# Week 4: Neonatology

## Neonatal General: NICU Care

**Tuesday, July 21 2:30-4:00 pm EDT**

**Moderators**
- Kevin Sullivan
- Jessica Fry

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<th>Abstract</th>
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<td>Bioenergetic homeostasis in late preterm and term infants during first 4 months of life</td>
<td>Lea Möllers</td>
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<td>Fumiyuki Gardner</td>
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<td>The Level IV Neonatal Intensive Care Unit (NICU) Experience of infants with Trisomy 18 (T18) and Trisomy 13 (T13): A report from the Children’s Hospital Neonatal Consortium (CHNC)</td>
<td>Krishna Acharya</td>
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Note: Schedule subject to change based on presenter availability.
Title: Bioenergetic homeostasis in late preterm and term infants during first 4 months of life

Authors: Möllers, Lea; Rochow, Niels; So, Hon Yiu; Sehdev, Lauren; Fusch, Gerhard; Fusch, Christoph

Authors/Institutions: L. Sehdev, G. Fusch, Pediatrics, McMaster University, Hamilton, Ontario, CANADA; H. So, University of Waterloo, Waterloo, Ontario, CANADA; L. Möllers, N. Rochow, C. Fusch, Paracelsus Medical University, Nuremberg, GERMANY;

Current category: Neonatology

Current subcategory: Neonatal General

Keywords: IGF, Body Composition, Nutrition.

Session title: Neonatal General: NICU Care | Neonatal General: NICU Care

Session type: Webinar/Platform

Abstract body:

Background: It has been established that early postnatal development is related to long-term health outcomes. Therefore, achieving ideal growth and body composition in preterm-born infants is desirable. Preterm-born infants should develop like a healthy fetus in-utero and also achieve similar functional outcomes. To create optimal growth in preterm infants, parameters impacting postnatal growth in healthy term-born infants have to be studied as a reference model. Furthermore, the entirety of the interplay between nutrition, hormonal and metabolic responses and resulting growth trajectories in these infants has to be established.

Objective: The aim of this study is to analyze this interplay, the bioenergetic homeostasis, in late-preterm and term-born infants to create a model for normal growth.

Design/Methods: This observational study collected data from healthy infants born at 34-42 weeks of gestation at three time points: \( t_1 = 0-5 \) days of life (DOL), \( t_2 = 55-65 \) DOL, \( t_3 = 115-125 \) DOL. Anthropometric data (weight, length, BMI, head-circumference, skinfold-thickness), body composition (fat-mass, lean-mass, FMI, FFMI, % body-fat), hormonal levels (IGF-1, IGF-2, IGFBP-2, IGFBP-3, insulin, leptin), biomarkers of metabolism (protein, albumin, triglyceride, cholesterol) and the energy expenditure were measured.

Results: In 94 infants (gestational age: 39.6±1.3 weeks, birth weight 3330±570g) and 18 preterm infants (35.0±1.0 weeks, 2520±660g) positive associations between postmenstrual age and hormonal levels (IGF-1, IGF-2) were found (Fig. 2). Furthermore, a positive relationship between body composition data and these growth promoting hormones was established (Tab. 1). Both, fat mass and lean mass are positively associated with IGF-1, however the association between IGF-1 and lean mass is stronger. Body composition data (percent body fat, fat mass and lean body mass) was found to be lower in the preterm-born group when compared to term-born infants. A positive relationship between lean mass and energy expenditure was observed. When infants were grouped by type of nutrition, formula-fed infants had higher levels of IGF compared with infants that were fed breast milk (Fig. 3).

Conclusion(s): The established interactions of multiple parameters indicating certain growth trajectories may allow for a possibility to fine-tune postnatal growth. At this point, the observed interactions need further studies, especially including preterm-born infants at different postmenstrual ages and levels of maturity.
Figure 1: Bioenergetic homeostasis – interaction of nutritional intake, growth promoting hormones, energy expenditure, metabolic parameters, anthropometric measurements and body composition contribute to postnatal growth in preterm and term-born infants (↑ - positive growth, ↓ - negative growth, IGF – insulin-like growth factor, IGFBP – insulin-like growth factor binding protein, HC – head circumference, BMI – body mass index, SFT – skinfold thickness, fm – fat mass, lbm – lean body mass, %bf – percent body fat, FMI – fat mass index, FFMI – fat-free mass index).

Figure 2: Relationship between postmenstrual age and IGFs in preterm and term born infants with respect to % fat mass. Panel A: PMA and IGF-1, B: PMA and IGF-2.

Figure 3: Effect of nutrition (formula vs. breast milk) on IGFs. Panel A: Correlation of PMA and IGF-1 levels in relation to lean body mass, B: Correlation of PMA and IGF-2 in relation to percent fat mass.

Table 1: Correlation between growth factors and body composition, anthropometry and energy expenditure, pearson correlation coefficients (r)

IMAGE CAPTION:
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Table 1: Correlation between growth factors and body composition, anthropometry and energy expenditure, pearson correlation coefficients (r)
Table 1: Sample characteristics

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<thead>
<tr>
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<th>Total Sample (N = 39)</th>
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<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Mothers (%)</td>
<td>74</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>31.9</td>
</tr>
<tr>
<td>Paternal Age (years)</td>
<td>35.2</td>
</tr>
<tr>
<td>Infant Age (months)</td>
<td>38.1</td>
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Table 2: Continuous and categorical variables by sex

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Female</th>
<th>P-value</th>
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<tr>
<td>Gestational Age (weeks)</td>
<td>37.4</td>
<td>37.2</td>
<td>0.6</td>
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<tr>
<td>Birth Weight (g)</td>
<td>2750</td>
<td>2670</td>
<td>0.8</td>
</tr>
<tr>
<td>Apgar Score 1 Min</td>
<td>7</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Apgar Score 5 Min</td>
<td>9</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>Ventilator Days</td>
<td>8</td>
<td>7</td>
<td>0.6</td>
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*P-values by Kruskal Wallis, CI = Confidence Interval

**Image Caption:**

CONTROL ID: 3379493

**Title:** The Level IV Neonatal Intensive Care Unit (NICU) Experience of infants with Trisomy 18 (T18) and Trisomy 13 (T13): A report from the Children's Hospital Neonatal Consortium (CHNC)

**Presenter:** Krishna Acharya

**Authors (Last Name, First Name):** Niehaus, Jason³; Acharya, Krishna⁴; Shah, Anita N.⁵; Datta, Ankur⁶; Wraith, Catherine L.⁷; Wymore, Erica⁸; Weiner, Julie⁹; Matoba, Nana¹⁰; O’Donnell, Brighid M.¹¹; Rose, Rebecca¹²; Schlegel, Amy¹³; Coghill, Carl H.¹⁴; Wojcik, Monica H.¹⁵; Nayar, Pritha¹⁶; DiGeronimo, Robert¹⁷; Natarajan, Girija¹⁸; Leuthner, Steven R.¹⁹; Ling, Con Y.²⁰; Dereddy, Narendra²¹; Seale, Jamie N.²²; Williams, Helen²³; Jackson, Laura²⁴; Fry, Jessica T.²⁵; Sullivan, Kevin M.²⁶

**Authors/Institutions:** K.M. Sullivan, Pediatrics/Neonatology, AI duPont Hospital for Children/Thomas Jefferson University, Wilmington, Delaware, UNITED STATES; J.T. Fry, Pediatrics/Neonatology, Northwestern University, Chicago, Illinois, UNITED STATES; J. Niehaus, Pediatrics, Indiana University, Indianapolis, Indiana, UNITED STATES; K. Acharya, Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, UNITED STATES; A.N. Shah, Neonatology, CHOC Children's Hospital, Rancho Santa Margarita, California, UNITED STATES; A. Datta, Pediatrics, Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, UNITED STATES; C.L. Wraith, Pediatrics, University of Wisconsin, Madison, Wisconsin, UNITED STATES; E. Wymore, Neonatology, University of Colorado, Aurora, Colorado, UNITED STATES; J. Weiner, Neonatology, Children's Mercy Hospital, Kansas City, Missouri, UNITED STATES; N. Matoba, Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, UNITED STATES;
Background: The experience of infants with T13 or T18 who are admitted to children's hospitals NICUs has not previously been reported. T18 and T13 are chromosomal anomalies, which were previously uniformly described as lethal; few interventions were performed on these neonates. A review of a large Canadian database showed that although early mortality was common, children who underwent surgery had high 1 year survival. Birth-weight and major anomalies have been described as influencers of medical decision-making but the surgical and level IV NICU experience has not been captured.

Objective: To characterize the level IV Children’s Hospital NICU experience for infants with T18 and T13.

Design/Methods: CHNC includes 34 level IV NICUs across the US and Canada that prospectively collects data on all neonates. This is a retrospective cohort analysis using data collected from 2010-2016. All infants admitted with the diagnosis of T13 and T18 were included. Statistical comparisons based on parametric and non-parametric tests were completed.

Results: During the study period, 467 patients (317 with T18 and 150 with T13) were admitted and 235 (50%) survived to discharge. A majority of patients were born at > 37 weeks (57%) with a median (IQR) admission age of 1 (0-4) day, birth weight of 1500-2499 grams (55%) and were outborn (88%). In the delivery room (DR), 130 (28%) infants had a 1-minute APGAR score of less than 2 and 284 (61%) received positive-pressure ventilation and a third underwent endotracheal intubation. No surgical interventions were performed in 350 (75%) infants, 52 (11%) received one surgical procedure and 65 (14%) received 2 or more surgical procedures. Tracheostomy (2.7%) was rare. Of survivors, 157(84%) were discharged home with a feeding ostomy and 92(49%) with home oxygen. Infants with T13 were of lower birth weight, less likely to be intubated in the DR and less likely to survive to discharge.

Conclusion(s): Among infants with T18 and T13 admitted to CHNC institutions survival to NICU discharge was possible. Surgery was performed in 25% of patients, mainly related to feeding stomas, while C-section and DR intervention were frequent. Surviving infants required significant discharge support with high rates of assisted feeding and oxygen. Next steps include identifying inter-center variations in care, changes in management over time and linking DR decision-making to surgical intervention and long-term parental satisfaction.
CONTROL ID: 3379522

TITLE: High Rates of Withdrawal of Life Sustaining Therapy (WLST) in Early Death (<12 hours) after Transfer to Level IV NICUs

PRESENTER: Devika Locke

AUTHORS (LAST NAME, FIRST NAME): Locke, Devika1; Niehaus, Jason3; Acharya, Krishna4; Shah, Anita N.5; Datta, Ankur6; Wraight, Catherine L.7; Wymore, Erica8; Weiner, Julie9; Matoba, Nana10; O’donnell, Brighid M.11; Rose, Rebecca12; Schlegel, Amy13; Coghill, Carl H.14; Wojcik, Monica H.15; nayak, Pritha16; DiGeronimo, Robert17; Natarajan, Girija18; Leuthner, Steven R.19; Ling, Con Y.20; Dereddy, Narendra20; Seale, Jamie N.22; Williams, Helen23; Jackson, Laura11; Fry, Jessica T.2; Sullivan, Kevin M.1

AUTHORS/INSTITUTIONS: D. Locke, K.M. Sullivan, Pediatrics/Neonatology, Al duPont Hospital for Children/Thomas Jefferson University, Wilmington, Delaware, UNITED STATES; J.T. Fry, Pediatrics/Neonatology, Northwestern University, Chicago, Illinois, UNITED STATES; J. Niehaus, Neonatal-Perinatal Medicine, Indiana University, Indianapolis, Indiana, UNITED STATES; K. Acharya, Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, UNITED STATES; A.N. Shah, Neonatology, CHOC Childrens Hospital, Rancho Santa Margarita, California, UNITED STATES; A. Datta, Pediatrics, Division of Neonatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, UNITED STATES; C.L. Wraight, Pediatrics, University fo Wisconsin, Madison, Wisconsin, UNITED STATES; E. Wymore, Neonatology, University of Colorado, Aurora, Colorado, UNITED STATES; J. Weiner, Neonatology, Children's Mercy Hospital, Kansas City, Missouri, UNITED STATES; N. Matoba, Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, UNITED STATES; B.M. O’donnell, L. Jackson, Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, UNITED STATES.
Background: The decision to transport a critically ill infant to a higher level NICU is designed to provide therapies to improve survival. Unfortunately, some infants die quickly following transport and little is known about the contributing factors or manner of their death.

Objective: To compare characteristics and end-of-life events of infants who died less than 12 hours after transfer to level IV NICUs with other infants that died later following transfer.

Design/Methods: Children’s Hospitals Neonatal Consortium (CHNC) is a group of 34 level IV NICUs across the US that prospectively collect data on all admitted neonates. This was a retrospective cohort analysis using data collected between 2010-2016. Infants who were inborn were excluded. Demographic factors including race, gestational age, medical diagnoses and interventions were compared for infants who died less than 12 hours after transfer and infants who died greater than 12 hours after transfer. These categories were analyzed using parametric and non-parametric testing as appropriate.

Results: A total of 6035 infant deaths were reviewed with 356 (5.9%) dying at less than 12 hours. Infants dying early were of younger gestational age, lower birth weight, had increased comorbidities, and were more likely to be intubated and paralyzed at admission. Infants who died early more commonly had as their primary cause of death intra-abdominal catastrophes (35.4% vs. 10.8%), including GI perforation (7% vs. 4%) (Table 1). Additionally, a higher percentage of infants with early death had do-not-resuscitate (DNR) orders in place (51.7% vs. 19.8%), and they were less likely to have withdrawal of life-sustaining therapies (WILST) (55.6% vs. 72.9%), or receive cardiopulmonary resuscitation (CPR) around death (38% vs. 55.6%) (Table 2).

Conclusion(s): Infants in this cohort with early mortality after transfer have predictably higher acuity at admission. Surprisingly, the majority of early deaths appear to be anticipated with preceding DNR and WLST along with lower rates of CPR. This study highlights the importance of interdisciplinary decision making to ensure that patient transfers to higher levels of care continue to align with overall family goals of care.
Background: Histologic chorioamnionitis (HCA) is a frequently ‘silent’ placental inflammation that may contribute to preterm birth. Calgranulins, inflammatory S100 proteins, have been identified in amniotic fluid in HCA. We hypothesized that circulating calgranulin expression levels in pregnant women or in cord blood might serve to identify gestations affected by HCA.

Objective: Our goal was to correlate S100A8 and S100A12 plasma levels in mother-baby pairs of preterm gestations with the presence or absence of HCA.
**Design/Methods:**
In this prospective observational study we enrolled a cohort of pregnant women (23-34 wk GA) admitted with preterm labor or preterm premature rupture of membranes (PPROM). Exclusion criteria included maternal inflammatory disorders or fetal abnormalities. Maternal peripheral venous blood was collected within 24 h peripartum and venous umbilical cord blood (CB) samples were obtained at delivery. Maternal (M-HCA) or fetal (F-HCA) or the absence of HCA (Ctrl) were identified by placental examination (Redline 2012). S100A8 and S100A12 levels were measured in replicate samples by commercial ELISA.

**Results:** Plasma S100 protein levels were determined in 41 mother-baby pairs. Demographic data, PPROM incidence and gestational age at delivery were similar between groups. In F-HCA, S100A8 and S100A12 levels were increased 4-fold in CB (P<0.001) relative to Ctrl. In contrast, S100A8 but not S100A12 levels were elevated in maternal blood (p<0.05). In paired comparisons, maternal S100A8 levels were higher (P=0.01 vs. CB) in M-HCA, while in F-HCA, maternal and CB levels were similar.

**Conclusion(s):** Fetal HCA is associated with elevated circulating levels of S100A8 and S100A12 in preterm gestations. Our data suggest that S100A8 blood levels may identify mothers and neonates exposed to fetal HCA, a diagnosis that currently depends on postpartum placental analysis. Studies to establish the utility of S100A8 and S100A12 as biomarkers of HCA exposure are underway. This work was funded in part by the Gerber Foundation (to JMK).

(No Image Selected)
Results: We considered all 15,625,734 infant births, including 103,703 HB and 71,394 FBC births. Table 2 displays risk factors by birth setting. Among planned HB, 39,705 (38%) /21,707 (21%) /18,944 (18%) did not meet AAP-ACOG/OHA/NICE criteria for low-risk compared with 24,602 (34%) /11,651 (16%) /10,584 (15%) in FBC, respectively (Table 2). Within setting comparisons revealed significantly increased odds of early neonatal mortality in HB for all guidelines, but only for OHA and NICE guidelines in the FBC setting (Figures 1a-f). For all guidelines, elevated-risk HB and FBC births exhibited significantly higher early mortality compared with non-vertex singleton healthy-birthweight term infants delivered by hospital midwives.

Conclusion(s): Between 18-40% of mothers with planned out-of-hospital birth do not meet criteria for low-risk under guidelines of several professional medical associations. Inadequate risk selection is associated with increased early neonatal mortality in out-of-hospital births.

Risk factors of births. Includes pregnancy and pre-pregnancy risk-factors. Guidelines from the American Academy of Pediatrics (AAP), (b) American College of Obstetricians and Gynecologists (ACOG), Oregon Health Authority (OHA), and the UK National Institute for Health and Care Excellence (NICE).

Guidelines for elevated-risk contraindications to home and birth center (H&BC) births by organization. American Academy of Pediatricians (AAP), American College of Obstetricians and Gynecologists (ACOG), Oregon Health Authority (OHA), and the UK National Institute for Health and Care Excellence (NICE).
Early mortality for elevated-risk vs low-risk infants for home birth (HB) and freestanding birth center births (FBC) using guidelines from (a) the American Academy of Pediatricians (AAP), (b) American Association of Gynecologists (ACOG), (c) Oregon Health Authority (OHA), and (d) the UK National Institute for Health and Care Excellence (NICE). Mortality is compared with hospital mortality for singleborn, non-vertex, term (>=37 week gestational age) infants of healthy birthweight (>=2500g) delivered by midwives. Non-overlap in confidence bands indicates significant difference between groups at the p=0.05 level.

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Guidelines for elevated-risk contraindications to home and birth center (H&BC) births by organization. American Academy of Pediatricians (AAP), American College of Obstetricians and Gynecologists (ACOG), Oregon Health Authority (OHA), and the UK National Institute for Health and Care Excellence (NICE).

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ABSTRACT BODY:

Background: Regenerative cell therapies for neonatal morbidities including bronchopulmonary dysplasia and preterm brain injury are entering early phase clinical trials. The reliable delivery of a known dose of cell therapy is fundamental to early safety studies. Infants, particularly extremely preterm infants, require small volume infusions. However, intravenous infusion protocols for delivering cells have been largely adopted from adult protocols and have not been evaluated in infants.

Objective: We aimed to explore the effects of different intravenous infusion parameters on cell delivery to define the optimum protocol for the administration of a leading cell therapy, human amnion epithelial cells (hAECs), to extremely preterm infants.

Design/Methods: Standard cell infusion protocols were modelled. To characterise hAEC delivery the infusate was collected at intervals over 60 minutes. The volume infused (mL) and hAEC density (hAEC/mL) measured. At the end of the 60-minute infusion the hAEC density of the suspension remaining in the syringe and the intravenous line was measured. Infusion parameters including albumin concentration (2% vs. 4%), syringe orientation (horizontal vs. vertical), intravenous line volume (0.2-2.2mL), and flow rate (3-15mL/hr) were varied to determine the influence on dose delivery.

Results: The standard (previously published) cell infusion protocol delivered a mean (SD) of 17.6(9)% of intended hAEC dose. Over the duration of the infusion the hAEC density of the infusate decreased and hAECs accumulated in the intravenous line. Increasing the albumin concentration to 4%, positioning the syringe and intravenous line vertically, and decreasing intravenous line volume to 0.6mL increased hAEC delivery to a mean (SD) of 98(6)% of intended cell dose (figure1). Flow rate had little effect on dose delivery when other conditions were optimised.

Conclusion(s): It is essential that cell infusion protocols are optimised for small volume delivery in preterm infants. We describe the refinement and validation of a cell therapy infusion protocol that offers reliable delivery of intended cell doses, suitable for extremely preterm neonates. Previously published work should be viewed with caution given the possibility that only a fraction of the intended cell dose may have been delivered.