What’s new in perinatal/neonatal medicine and how it should change health care?

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Disclosure Statements:

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.
• The off-label use of any drug will be identified, discussed and strongly discouraged.

We still do not know how to diagnosis or treat hypoglycemia.
Fourth-grade achievement test scores in 1395 newborn-student pairs (71.8%). Transient neonatal hypoglycemia (glucose level <35, <40, and <45 mg/dL) was observed in 6.4% (89 of 1395), 10.3% (143 of 1395), and 19.3% (269 of 1395) of newborns, respectively.

- After controlling for gestational age group, race, sex, multifetal gestation, insurance status, maternal educational level and socioeconomic status, and gravidity, transient hypoglycemia was associated with decreased probability of proficiency on literacy and mathematics fourth-grade achievement tests.
Of 614 children, 528 were eligible, and 404 (77% of eligible children) were assessed; 216 children (53%) had neonatal hypoglycemia (blood glucose concentration, <47 mg per deciliter).

Hypoglycemia, when treated to maintain a blood glucose concentration of at least 47 mg per deciliter, was not associated with an increased risk of the primary outcomes of neurosensory impairment.

The lowest blood glucose concentration, number of hypoglycemic episodes and events also did not predict the outcome.


Babies aged 35-42 weeks’ gestation, younger than 48 h-old, and at risk of hypoglycemia were randomly assigned to 40% dextrose gel 200 mg/kg or placebo gel.

Randomization was stratified by maternal diabetes and birthweight.

The primary outcome was treatment failure, defined as a blood glucose concentration of less than 2.6 mmol/L (48 mg/dl) after two treatment attempts.

Of 514 enrolled babies, 242 (47%) became hypoglycaemic and were randomised.

Dextrose gel reduced the frequency of treatment failure compared with placebo (16 [14%] vs 29 [24%]; relative risk 0.57, 95% CI 0.33-0.98; p=0.04).

There were no serious adverse events. Three (3%) babies in the placebo group each had one blood glucose concentration of 0.9 mmol/L (16 mg/dl). No other adverse events took place.

Treatment with dextrose gel is inexpensive and simple to administer.

Dextrose gel should be considered for first-line treatment to manage hypoglycaemia in late preterm and term babies in the first 48 h after birth.
<table>
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<tbody>
<tr>
<td>Follow-up study of 184 children with hypoglycemia (&lt;2.6 mM [47 mg/dL]) in the first 48 hours and randomized to either dextrose (90/118, 76%) or placebo gel (94/119, 79%).</td>
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<tr>
<td>Co-primary outcomes were neurosensory impairment (cognitive, language or motor score below 1 SD or cerebral palsy or blind or deaf) and processing difficulty (executive function or global motion perception worse than 1.5 SD from the mean).</td>
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<td>Sixty-six children (36%) had neurosensory impairment (1 severe, 6 moderate, 59 mild) with similar rates in both groups (dextrose 38% vs placebo 34%, relative risk 1.11, 95% CI 0.75-1.63).</td>
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<td>Processing difficulty also was similar between groups (dextrose 10% vs placebo 18%, relative risk 0.52, 95% CI 0.23-1.15).</td>
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<tr>
<td>Conclusions: Dextrose gel is safe for the treatment of neonatal hypoglycemia, but neurosensory impairment is common among these children.</td>
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<tr>
<td>Two trials involving 312 infants.</td>
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<tr>
<td>Dextrose gel compared with placebo gel or no gel did not alter the need for intravenous treatment for hypoglycaemia (typical RR 0.78, 95% CI 0.46 to 1.32; two trials, 312 infants; quality of evidence very low).</td>
</tr>
<tr>
<td>Infants treated with dextrose gel were less likely to be separated from their mothers for treatment of hypoglycaemia (RR 0.54, 95% CI 0.31 to 0.93; one trial, 237 infants; quality of evidence moderate) and were more likely to be exclusively breast fed after discharge (RR 1.10, 95% CI 1.01 to 1.18; one trial, 237 infants; quality of evidence moderate).</td>
</tr>
<tr>
<td>CONCLUSIONS: Treatment of infants with neonatal hypoglycemia with 40% dextrose gel reduces the incidence of mother-infant separation for treatment and increases the likelihood of full breast feeding after discharge compared with placebo gel. No evidence suggests occurrence of adverse effects during the neonatal period or at two years’ corrected age. Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycaemia.</td>
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<td>NOT FDA APPROVED FOR THIS INDICATION</td>
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| NRP 2017: What’s New? |
New Neonatal Resuscitation Guidelines

Meconium
Non-vigorous newborns with meconium-stained fluid do not require routine intubation and tracheal suctioning; however, meconium-stained amniotic fluid is a perinatal risk factor that requires presence of one resuscitation team member with full resuscitation skills, including endotracheal intubation.

Delayed Cord Clamping
Current evidence suggests that cord clamping should be delayed for at least 30 to 60 seconds for most vigorous term and preterm newborns. If placental circulation is not intact, such as after a placental abruption, bleeding placenta previa, bleeding vasa previa, or cord avulsion, the cord should be clamped immediately after birth. There is insufficient evidence to recommend an approach to cord clamping for newborns who require resuscitation at birth.

Oxygen Use, Positive Pressure, ECG Monitoring
- Resuscitation of newborns greater than or equal to 35 weeks' gestation begins with 21% oxygen (room air).
- Resuscitation of newborns less than 35 weeks' gestation begins with 21% to 30% oxygen.
- If the newborn has labored breathing or SpO2 cannot be maintained within target range despite 100% free-flow oxygen, consider a trial of continuous positive airway pressure (CPAP).
- When PPV begins, consider using an electronic cardiac monitor for accurate assessment of the heart rate.

Antenatal Corticosteroid Therapy Before 24 Weeks of Gestation?

CONCLUSION:
The available data, all observational, show reduced odds of mortality to discharge in neonates born before 24 weeks of gestation who received antenatal corticosteroids and active intensive treatment.

Antenatal corticosteroids should be considered for women at risk of imminent birth before 24 weeks of gestation who choose active postnatal resuscitation.

Primary Outcome: Mortality by Gestational Age
Transfusion and Necrotizing Enterocolitis:
What’s New?


EXPOSURES: The primary exposure was RBC transfusion. The secondary exposure was severe anemia, defined a priori as a hemoglobin level of 8 g/dL or less.

RESULTS: Of 600 VLBW infants enrolled, 598 were evaluated. Forty-four (7.4%) infants developed NEC. Fifty-three percent of infants (319) received a total of 1430 RBC transfusion exposures. In multivariable analysis, RBC transfusion in a given week was not significantly related to the rate of NEC. The rate of NEC was significantly increased among VLBW infants with severe anemia in a given week compared with those who did not have severe anemia (adjusted cause-specific hazard ratio, 3.99 [95% CI, 2.00-18.0]; P = .001).

CONCLUSIONS: Among VLBW infants, severe anemia, but not RBC transfusion, was associated with an increased risk of NEC.

Bevacizumab Intravitreal Injections for Retinopathy of Prematurity: Long Term Adverse Effects?

Canadian Neonatal Follow-Up Network databases were retrospectively reviewed. Infants born at <29 weeks’ in 2010–2011 with treated ROP were studied. Neurodevelopmental outcome at 18 months was assessed by using neurologic examination and the Bayley Scales of Infant and Toddler Development.

RESULTS: Of 125 treated infants, 27 received bevacizumab and 98 laser. Odds of severe neurodevelopmental disabilities (Bayley scores <70, severe cerebral palsy, hearing aids, or bilateral blindness) was 3.1 times higher (95% confidence interval: 1.2-8.4) in infants treated with bevacizumab versus laser after adjusting for gestational age, gender, maternal education, Score for Neonatal Acute Physiology-II score, bronchopulmonary dysplasia, sepsis, and severe brain injury.

Bevacizumab IS NOT FDA approved for this indication

Oxygen Targeting: Lost in Translation?


Conclusions
Use of an oxygen-saturation target range of 85 to 89% versus 91 to 95% resulted in non-significantly higher rates of death or disability at 2 years in each trial.

Post hoc combined analyses, showed a significant increased risks of death.
Targeting different oxygen saturation ranges between 85% and 95% from birth did not impact growth velocity or reduce growth failure in preterm infants.
What is important?  
Real important?  

Did we study the wrong thing?

COMP-ROP

Identification of the multidisciplinary COMP-ROP  
Team

Baseline Data  
Hyperoxia Assessment  
Staff Education  
System Redesign

Baseline Data  
Hyperoxia

Eliminate Sources of Hyperoxia  
ROP Presentation  
Pre/Post Test

Standard Orders, Signs, Contracts, etc

Baseline Alarm Audits  
Oxygen Saturation Trending  
Implementation

Oximeter Alarm Audits  
Oxygen Saturation Trending  
ROP Rates

PDSA cycles as needed to optimize alarm compliance and trending results

COMP ROP

- Narrowing oxygen targets/limits increases the frequency of alarms and we begin to ignore alarms (especially the high alarms), and that is a mistake.
- We manage the high end; the baby more often determines the low end. We can make a baby have a 100% oxygen saturation. Providing oxygen treatment to an infant who is not breathing will not make their oxygen saturation better.
- Our “therapeutic response” to pulse oximeter alarms is likely to be more important than the limits/targets themselves.
The ideal physiologic target range for oxygen saturation for infants of extremely low birth weight is likely patient-specific and dynamic and depends on various factors, including gestational age, chronologic age, underlying disease, and transfusion status.

The ideal physiologic target range is a compromise among negative outcomes associated with either hyperoxemia (eg, ROP, bronchopulmonary dysplasia) or hypoxemia (eg, necrotizing enterocolitis, cerebral palsy, death).

Recent RCTs suggest that a targeted oxygen saturation range of 90% to 95% may be safer than 85% to 89%, at least for some infants.

However, the ideal oxygen saturation range for extremely low birth weight infants remains unknown.

Alarm limits - avoid potentially harmful extremes of hyper or hypoxemia.

Given the limitations of pulse oximetry and the uncertainty that remains regarding the ideal oxygen saturation target range for infants of extremely low birth weight, these alarm limits could be fairly wide.

Regardless of the chosen target, an upper alarm limit approximately 95% while the infant remains on supplemental oxygen is reasonable.

A lower alarm limit will generally need to extend somewhat below the lower target, as it must take into account practical and clinical considerations, as well as the steepness of the oxygen saturation curve at lower saturations.

We can and should decrease the use of poorly study drugs and devices.
Choosing Wisely in Newborn Medicine: Five Opportunities to Increase Value

1. Avoid routine use of antireflux medications for treatment of symptomatic gastroesophageal reflux disease or for treatment of apnea and desaturation in preterm infants.

2. Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection.

3. Avoid routine use of pneumograms for predischarge assessment of ongoing and/or prolonged apnea of prematurity.

4. Avoid routine daily chest radiographs without an indication for intubated infants.

5. Avoid routine screening term equivalent or discharge brain MRIs in preterm infants.
136 very preterm neonates (24-32 weeks gestational age) was serially scanned with MRI near term-equivalent age for volumetric measurements of the cerebellum and cerebrum.

• A 10-fold increase in morphine exposure was associated with a 5.5% decrease in cerebellar volume, after adjustment for multiple clinical confounders and total brain volume (P = .04).

• Greater morphine exposure also predicted poorer motor (P < .001) and cognitive outcomes (P = .006) at 18 months CA, an association mediated, in part, by slower brain growth.

• Alternatives to better manage pain in preterm neonates that optimize brain development and functional outcomes are urgently needed.

- Retrospective cohort analysis of 981 infants who completed pharmacologic treatment of NAS with methadone or morphine from January 2012 through August 2014.
- After adoption of treatment protocol, infants treated by the 3 groups previously without stringent weaning guidelines experienced shorter duration of opioid treatment (23.0 vs 34.0 days, P<.001) and length of inpatient hospital stay (23.7 vs 31.6 days, P<.001).
- Protocol-adopting sites also experienced a lower rate of adjunctive drug therapy (5% vs 21%, P = .004).
- Improvements were sustained.
- Adoption of a stringent weaning protocol resulted in improved NAS outcomes, demonstrating generalizability of the protocol-driven weaning approach.

Why we need to continue to reduce the late preterm births that are not medically indicated.


- Population-based study, 10 321 patients with ADHD, diagnosed according to the International Classification of Diseases.
- 38 355 controls individually matched for gender, date and place of birth, in Finnish nationwide registers.
- Risk of ADHD increased by each declining week of gestation.
- The associations were robust after adjusting for confounders.
- An elevated risk also was seen among late preterm and early term infants.
- The odds ratio showed a U-shaped curve with an increased risk seen when the weight for gestational age was 1 SD below and 2 SD above the mean.
Prachi Shah et al. Developmental Outcomes of Late Preterm Infants From Infancy to Kindergarten. Pediatrics 2016;138:e20153496

- Sample included 1000 late preterm, 1800 early term, and 3200 term infants ascertained from the Early Childhood Longitudinal Study, Birth Cohort.
- With covariates controlled at all timepoints, at 9 months late preterm infants demonstrated less optimal developmental outcomes (T = 47.31) compared with infants born early term (T = 49.12) and term (T = 50.09) (P < .0001).
- This association was not seen at 24 months, (P = .66) but reemerged at preschool. Late preterm infants demonstrated less optimal scores in preschool reading (P = .0006), preschool mathematics (P = .0014), and kindergarten reading (P = .0007) compared with infants born at term gestation.


PERCENT WITH POOR PERFORMANCE

Is there a better way to give surfactant?

- Of 211 infants who were randomized, 104 were randomized to the control group and 107 to the less invasive surfactant application protocol (LISA) group.
- Of the infants who received LISA, 72 (67.3%) survived without BPD compared with 61 (58.7%) of those in the control group. The reduction in absolute risk was 8.6% (P = .20).
- Intervention group infants were less frequently intubated (80 infants [74.8%] vs 103 [99.0%]; P < .001) and required fewer days of mechanical ventilation.
- Significant reductions were seen in:
  - Pneumothorax: 5/105 treated (4.8%) vs 13/103 controls (12.6%); p = .04
  - Severe IVH: 11 infants (10.3%) vs 23 (22.1%); p = .02
  - The combined survival without severe adverse events was increased in the intervention group (54 infants [50.5%] vs 37 [35.6%]; p = .02)

How long can lines stay in and is CLABSI a good measure?
The overall incidence of CLABSI was 0.93 per 1000 catheter days.
Increased dwell time was not associated with increased risk of CLABSI for PICCs.
For tunneled catheters, infection incidence was significantly higher in weeks 7 and 9 compared with week 1.
CONCLUSIONS: Clinicians should not routinely replace uninfected PICCs for fear of infection but should consider removing tunneled catheters before week 7 if no longer needed.

### Table 2: Effect of Dwell Time on CLABSI

<table>
<thead>
<tr>
<th>Week</th>
<th>PICCs</th>
<th>CLABSI</th>
<th>PICCs</th>
<th>CLABSI</th>
<th>Tunneld Catheters</th>
<th>CLABSI</th>
<th>Tunneld Catheters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1445</td>
<td>33 (0.0)</td>
<td>Reference</td>
<td>1118</td>
<td>3 (0.0)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8206</td>
<td>58 (0.7)</td>
<td>1.2 (0.9–1.7)</td>
<td>9808</td>
<td>5 (0.0)</td>
<td>1.0 (0.4–4.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4951</td>
<td>51 (0.8)</td>
<td>1.2 (0.9–1.6)</td>
<td>7480</td>
<td>5 (0.0)</td>
<td>1.0 (0.2–4.8)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1360</td>
<td>13 (0.9)</td>
<td>0.7 (0.4–1.0)</td>
<td>906</td>
<td>2 (0.0)</td>
<td>0.9 (0.2–4.7)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1206</td>
<td>7 (0.6)</td>
<td>0.8 (0.4–1.0)</td>
<td>452</td>
<td>3 (0.7)</td>
<td>1.6 (0.4–7.6)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>769</td>
<td>7 (0.9)</td>
<td>1.5 (0.7–3.0)</td>
<td>338</td>
<td>4 (1.1)</td>
<td>2.2 (0.8–7.9)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>458</td>
<td>4 (0.9)</td>
<td>1.4 (0.5–4.0)</td>
<td>268</td>
<td>4 (1.4)</td>
<td>4.6 (1.1–15.6)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>276</td>
<td>1 (0.4)</td>
<td>1.4 (0.5–4.0)</td>
<td>218</td>
<td>1 (0.4)</td>
<td>1.0 (0.2–4.6)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>102</td>
<td>2 (1.1)</td>
<td>1.5 (0.4–6.0)</td>
<td>178</td>
<td>2 (1.1)</td>
<td>4.7 (1.1–28.8)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>125</td>
<td>9</td>
<td>1 (0.7)</td>
<td>151</td>
<td>3 (1.9)</td>
<td>2.5 (0.3–21.7)</td>
<td></td>
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</table>

G: confidence interval; HR, hazard ratio.
* HRs are adjusted for PMA, year of catheter insertion, and site.

Human Milk is best and exclusive use of human milk is even better.

- Used aORs derived from the Glutamine Trial to perform Monte Carlo simulation of a cohort of ELBW infants under current suboptimal feeding practices, compared with a theoretical cohort in which 90% of infants received at least 98% human milk.
- NEC incidence among infants receiving <98% human milk was 1.3%; 11.1% among infants fed only PF, and 8.2% among infants fed a mixed diet (P = .002). In adjusted models, compared with infants fed predominantly human milk, we found an increased risk of NEC associated with exclusive PF (aOR = 12.1, 95% CI 1.5, 94.2), or a mixed diet (aOR 8.7, 95% CI 1.2-65.2).
- In Monte Carlo simulation, current feeding of ELBW infants was associated with 928 excess NEC cases and 121 excess deaths annually, compared with a model in which 90% of infants received >98% human milk.
- Estimated an annual cost of suboptimal feeding of ELBW infants of $27.1 million in direct medical costs, $563,655 in indirect nonmedical costs, and $1.5 billion in cost attributable to premature death.


- Number of days on which infants received >50% of enteral intake as breast milk from 0-28 days of life.
- A greater number of days on which infants received >50% breast milk was associated with greater deep nuclear gray matter volume at term equivalent age (0.15 cc/d; 95% CI, 0.05-0.25); and with better performance at age 7 years of age on IQ (0.5 points/d; 95% CI, 0.2-0.8), mathematics (0.5; 95% CI, 0.1-0.9), working memory (0.5; 95% CI, 0.1-0.9), and motor function (0.1; 95% CI, 0.0-0.2) tests.

BPD is a hard thing to define but it is still and important morbidity to measure.
BPD is the most common morbidity of prematurity, but the validity and utility of commonly used definitions have been questioned.

Compare three commonly used definitions of BPD in a prospective, multicenter observational cohort of extremely preterm infants.

At 36 weeks postmenstrual age, the following definitions were applied to surviving infants with and without imputation:

- Need for supplemental oxygen (Shennan definition).
- National institutes of health workshop definition.
- And "physiologic" definition after a room-air challenge.

Of 765 survivors assessed at 36 weeks, BPD was diagnosed in 41, 59, and 32% of infants, respectively, with the Shennan, workshop and physiologic definitions.

The number of unclassified infants was lowest with the workshop definition (2.1%) and highest with the physiologic definition (16.1%).

After assigning infants discharged home in room air before 36 weeks as no BPD, the modified Shennan definition compared favorably to the workshop definition, with 2.9% unclassified infants.

Newer management strategies with nasal cannula flows up to 4 L/min or more and 0.21 FiO2 at 36 weeks obscured classification of BPD status in 12.4% of infants.

BPD, serious brain injury, and severe ROP occurred in 43%, 13%, and 6% of the infants, respectively.

Each of the 3 morbidities was similarly and independently correlated with poor 5-year outcome.

Rates of death or disability in children with none, any 1, any 2, and all 3 morbidities were 11.2% (8.0%-13.7%), 22.9% (19.6%-26.5%), 43.9% (35.5%-52.6%), and 61.5% (40.6%-79.8%), respectively.

In VLBW infants who survive to 36 weeks PMA, a count of BPD, serious brain injury, and severe ROP predicts the risk of a late death or survival with disability at 5 years.

Univariate relationships between individual neonatal morbidities and poor outcome at 5 years

<table>
<thead>
<tr>
<th>Neonatal morbidity</th>
<th>Morbidity absent</th>
<th>Morbidity present</th>
<th>Observed OR (95% CI)</th>
<th>P value</th>
<th>Model estimated OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>1104657 (12.5)</td>
<td>1874657 (20.5)</td>
<td>2.7 (2.1-3.5)</td>
<td>&lt; .001</td>
<td>2.3 (1.5-3.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Brain injury</td>
<td>2221518 (23.9)</td>
<td>75196 (8.3)</td>
<td>3.0 (2.4-4.2)</td>
<td>&lt; .001</td>
<td>2.6 (1.9-3.6)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Severe RCP</td>
<td>2561461 (31.3)</td>
<td>43063 (46.2)</td>
<td>4.0 (2.6-5.5)</td>
<td>&lt; .001</td>
<td>2.5 (1.6-3.6)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Schmidt et al. Prediction of Late Death or Disability at Age 5 Years Using a Count of 3 Neonatal Morbidities in Very Low Birth Weight Infants.