for rainbow Acoustic Monitoring® (RAM®), for infant and neonatal patients. RAM could previously be used to monitor adult and pediatric patients greater than 10 kg using RAS-125c and RAS-45 sensors. With clearance of the RAS-45 sensor for infant and neonatal patients, acoustic respiration rate measurement is now, for the first time, possible for patients of all sizes, including neonates, in the United States.

RAM noninvasively and continuously measures respiration rate using an innovative adhesive sensor with an integrated acoustic transducer, the RAS-45 and RAS-125c, applied to the patient's neck area or, for infant and neonatal patients under 10 kg, the chest. Using acoustic signal processing that leverages Masimo Signal Extraction Technology® (SET®), the respiratory signal is separated and processed to display continuous respiration rate (RRa®) and an acoustic respiration waveform, a visualization of the vibrations caused by the patient's airflow. The acoustic sensor also allows clinicians to listen to the sound of a patient's breathing, whether at the bedside, through a point-of-care device like the Radical-7® Pulse CO-Oximeter®, or remotely, from a Patient SafetyNet™ view station.

The RAS-45 sensor for infant and neonatal patients offers multiple benefits of particular importance for successfully monitoring these youngest and most fragile patients. With the clearance for newborns and neonates, RRa's accuracy range has been expanded up to 120 breaths per minute, while still providing accuracy of ± 1 breath per minute, facilitating accurate measurement of the higher respiratory rates common in this population. The sensor itself is significantly smaller than the RAS-125c sensor, and in fact with a diameter of ap-

proximately 2.2 cm without adhesive is only slightly larger than a nickel. Similarly, it weighs so little, 13 grams, that its presence may be barely noticeable, and features an adhesive that is transparent, light, and flexible. The size, weight, and adhesive advantages make it particularly suitable for the smaller stature and delicate skin of infants and neonates.

RRa has been shown not only to be accurate[1,2] and reliable[1], but also easy-to-use1, easy-to-tolerate[1,3], and to enhance patient compliance with respiration monitoring. In a study comparing pediatric patient tolerance of sidestream capnography with a nasal cannula to respiration rate monitoring with an RAS-125c acoustic sensor, 15 out of 40 patients removed the capnography cannula, while only one removed the RAM acoustic sensor.[3] In a study of 98 patients consciously sedated during upper gastrointestinal endoscopy, researchers found that RRa monitoring with the RAS-125c sensor more accurately assessed respiration rate than impedance pneumography.[2]

Joe Kiani, Founder and CEO of Masimo, commented, "From the beginning, we have focused our R&D on neonates and children for many reasons, including our belief that helping clinicians care for children will provide more benefit to society. RAM harnesses the power of our breakthrough signal processing and sensor technology and applies it to a measurement that has either been unreliable or difficult to use, respiration measurement, the third vital sign."

RAM is available on most rainbow SET™-ready platforms. Continuous monitoring of respiration rate can be helpful in cases such as sedation-based procedures and post-surgical patients receiving patient-controlled analgesia for pain management.[4,5]

@MasimoInnovates || #Masimo

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About Masimo

Masimo (NASDAQ: MASI) is a global leader in innovative noninvasive monitoring technologies. Our mission is to improve patient outcomes and reduce the cost of care. In 1995, the company debuted Masimo SET® Measure-through Motion and Low Perfusion™ pulse oximetry, which has been shown in multiple studies to significantly reduce false alarms and accurately monitor for true alarms. Masimo SET® has also been shown to help clinicians reduce severe retinopathy of prematurity in neonates,[1] improve CCHD screening in newborns,[2] and, when used for continuous monitoring with Masimo Patient SafetyNet™ in post-surgical wards, reduce rapid response activations and costs.[3,4,5] Masimo SET® is estimated to be used on more than 100 million patients in leading hospitals and other healthcare settings around the world, 6 and is the primary pulse oximetry at 9 of the top 10 hospitals listed in the 2018-19 U.S. News and World Report Best Hospitals Honor Roll.7 In 2005, Masimo introduced rainbow® Pulse CO-Oximetry technology, allowing noninvasive and continuous monitoring of blood constituents that previously could only be measured invasively, including total hemoglobin (SpHb®), oxygen content (SpOC™), carboxyhemoglobin (SpCO®), methemoglobin (SpMet®), Pleth Variability Index (PVi®), and more recently, Oxygen Reserve Index (ORi™), in addition to SpO2, pulse rate, and perfusion index (Pi). In 2014, Masimo introduced Root®, an intuitive patient monitoring and connectivity platform with the Masimo Open Connect® (MOC-9®) interface, enabling other companies to augment Root with new features and measurement capabilities. Masimo is also taking an active leadership role in mHealth with products such as the Radius-7® wearable patient monitor, iSpO2® pulse oximeter for smartphones, and the MightySat™ fingertip pulse oximeter. Additional information about Masimo and its products may be found at www.masimo.com. Published clinical studies on Masimo products can be found at http://www.masimo.com/evidence/featured-studies/feature/.

ORi has not received FDA 510(k) clearance and is not available for sale in the United States.

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NT

Federal grant to support prenatal, early childhood program

New Neonatal Perinatal grant program.

Updated 2:53 am CDT, Monday, October 8, 2018

FRANKFORT, Ky. (AP) — Kentucky officials say a new $7.5 million grant will support a statewide program aimed at decreasing the number of premature deliveries and low birth weight babies.

The state Cabinet for Health and Family Services say the federal grant will support the Maternal, Infant and Early Childhood Home Visiting Program, often called Kentucky's HANDS program.

Officials say the program is offered in all 120 Kentucky counties through local health departments. It serves high-risk populations by providing assistance to overburdened parents during the prenatal period until a child's third birthday.

They say the outcomes of the home visitation program include decreased maternal complications in pregnancy, fewer premature deliveries, fewer low birth weight babies and a decrease in child abuse and neglect.

Officials say the program is offered in all 120 Kentucky counties through local health departments. It serves high-risk populations by providing assistance to overburdened parents during the prenatal period until a child's third birthday.

They say the outcomes of the home visitation program include decreased maternal complications in pregnancy, fewer premature deliveries, fewer low birth weight babies and a decrease in child abuse and neglect.

In the 2017 fiscal year, the program served about 4,040 participants.

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NT

Outcomes worse for Hispanic infants with congenital heart diseases

Hispanic infants born with heart disease have worse outcomes in the first year than those born to white mothers.

Health News Oct. 10, 2018 / 11:08 AM

By Allen Cone

Oct. 10 (UPI) -- Hispanic infants born with heart disease have worse outcomes in the first year than those born to white mothers, with researchers linking the finding to the mother's level of education and insurance coverage, according to a study.

Researchers studied two heart defects that require neonatal surgery. With hypoplastic left heart syndrome, the left side of the heart is underdeveloped in the womb, and the aorta and left ventricle are too small. And with d-transposition of the great arteries, two of the main arteries are connected to the wrong side of the heart.

In the case of both, the researchers found less-favorable rates of mortality for Hispanic infants than for non-Hispanic white infants with the same conditions, report report in the new study, published Wednesday in the Journal of the American Heart Association.

Congenital heart disease affects nearly 1 percent of births -- about 40,000 babies -- in the United States each year. About 25 percent them have a critical CHD, and they generally need surgery or other procedures in their first year of life.

"The findings from this paper begin to increase our awareness of non-medical factors that can impact the outcome of children with complex congenital heart disease," Dr. Shabnam Peyvandi, an assistant professor at the University of California, San Francisco, said in a press release.

The research is consistent with other studies. Hispanic infants had less favorable outcomes in one-year mortality or the number of readmissions up to 1 year of age as compared with non-Hispanic white infants with the same defects.

In the latest study, researchers studied the outcomes and key socioeconomic variables from a database maintained by the California Office of Statewide Health Planning and Development. It includes data on 3.1 million live births from the years 2007-12.

The number of liveborn infants with the defects include 1,796 patients, of which 838 were Hispanic patients and 477 were non-Hispanic. The study only included gestational age 22 to 42 completed weeks and researchers excluded those with other major structural birth defects aside from the two they were focused on.

The researchers found Hispanic mothers were younger, had fewer years of education, higher rates of public insurance, lived in cities and their infants were more likely to have been born in community hospitals. Infants born to Hispanic mothers were also found to be smaller for their gestational age.

Only 22 percent of Hispanic mothers had more than 12 years of school, compared with 70 percent for non-Hispanic white mothers. And 69 percent of non-Hispanic white mothers had private insurance coverage compared with 23.5 percent of Hispanic women.

The researchers also note that income, ac-

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cess to care and occupation could have contributed to a large percentage of the disparity.

"This study demonstrates the socioeconomic factors that can in part explain the disparities seen between Hispanic infants with congenital heart disease compared to white infants," Peyvandi said. "Maternal education levels likely act as a proxy for other socioeconomic factors that may impede access to care and available resources to certain communities."

He said this data can be valuable in improving healthcare.

"Community engagement and outreach to at-risk communities are initial steps in identifying specific barriers to healthcare access with a goal of improving outcomes for all children with congenital heart disease," Peyvandi said.

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NT

Neonatal seizures: Closing the knowledge and treatment gap

Released: 10-Oct-2018 12:05 PM EDT

Source Newsroom: International League Against Epilepsy

PNewswise — Seizures are more common during the neonatal period than any other time in life, occurring in 2 to 3 neonates per 1,000. Incidence is even higher in preterm infants, with some studies finding rates of up to 130 per 1,000.

Despite their frequency, the topic as a focus of research "is so neglected," said Ronit Pressler, UCL Institute of Child Health & Great Ormond Street Hospital, UK. Pressler gave a presentation on neonatal seizures as part of the Chairs' Symposium at the 13th European Congress on Epileptology (Aug. 26-30) in Vienna.

Most neonatal seizures occur during the first 24 hours after birth, and are most often caused by something other than epilepsy. The most common cause is hypoxia, a loss of the oxygen supply to the brain. In premature infants, the seizures are often due to cerebrovascular hemorrhage or infarction. Other causes include brain malformations, infections, genetic syndromes and metabolic issues.

The cause of the seizures determines the prognosis, as well as the treatment strategy.

Diagnosis requires EEG

Diagnosis is difficult due to the seizures' subtlety, Pressler said. Some normal infant movements may be misdiagnosed as seizures, while some seizures are overlooked as normal movements. As a result, using only clinical observations to diagnose neonatal seizures may be no more accurate than a coin flip.

Pressler reviewed a 2009 study that asked 137 health professionals (91 physicians, 46 others) to evaluate 20 video clips of neonates for seizures. (Eleven of the 20 were having seizures.) The average percentage of correct diagnoses was 50%, and physicians were no more accurate than other health care professionals.

To further complicate the picture, more than half of neonatal seizures are clinically invisible, seen only on EEG. Because of this phenomenon, the generally accepted definition of a neonatal seizure refers to abnormal EEG activity, rather than clinical signs.

Because the excitatory and inhibitory neurotransmitter systems are not fully developed, the neonatal brain is relatively prone to seizures. In the past, said Pressler, it was thought that the still-developing brain also was more resilient; as a result, neonatal seizures were not viewed with much concern. But research has shown that seizing neonates are at higher risk for death, as well as later developmental delays, cerebral palsy and post-neonatal epilepsy.

Open treatment questions

Given that seizures usually indicate an underlying, serious issue—"These babies are already critically ill," said Pressler—it's still not clear which long-term complications result from the seizures themselves and which stem from the underlying cause. Still, there's general agreement that neonatal seizures should be treated promptly and aggressively; how to do that is an open question

Only one drug—phenobarbital—is approved for treating neonatal seizures. Effective in only 30% to 40% of cases, the drug may extinguish the clinical signs of seizures but not the electrographic ones (visible on EEG), a phenomenon known as uncoupling.

"Phenobarbital has been used for seizures for the past 100 years," Pressler noted. "It's hardly used for adults and older children anymore because of its side effects. But it's so difficult to do drug trials in babies, which is why no other drug has been approved so far."

Neonatal status epilepticus

Because neonates tend to have short-lived seizures—most are under 2 minutes—there's also no good data on what constitutes neonatal status epilepticus (SE). "A seizure over 2 minutes is definitely not good," said Pressler. "But there are no guidelines on when to start treatment [for SE], and without a definition that all doctors use, it will not be treated."

Pressler cited three variations on the definition of neonatal SE, culled from published studies:

Continuous seizures for at least 30 minutes, or recurrent seizures over at least 30 minutes without a return to baseline neurological activity

Seizure activity for at least 30 minutes of an arbitrarily defined 1-hour time period

Electrographic seizure activity that occurs for more than 50% of the recording time (usually 30 minutes)

Based on these definitions, said Pressler, between 10% and 30% of babies with seizures experience neonatal SE. But studies have found an increased risk for poor outcome above a lower threshold of 12 to 13 minutes of seizure activity per hour.

Though new treatment options are limited, increasing adherence to current treatment standards can improve outcomes. A 2016 study followed the implementation of a standardized protocol for neonatal SE at the Riley Hospital for Children, Indianapolis. The 12-month project led to several improvements:

Reduced progression to neonatal SE (46% to 36%)

Decreased maximum concentrations of phenobarbital (56.8 ug/ml to 41.0 ug/ml)

Decreased length of stay by 9.7 days

Proposed neonatal seizure classification

The ILAE task force's proposed neonatal classification framework emphasizes the role of EEG in the diagnosis of seizures in the neonate and includes a classification of seizure types relevant to this age group. Pressler and her colleagues hope that the classification system will lead to improved awareness of the diversity in the causes of neonatal seizures, which may, in turn, lead to more tailored treatments and improved long-term outcomes.

The task force's proposed Neonatal Seizure Classification is open to public review and comments until October 15.

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Founded in 1909, the International League Against Epilepsy (ILAE) is a global organization with more than 115 national chapters.

Through promoting research, education and training to improve the diagnosis, treatment and prevention of the disease, ILAE is working toward a world where no person's life is limited by epilepsy.

To learn more, visit the ILAE website or find us on Facebook, Twitter or YouTube.

NT

Brain Circuits for Successful Emotional Development Established During Infancy

Results from the UNC Early Brain Development Study, led at UNC by John Gilmore, MD, suggest that early detection and intervention could help children at risk for emotional problems..

Released: 9-Oct-2018 2:05 PM EDT
Source Newsroom: University of North Carolina School of Medicine

Newswise — CHAPEL HILL, N.C. – Researchers in the UNC Early Brain Development Study tracking the development of the brain's emotion circuitry in infancy found that adult-like functional brain connections for emotional regulation emerge during the first year of life. And the growth of these brain circuits during the second year of life predicted the IQ and emotional control of the children at 4 years old, suggesting new avenues for early detection and intervention for children who are at risk for emotional problems.

These results were published in Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.

"If confirmed in future studies, these findings suggest that it may be possible to identify children at risk for behavioral dif-

ficulties associated with psychiatric disorders very early in life, allowing early intervention to reduce risk and improve long term behavioral outcomes," said John Gilmore, MD, co-senior author of the study, the Thad and Alice Eure Distinguished Professor and Vice Chair for Research & Scientific Affairs in UNC's Department of Psychiatry, and director of the UNC Center for Excellence in Community Mental Health.

The results were based on an analysis of brain imaging findings from 223 infants in the ongoing UNC Early Brain Development Study. Gilmore and colleagues focused on a core hub of emotion processing in a region of the brain called the amygdala and its connections with other emotion-related brain areas. Atypical processing in the amygdala is linked to disorders such as depression, anxiety, and schizophrenia in adults. The new findings that track the development of the emotional control system during infancy provide a clue as to when atypical development may lead to enduring effects on emotion and cognition later in life.

"Through the lens of functional MRI, this study shows that the brain circuits essential for successful emotional regulation in adults are absent in neonates but emerge in 1 and 2-year-olds, providing the foundation for successful emotional development," said co-senior author Wei Gao, PhD, who was a faculty member in the UNC School of Medicine when this work began. Now he is an associate professor and director of neuroimaging research at Cedars-Sinai Medical Center in Los Angeles.

Growth rates of the emotion circuitry during the second year of life predicted anxiety and emotional regulation in the children at 4 years old. Growth also predicted IQ at 4 years old, indicating its importance not just for the development of emotional control later in life, but also cognition.

Co-authors of the study were Andrew P. Salzwedel, PhD; Rebecca L. Stephens, PhD; Barbara D. Goldman, PhD; and Weili Lin, PhD.

This work was supported by the National Institutes of Health (R01DA042988, R01DA043678, R21NS088975, R21DA043171, R03DA036645, T32-MH106440, U01MH110274, R01MH064065 and R01HD05300), and Cedars-Sinai Precision Precision Health. obstetrics clinic.

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Study Finds Human Milk Components in Amniotic Fluid

Results open new field of inquiry, expanding potential roles of components from postnatal to prenatal.

Released: 2-Oct-2018 11:05 AM EDT
Source Newsroom: University of California San Diego Health

Newswise — Human milk oligosaccharides (HMOs) are complex carbohydrates that are highly abundant and unique to human milk. Accumulating evidence indicates that exposure to HMOs in the postnatal period has both immediate and long-term benefits to infant health and development. Previous studies have shown that HMOs are present in maternal urine and blood during pregnancy, as early as the first trimester, but researchers at University of California San Diego School of Medicine report for the first time that HMOs are also present in amniotic fluid.

The study is published in the October 2 issue of Frontiers in Pediatrics-Neonatology.

"So far, research around human milk oligosaccharides has focused on the breast-fed infant, but our latest discovery suggests that the benefits of HMOs may begin much earlier and affect the growing fetus," said Lars Bode, PhD, associate professor of pediatrics at UC San Diego School of Medicine and director of the Larsson-Rosenquist Foundation Mother-Milk-Infant Center of Research Excellence (LRF MOMI CORE).

HMOs are natural prebiotics that contribute to the shaping of the infant gut microbiome, which may affect disease risk, such as infectious diarrhea or necrotizing enterocolitis, a condition that impacts the intestine of premature infants, and potentially also non-communicable diseases like asthma, allergies and obesity later in life. "Our findings that HMOs appear in amniotic fluid opens up an entirely new field of research and expands the HMO focus throughout development and after birth," said Bode.

The study enrolled 48 pregnant women and collected their urine and amniotic fluid at delivery, as well as their milk four days postpartum.

Similar to the effects reported for the postnatal phase, HMOs in amniotic fluid may influence the early microbiome and also prevent infections and regulate immune responses that would otherwise raise the risk for preterm birth.

"HMOs could also potentially be involved in prenatal lung or brain development," said Bode. "We don't know yet how early during pregnancy HMOs appear in the amniotic fluid, but imagine if we could screen HMOs in amniotic fluid as a marker for preterm delivery risk."

The new findings, he said, warrant additional research in how HMOs impact maternal and infant health at the perinatal and neonatal stage, including investigation of their potential life-long consequences.

Co-authors include: Audra Wise and Bianca Robertson, UC San Diego and Rady Children's Hospital–San Diego; Biswa Choudhury, UC San Diego; Samuli Rautava and Erika Isolauri, University of Turku and Turko University Hospital; Seppo Salminen, University of Turku.

Funding for this research came from the UC San Diego Academic Senate (RO192H-BODE).

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36th Annual Advances in Therapeutics and Technology: Critical Care of Neonates, Children, and Adults

March 26 to March 30, 2019
The Cliff Lodge - Snowbird, Utah

Registration: http://paclac.org/advances-in-care-conference/

Topics and Speakers Include:

Rashmin Savant, MD BPD New Concepts in Pathogenesis and Prevention

Cynthia Blanco, MD Metabolic Disturbances of Prematurity When How and Who to Treat

Sinjo Hirose, MD Fetal Surgery

Arun Pramanick, MD Game Changers in Neonatal-Perinatal Medicine- A View Through a Retroscope

Don Null Persistent Pulmonary Hypertension in the Preterm Newborn Etiologies and Cardiopulmonary Management

Marty Keszler, MD New Modalities in High Frequency Ventilation

Mitchell Goldstein, MD Rediscovering the Denominator

Steve Derdak, DO Pediatric Origins of Adult Disease

Conference Description

This conference will present high quality education to advance pediatric health and well-being through collaboration, communication and education on the discovery and development of therapeutics and technology and their successful translation into practice. The conference aims to improve communication and relationships within industry, academia and government agencies as well as educate on the discovery, development, and implementation processes. Networking opportunities for healthcare professionals who provide care for patients with a focus on advances in therapeutics and technology will be provided. Along with featured speakers, the conference includes abstract presentations on research.

Special Panel Discussion

Avoiding the Conflict, Working to Develop Better Relations with Industry. Don Null, MD and Mitchell Goldstein, MD.

Special Lecture: President of AAP, Colleen Kraft, MD

Continuing Education Credit

The Perinatal Advisory Council: Leadership, Advocacy, And Consultation is providing physician, nursing, and respiratory continuing education units.

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99nicu – A Forum with a Future. And a Meetup Next April!

Stefan Johansson, MD, PhD and Francesco Cardona, MD, MSc

Welcome to this new column in Neonatology Today! Here Dr. Francesco Cardona and I will share bits and pieces from the 99nicu community, mixed with more general reflections.

As a starting point, I would like to share some background for those who are not familiar with 99nicu.

The online community 99nicu.org started off with a few colleagues in my kitchen in late 2005. This was a time before the social web was on everyone's fingertip. Instead, Internet-savvy people gathered on so-called Bulletin Boards or Discussion Forums, often niched to specific topics or interests and managed by enthusiasts. Being an active member of a computer forum, I got the idea to bring neonatal staff together online. After plenty of hours, fiddling with software and web stuff, we opened the 99nicu web site on May 11, 2006. But what did the "99" stand for? That people would gather to discuss 99% of neonatology, and 1% of everything else. :)

Since the launch in 2006, I think we have reached the main purpose: to create an international neonatal community for sharing experience and expertise, not restricted by geographical boundaries. We now count more than 7,000 registered members. Although the majority are doctors, members represent all neonatal staff categories. Moreover, our server gets a lot of traffic! During the latest 3-month period, there were 42,000 pageviews, from all over the world (Figure 1).

> ***"We now count more than 7,000 registered members. Although the majority are doctors, members represent all neonatal staff categories."***

What's the future of online forums, when there's an app for everything? Will 99nicu be out-competed by the big players of the social web? Services like WhatsApp and Twitter do offer great tools for discussions in closed and open groups. But still,

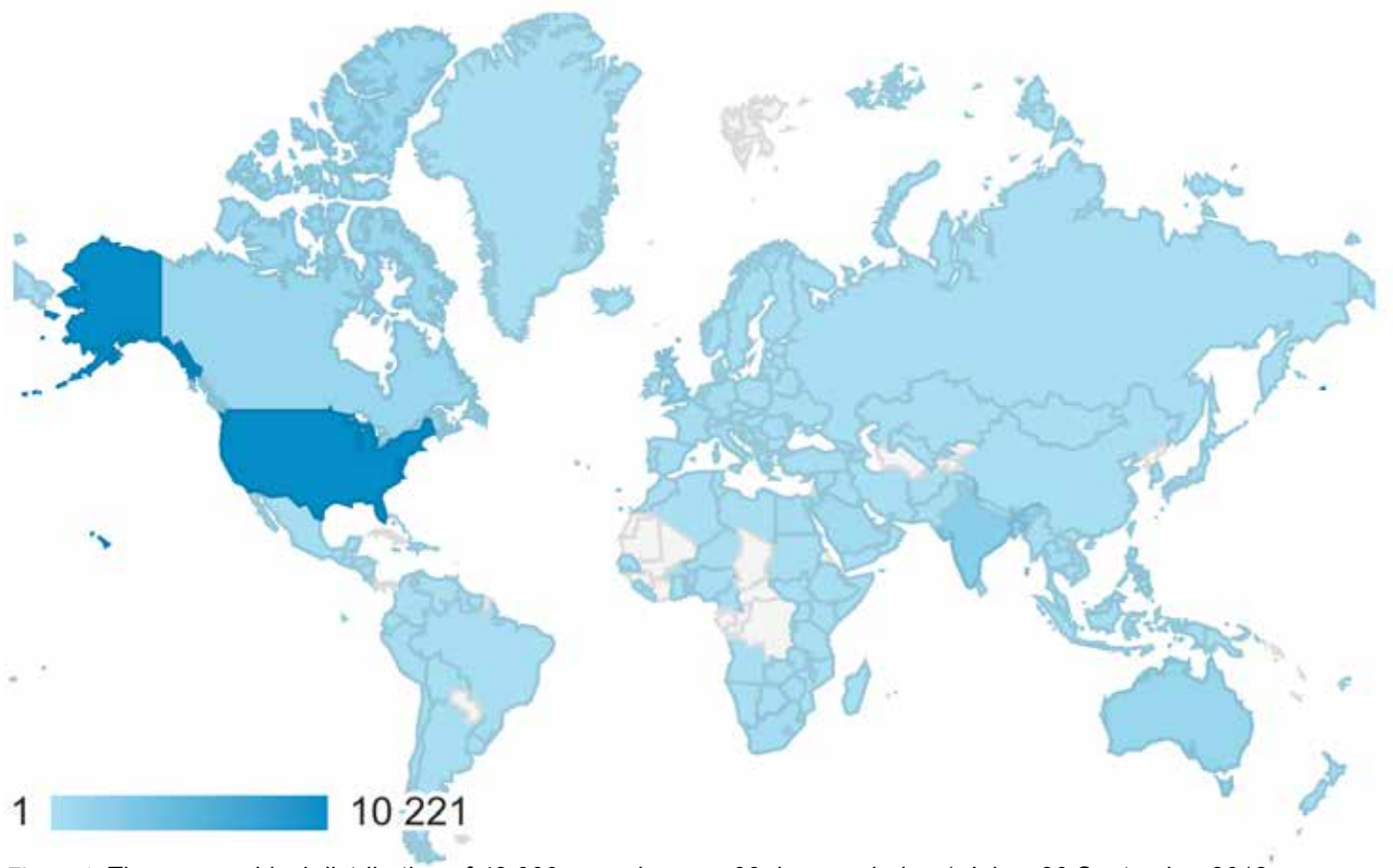

Figure 1: The geographical distribution of 42.000 pageviews on 99nicu.org during 1 July – 30 September 2018. The color coding represent the number of pageviews.

I believe that niched forums will outlive social media platforms when it comes to professional content. For two principal reasons. First, I assume that professionals will want to keep out of the business model of the social media companies, where free-of-charge turns users into data-for-sale ("if it is free online, you are the product"). Second, social media companies, despite smart algorithms, will not bring enough focus to your feeds. If you are primarily interested in neonatal medicine, your content will still be diluted with images of pets and food plates. On the contrary, "old-school" communities are comprehensible and focused. You know why you are there, you know why other people are there, and you know what content to expect.

"When we meet up in Copenhagen, 7-10 April 2019, we hope to bring more than 250 people together, from an even larger number of countries."

While 99nicu gravitates around the website, we have also realized the potential in meeting up IRL. Getting to know each other online is fantastic, but personal meetings will always be very powerful for networking and sharing. That is why we are now preparing our third conference "Future of Neonatal Care." At our previous conference in Vienna, we had 150 delegates from 33 countries. When we meet up in Copenhagen, 7-10 April 2019, we hope to bring more than 250 people together, from an even larger number of countries.

Interested in joining us in Copenhagen?

Keep updated on 99nicu.org!

Stefan Johansson, MD PhD

Consultant neonatologist, Sachs' Children and Youth Hospital
Associate professor, Karolinska Institutet
Stockholm, Sweden

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The authors indicate that they have no disclosures

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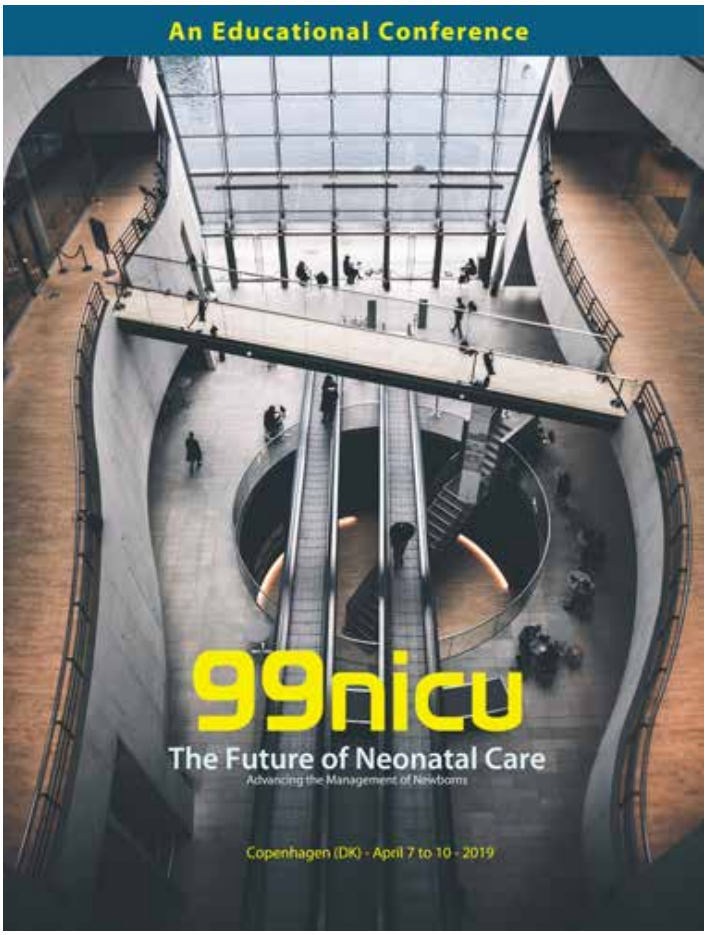

Family Centered Care is trendy, but are providers really meeting parents needs in the NICU?

Consider the following:

Surveys show hospital support groups are being widely underutilized by parents.

And only 10% of NICUs surveyed connect parents with non-hospital support.

Graham's Foundation, the global support organization for parents going through the journey of prematurity, set out to find the missing piece that would ensure all parents have real access to the support they need.

See what they found by emailing info@grahamsfoundation.org to request a free copy of the 2017 whitepaper, "Reaching Preemie Parents Today" (*Heather McKinnis, Director, Preemie Parent Mentor Program, Graham's Foundation*).

You may be surprised to see what NICUs are doing right and where their efforts are clearly falling short.

Graham's Foundation empowers parents of premature babies through support, advocacy and research to improve outcomes for their preemies and themselves.

Graham's FOUNDATION
Fighting for Premature Babies

Visit **www.GrahamsFoundation.org** to learn more.

Readers can also follow **NEONATOLOGY TODAY at its Twitter account:** @NeoToday

Save the Date

23rd Annual PAC/LAC Conference
Quality of Life for Families

June 13, 2019

The California Endowment
Downtown Los Angeles

A Genetics Consultation for Family History of Hearing Loss

Subhadra Ramanathan, M.Sc., M.S and. Robin Clark, MD

Case History:

A 4-day old term non-Hispanic Caucasian male was evaluated by Genetics for a family history of hearing loss. He was admitted to the neonatal intensive care unit at Loma Linda University Children's Hospital for suspected Congenital Pulmonary Airway Malformation (CPAM). The infant was born vaginally at 38 weeks five days gestation to a 27-year-old G2P1 mother. The prenatal history was significant for maternal gestational diabetes and CPAM of the left lung on fetal ultrasound, both detected in the second trimester. The infant cried spontaneously at birth, his color was dusky but improved, and his tone was normal. Post-birth imaging demonstrated left lower lobe pulmonary sequestration. He is followed by Peds Surgery, with the lesion decreasing in size over time; no indication for surgery in this now 18-month old.

On physical exam, the infant was noted to have a white lock of hair in the frontal region and a white patch on his right eyebrow, with a hypopigmented skin lesion on his forehead. The infant was referred bilaterally on newborn hearing screen and has subsequently been diagnosed with profound sensorineural hearing loss.

The family history was significant for hearing loss in both parents. Mother's hearing loss was attributed to meningitis in childhood. Father had been diagnosed with Waardenburg syndrome; he had heterochromia irides (one brown, one blue) and a white forelock of hair. Father's paternal half-brother, his father, and his paternal half-uncle also have Waardenburg syndrome.

Consultant's Report:

This pattern of pigmentary abnormalities and hearing loss in the infant and his father are consistent with a clinical diagnosis of Waardenburg syndrome. Molecular genetic testing identified a likely pathogenic variant in the SOX10 gene, c.356G>T, p.Arg119Leu. On follow-up, no new concerns were identified. The family declined hearing aids and assessment for cochlear implants. He is growing well.

There is extreme heterogeneity in the underlying etiology of human deafness and hearing loss (figure 1). Hereditary hearing loss and deafness can be syndromic or non-syndromic. Syndromic hearing impairment is associated with malformations of the external ear, with malformations in other organs, or with medical problems involving other organ systems. Nonsyndromic hearing impairment has no associated visible abnormalities of the external ear or any related medical problems; however, it can be associated with abnormalities of the middle ear and/or inner ear.

"Waardenburg syndrome (WS) is the most common type of autosomal dominant syndromic hearing loss."

More than 400 syndromes are known to be associated with hearing loss. The underlying etiology of syndromic hearing loss will guide clinical management and surveillance. For example, here are three syndromes, each associated with congenital severe to profound sensorineural hearing loss, with very different clinical surveillance and management. Usher syndrome is associated with adolescent-onset retinitis pigmentosa. Pendred syndrome is associated with the development of euthyroid goiter in late childhood to early adulthood. Jervell and Lange-Nielsen syndrome is characterized by long QTc, associated with tachyarrhythmias, including ventricular tachycardia, episodes of torsade de pointes ventricular tachycardia, and ventricular fibrillation, which may culminate in syncope or sudden death.

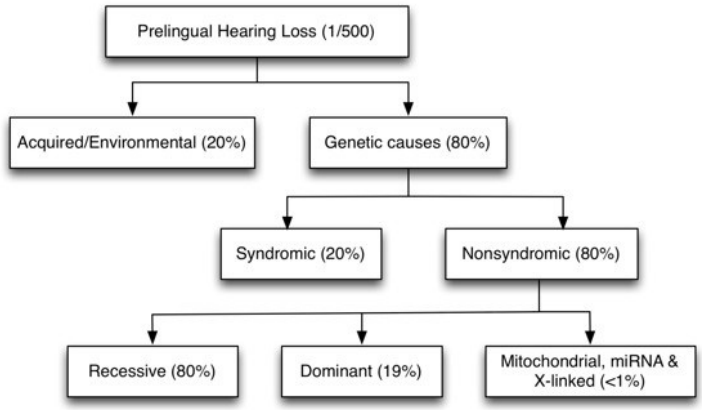

Figure 1: www.genereviews.org

Waardenburg syndrome (WS) is the most common type of autosomal dominant syndromic hearing loss. It is characterized by congenital sensorineural hearing loss and pigmentary abnormalities of the hair, skin, and eyes. There are four recognized types of Waardenburg syndrome, which are distinguished by their physical characteristics and sometimes by their genetic cause. Types 1 and 2 have very similar features, although individuals with type 1 almost always have a lateral displacement of the inner canthi (dystopia canthorum) and those with type 2 do not. In addition, hearing loss occurs more often in people with type 2 than in those with type 1. Type 3 (sometimes called Klein-Waardenburg syndrome) includes abnormalities of the arms and hands in addition to hearing loss and changes in pigmentation. Type 4 (also known as Waardenburg-Shah syndrome) has clinical features of Waardenburg syndrome and Hirschsprung disease.

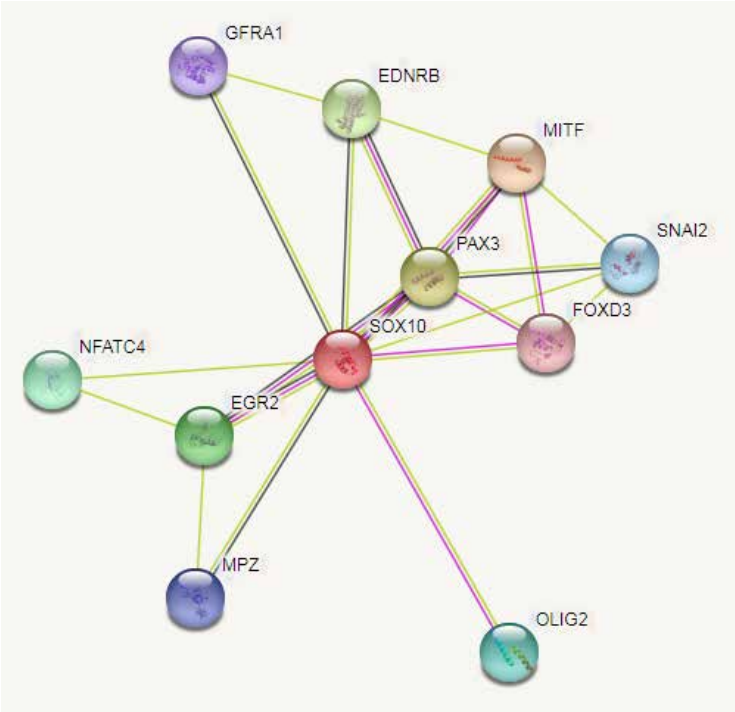

Figure 2: http://string-db.org

Type 1 and 3 are due to pathogenic variants in the PAX3 gene; type 2 is associated with pathogenic variants in the MITF or SOX10 genes. Type 4 can be due to pathogenic variants in any one of three genes, EDNRB, EDN3, and SOX10.

About half the patients with WS4 and 15% of WS2 patients have heterozygous pathogenic variants (mutations) in the SOX10 gene. All features show incomplete penetrance and variable expressivity. This clinical variability in patients carrying the same (or similar) mutations suggests that the genetic environment modifies the phenotypic expression of the intestinal phenotype (Pingault V et al., 2014).

Waardenburg syndrome is a neurocristopathy, a class of disorders resulting from abnormal expression, migration, differentiation or death of neural crest cells during embryonic development. The SOX10 protein belongs to the high mobility group (HMG) box superfamily of DNA binding proteins and modulates other transcription factors. It is first expressed during neural crest cell development and can be detected in the sensory, sympathetic and enteric ganglia and along nerves. It is also transiently expressed in the melanoblast.

The SOX10 protein interaction network includes the other WS genes (figure 2). The SOX10 protein modulates PAX3 expression and transactivates the MITF promoter. The microphthalmia-associated transcription factor (MITF) plays a pivotal role in the survival and differentiation of melanocytes, the cells that produce melanin pigment. Thus, there is an epistatic relationship between SOX10 and MITF, resulting in the audio-pigmentary defect in patients with WS with pathogenic variants in SOX10.

The recurrence risk for WS is 50% to each of father's offspring (and to each of the child's offspring). Prenatal diagnosis for the likely pathogenic variant in the SOX10 gene will be available if desired.

The patients' parents identify themselves as members of the Deaf community and use American Sign Language. Members of the Deaf community do NOT consider themselves to be hearing "impaired," nor do they feel that they have a hearing "loss." Rather, they consider themselves deaf. Their deafness is not considered to be a pathology or disease to be treated or cured.

Practical Applications:

1. An evaluation for hearing loss should include detailed family history and, where possible, physical examination of parents, including looking for pigmentary anomalies.

2. Establishing the diagnosis of hearing loss allows for appropriate clinical surveillance and management and allows for accurate recurrence risk counseling.

3. The Deaf community has its own social attributes and culture and does not view deafness or hearing loss as a disability. Health care providers should respect this, in order to communicate effectively on the care of the child and while counseling regarding recurrence risks.

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How to Care for a Baby with NAS

Use the Right Words

I was exposed to substances in utero. I am not an addict. And my mother may or may not have a Substance Use Disorder (SUD).

Treat Us as a Dyad

Mothers and babies need each other. Help my mom and me bond. Whenever possible, provide my care alongside her and teach her how to meet my needs.

Support Rooming-In

Babies like me do best in a calm, quiet, dimly-lit room where we can be close to our caregivers.

Promote Kangaroo Care

Skin-to-skin care helps me stabilize and self-regulate. It helps relieve the autonomic symptoms associated with withdrawal and promotes bonding.

Try Non-Pharmacological Care

Help me self-soothe. Swaddle me snugly in a flexed position that reminds me of the womb. Offer me a pacifier to suck on. Protect my sleep by "clustering" my care.

Support Breastfeeding

Breast milk is important to my gastrointestinal heath and breast feeding is recommended when moms are HIV-negative and receiving medically-supervised care. Help my mother reach her pumping and breastfeeding goals.

Treat My Symptoms

If I am experiencing withdrawal symptoms that make it hard for me to eat, sleep, and be soothed, create a care plan to help me wean comfortably.

Learn more about
Neonatal Abstinence Syndrome
at www.nationalperinatal.org

National Perinatal Association

MARCH OF DIMES

2018 California Conference

Advancing Health Equity to Improve Maternal & Neonatal Outcomes

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- Implicit bias and trauma-informed care in the NICU Setting
- Co-designing mobile technology & care delivery to improve family integrated care in NICUs
- Management of neonatal early-onset sepsis
- California Newborn Screening Program updates
- Rapid DNA Sequencing in the NICU
- Hospital-based maternal mental health screening

Register and view agenda, faculty, and CME credits at: www.regonline.com/marchofdimes

Protecting Premature Infants From Infectious Diseases?

NCfIH National Coalition for Infant Health

Protecting Access for Premature Infants through Age Two

The National Coalition for Infant Health is a collaborative of more than 180 professional, clinical, community health, and family support organizations focused on improving the lives of premature infants through age two and their families. NCfIH's mission is to promote lifelong clinical, health, education, and supportive services needed by premature infants and their families. NCfIH prioritizes safety of this vulnerable population and access to approved therapies.

Dear Colleagues,

Protecting newborn babies—especially those born prematurely—should be a top priority in any healthcare system. But public policy and insurance standards don't always provide for proper prevention against some of the greatest threats to preemies.

While all newborns are highly susceptible to infectious diseases, premature infants are even more at risk. Essential growth and development, particularly of the immune system, occurs throughout pregnancy. Thus, children born prematurely are less able to fight infection because they do not benefit from the additional passage of their mothers' antibodies during their final weeks in the womb. Preemies often have underdeveloped airways as well, which can further complicate any infection they contract. Their weaker physical condition enhances the likelihood of additional co-morbidities and their overall ability to endure health challenges. For all of these reasons, public policies and insurance practices must help to prevent infections so every baby has the chance to thrive and grow.

"Policymakers must continue to champion logical, evidence-based legislation and promote public dialogue rooted in science."

IMMUNIZATION IS CRITICAL TO PREVENTION

The science is clear. Immunizations safely protect children against many potential infections. They represent the easiest, most effective way to prevent a number of infectious diseases and are essential to protect premature babies. Nevertheless, confusion and misleading information still exists among the public. Parents' and health care providers' decisions during infants' first few weeks of life can have profound and long-lasting consequences, including death. These decisions may be influenced by a handful of celebrities with minimal medical knowledge as well as a few researchers who have made baseless claims against immunizations. Some scientists and physicians may mislead patients based on their own conclusions drawn from anecdotal cases.

These naysayers have managed to stoke enough fear about alleged connections between various vaccines and autism to make a significant impact in immunization rates in recent years. Thirteen separate scientific studies have demonstrated that no evidence supports such a link. Major authorities such as the World Health Organization, the Center for Disease Control, and the American Academy of Pediatrics unequivocally endorse immunization.

Parents tend to make informed decisions and even advocate for immunization publicly when they understand the data. A vast majority (83 percent) of Americans say vaccines are safe for healthy children(1), and two-thirds of Californians supported aspects of a measure to require immunization for all students (2).

"Public awareness efforts need to proactively discredit myths about immunization. Shielding infants from avoidable infectious diseases protects individual families and ensures the public welfare."

Public awareness efforts need to proactively discredit myths about immunization. Shielding infants from avoidable infectious diseases protects individual families and ensures the public welfare.

Prevention Against Respiratory Syncytial Virus

A less widely known issue, but one that is perhaps an even greater health concern to preemies, is protection against a highly contagious and potentially deadly virus known as Respiratory Syncytial Virus (RSV). In adults, children, and full-term infants, its symptoms usually resemble those of the common cold. However, RSV frequently causes severe problems in pre-term and other at-risk babies who do not have fully developed airways or mature im-

Figure 1. Studies that Demonstrate No Evidence Linking Autism and Immunizations

Source	Study design	Study location
Taylor et al., 1999 [5]	Ecological	United Kingdom
Farrington et al., 2001 [6]	Ecological	United Kingdom
Kaye et al., 2001 [7]	Ecological	United Kingdom
Dales et al., 2001 [8]	Ecological	United States
Fombonne et al., 2006 [9]	Ecological	Canada
Fombonne and Chakrabarti, 2001 [10]	Ecological	United Kingdom
Taylor et al., 2002 [11]	Ecological	United Kingdom
DeWilde et al., 2001 [12]	Case-control	United Kingdom
Makela et al., 2001 [13]	Retrospective cohort	Finland
Madsen et al., 2002 [14]	Retrospective cohort	Denmark
DeStefano et al., 2004 [15]	Case-control	United States
Peltola et al., 1998 [16]	Prospective cohort	Finland
Patja et al., 2000 [17]	Prospective cohort	Finland

mune systems.

Chronic lung disease, bronchopulmonary dysplasia, congenital heart disease, and other conditions frequently lead to RSV-related hospitalization. Environmental factors, such as child care, contagions from siblings, or complications from parental smoking can increase the risk and chance of hospitalization. Neurological, immunologic, and transplant complications may place babies at even higher cumulative risk. RSV is the leading cause of hospitalization in babies less than one year old (3).In fact, RSV is the most common cause of bronchiolitis and pneumonia (4).

RSV causes approximately 90,000 hospitalizations and 4,500 deaths per year in children five years of age and under (5). Worldwide, there are up to 200,000 deaths per year from RSV.The main approach to preventing the effects of viruses like RSV is through the use of a prophylactic biologic medication. Though it does not stop infection, prophylaxis does diminish its severity. RSV prophylaxis with a drug called palivizumab has been shown to reduce RSV infections and decrease hospitalizations of premature babies by at least 55 percent and as much as 80 percent in certain subgroups (6).

Despite product labeling from the FDA based on clinical research, the current American Academy of Pediatrics Committee on Infectious Diseases' (COID) guidelines recommend prophylaxis only for premature infants born at 29 weeks gestation or earlier. There are few exceptions. Medicaid systems and private insurers who adopted the COID's stance into their coverage policies effectively shut the majority of premature infants out of RSV prevention. Their policies compound existing disparities; for instance, restricting access to RSV prophylaxis disproportionately affects African-American babies as they are more likely to be born prematurely and often have increased risk factors for the virus.

"Palivizumab reduces RSV infections by at least 55 percent — Yet inadequate insurance coverage prohibits as many as three-quarters of infants who need it from receiving the indicated dosing."

Another concern surrounding palivizumab is aligning standard practices. A great deal of confusion exists among patients and providers regarding disease risks, prophylaxis use, and coverage. Inconsistent reporting and documentation, along with variable insurance coverage, prevent as many as 75 percent of infants who would benefit from prophylaxis from receiving it (7).

There is a renewed focus on prevention in the wake of recent skyrocketing rates of RSV infections in states such as Arizona and California. Private and public health insurers must reconsider the importance of RSV prevention, allowing for risk-based assessment that incorporates the insight of neonatal and pediatric care providers and families. Risk-based prevention also mitigates misdiagnoses that confuse RSV symptoms for flu symptoms.

Moreover, the COID guidelines should align with the FDA's indication for palivizumab, allowing health care providers to administer preventative treatment based on their clinical judgement. Families need expanded education about RSV and how to properly protect their infants against the virus during "RSV Season," defined as the time when the virus is circulating in any given state, as outlined by the Center for Disease Control (CDC).

Conclusions:

Public policies regarding immunization and prophylaxis should work to prevent infectious diseases that are particularly dangerous for premature babies.

Loving parents need to be empowered with accurate information about immunizations in order to do what is best for their preemie babies. The first fragile weeks of premature infants' lives are extraordinarily stressful for their new parents. Misinformation should not cloud their choices. Educating the public about the evidence supporting immunization must be continually emphasized.

For prophylaxis against RSV, uniform risk assessments and reporting will encourage better, more consistent insurance coverage. Health care providers must regain the ability to provide preventative treatment as needed for their fragile patients in accordance with palivizumab's FDA indication. Congressional leadership and sound, evidence-based public policy can significantly reduce or eliminate the threat of infectious diseases that pose great risks to premature babies.

Mitchell Goldstein, MD
Medical Director
National Coalition for Infant Health

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The author has no relevant disclosures.

NT

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National Coalition for Infant Health Values (SANE)

Safety. Premature infants are born vulnerable. Products, treatments and related public policies should prioritize these fragile infants' safety.

Access. Budget-driven health care policies should not preclude premature infants' access to preventative or necessary therapies.

Nutrition. Proper nutrition and full access to health care keep premature infants healthy after discharge from the NICU.

Equality. Prematurity and related vulnerabilities disproportionately impact minority and economically disadvantaged families. Restrictions on care and treatment should not worsen inherent disparities.

Medicolegal Forum: Oversight

Gilbert Martin, MD and Jonathan Fanaroff, MD, JD

In a commentary appearing in the Winter 1984 issue of the Journal of Perinatology, a tongue-in-cheek "Timely Scenario" discussed the Baby Doe dilemma and its effect on the approach to some aspects of neonatal care.

Over the past few months, as the Justice Brett Kavanaugh confirmations hearings were presented, there was some discussion regarding Roe vs. Wade. In the early comments dealing with Roe vs. Wade, the divide between pro-life and pro-choice views extended into a debate which concerned withholding or withdrawing treatment for severely impaired newborns. This discussion resulted in the Baby Doe regulations (1) which required aggressive care for newborns unless such care: would merely prolong dying, not be effective in ameliorating or correcting all of the infant's life-threatening conditions or otherwise be futile in terms of the survival of the infant (2). It was clear that by the end of 1984 the American Academy of Pediatrics (3) and the American Hospital Association (4) issued statements supporting the employment of interdisciplinary ethics as an alternative to governmental investigation. Was this an alternative to governmental investigation or was this an alternative to government intrusion?

Ethical issues and decisions frequently arise in neonatal clinical settings and the AMA Council on Ethical and Judicial Affairs has become involved. In today's hospital setting, an "Ethics Committee" is often part of the medical staff's responsibility.

We now have hospital quality oversight by The Joint Commission (TJC), formerly known as the Joint Commission Accreditation of Healthcare Organizations (JCAHO) which is tied to payments from the Centers for Medicare and Medicaid Services (CMS). Historically, TJC reviews hospitals every three years on a scheduled basis. These surveys and visits are typically unannounced and often produce great anxiety for both hospital staff and administration. The AAP has a committee called the Council on Quality Improvement and Patient Safety (COQIPS). There is also a National Perinatal Information Center which collects data on quality metrics in obstetrical and neonatal care. The Vermont Oxford Network (VON) founded in 1988 stated that its mission was "to improve the quality and safety of medical care for newborn infants and their families through a coordinator program of research, education and quality improvement projects." There are Global Health Initiatives throughout the world. There are also State organizations which are imperative in collecting data with the goal of improving neonatal care (California Perinatal Quality Care Collaborative CPQCC, is an example).

The question of "oversight" and monitoring of morbidity and mortality continues to be important to the Neonatal/Perinatal Section of the American Academy of Pediatrics. The AAP has a Steering Committee on Quality Improvement and Management. There is now a section in the Journal of Perinatology focusing on Quality Improvement.

So…..we are in fact policing ourselves. We may have reached the limits of viability and mortality rates for the Extremely Low Birthweight Infant (ELBW) may not improve much in the future. Our mission, however, is morbidity. We want to produce a generation of ELBW NICU graduates who live long, happy, healthy, and productive lives.

Oversight on all levels is indicated. Baby Doe is watching over us and saying…..Thank You.

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NT

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Rainbow Babies & Children's Hospital
Cleveland, Ohio

New Moms Need Access to Screening & Treatment for POSTPARTUM DEPRESSION

1 IN **7** MOMS FACE POSTPARTUM DEPRESSION, *experiencing*

- Uncontrollable crying
- Disrupted sleep
- Anxiety
- Shifts in eating patterns
- Thoughts of harming self or baby
- Withdrawal from friends and family

15%

Yet only 15% receive treatment[1]

UNTREATED POSTPARTUM DEPRESSION CAN IMPACT:

- *Mother's health*
- *Baby's sleeping, eating, and behavior as he or she grows*[2]
- *Ability to care for a baby and siblings*

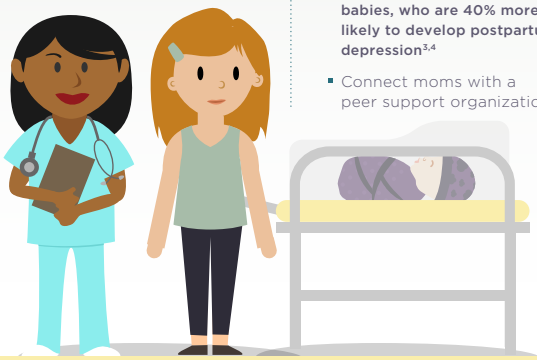
TO HELP **MOTHERS FACING POSTPARTUM DEPRESSION**

POLICYMAKERS CAN:

- Fund Screening Efforts
- Protect Access to Treatment

HOSPITALS CAN:

- Train health care professionals to provide psychosocial support to families... **especially those with preterm babies, who are 40% more likely to develop postpartum depression**[3,4]
- Connect moms with a peer support organization



NCfIH National Coalition for Infant Health

Protecting Access for Premature Infants through Age Two

www.infanthealth.org

[1] American Psychological Association. Available at: http://www.apa.org/pi/women/resources/reports/postpartum-depression.aspx

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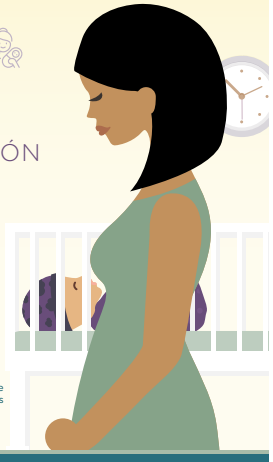
Las nuevas mamás necesitan acceso a la detección y tratamiento para LA DEPRESIÓN POSPARTO

1 DE CADA **7** MADRES AFRONTA LA DEPRESIÓN POSPARTO, *experimentando*

- Llanto incontrolable
- Sueño interrumpido
- Ansiedad
- Desplazamientos en los patrones de alimentación
- Ideas de hacerse daño a sí mismas o al bebé
- Distanciamiento de amigos y familiares



15%

Sin embargo, sólo el 15% recibe tratamiento[1]

LA DEPRESIÓN POSTPARTO **NO TRATADA** PUEDE AFECTAR:

- *La salud de la madre*
- *El sueño, la alimentación y el comportamiento del bebé a medida que crece*[2]
- *La capacidad para cuidar de un bebé y sus hermanos*

PARA AYUDAR **A LAS MADRES A ENFRENTAR LA DEPRESIÓN POSPARTO**

LOS ENCARGADOS DE FORMULAR POLÍTICAS PUEDEN:

- Financiar los esfuerzos de despistaje y diagnostico
- Proteger el acceso al tratamiento

LOS HOSPITALES PUEDEN:

- Capacitar a los profesionales de la salud para proporcionar apoyo psicosocial a las familias... **Especialmente aquellas con bebés prematuros, que son 40% más propensas a desarrollar depresión posparto**[3,4]
- Conectar a las mamás con una organización de apoyo

NCfIH National Coalition for Infant Health

Protecting Access for Premature Infants through Age Two

www.infanthealth.org

[1] American Psychological Association. Accesible en: http://www.apa.org/pi/women/resources/reports/postpartum-depression.aspx

[2] National Institute of Mental Health. Accesible en: https://www.nimh.nih.gov/health/publications/postpartum-depression-facts/index.shtml

[3] Journal of Perinatology (2015) 35, 529–536; doi:10.1038/jp.2015.147.

[4] Prevalence and risk factors for postpartum depression among women with preterm and low-birth-weight infants: a systematic review. Vigod SN, Villegas L, Dennis CL, Ross LE BJOG. 2010 Apr; 117(5):540-50.

Peer Reviewed

Monthly Clinical Pearl: "He Looks Very Much Alive to Me!"

Joseph R. Hageman, MD

Depending on your perspective, this could be considered one of those clinical experiences consistent with having a "black cloud." My neonatal rotations at Prentice Women's Hospital were labor intensive and loaded with a wide variety of clinical experiences. But as I had decided by my second year of residency that critical care was what I wanted to pursue and I had made the decision to do neonatal intensive care, these experiences were very valuable and actually exciting, especially since most of them occurred during my call nights. We went to the delivery room, this was 1979, and many of the unusual newborns I saw were born to Moms who had not had prenatal ultrasounds and whose prenatal care was sometimes dictated by their social situation or economic status and access to OB care. On this particular night, a term infant was born, and we noted that he had a relatively large head, a "stork bite" on his forehead, relatively short extremities and a small chest. I had not seen an infant with this constellation of anomalies before so we intubated him, stabilized him and transported him back to the neonatal intensive care unit (NICU). Once we got him admitted, we had a chance to call our attending neonatologist, and I went to get our copy of 'Smith's Recognizable Patterns of Human Malformations' which was our "bible" when we saw a dysmorphic infant (1).

Image Credit: Alsulaimani AA. Thanatophoric dysplasia Variant in Identical Saudi Twins. Prenatal Diagnosis and Genetic Analysis Journal of Taibah University Medical Sciences 2009; 4(2): 170 - 173. Copyright: Creative Commons ©. License Terms: https://creative-commons.org/licenses/by-nc-nd/3.0/legalcode

I have to say I felt an immediate closeness to this baby as even those his chest was small and he was having trouble with his own spontaneous respirations; he seemed very "full of life" to me. Our concern was that he appeared to be a type of "dwarf" with his shortened extremities, relatively large head and "stork bite" on his forehead. When you evaluate a dysmorphic newborn, after they are stable and you have some time to spend at the bedside, please take your time, have your resources (like Smith's or nowadays your computer with access to OMIM and other websites) and study your patient carefully. Again, as I summarized in "genetics detective work key to difficult NICU conversations," this is how I learned (self-learning) to approach and recognize syndromes… and then I called the geneticist (2-7).

From what I have presented so far, do you have an idea of what syndrome this baby has? Once again, our geneticist came to the bedside and said, "this baby has thanatophoric dysplasia." I have to say as a pediatric resident and aspiring neonatal fellow to be, I looked this up immediately and have never forgotten him. I have attached an example of thanatophoric dysplasia or dwarfism just to give you some perspective (8). The name thanatophoric means 'Death bearing" or "leading to death" as per the http://medical-dictionary.thefreedictionary.com/thanatophoric (9)

For a more contemporary evaluation of the neonate with congenital anomalies, I refer you to this article by Wenger and Bhoj in the September issue of NeoReviews (6). The "overarching goal of this review is to provide neonatal clinicians the tools to assess, contextualize, and discuss congenital anomalies in neonates to improve communication and the diagnostic process" (10).

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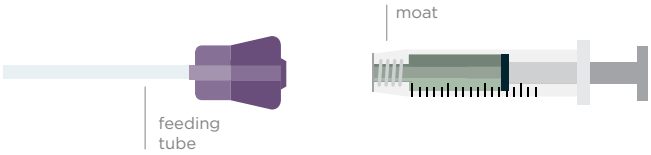

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Letters to the Editor

From: Truong, Giang (by e-mail)
Sent: Tuesday, October 16, 2018 10:02 AM
To: Goldstein, Mitchell <MGoldstein@llu.edu>
Subject: Letter for the editors

Dear Dr. Goldstein,

I heard that Neonatology Today was promoted for the EBSCO database. Could you explain what this means to authors and readers?

G. Truong

Dear Dr. Truong:

Last month we received an e-mail from EBSCO information services. EBSCO (www.ebsco.com) is a prestigious institution that maintains academic libraries (as well as a number of other academic indexing services). " EBSCO provides high-quality content and technology for academic libraries including academic research databases, discovery service, academic journals, academic ebooks, scholarly journals and more"

Please find the initial e-mail below.

From: Allison Connolly [mailto:aconnolly@EBSCO.COM]
Sent: Wednesday, September 12, 2018 7:34 AM
To: LomaLindaPublishingCompany@gmail.com
Subject: Neonatology Today~ Nomination

Hello from EBSCO,
Neonatology Today has been nominated for inclusion on our research databases that are used in libraries.

This is a great way to ensure your publication is gaining exposure and web traffic originating from those using an EBSCO database in a library. We currently have a near perfect renewal rate of over 99% with over 16,000 Publisher Partners.

There is no cost to participate and I am happy to elaborate over phone or email.

Thank you,
Allison
Allison L. Connolly, EBSCO Information Services
E: aconnolly@ebsco.com

We had a nice discussion, and I received this e-mail in response.

From: Allison Connolly
Sent: Tuesday, September 18, 2018 3:15 PM
To: 'Loma Linda Publishing Company' <lomalindapublishingcompany@gmail.com>
Subject: Neonatology Today

Hello Dr. Goldstein,

Thanks so much for the phone call today.

As we discussed, there are no costs to participate and moving forward is simple. We ask that you give EBSCO permission to display (not edit) your articles via our databases by signing a license agreement. This is a nonexclusive arrangement, so you are free to explore similar partnerships with other companies as you wish. There is also no transfer of copyright, so you are not signing over the rights to any of your content to EBSCO. After you sign the agreement and return it to me, we set you up with an ftp transfer site where you can easily drop a pdf of each issue as it is published. This is your only obligation as a result of this agreement and although I am always here if you need something this relationship will not be high maintenance or something that you think about very often.

I have attached a copy of our standard license agreement. If you would like to move forward, please return the attached with a handwritten signature via email or fax. I would suggest you decline the sublicensing options. I am happy to elaborate on any points.

Kind regards,
Allison

As of 10/13/2018, we are now partnering with EBSCO. We believe this partnership will increase the readership and distribution of NT as well as enhance the value of NT as a publishing platform.

Sincerely,

Mitchell Goldstein, MD
Editor in Chief

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Neonatology Today welcomes your editorial commentary on previously published manuscripts, news items, and other material relevant to the fields of Neonatology and Perinatology.

Please address your response in the form of a letter. For further formatting questions and submissions, please contact Mitchell Goldstein, MD at LomaLindaPublishingCompany@gmail.com.

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Erratum (Neonatology Today September, 2018)

Neonatology Today has not identified any erraturm affecting the September, 2018 edition. Corrections can be sent directly to LomaLindaPublishingCompany@gmail.com. The most recent edition of Neonatology Today including any previously identifed erratum may be downloaded from www.neonatology-today.net.

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National Perinatal Association
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Providence, Rhode Island
http://nationalperinatal.org/2019Conference

Pediatrics Academic Societies Meeting
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Editorial Board

Neonatology and the Arts

This section focuses on artistic work which is by those with an interest in Neonatology and Perinatology. The topics may be varied, but preference will be given to those works that focus on topics that are related to the fields of Neonatology, Pediatrics, and Perinatology. Contributions may include drawings, paintings, sketches, and other digital renderings. Photographs and video shorts may also be submitted. In order for the work to be considered, you must have the consent of any person whose photograph appears in the submission.

Works that have been published in another format are eligible for consideration as long as the contributor either owns the copyright or has secured copyright release prior to submission.

Logos and trademarks will usually not qualify for publication.

This month's selection is actually one of the conference flyers from 99NICU's upcoming conference in 2019. This is a nice example of how photography can be used to create interest and drive attendance. Francesco Cardona, MD, MSc of 99NICU submitted this piece. This Grey Pointed Building photo is by Kasper Rasmussen and is of Aller Media A/S headquarters, København, Denmark and sourced from Unsplash

Herbert Vasquez, MD
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Manuscript Submission: Instructions to Authors

1. Manuscripts are solicited by members of the Editorial Board or may be submitted by readers or other interested parties. Neonatology Today welcomes the submission of all academic manuscripts including randomized control trials, case reports, guidelines, best practice analysis, QI/QA, conference abstracts, and other important works. All content is subject to peer review.

2. All material should be emailed to: LomaLindaPublishingCompany@gmail.com in a Microsoft Word, Open Office, or XML format for the textual material and separate files (tif, eps, jpg, gif, ai, psd, or pdf) for each figure. Preferred formats are ai, psd, or pdf. tif and jpg images should have sufficient resolution so as not to have visible pixilation for the intended dimension. In general, if acceptable for publication, submissions will be published within 3 months.

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