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Because jaundice can translate to big risk for newborns

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Each year, more than 800,000 newborns in the United States are diagnosed with neonatal jaundice.[1] Some babies may not fully respond to current therapies and may require additional interventions, leaving them exposed to elevated levels of bilirubin for a long duration of time.[2]

It is unknown what levels of bilirubin start to trigger potentially toxic effects in an individual newborn. Left uncontrolled, elevated bilirubin can lead to neurologic dysfunction, encephalopathy, or irreversible brain damage.[3,4]

In 2004, the American Academy of Pediatrics published guidelines for the management of hyperbilirubinemia.[3] Since then, there have been only modest treatment advancements in jaundice. The current standard of care requires periods of isolation that can compromise the potential of the mother-infant bond.[5]

Mallinckrodt is committed to researching and advancing the understanding of neonatal jaundice.

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What is the "Best" Way to Administer Surfactant in 2018? The Case for the Laryngeal Mask Airway (LMA).

By: Kari Roberts, MD, T. Allen Merritt, MD, and Mitchell Goldstein, MD

The discovery and clinical use of surfactant in the treatment of respiratory distress syndrome (RDS) was a landmark breakthrough in the field of neonatology and discussions are often referred to in terms of the "before surfactant" and "after surfactant" eras. In the initial "after surfactant" era, infants with RDS were intubated, mechanically ventilated and administered surfactant via an endotracheal tube (ETT). In 2018, clinicians are now practicing in the distant "after surfactant" era, where the focus is avoidance of intubation and mechanical ventilation. While the increased use of non-invasive ventilation is beneficial for avoiding ventilator-related lung injury, it has left infants without an ETT- the only approved mode available previously for surfactant delivery- and therefore, without the benefit of "prophylactic" or "early" surfactant. In this current era, is there a way to have non-invasive mechanical ventilation and "early" surfactant administration? The answer is, "Yes." This review explores the current methods available for "non-traditional" surfactant administration and suggest the laryngeal mask airway (LMA) is the "best" method for delivering surfactant.

METHODS AVAILABLE FOR SURFACTANT ADMINISTRATION

Intubation and placement of an ETT has been the traditional method of surfactant administration for years. Over the past decade, however, alternative or "less-invasive" methods to deliver surfactant into the lungs have become the subject of many trials. Among these methods are: INSURE (intubate, administer surfactant, and extubate), MIST (minimally invasive surfactant therapy), LISA (less invasive surfactant therapy), LMA (laryngeal mask airway) and aerosol administration.

The INSURE technique was first described in a pilot study by Victorin[1] in 1990 and further by Verder et al[2] in Denmark in 1999. The traditional method of intubation and surfactant administration through an ETT are used with the variance from traditional method being immediate or rapid (within minutes or hours) extubation rather than being maintained or slowly weaned (hours to days) off mechanical ventilation.

The MIST technique (also called the Hobart method), first described by Dargaville[3] in Hobart, Australia in 2011 involves use of a laryngoscope to guide a 16 gauge vascular catheter through the vocal cords into the trachea for surfactant administration. With this technique, infants remain on CPAP, surfactant is administered in 3-4 boluses over 15-30 seconds, and infants remain spontaneously breathing throughout the procedure[4].

The LISA technique, introduced by Kribs[5] and co-workers in Cologne, Germany in 2007 involves use of a laryngoscope and McGill forceps to pass a 4 to 5 French feeding tube through the vocal cords into the trachea for surfactant administration. Infants remain on CPAP, surfactant is administered over 1-3 minutes, and infants remain spontaneously breathing throughout the procedure.

Use of an LMA for surfactant administration was first described in 2004 in a case report of 2 infants[6] and in 2005 with a prospective study of 8 infants[7]. Placement of the LMA is achieved with the thumb and index finger and does not require use of a laryngoscope or other instrumentation. Positive pressure ventilation (PPV) is used to distribute the surfactant, infants remain on CPAP and are spontaneously breathing throughout the procedure.

Nebulization or delivery of surfactant by an aerosol device to human infants was first described by Jorch[8] and coworkers in 1997. While potentially the least invasive and most promising of all the techniques, clinical use has been limited by technical problems including attaining a particle size that is inhaled, but not exhaled, stability during nebulization, delivery over a reasonable time-frame to deliver an appropriate dose to the lungs.

"In 2018, clinicians are now practicing in the distant "after surfactant" era, where the focus is avoidance of intubation and mechanical ventilation. "

CONSIDERATIONS

Determining what method of surfactant delivery is "best" requires evaluating several aspects of the procedure. Among these under consideration are:

- Efficacy of treating RDS
- Physiologic effect on the infant
- Premedication
- Patient Population
- Effect on functional residual capacity (FRC)
- Need for positive pressure ventilation (PPV)
- Potential adverse effects
- Provider skill and familiarity with the device

EFFICACY OF TREATING RDS

The INSURE technique has been around the longest and is the most widely studied of the techniques. Results have been inconclusive with some studies noting a decrease in need for mechanical ventilation2 and other studies showing similar rates compared to CPAP alone[9,10]. Results with the outcome of ability to achieve rapid extubation and/or need for reintubation are difficult to interpret as they may be due to a lack of response to surfactant or secondary to the adverse respiratory or hemodynamic effect of premedication with an analgesic and/or muscle relaxant.

Studies investigating use of a thin catheter (Hobart method) or feeding tube (Kribs method) have shown a decrease need for mechanical ventilation. An initial multicenter trial was followed by a larger German Neonatal Network: Avoidance of Mechanical Ventilation (AMV) trial[11]. Infants 26-28 weeks gestational age were initially managed by CPAP, and when FiO_2 > 0.3, were randomized to receive surfactant through a thin catheter (n=108) or continued on CPAP (n=112). They found a significant reduction in the number of infants mechanically ventilated on days 2 or 3 after birth in the intervention group compared with the CPAP alone group (28% vs 46%, p=0.008 (RR 0.68, 95% CI 0.42-0.88). There

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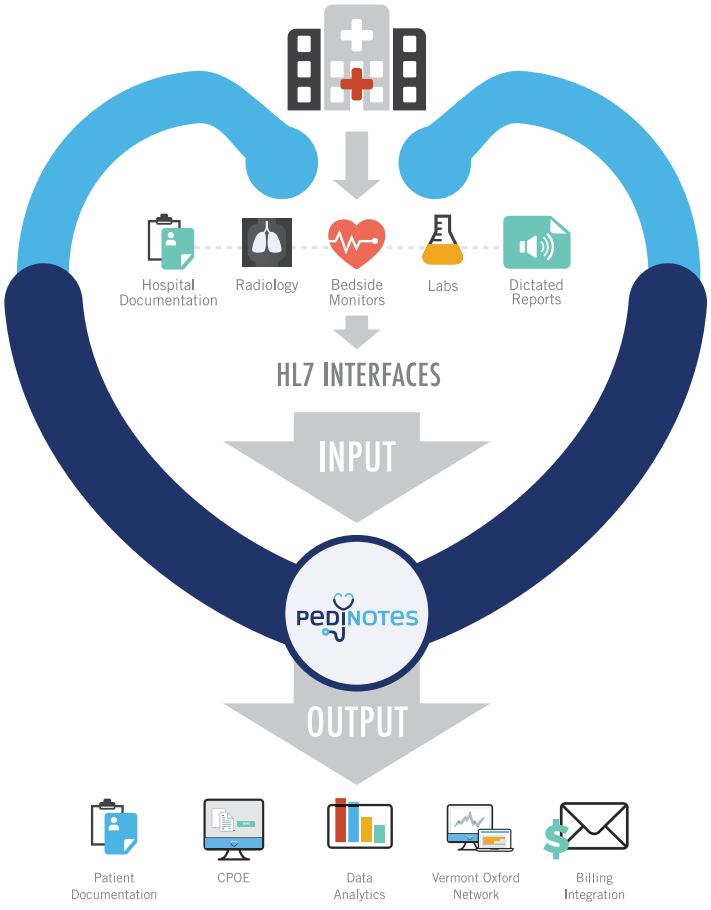

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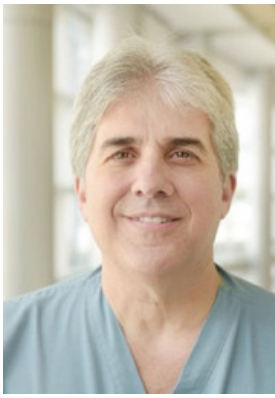

Steve Spedale, MD, FAAP, is the director of neonatology for one of the country's largest women's hospitals. As an early adopter of electronic medical records in the NICU, Spedale recognized the need for improved technology not provided by the available EMRs. With that in mind, he began developing software add-ons independently to give him the tools he needed.

In 2011, Dr. Spedale realized his ideas could benefit other doctors and caregivers, so he built a development team to execute them. Together, they created PediNotes.

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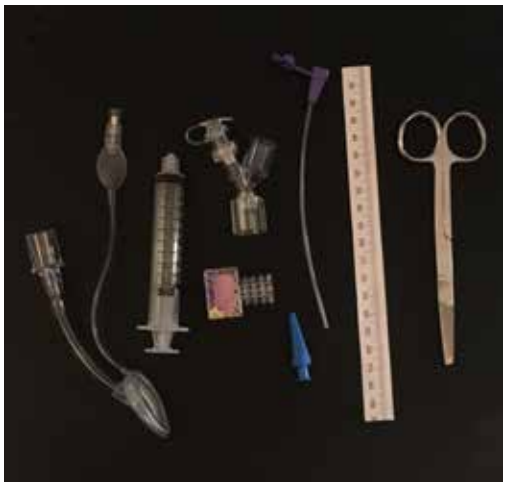
Picture 1. Placement of Laryngomask Airway. Note surfactant administration in progress

was a lower need for oxygen therapy at 28 days and fewer infants required mechanical ventilation at any time during their NICU stay in the intervention group (33% vs 73%, p<0.001, RR 0.42 (95% CI 0.3, 0.59).

In the Vienna trials, Klebermass-Schrehof[12] focused on extremely premature infants of 23-27 weeks' gestation and modified the technique of Kribs by treating infants within 30 minutes after birth while maintaining infants on higher pressure CPAP (10-15 cm H_2O). Using this modified technique in 224 infants, mechanical ventilation was avoided in 65% of infants during the first week and 41% of infants in the intervention group required no mechanical ventilation during the entire hospitalization. When compared to institutional historic controls, overall survival was increased (76% vs 64%, p<.002) and among infants 23-25 weeks gestation, survivors increased from 43% to 68%, p<0.0001. In this non-randomized study, surprisingly the occurrence of BPD was not significantly different. In Spain, Aguar[13] compared minimally invasive surfactant treatment with an orogastric tube inserted into the trachea by direct laryngoscopy and without sedation, and compared outcomes in infants from 24-35 weeks to their units historic comparison group treated with INSURE. No differences were found in the need for intubation rates or in the need for mechanical ventilation in the first 72 hours. Additionally, more infants required a second dose of surfactant using the minimally invasive technique than INSURE (35% vs 6.5%, p=0.0001) raising the question of whether surfactant dosing was actually achieved with initial instillation. The authors comment that using the minimally invasive approach may require increases in surfactant dose and/or higher end expiratory pressures may be necessary to optimize the technique. In the Take Care[14] randomized controlled trial, surfactant administration using the Krib's technique was compared to classical INSURE. Infants receiving CPAP were randomized when the FiO_2 ≥0.4. Compared with the INSURE group, those receiving less invasive surfactant administration had a lower rate of intubation of <72 hours (30% vs 45%, p=0.02), a significantly shorter duration mechanical ventilation and CPAP, and a lower rate of BPD (10% vs 20%, p=0.009). These and others studies are summarized in Table 1.

Studies investigating the use of the LMA have been universally favorable. Use of the animal model comparing surfactant administration via LMA compared to an ETT showed similar improvements in oxygenation[15]. To date, there have been 3 case reports and 5 published randomized controlled trials investigating the use of the LMA for surfactant administration in humans. Attridge[1] compared infants on CPAP who received surfactant via an LMA to those who did not receive surfactant and found a decrease in oxygen requirement for 12 hours after the intervention with no significant difference in the need for mechanical ventilation or incidence of BPD. Roberts[17] compared similar groups and found a 26% decrease in the need for mechanical ventilation in the group who received surfactant via an LMA compared to controls maintained on CPAP alone (38% vs 64%, OR 0.30 (95% CI: 0.13, 0.70), p=0.006, NNT=4). Studies comparing LMA administration vs INSURE have found the LMA to be superior in improvement in oxygenation[18] and decreased failure rate (77% in the INSURE group compared with 30% in the LMA group with similar efficacy in decreasing severity of RDS[19]. The high failure rate in the INSURE group was largely secondary to difficulty with extubation due to premedication with narcotics. A similar comparison by Barbosa found that short-term efficacy was similar between groups20. A recent study combined the use of an LMA and catheter by passing an 8 French umbilical vein catheter through the LMA into the trachea for surfactant administration. This technique was evaluated in 4 patients. The procedure was correctly performed on the first attempt and all patients experienced improvement in the patient's FiO_2 requirement at 3 hours post administration[21]. These studies are summarized in Table 2.

As mentioned previously, the use of aerosolized or nebulized surfactant has been hindered by technical issues. The few studies that have investigated this method in humans are summarized in Table 3.



Picture 2. Equipment for LMA Placement

Table 1: Clinical studies of surfactant administration via thin catheter

Trial	Intervention vs. control	Gestation range	Entry criteria	Primary outcomes	Findings
Procedure Trials					
Dargaville[4] 2013	Hobart (n=61) vs historical controls (n=97)	25–32 wks	Age < 24 hrs FiO_2>30% (25-28 wks), FiO_2 > 35% (29-32 wks)	Intubation < 72 hrs	MV within 72 hrs: 25-28 wks 32% vs 68% (p=.0011); 29-32 wks 22% vs 45% (p=.057). No difference in duration of ventilation or BPD. Short duration of oxygen in the Hobart method group
Kribs[5] 2007	Kribs (n=29) vs historical controls (n=34)	23-27 wks	FiO_2 > 40%	Intubation < 72 hrs	MV within 72 hrs: 34% vs 77%; decreased mortality, severe IVH and pulmonary interstitial emphysema
Klebermass-Schrehof[12] 2013	Kribs (n=224) vs historical controls (n=182)	23-27 wks	FiO_2 > 30%	Intubation < 72 hrs	MV within 72 hrs 32%; MV within 7 days 25%; MV during hospital stay 59%; higher survival rates 76% vs 64% ; less IVH 28% vs 46%; less severe IVH 13% vs 24%, less cystic periventricular leukomalacia 1% vs 6%; more PDA 75% vs. 53%, more ROP 41% vs 21%
Aguar[13] 2014 SONSURE (Sonda Nasogastica Surfactante Extubacion, Spanish)	Kribs (n=44) vs historical controls with INSURE (n=31)	24-35 wks	FiO_2 > 21%	Intubation < 72 hrs	MV within 72 hrs 34% vs 26%, p=.44; trend toward reduction in NEC 0% vs 9%, p=.067, more need for second surfactant dose 35% vs 6%, p<.0001; no difference in duration of MV or CPAP
Teig[54] 2015	Kribs (n=53) vs historical controls (n=44)	23-28 wks	FiO_2 30-50%	Intubation < 72 hrs	MV within 72 hrs 42% vs 77%, p<0.0005; MV during hospital stay 55 % vs 77%, p=0.02; duration of MV 2 vs 3 days, p=0.056; No difference in survival without BPD. Improved Mental Developmental Index (89 vs. 98, p=0.16) and Physical Developmental Index (83 vs. 91, p=0.03) at 3 years
Gopel[55] 2015	Kribs (n=1103) vs historical controls (n=1103)	< 32 wks (22-32 wks)	Matched controls, FiO_2 not specified	Need for MV	MV during hospitalization 41% vs 62%, p<.001; postnatal dexamethasone use 3% vs 7%, p < 0.001; BPD 12% vs 18%, p = 0.001; BPD or death 14% vs 21%, p < 0.001
Krajewski[56] 2015	MIST (n=26) vs historical controls with INSURE				MV 19% vs 65%; duration of MV 5 d vs 3.5 d, duration of CPAP 5.5 d vs 4 d; higher IVH≥ 2 50% vs 30%, less NEC 12% vs 23%, increased PDA 54% vs 45%, less BPD 15% vs 40%, less ROP 4% vs 12%
Templin[57] 2017	MIST (n=52) vs historical controls (n=40)	24-27 wk		Intubation in the delivery room	Intubation in the delivery room 31% vs 90%, p=.001; MV at 72 hrs 28% vs 62%, p=.002); MV during hospitalization 75% vs 93%, p<.05)
Randomized Controlled Trials					
Göpel[11] 2011 Avoidance of Mechanical Ventilation (AMV) Trial	MIST (n=108) vs. CPAP followed by ET instillation (n=112)	26–28 wk	Age <12 hr FiO_2> 30%	Intubation days 2–3	MV days 2–3 28% vs 46% (NNT: 6, 95% CI: 3–20, *P*=0.008); intubation at any time: 33% vs 73% (*P*<0.001); median days on MV: 0 vs 2; Oxygen at 28 days: 30% vs 45% (*P*=0.032)
Kanmaz[14] 2013 Take Care Trial	MIST (n=100) vs. INSURE (n=100)	<32 wk	Age<72 hr FiO_2>40%	Intubation <72 hr	MV within 72 hr: 30% vs. 45% (*P*=0.02); MV at any time: 40% vs. 49% (*P*=0.08); BPD: 10% vs. 20% (*P*=0.009)
Heidarzadeh[58] 2013	MIST (n=38) vs. INSURE (n=42)	≤32 wk	Immediately after birth	Feasibility, description of outcomes	Lower rate of NEC and shorter duration of CPAP and hospital stay in the intervention group, no further differences
Kribs[34] 2015 NINSAPP Trial (Non-intubated Surfactant Application)	MIST (n=104) vs. CPAP, ET instillation (n=107)	23–26 wk	Age<2 hr FiO_2≥ 30% or Silverman score ≥5	Survival without BPD at 36-wk GA	Survival without BPD 67.3% vs. 58.7% (*P*=0.20); intubation: 74.8% vs. 99.0% (*P*=0.04); pneumothorax: 4.8% vs. 12.6% (*P*=0.02); Severe IVH: 10.3% vs. 22.1% (*P*=0.02); survival without major complications: 50.5% vs. 35.6% (*P*= 0.02).
Mohammadizadeh[59] 2015	MIST (n=19) vs. INSURE (n=19)	≤34 wk	Age<1 hr FiO_2≥ 30% or Silverman score ≥5	Need for MV and duration of oxygen therapy	No difference in need for MV, but duration of surfactant therapy significantly shorter in intervention group
Bao[60] 2015	MIST (n=47) vs. INSURE (n=43)	28–32 wk	Age<2 hr FiO_2≥ 30% (28^{+0}–29^{+6} wk) or FiO_2≥ 35% (30^{+0}–32^{+6} wk)	Feasibility, rate of MV in the first 72 hr, duration of MV, CPAP, and oxygen requirement, neonatal morbidities	No differences in rate of MV in the first 72 hr, duration of oxygen and neonatal morbidities, duration of MV and CPAP significantly less in the intervention group

MIST, minimally invasive surfactant therapy (Hobart or Kribs method); CPAP, continuous positive airway pressure; ET, endotracheal; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; NNT, number need to treat; CI, confidence interval; INSURE, intubation, surfactant and extubation; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; GA, gestational age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity

Assuming correct placement of the device, the INSURE, MIST and LISA methods offer direct instillation of surfactant into the lungs. However, reflux into the pharynx can occur, which occurred in over 30% of the patients in the MIST trial[4]. Objective means to qualify the amount of surfactant that is refluxed and where the refluxed medication ends up is not feasible given the surfactant is likely swallowed, aspirated back into the lungs or spit up by the infant. In contrast to direct tracheal administration, the LMA rests in the posterior pharynx and has the potential for leakage around the inflatable cuff. In the Roberts[17] study, objective means to quantify leakage was made by aspirating gastric contents before LMA placement and after surfactant administration. They found that over 50% of the infants had gastric aspirates that were <10% of the administered dose. Gastric aspirate is an imprecise indicator however, as all of the surfactant may not have been aspirated and/or the gastric aspirate may represent gastric secretions or other medications in addition to surfactant. Clinical response to the surfactant dose is currently the best indicator of whether surfactant reached the lungs.

"In summary, all methods have been shown to reduce the need for mechanical ventilation."

In summary, all methods have been shown to reduce the need for mechanical ventilation. Studies comparing INSURE to the Hobart or Kribs methods have found Hobart or Kribs to be superior, while studies investigating LMA compared to INSURE or CPAP alone have found the LMA to be superior. Currently there are no studies comparing LMA to the Hobart or Kribs method.

PHYSIOLOGIC EFFECT ON THE INFANT

Direct comparison of the physiologic effect on the infant during placement of an ETT, feeding tube or thin catheter is difficult given the wide variation in whether premedication is used, and if so, what agents. However, since these devices all require use of a laryngoscope and advancement of a device through the vocal cords, adverse physiologic effects can be

generalized as a being similar. Studies investigating intubation without premedication have shown adverse physiologic effects such as bradycardia[22,23], hemodynamic instability including hypo- and hypertension[22-28], hypoxia[22,23,27,29-31] and increased intracranial pressure[23,24,26,28,32,33].

Studies comparing INSURE and MIST/LISA techniques have shown higher rates of transient hypoxia and bradycardia in infants treated with MIST/LISA[3,11,14,34]. Bertini compared cerebral oxygenation during MIST (using a feeding tube) and INSURE with infants in both groups not receiving premedication. They found both strategies were associated with a decrease in cerebral regional oxygenation (as measured by near-infrared spectroscopy (NIRS)), with the decrease significantly higher in the MIST group during the procedure and at 2 hours after the procedure (45 vs 61, p=0.005 and 77 vs 84, p=0.01). They also found SpO_2 during the procedure to be lower in the MIST group (61% vs 74%, p=0.001). Cerebral blood flow velocity and transient bradycardia during the

Table 2: Clinical studies of surfactant administration via an LMA

Trial	Intervention vs. control	Gestation range	Entry criteria	Premedication	Findings
Case Reports					
Brimacombe[6] 2004	n=2	30 wk 37 wks	FiO_2 50% FiO_2 80%	None Midazolam	Improvement in respiratory function
Trevisanuto[7] 2005	n=8	28-35 wks	Age < 72 hrs a/A PO_2 <.2	None	a/A PO_2 at 3 hrs after surfactant increased 0.13 to 0.34, p<0.01
Vannozzi [21] 2017 CALMEST (Catheter and laryngeal mask endotracheal surfactant therapy)	n=4	BW >1.5 kg	FiO_2 ≥ 35%	None	Improvement on FiO_2 requirement, respiratory rate and Silverman score at 3 hrs after surfactant
Randomized Controlled Trials					
Attridge[16] 2013	LMA (n=13) vs CPAP alone (n=13)	BW ≥1.2 kg	Age <72 hr FiO_2 30-60%	None	FiO_2 at 1 hr 25% vs 37%, p=0.002; FiO_2 at 12 hrs 27% vs 40%, p=.04; Required MV 8% vs 23%, p=0.59
Sadeghnia[18] 2014	LMA (n=35) vs INSURE (n=35)	BW ≥2 kg	Age < 48 hrs FiO_2 ≥ 30%	None	a/A PO_2 after surfactant dose 0.48 vs 0.43, p=.014
Penheiro[19] 2016	LMA (n=30) vs INSURE (n=31)	29-36 wks	Age < 48 hrs FiO_2 30-60%	LMA: Atropine INSURE: Atropine and Morphine	Failure requiring MV 30% vs 77%, p<0.001; Early failure 3% vs 67%, p<0.001; Late failure 10% vs 27%, p=0.181; FiO_2 decrease and adverse events similar between groups
Barbosa[20] 2017	LMA (n=26) vs INSURE (n=22)	28-35 wks BW > 1 kg	FiO_2 ≥40%	LMA: Lidocaine gel on mask INSURE: Remifentanil and Midazolam	FiO_2 ≤30% at 3 hrs post surfactant 77% vs 77%, p.977; 54% of LMA group did not require MV; lower Silverman- Anderson score at 3 and 6 hrs after surfactant 2 vs 0, p=0.0001 and 0.5 vs 0, p=0.017; similar second dose of surfactant 23% vs 18%,p=0.735
Roberts[17] 2017	LMA (n=50) vs CPAP alone (n=53)	28-35 wks BW ≥1250g	Age ≤ 36 hrs FiO_2 30-40%	LMA: Atropine and 24% sucrose solution	MV in first 7 days 38% vs 64%, p=0.006; Duration of MV, CPAP and supplemental oxygen at 7 days of age similar between groups

LMA, laryngeal mask airway; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; a/A PaO_2, arterial/alveolar ratio; BW, birth weight; INSURE, intubation, surfactant and extubation

Table 3: Clinical studies of surfactant administration via aerosolization

Trial	Intervention vs. control	Gestation range	Entry criteria	Primary outcomes	Findings
Procedure Trials					
Berggren[61] 2000	Jet nebulizer (n=16) vs CPAP alone (n=16)		Age < 36 hrs FiO_2>40%	Intubation	MV 31% vs 38%
Minocchieri[62] 2013	Vibrating membrane nebulizer (n=64) vs CPAP alone	29-33 wks	Age < 6 hrs FiO_2 22-30%	Intubation < 72 hrs	MV within 72 hrs: RR 0.56 (95th CI .34,.93); No difference in BPD
Windtree Therapeutics[63] 2017	Heated capillary nebulizer (n=221) vs CPAP alone	28-32 wks	FiO_2>30% CPAP=5 Aerosol 25 or 50 minutes	NCPAP failure, Time of Failure, Physiologic criteria for CPAP failure	"Aerosurf nebulizer did not meet the desired end-point of a reduction in CPAP failure" In 50 minute aerosol group nCPAP failure was 31% vs 44% in CPAP group Overall results of Trial are P=NS

CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia

procedure were similar between groups[35]. Skov also showed a decrease in cerebral oxygenation with the INSURE technique[36]. In contrast, van der Berg found that the INSURE technique did not affect cerebral oxygenation[37]. However, infants in the van der Berg study did receive premedication with morphine.

Premedication has been shown to mitigate the adverse effects of intubation; with atropine mitigating bradycardia[23,26-28], an analgesic mitigating hemodynamic instability[31] and a muscle relaxant mitigating the increase in intracranial pressure[23,24,26,28,32]. However, use of premedication may lead to difficulty with rapid extubation with the INSURE technique or failure to remain spontaneous breathing with the MIST and LISA techniques.

In the Roberts trial[17], placement of an LMA was accomplished with premedication with atropine and 24% sucrose solution. Infants tolerated the procedure well with heart rate and oxygen saturation (SaO_2) maintained close to baseline (1 bpm and 6% respectively)[38].

PREMEDICATION

The American Academy of Pediatrics[39] and Canadian Society[40] have issued statements that premedication with an anticholinergic, analgesic and muscle relaxant should be used for all non- emergent intubations. Despite these statements, there is a great deal of variation amongst clinicians on whether premedication is given for intubation and, if so, what medications are used[41]. For traditional intubation, premedication with the recommended triple combination is possible. However, if using the INSURE technique, a muscle relaxant needs to be avoided or rapid extubation delayed until the muscle relaxant wears off. With the MIST and LISA techniques, the infant must remain spontaneously breathing so a muscle relaxant can not be used. Given the need for a laryngoscope and identification and passage through the vocal cords, the inability to use a muscle relaxant may prolong the procedure as a muscle relaxant has been shown to decrease the time and number of attempts required to successfully place the device[42].

Placement of an LMA does not require a laryngoscope or direct visualization of the vocal cords. In the Roberts LMA trial[17], infants in the LMA group (premedication with atropine and 24% sucrose solution) and those who reached treatment failure criteria and were intubated for ETT placement (premedication with atropine, fentanyl and rocuronium) were videotaped during the procedure. Results showed duration of attempts were shorter for LMA as compared to ETT placement (32 sec vs 66 sec, p<0.001). Mean total procedure time for successful LMA placement was 88 sec as compared to 153 sec for ETT (p=0.065) and mean number of attempts for successful placement was fewer for LMA placement (1.5 vs 1.9, p=0.106).

PATIENT POPULATION

The INSURE, MIST and LISA techniques are all very similar to the traditional method of endotracheal intubation and have been investigated in infants down to 23 weeks gestation[5,12,34]. Previously, the LMA did not fit well in infants < 28 weeks and <1.2 kg. However, a smaller LMA has recently became available that fits infants as small as 500 grams (Air-Qsp Reusable 0.5 Laryngeal Mask, Ref 6005, Cookgas, St. Louis, MO). This is encouraging as the < 28 weeks gestation population represents about one-third of the infants with RDS[44].

EFFECT ON FUNCTIONAL RESIDUAL CAPACITY

Intubation, INSURE, MIST and LISA require the use of a laryngoscope during placement of the device without the ability to maintain FRC. Immediately after insertion of the LMA, a "Y" piece can be placed on distal end allowing for CPAP to be re-established using one end of the "Y" piece. A catheter is threaded through the port on the other end of the "Y" piece for surfactant administration thereby allowing CPAP and FRC to be maintained throughout the duration of surfactant administration. In contrast, Jourdian and co-workers[45] reported in a physiologic study using maneuvers for minimally invasive surfactant therapy using a fine catheter into the trachea resulted in a 99% loss of distending pressure during mouth opening and closing in both an in vitro airway-lung model and in 19 neonates under the same conditions. These findings are important because maintaining continuous distending pressure during surfactant administration improves surfactant distribution throughout the lungs and maintenance of FRC.

POSITIVE PRESSURE VENTILATION

Studies have shown that even a short duration of PPV can be associated with barotrauma, volutrauma and excitation of the inflammatory cascade[46]. However, PPV has also been shown to be beneficial in the recruitment of alveoli and result in an increase in functional residual capacity[47]. Whether PPV or spontaneously breathing results in better surfactant distribution is an area of debate. Animal studies have resulted in conflicting results with one study showing spontaneous breathing to be superior[48] while another found that surfactant deposition was significantly lower in preterm lambs who were spontaneously breathing[49]. Clinical trials in humans comparing the Hobart and Kribs methods (which do not use PPV) to the INSURE technique (which does use PPV) found the Hobart/Kribs method to be superior. However, it is worth noting that infants receiving surfactant via the Hobart or Kribs method may require PPV due to hypoxia or bradycardia, with 44% of infants in the Dargaville trial requiring PPV[4] and 56% in the Kribs trial experienced hypoxia that resolved with PPV[34].

POTENTIAL ADVERSE EFFECTS

In addition to the adverse physiologic effects already discussed, intubation, INSURE, MIST and LISA have the potential for mouth

and pharyngeal trauma and bleeding secondary to use of the laryngoscope and/or vocal cord or subglottic injury from the device passed thru the vocal cords. Because the LMA rests in the posterior pharynx, these potential adverse effects are negated but does raise the possibility of laryngospasm since surfactant is administered above the vocal cords. While a theoretic risk, laryngospasm has not been reported in the animal study[15] or human case reports or randomized, controlled trials[6,7,16-21]. Because of the theoretic risk however, clinicians should be prepared with a muscle relaxant and intubation supplies readily available during the procedure.

PROVIDER SKILL AND FAMILIARITY

Intubation, INSURE, MIST and LISA have similar skill requirements given the need for use of a laryngoscope and direct visualization of the vocal cords. While intubation was a frequently performed procedure in the past, the change in the American Academy of Pediatrics and the American Hospital Association Neonatal Resuscitation Program (NRP) guidelines[50] in 2006 discouraging routine suctioning of meconium for vigorous infants born through meconium stained fluid and the increased use of non-invasive ventilation have led to a significant decrease in the number of intubations available for providers to obtain or maintain this skill. For those comfortable with intubation, use of a McGill forceps to aid in the placement of a device may be a foreign concept, potentially making the LISA technique less attractive to those providers.

While becoming more common, many neonatologists and neonatal nurse practitioners have had little or no experience placing an LMA in neonates. In the past, the NRP guidelines mentioned the LMA as an alternative device to establish an advanced airway in the event that intubation was not successful or feasible[51]. However, the 7th edition of the guidelines[52] (2016) now recommend and incorporate training of placement of an LMA. This recommendation will result in increased exposure and familiarity with the device, as most neonatal clinicians are NRP certified.

In a recent editorial supporting the MIST technique, the author states "learning the essentials may be only a matter of training, but as with most neonatal procedures, full mastery of laryngeal mask placement will inevitably require some good and bad experiences." In this respect, the author concludes that "surfactant delivery by LMA is trumped by tracheal catheterization, because direct laryngoscopy is familiar to any neonatal proceduralist and the insertion of a thin catheter through the vocal cords is not dissimilar to insertion of an endotracheal tube."[53] We agree that learning a new technique is a matter of training, but come to the opposite conclusion in terms of what device should be used. We believe providers should stop subjecting infants to laryngoscopy and become familiar with placement of an LMA, the least invasive method available.

In the Roberts[17] study, a successful placement of the LMA was achieved in the majority of infants in a single attempt and was completed within 35 seconds[38]. Providers involved in the study stated they felt comfortable with the technique after their second experience. While there is a learning curve, it may be much less steep than for the techniques that require direct visualization and insertion through the vocal cords.

Now is the time to become familiar with placement of an LMA and reserve endotracheal intubation for those who fail less invasive measures. We believe that intubation will have a fate similar to placement of a chest tube- where the procedure is performed on an infrequent basis, skills will need to be maintained by a designated group of providers and skills will largely need to be maintained through use of simulation on mannequins.

LMA surfactant administration photo and required supplies are shown in Figures 1 and 2. Training for placement and surfactant administration can be obtained from the methods described in the publication by Roberts[17], a workshop at the upcoming Pediatric Academic Society (PAS) meeting in Toronto, Canada and a training video which is currently in progress.

CONCLUSION

In conclusion, in this era of increased non-invasive ventilation, methods are available to provide the benefits of early surfactant without resorting to conventional means of intubation and mechanical ventilation. While all of the methods are effective, the ease, short duration, physiologic stability and ability to maintain FRC during the procedure make the LMA the "best" way to administer surfactant.

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Commentary: Surfactant Administration in 2018: A Program Director's Perspective

By Elba Simon-Fayard, MD

Roberts and co-author's present a strong case using Laryngotracheal Masks (LMA) for the administration of surfactant to infants failing nasal continuous positive airway pressure (nCPAP). The benefit was shown through the management of respiratory distress syndrome (RDS) in their multicenter randomized trial as well as others that have used this technique with similar results. Neonatologists and their trainees can better serve these struggling infants with RDS with an easier mode of surfactant administration while avoiding endotracheal intubation, use of a laryngoscope or McGill forceps, and loss of distending airway pressures during surfactant administration that are so critical for a more uniform intra-pulmonary distribution of the surfactant. Yet, having a smaller size LMA could allow the extremely low birth weight infants to also benefit from this practice.

Neonatologists now perform endotracheal intubation fewer times than before, thus presenting less opportunity to teach trainees the techniques of intubation. Neonatal Nurse Practitioners and Respiratory Therapists also need training, and thus pediatric residents are afforded fewer and fewer opportunities to learn this infrequently used, but critical procedure. Leone in the US and Bismilla and co–workers in Canada demonstrated that the success rate and overall quality of neonatal intubations performed by pediatric trainees and neonatal trainees did not meet the standards articulated by the Neonatal Resuscitation Program, particularly in the time taken to successfully intubate the trachea of these fragile infants.[1,2] There is also the effect of time where the trainee loses competency to perform endotracheal intubation if the procedure is not practiced after completion of training.

The 7th edition of the Neonatal Resuscitation Program textbook dedicates 23 pages of discussion and illustration of endotracheal intubation, equipment, and problems associated with intubation while only 7 pages are dedicated to placement of an LMA and ventilation through this alternative advanced airway. This may be due to the fact that LMA placement and a shorter interval of ventilation is easier and has fewer steps and complications. Given this advantage, perhaps more training time should be dedicated to the use of LMA's for advanced airway placement and, in addition, to its use for delivering surfactant.

Two recent publications have highlighted the benefits of using video-laryngoscopes for teaching trainees.[3,4] Both trials showed that success on initial attempt was much higher with the video laryngoscope. The screen images were useful for instructors to assist trainees in identifying critical anatomy and given them guidance, although the times of intubation were still longer than the desired 30 seconds. O'Shea, et al[5,6] provides an analysis of unsuccessful intubations; it seems that main reason is failure to recognize the vocal cords, and poor visualization of the glottis. Of course, during placement of an LMA these structures do not need to be visualized as the mask is guided with the fingers under the palate and over the tongue until it covers the glottis.

In none of the LMA trials conducted for administering surfactant were there reports of serious adverse events. Only sugar water and atropine were used with LMA technique whereas with INSURE, MIST and LIST techniques opioid sedation was frequently used. Sedation is to be avoided in infants with impending ventilatory failure, but with elective intubations sedation it is advisable, if not, always needed. Yet, this is not the case for LMA ventilation, another positive for using it as a preferred initial advanced airway.

At this point there are no randomized trials comparing MIST, LIST, or LMA in head to head trials, but hopefully there will be one. Currently, in 2018, we can conclude that the balance on the scale of benefit to harm is clearly weighted on the benefit of using the LMA technique for surfactant administration.

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Letters to the Editor

To the Editor,

The article in the March, 2018 issue by Salama et al entitled "Clinical Outcome of Complete Integration of Electronic Health Record System Technologies Inside the Neonatal Intensive Care Unit - Four 4-Year Evaluation" identifies an important area for research. The authors' conclusion merits further reflection: "Complete transformation into EHRs was not accompanied with significant improvement in clinical outcomes in newborn infants admitted to the NICU. Health care policy makers may consider goals other than patient clinical outcome when they plan to implement the EHRs."

Salama et al state in their introduction that "In this study, the authors are exploring the clinical impact of such modern technology on newborn morbidity and mortality inside the neonatal intensive care." This greatly oversimplifies an extremely complicated reality and thereby risks promoting misleading inference.

The process of evaluating a NICU EHR must rest upon detailed knowledge of the data model and software implementation, along with the specific goals they reflect.[1-3] Too often for NICU EHRs, the specific design goals are restricted to regulatory compliance and financial optimization. Readers should appreciate that merely to articulate a testable research question about EHR impact whose answer might yield operational insight for improvement requires that question to derive from explicit knowledge of the design and goals of the EHR.

To expect to see a change in specified clinical outcomes after implementation of a new data management system rests on key assumptions the authors do not address, including: 1) The important determinants of the clinical outcomes are known and are captured in the data model and implementation; 2) The EHR was designed to help manage the specified outcome determinants and thereby improve the specified clinical outcomes; 3) Before the start of the study (2013), year-to-year changes in outcomes did not vary as they did during the two study periods; 4) During the study period, no other changes in the processes of care were implemented. A comparatively more minor point, but worth mentioning, is that p-value computations for outcomes should have reflected multiple comparisons.

Thus, it is not surprising that the authors found no evidence that their EHR did not improve clinical outcomes. However, it is by asking ourselves "why not?" that we can identify the path by which our EHRs can help us achieve our goals.

Sincerely,

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NT

Dear Dr. Joseph Schulman

Thank you for your letter to the editor, which stimulated important pressing questions,

1. What, when and why we need to introduce new technology to intensive care?
2. What are the category of indicators the policy makers need to consider before inviting new technology to the NICU: clinical outcome versus logistic support.?
3. What parents want to see and get?

Many, if not the majority of practitioners agree on the following neonatal outcome indicators:

1. Survival rate with its variations.
2. Pulmonary complications of prematurity & chronic lung disease.
3. Neurologic and developmental complications .
4. Ventilation days.
5. Days of Hospitalization.
6. Delivery room performance as hypothermia, resuscitation, and transport.
7. Healthcare related infection rate.
8. Visual complications of prematurity.
9. Surgical complications as necrotizing enterocolitis.
10. Breast milk utilization.
11. Growth velocity.
12. Parent's communication, understanding & satisfaction.

With no doubt, complete integration to EHR system does guarantee many benefits to our practice and does solve several logistic problems. But, in our study, we focused merely on what matters to the parents as well as to the clinicians in every day practice. We as well, tried to address to health care decision makers that while complete integration of EHR is facilitated with documentation, security, monitoring and logistic support inside the NICU, it still has little to add to the above mentioned indications. The authors do understand the efforts to develop, implement and disseminate new core outcome sets for neonatal medicine but until it prove its validity and convenience, the clinician will continue to associate any new development with the well established indicators.

We state in the manuscript a clear statement which is:

"Nevertheless, we cannot exclusively link or associate our NICU outcome solely on the EHR's application. Within the capacity of this study, the authors can conclude that introducing EHRs to our NICU

facility did not demonstrate a momentous improvement in morbidity and/or mortality rates inside our NICU. Healthcare policy makers are required to consider clinical outcomes when they endorse complete integration of EHRs."

Thank you for your interaction

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Maternal Mortality in the US is Due to Inefficiency in the Healthcare System

Viveka Zawisza, MD FACOG

Members of the NPA write a regular column in *Neonatology Today*.

National Perinatal Association

Educate. Advocate. Integrate.

Maternal mortality, defined as the death of a woman while pregnant or within 42 days of giving birth or termination of pregnancy, is a scourge that afflicts every nation in the world. The death of a new mother is often measured by the people it leaves behind: a newborn infant, sometimes other children, and a spouse or partner, and thus it can impact a community in a uniquely devastating way. It is easy to picture mothers dying in poor countries with minimal resources and rampant economic inequality. Therefore, it might seem unthinkable that a country as wealthy as the United States, the land where immigrants come to enjoy access to opportunities unavailable in their own countries, and which spends almost 20% of its gross domestic product on healthcare, should have one of the highest maternal mortality rates in the world. And yet it does. While many experts have studied this problem and proposed explanations, it is undeniable that major inefficiencies in the way the US healthcare system provides prenatal and peripartum care contribute a great deal to the problem.

As of 2016, the maternal mortality ratio in the US was estimated to be 14 maternal deaths per 100,000 live births (World Bank, 2017). To put this in perspective, this is more than double that of similar countries, such as Switzerland and Australia which have maternal mortality ratios around 6 maternal deaths per 100,000 live births. It may be heartening to known that 97% of pregnant women in the US receive at least four antenatal visits (UNICEF, 2016) but that number doesn't tell the whole story. Simply getting prenatal care is not enough if that care is not making an impact in reducing mortality rates. When it comes to providing antenatal care to pregnant and laboring women, the biggest difference between the US and other developed nations is the inefficient and inconsistent way in which that care is provided in the US.

Because American health insurance policies vary state by state, a woman may not have consistent coverage for antenatal care. This is an inefficiency that is maddening, both for patients and providers, because it is purely a result of policies based on the divisive political climate in the US. Imagine Jane Doe, an average American woman, who finds out she is pregnant. Luckily, she is employed so she uses her insurance benefit for prenatal care to see Dr. Smith. Now let's say her company changes its benefits plan and she can no longer see Dr. Smith because he is not covered under the new plan. She must find a new doctor and transfer of her health records must be coordinated between the previous doctor and the new doctor, a notoriously inefficient process that may not be completed before she goes into labor.

"We must…provide efficient continuity of care for pregnant women and consistent, evidence-based practices in uniform, enforceable ways if we are ever going to be serious about reducing our unacceptably high maternal mortality rates."

In a different scenario, let's say Jane loses her job during her pregnancy, and would then need to rely on her spouse's insurance (if that's even an option), or apply for state-funded insurance. In either scenario, while the administrative quagmire at the insurance company is processing her application, Jane's pregnancy is progressing and she isn't getting the care she needs. If she develops any complications in the pregnancy, they will remain undiagnosed, or if they were diagnosed early on, they will not be managed properly due to lost continuity of care. Ultimately, Jane will show up at a hospital ready to give birth with limited prenatal records, and the physicians and nurses will have to quickly piece together her clinical situation. In many cases, the fatal or near-fatal events that occur during labor and the immediate postpartum period could have been prevented if there was better management of complications during pregnancy. Uninsured women in the US are up to four times more likely to die of pregnancy-related complications (Agrawal, 2015).

Inefficiency rears its ugly head yet again in actual obstetric provider practices. Despite regular updates and recommendations from the American College of Obstetricians and Gynecologists, the central body that reviews and issues evidence-based guidelines for the care of pregnant and postpartum women, there remains wide variation in the implementation of these guidelines across hospitals and practices. One way to address this issue is to enforce mechanisms for state-based maternal mortality review. Some states have passed legislation for formal reporting of maternal mortality cases, and some states have convened committees comprised of healthcare providers and policy leaders. However, as of May 2017, less than half of the 50 states had active legislation requiring some type of maternal mortality review (Adesomo et al., 2017).

The conversation around poor health outcomes in the US often centers on access as a factor dependent on health insurance. The story is more complex and deeper than

that. Until we acknowledge that efficiency is an often-overlooked casualty of a broken health insurance system, we won't be able to adequately tackle any major health issue. State-based initiatives to review maternal mortality are a good first step, but practice variation will never truly be addressed until there are federal mandates in place. Without addressing inconsistency and inefficiency, new mothers will keep dying in the US. American women deserve better, and we have the resources to do better. We must utilize these resources to provide efficient continuity of care for pregnant women and consistent, evidence-based practices in uniform, enforceable ways if we are ever going to be serious about reducing our unacceptably high maternal mortality rates.

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Compiled and Reviewed by Mitchell Goldstein, MD Editor in Chief

Study confirms that inflammation during pregnancy is linked to baby's brain

Machine-learning algorithm able to predict long-term brain impact, may identify early treatment opportunities for children

OREGON HEALTH & SCIENCE UNIVERSITY

Inflammation is a normal part of the body's response to infection, chronic stress or obesity. In pregnant women, it is believed that heightened inflammation increases the risk of mental illness or brain development problems in children.

A study conducted by researchers at OHSU in Portland, Oregon, has established a link between inflammation in pregnant women and the way the newborn brain is organized into networks. The results, published today in Nature Neuroscience, may provide promising avenues to explore treatments with potential to change these negative impacts on newborn brain function.

The research team, led by Damien Fair, P.A.-C., Ph.D., associate professor of behavioral neuroscience and psychiatry in the OHSU School of Medicine, and Claudia Buss, Ph.D., professor at the Charité - Universitätsmedizin Berlin, Berlin, Germany and associate professor at University of California, Irvine, collected blood samples from 84 expectant mothers at each pregnancy trimester. The samples were measured for levels of the cytokine interleukin-6, or IL-6, an inflammatory marker known to play a role in fetal brain development.

Four weeks following birth, brain connectivity patterns of the offspring were assessed using functional magnetic resonance imaging, or fMRI, scans. At age 2, the children were also tested for working memory performance, a key skill that supports academic achievement and is frequently compromised in mental health disorders.

The data from mother and child show that differences in the levels of inflammatory markers are directly associated with differences in newborn brain communication, and later to working memory scores at age 2. Higher levels of the marker during pregnancy tended to result in less working memory capacity in the child.

"Importantly, this doesn't mean that every exposure to inflammation will result in a negative impact to the child; however, these findings provide new avenues for research, and can help health care providers think about how, and when, inflammation might impact a child's long-term learning development and mental health," said Alice Graham, Ph.D., postdoctoral fellow in behavioral neuroscience in the OHSU School of Medicine.

A notable aspect of the study, according to Graham, is the development of a model that can accurately estimate information about maternal inflammation during pregnancy based only on newborn brain functioning. Created using artificial intelligence known as machine-learning, the model is based on the biomarkers identified in the study and can be applied to cases beyond the initial research group.

"Now, we have an approach that can utilize MRI brain scans of a newborn to accurately estimate the mother's overall levels of inflammation during the time of her pregnancy," she said. "This understanding provides some information about future memory function of that child approximately two-years later, creating a potential opportunity for research surrounding early clinical intervention, if necessary."

In the future, Fair believes that research should focus on how factors before and after birth - such as society and environment - interact to influence the impacts to brain function and cognition in newborns.

"Increased stress and poor diet are considered normal by today's standards, but greatly impact inflammation rates in all humans, not just expectant mothers," he said. "Just as important to understanding how the immune system and inflammation affect early brain development, we also need to understand what common factors contribute to heightened inflammation so that we may target therapies to help reduce the rates of inflammation and overall impact on the developing brain."

###

This study was completed in collaboration with University of California, Irvine. Marc Rudolph, a former research assistant in the OHSU School of Medicine, and current doctoral student in Cognitive Psychology at the University of North Carolina at Chapel Hill, is the study's lead author.

Funding was provided by the Bill & Melinda Gates Foundation, The Destefano Innovation Fund, National Institutes of Mental Health (grants MH091351 and MH091351), National Center for Advancing Translational Sciences (award UL1TR0002369) and the National Institutes of Health (grants MH096773 and MH091238). Additional support was provided by the Oregon Clinical and Translational Research Institute, and the National Library of Medicine Postdoctoral Fellowship.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Life after the NICU

Checking in at the Tiny Tot Clinic at UT Physicians

Newswise — Shortly after Luke Lombardi and his twin sister Sofia were discharged from a newborn intensive care unit or NICU, they

were enrolled in a special clinic for premature babies operated by UT Physicians.

The twins needed help accomplishing developmental milestones that many parents take for granted such as rolling over, pushing up and sitting up.

The Tiny Tot Clinic is helping the Lombardi twins and other premature babies realize their full potential and is for children up to 6 years of age. UT Physicians is the medical practice of McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth).

"These smallest of patients require very close follow-up," says Andrea Duncan, M.D., the clinic's medical director and an associate professor of pediatrics at McGovern Medical School at UTHealth. "In a NICU, the babies are cared for 24/7. When they're released, it's up to the parents to provide that care."

The clinic was opened in 2016 to provide follow-up care for babies born at 30 weeks of pregnancy or less, as well as other children born with critical illnesses. Forty weeks of pregnancy is considered full term.

That follow-up care is particularly important for premature babies who have a heightened risk of developmental issues such as movement, speech, cognitive and behavioral disorders that, in some instances, ultimately lead to school failure.

"Because they were born so early, many of these children are playing catch up," says Duncan, noting that about 80 children that are seen in the clinic right now, with 20 new children being added per month on average. "There are a number of things we can do to support their strengths, prepare them for the next milestone and to intervene when we see that something is amiss."

In the last weeks of pregnancy, organs such as the brain, lungs and liver are still being developed. In addition to developmental issues, preterm babies have a heightened risk of lung disease, heart complications, brain injury and cerebral palsy.

"Our services reduce the risk for neurodevelopmental and behavioral deficits, school failure, social difficulties, family stress and medical complications," Duncan says.

In a perfect world, Luke and Sofia would have been born in May of 2017 but instead arrived in January of that year. Born at 24 weeks of pregnancy, each weighed less than two pounds and had critical health challenges that had to be dealt with immediately.

In the NICU at Children's Memorial Hermann Hospital, Luke had three surgeries for bleeding on the brain and Sofia, treatment for a collapsed lung. Sofia was discharged in May and Luke in June.

Luke and Sofia now weigh 17 pounds and are doing much better but will still have to deal with chronic health issues. Sofia has a hole in her heart and Luke, hydrocephalus.

"The Tiny Tot Clinic has been a godsend for us," says Christine Lombardi, the twin's mother and a Houston realtor. "They've been with us every step of the way."

Luke and Sofia are the first children for Christine and her husband Federico, an importer/exporter. "It has been a roller coaster ride, and we have received help along the way," she says.

Born at The Woman's Hospital of Texas, the twins were later transferred to Children's Memorial Hermann Hospital. "I was terrified. Neither of us had ever had any medical issues. We were told that they had a low chance of survival at that weight," Christine recalls.

It would be two weeks before Christine would be able to hold Luke.

"The NICU experience is one if the hardest things anyone can go through but it is a rewarding experience. You celebrate every little milestone. You celebrate every gram gained, every milliliter eaten, every notch weaned from oxygen support," she says.

At the Tiny Tot Clinic, Duncan and her colleagues are helping Sofia and Luke develop their fine motor skills.

"With Dr. Duncan and the rest of the Tiny Tot Clinic team, our children are getting the best chance of development. We are realistic and are giving them the best life we can," Federico adds.

In addition to counseling and therapy, Duncan's team assists with issues regarding sleep, feeding, behavior, movement and other developmental difficulties.

"The parents and families of children born with these types of concerns often experience high stress, worry and difficulty with adjustment," she says. "We're here to help."

"The Tiny Tot Clinic fulfills a critical need in a specialized patient population by providing developmental components that are critical to creating a medical home for NICU graduates and other children at high risk for neurodevelopmental and behavioral deficits," Duncan says.

The Tiny Tot Clinic receives support from the Memorial Hermann Foundation, the Baxter Foundation and the Cerebral Palsy Foundation.

"We will come to the Tiny Tot Clinic for as long as we can," Federico says. "You can tell they really care about the babies. They always want to see pictures, and we have lots of those."

MicroRNA predicts and protects against severe lung disease in extremely premature infants

This exosomal microRNA is a biomarker for bronchopulmonary dysplasia, a disease that can lead to death or long-term disease in extremely low birth-weight infants.

University of Alabama at Birmingham

BIRMINGHAM, Ala. - Extremely low birthweight babies are at risk for a chronic lung disease called bronchopulmonary dysplasia, or BPD. This condition can lead to death or long-term disease, but clinical measurements are unable to predict which of the tiny infants -- who get care in hospital intensive-care units and often weigh just one and a half pounds -- will develop BPD.

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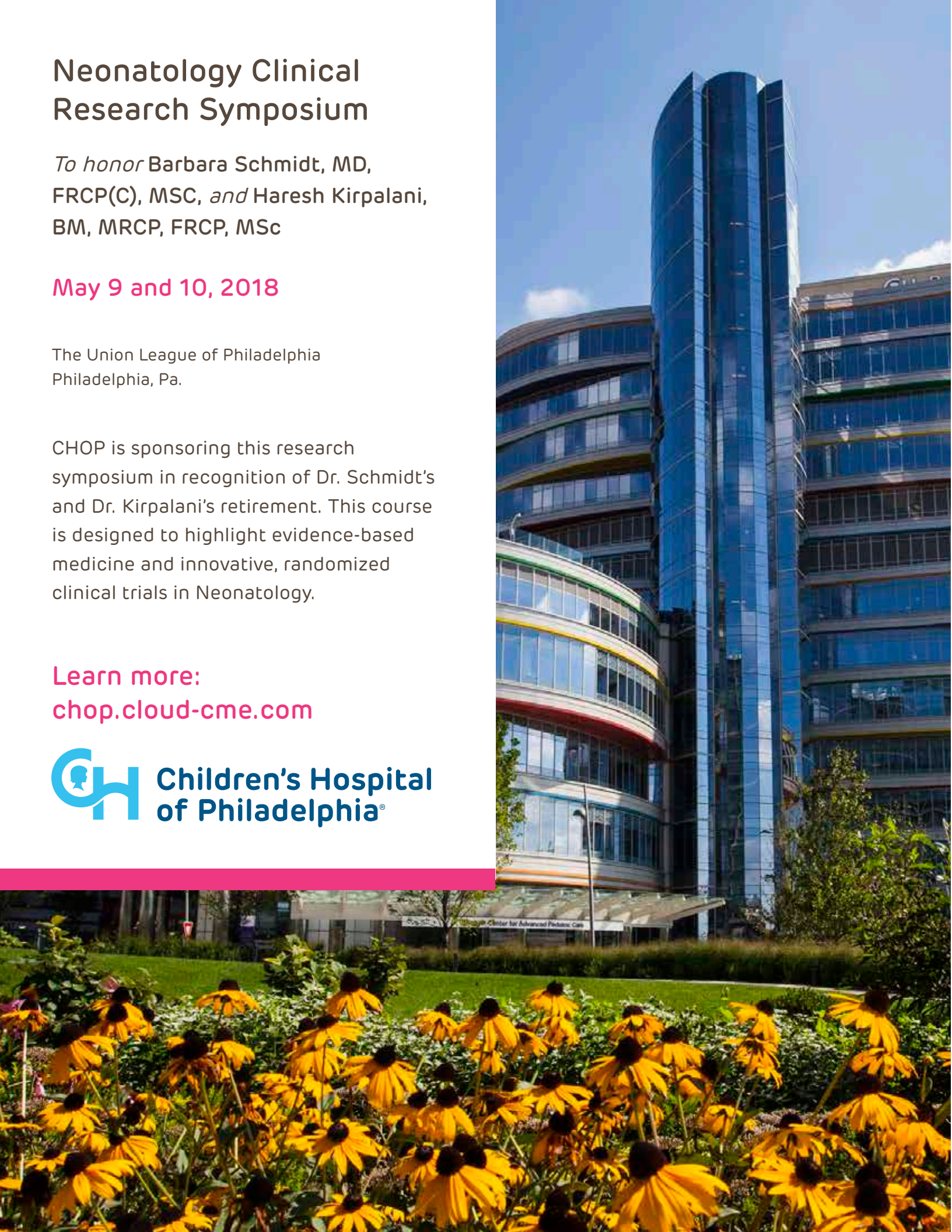

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University of Alabama at Birmingham researchers now report discovery of a strong predictive biomarker for BPD, and they show a role for the biomarker in the pathogenesis of this neonatal lung disease. These results open the path to possible future therapies to prevent or lessen BPD, which is marked by inflammation and impaired lung development.

This biomarker could also help neonatologists plan optimal management and risk stratification of their tiny patients, and it could guide targeted enrollment of high-risk infants into randomized trials of potentially novel treatment strategies.

The UAB work, published in the journal JCI Insight, is an example of "bedside to bench" research. It began with prospective studies of extremely premature infants to identify potential biomarkers, and then proceeded to lab experiments using animal models and cells grown in culture to learn how the biomarker functions in disease progression.

The study was led by Charitharth Vivek Lal, M.D., assistant professor in the UAB Pediatrics Division of Neonatology, and it builds upon Lal's 2016 report that early microbial imbalance in the airways of extremely premature infants is predictive for development of BPD.

The biomarker in the JCI Insight study is microRNA 876-3p.

Study details

The hunt for the biomarker began with a prospective cohort study at the UAB Regional Neonatal Intensive Care Unit, looking at exosomes obtained from tracheal aspirates of infants with severe BPD, compared with full-term controls. Exosomes are small, membrane-bound blebs or vesicles that are actively secreted by a variety of cells. They are known to contain microRNAs and proteins, and the exosomes act in cell-to-cell signaling. MicroRNAs can regulate gene expression in cells.

Lal and colleagues found that airway cells in infants with severe BPD had greater numbers of exosomes, but those exosomes were smaller sized. They also experimentally found that high oxygen exposure for newborn mice or human bronchial epithelial cells grown in culture also caused the release of more exosomes, and the exosomes were smaller in size that those secreted at normal oxygen level. Premature infants often receive extra oxygen to aid their underdeveloped lungs.

The UAB researchers then did a prospective discovery cohort study at UAB -- they collected tracheal aspirate samples from extremely premature infants within six hours of birth, purified exosomes from the samples and looked for microRNAs in the exosomes. Out of 810 microRNAs that were found, 40 showed differences between infants who later developed BPD and those who were BPD-resistant.

Next, in cooperation with researchers at Thomas Jefferson University and Drexel University, a validation cohort was studied in Philadelphia. Thirty-two of the 40 microRNAs were confirmed; six had a higher statistical significance; and one biomarker, a low concentration of microRNA 876-3p, was found to have the highest sensitivity to predict severe BPD in extremely low birth-weight infants.

The researchers then showed changes in expression of microRNA 876-3p in BPD in three types of experiments. First, tracheal-aspirate, exosomal microRNA 876-3p expression was decreased in infants with severe BPD, as compared with full-term infant controls.

Second, using an animal model of BPD where mouse pups are exposed to high levels of oxygen, microRNA 876-3p expression from exosomes in bronchoalveolar lavage fluid was found to progressively decrease over 10 days of oxygen exposure. At the same time, the gene expression of two targets of microRNA 876-3p increased.

Third, exosomal microRNA 876-3p was decreased in supernatants of normal human bronchial epithelial cells exposed to high levels of oxygen for 24 hours, another model for BPD. This was accompanied by higher gene expression of the two targets of the microRNA. Experimental addition of a mimic of microRNA 876-3p, which causes gain of function, increased the expression of microRNA 876-3p and reduced the expression of the two targets.

Since Lal and colleagues had previously shown presence of increased Proteobacteria in the airways of infants with severe BPD, they tested the effect of adding Proteobacteria lipopolysaccharide, or LPS, to the animal and cell culture models of BPD. In both models, LPS alone had an effect similar to high levels of oxygen. When LPS and high oxygen were used together in double-injury tests, the researchers found even greater decrease in exosomal microRNA 876-3p; in the animal model, the double injury caused greater impairment of lung development and higher expression of inflammatory cytokines than either high oxygen or LPS alone.

Finally, the researchers tested the effect of giving a gain-of-function mimic of microRNA 876-3p to pups in the animal model of BPD. For both the high-oxygen model and the double-injury model of high oxygen and LPS, mice given the mimic showed protection as measured by less alveolar hypoplasia and decreased neutrophilic inflammation.

"These data establish that exosomal microRNAs have critical and causative roles in neonatal chronic lung disease pathogenesis," Lal said.

###

Co-authors with Lal on the paper "Exosomal microRNA 876-3p predicts and protects against severe bronchopulmonary dysplasia in extremely premature infants" are Nelida Olave, Colm Travers, Gabriel Rezonzew, Kalsang Dolma, Alexandra Simpson, Brian Halloran and Namasivayam Ambalavanan, UAB Department of Pediatrics; Zubair Aghai, Thomas Jefferson University Department of Pediatrics; Pragnya Das, Nirmal Sharma and Vineet Bhandari, Drexel University Department of Pediatrics; Xin Xu, Kristopher Genschmer, Derek Russell, Tomasz Szul, J. Edwin Blalock and Amit Gaggar, UAB Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; and Nengjun Yi,

Department of Biostatistics, UAB School of Public Health.

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UC Davis, NEC Society launch major project to examine the use of probiotics in preemies

UNIVERSITY OF CALIFORNIA - DAVIS HEALTH SYSTEM

CREDIT: UC REGENTS

Thanks to the leadership of Mark Underwood, chief of neonatology at UC Davis Children's Hospital, and the NEC Society's Scientific Advisory Council, the NEC Society is launching a Multi-NICU Probiotic Quality Improvement (QI) Project. It is the first project of its kind to capture data from neonatal intensive care units (NICUs), that are ready to start routine administration of probiotics to very low birthweight infants at risk for necrotizing enterocolitis.

Necrotizing enterocolitis (NEC) is a leading cause of death in premature infants, with case-fatality rates of 20 to 30 percent. For fragile and premature infants in the NICU, NEC is a relatively common disease of the intestinal tract in which the tissue lining the intestine becomes inflamed and dies. It is the most common, serious gastrointestinal disease affecting newborn infants, and is considered a medical, and oftentimes a surgical, emergency.

Providing mothers' milk to premature infants helps to reduce the NEC risks by fostering a healthy gut microbiome. There is also solid empirical evidence demonstrating improved outcomes in fragile neonates with probiotic administration, including decreased risk of necrotizing enterocolitis, death and feeding intolerance. Yet despite probiotics' promising protective qualities for preemies, many NICUs are not utilizing this potentially lifesaving intervention.

The NEC Society's Probiotic QI Project seeks to change this.

Three probiotic products have been selected, based on the literature and on testing conducted at UC Davis.

"This project is the result of feedback gathered at the 2017 Necrotizing Enterocolitis Symposium, presented by the NEC Society and the UC Davis Department of Pediatrics. Many NICU representatives voiced interest in offering probiotics to their most fragile and premature patients, but did not know where or how to begin this intervention," said Jennifer Canvasser, founder and executive director of the NEC Society.

Participating NICUs can choose which product they use (they can also choose a different product if they wish). Those who participate will collect data before, during and after probiotics are administered. They then will share the de-identified data with the NEC Society for eventual publication. The goal is to have the participation of approximately 100 NICUs.

"We hope that this novel project will help empower more NICUs to use probiotics to improve outcomes and reduce risks of necrotizing enterocolitis, death and feeding intolerance among our most vulnerable babies," said Underwood.

This is not a clinical trial and there is no placebo arm, no randomization and no blinding, he added.

The results of this multi-center QI project will be shared with clinicians and researchers. The more NICUs that provide the secondary outcomes data, the more robust the final published data will be to improve the care of very low birthweight babies.

To learn more, please visit https://necsociety.org/probiotics-quality-improvement-project/

NT

From the National Perinatal Information Center: The Administrative Data Set: A Primer

By Janet H. Muri, MBA

Janet H. Muri has been with the National Perinatal Information Center since 1986 and it's President since 2007. Ms. Muri oversees all collection, processing and analysis of clinical and financial data submitted by NPIC member hospitals and other state, federal and private data sources related to contract work. She is the principal on many of the NPIC contracts including the Department of Defense Perinatal Performance Information Project, the Georgia Regional Intensive Care Network project, The Joint Commission Core Measure Services activities and the Alliance for Innovation in Maternal Health (AIM) Ms. Muri represents NPIC on the AHA Maternal and Child Health Governing Council, is a member of the Technical Advisory Panel for the Joint Commission Perinatal Care Core Measure set and the ACOG AIM Data Work Group. Ms. Muri received a Master in Business Administration with a concentration in Health Care Management from Boston University in 1986.

The administrative data set, also referred to as billing, discharge or UB 04 data, is a data set that is collected on every patient discharged from every hospital in the US. The data set is patient specific (mother and infant have their own record) and include all med/surg, pediatric, and OB/GYN discharges. Hospitals in forty-seven states send their administrative data sets to their state Department of Health, Hospital Association or vendor on a quarterly or bi-annual basis. In turn most states send their data to the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HUCP) which creates sample data sets available for analysis and research: The National Inpatient Sample (NIS), Kids Inpatient Sample (KID), Nationwide Emergency Department Sample (NEDS) to name a few.

The administrative data set contains demographic, clinical and financial data and has many standard coded items. Some states will add unique perinatal variables such as numeric birthweight, APGAR 5 and 10 or a variable to link mother and baby records but this is rare. What is true is that the administrative data contains a wealth of perinatal information that is often overlooked by clinicians as a valid, easy and inexpensive data set to analyze and jump start a quality initiative, support a grant application or benchmark outcome metrics across hospitals.

Jeffrey Gould, MD, Director of the Perinatal Epidemiology and Outcome Unit at Stanford University has appropriately described the administrative data set as the ultimate "green" data set and recommends "Building a hospital/statewide culture of excellence– minimize data collection burden by using "green data" – data that is collected for another purpose but can support QI activities".

The National Perinatal Information (NPIC) has collected, analyzed and reported on the administrative data set for members and contracted hospitals for the last thirty-three years. In addition to quarterly membership benchmark reporting, the data set has been used in QI activities funded by Agency for Health Care Research and Quality, Premier Inc., Ariadne Labs, the states of Georgia, Louisiana, Florida, Pennsylvania, Illinois, and Wisconsin to name a few. The data set has been used to analyze region and state-wide maternal and neonatal regionalization patterns, identify outcomes by maternal and neonatal levels of care, and identify the volume and acuity of high risk patients to allocate annual Medicaid funding. It has helped support research of very rare conditions that require a very large data set to identify a reasonable cohort of cases, complemented team training initiatives with multi-year baseline analysis prior to initiating team training, during the training period and post-training monitoring to continue reducing adverse events. The administrative data set is the primary data set that is supporting the national Alliance for Innovation on Maternal Health (AIM) outcome metrics overall and for the Hemorrhage, Hypertension and Venus Thromboembolism Patient Safety Bundles specifically.

The Joint Commission uses the administrative data set to define the initial patient population for the Perinatal Care Measure set and all of the Agency for Health Research and Quality Inpatient Quality, Patient Safety and Pediatric Quality Indicators are calculated using this data set.

While the administrative data set may not be the "gold standard" of manually abstracted or prospectively collected data, its flexibility, standardization, and cost effectiveness should not be overlooked. In addition, the transition from the 16,000 diagnosis and procedures codes in ICD 9 to 155,000 ICD 10 codes has greatly increased the precision of documented diagnoses and procedures.

NPIC is unique in its use of the administrative data set since we collect the data directly from member and contracted hospitals under the protection of a Data Use Agreement and Business Associate Agreement which allows for the submission of Protected Health Information (PHI), identifying data. Clinicians and hospitals are able to securely receive cases lists that can be used to audit the accuracy of provider documentation and coding to insure high quality information. NPIC also requests specific perinatal variables not always found in the state data files—numeric birthweight and gestational, APGAR, mother's medical record number on the infant's record. The latter allows for the linking of the mother and infant and analysis of maternal complications or co-morbidities and their impact on the infant. With more than 730,000 mother/baby records processed annually, of which greater than 80% are linked, our experience with the value of this data set to assist hospitals in a range of quality and process improvement activities is extensive.

Like NPIC, many states (California and Florida being the most mature users) provide their hospitals with comparative benchmarking reports allowing end users to identify where they may be outliers relative to a peer group of hospitals. This is turns helps their risk managers and perinatal leaders to focus their limited QI dollars most appropriately.

The obvious next enhancement to this data set is to integrate IP/OP electronic health data that allows for the analysis of process and outcome data together. NPIC, and many others, are working on this and look forward to moving this opportunity forward in spite of the variability of formats across vendors and within vendors across hospitals.

NPIC is looking forward to sharing summaries of the analyses we provide our member and contracted hospitals. We recently completed an analysis on Maternal Obesity, looking at rates of obesity among women coded with "obesity complicating childbirth", their comparative rates of delivery by Cesarean section, length of stay and impact on their infant. We are currently updating two analyses on Neonatal Abstinence Syndrome that we completed in 2010 and 2015 respectively and will be reported on in future Neonatology Today issues.

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New Tubing Connectors Create Unforeseen Challenges for Neonates

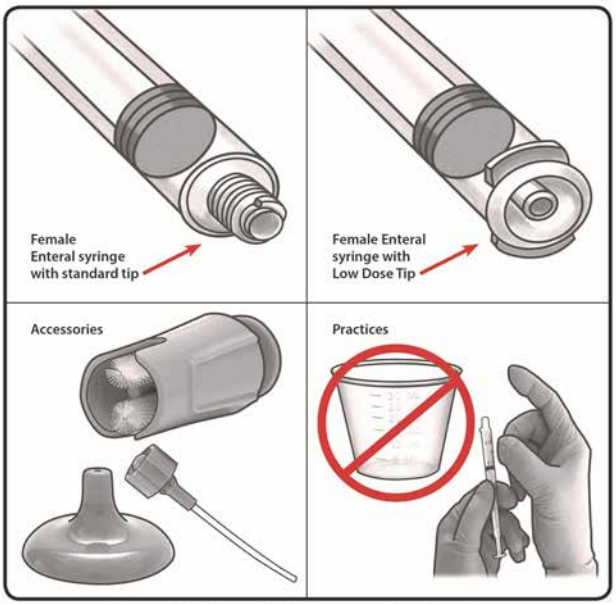
NCfIH National Coalition for Infant Health

Protecting Access for Premature Infants through Age Two

Dear Colleagues,

As practitioners, we expect that the products used for treating our patients are safe. But sometimes the best inventions, and intentions have unintended consequences.

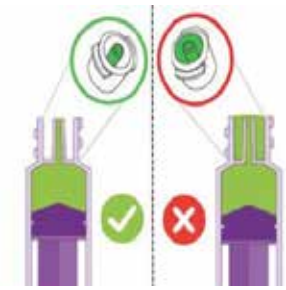
Such is the case with the ENFitTM tubing connector. Experts devised it to ensure that feeding tube connectors are compatible



only with one another, which can reduce the frequency of dangerous tubing misconnections and enhance patient safety. But, as pediatricians and neonatologists, we must be aware that the ENFit design poses new challenges to patients in the neonatal intensive care unit.

The new moat design is wider, increasing dead space which leads to inconsistent delivery of medications (over or under delivery). The moat carries risk for infection if residual breast milk or formula remains in the moat and is then connected to the feeding tube. For nurses, the new design requires accessories to draw up meds, clear moats, and clean tubes. For pharmacists, the design requires making sure the medication is not displaced when the syringe is capped and the moat is clear of additional medication.

NICU patients frequently have a feeding tube and an IV, both of which require multiple connections every day. The risk of misconnection occurs each time a baby needs medicine or nourishment. Limiting the risk of possible tubing misconnections is important, but our fragile patients should not be introduced to different potential harms in the process.

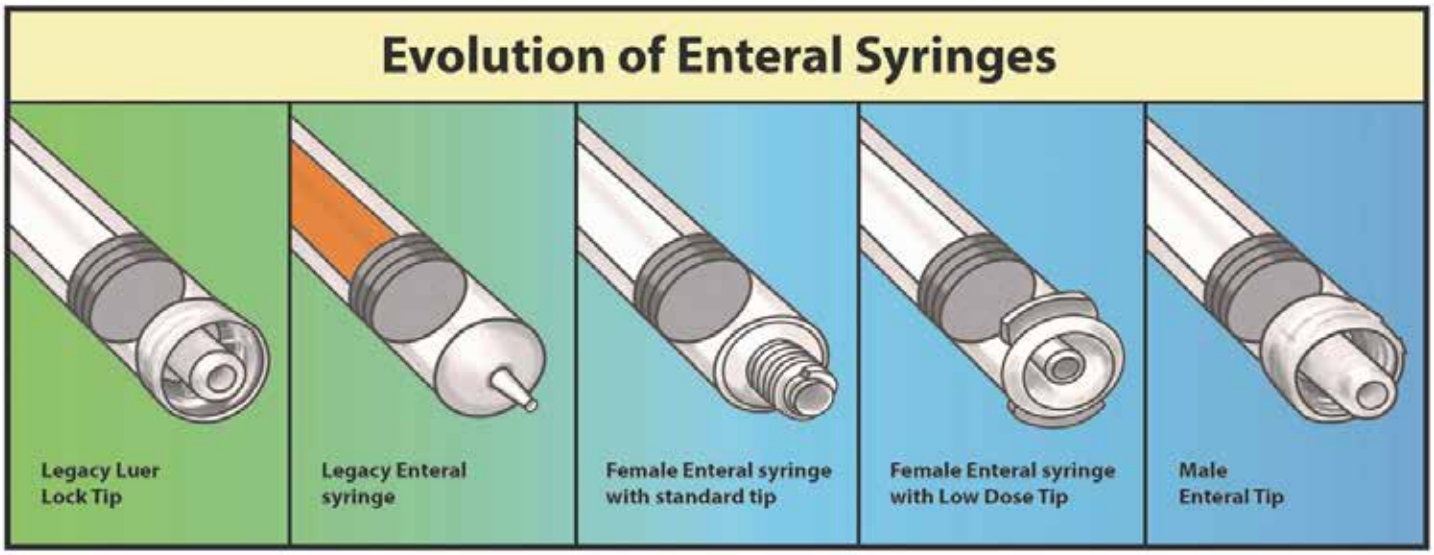


For these tiny, vulnerable infants, concerns about inaccurate dosing of medications must be taken very seriously. In addition to adding extra steps to nursing workflow, the ENFit design also creates new risks by increasing the delivered drug variance and the risk of infection.

Neonates receive very small volumes of medicine making dosing accuracy of paramount importance. There is no room for error, yet the new ENFit connector design makes this difficult because the moat, or area around the syringe barrel, is difficult to clear. Leftover medication can "hide" there, inadvertently increasing the dosage delivered when the syringe is inserted into the feeding tube. If the moat is not cleared, a tiny patient may inadvertently receive up to 30 percent more medication per dose. This places the baby at risk for an overdose, adverse drug reactions, and even death.

This moat design also increases the risk for infection if residual breast milk or formula remains in the moat and is then connected to the feeding tube. The potential for bacterial colonization of the moat increases by design with the ENFit connector because these feeding tubes are in place for up to 10 days at a time.

The accepted method for clearing the moat by "flicking" the receptacle is also risky and can potentially spread bacteria to the patient care area via droplet dispersal, putting other patients at risk. Hospitals should know that medication safety experts have



concerns about the ENFit design.

The ENFit connector also poses workflow issues. Nursing staff face the added steps of regularly clearing syringe moats and feeding tubes and using multiple connectors and adapters for oral or enteral administration of medication.

Hospitals need to understand these risks as they work to comply with ISO 80369-3 standards as well as their own state laws related to tubing connectors. Policymakers should consider these unintended consequences before enacting laws that mandate use of the ENFit design.

Adopting a new tubing design should not jeopardize patient care and safety.

Sincerely,

Mitchell Goldstein, MD

Medical Director

National Coalition for Infant Health

The National Coalition for Infant Health is a collaborative of more than 150 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.

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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.

Monthly Clinical Pearls: Just Shake Her Hand

By Joseph R. Hageman, MD

We had had a pretty eventful evening on call at Prentice Women's Hospital, but this was how my pediatric residency had gone for the entire 3 years. Now I was toward the last part of my third year and was going to be a neonatal fellow in this same challenging but fun program at Northwestern University. I had spent a lot of time with what some people would refer to as a "black cloud", Although one of my friends, once he finished a year ahead of me, decided to study it (Bob Tanz, subsequently a renowned academic ambulatory pediatrician at Children's Memorial Hospital) and concluded that "black clouds" really did not exist[1]. With this N of 1, I respectfully disagree…but having a black cloud meant you got to see and do a lot, and learn a lot.

Well, back to our evening on call, and we went to the delivery room and brought back a term infant who had some respiratory distress and was hypotonic. We got a chest radiograph and found the right hemi diaphragm to be elevated. We called our neonatal attending and after he examined the baby and reviewed the radiograph, was concerned. Then a rather remarkable and, for me, once in a lifetime clinical moment occurred. When the baby's Mom came to visit, our attending introduced himself and offered his hand to Mom. He shook her hand and the extensive differential diagnosis of hypotonia in the infant disappeared. Really! He explained it to us and then to Mom and then we got the chance to experience the "grip myotonia' of the Mom. I think Bob Tanz is really right! Depending on your perspective as you practice, these experiences are remarkable, wonderful clinical experiences you will never forget and are not negative or "black cloud" experiences.

I refer you to the new article by Hunter and Johnson entitled 'Diagnosis and management of pediatric myotonic dystrophy in the September issue of NeoReviews[2]. Grip myotonia in a parent can be of help in making the diagnosis of pediatric myotonic dystrophy in an infant or child. In our case, the Mom was not diagnosed at the time. He also mentioned the elevation of the right hemi diaphragm is a finding in a newborn with congenital myotonic dystrophy and what is interesting, I refer you to this reference from that same year of my "black cloud" experience, 1979[3].

It's funny how these clinical experiences that are linked to "abstract concepts" tend to stay with you throughout your professional life.

More black cloud experiences anyone? I have a bunch of them. More to follow.

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1 Tanz R. Black clouds in residency. Do they really exist?
2 Hunter M, Johnson N. Diagnosis and management of pediatric myotonic dystrophy. NeoReviews 2017;18(9): e513-e521.
3 Chudley, AE, Mamdouha AB. Diaphragmatic elevation in neonatal myotonic dystrophy. Am J Dis Child 1979; 133:1182-1185.

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1250 word limit not including references or title page.

May begin with a brief case summary or example.

Summarize the pearl for emphasis.

No more than 3 references.

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http://2018.worldneonatology.com

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