

## What's New and How Do We Implement the Evidence?

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### Disclosure Statements

- We 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.

Low dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. Andrikopoulou M et al. Am J Obstet Gynecol. June 2018

- The authors sought to determine whether low dose aspirin (ASA) reduces the rate of spontaneous pre-term birth (PTB) in nulliparous women without medical comorbidities.
- In 2543 subjects, the rate of spontaneous PTB <34 wks was 1.03% and 2.34% in the ASA and placebo group, respectively (OR 0.43, 95% CI 0.26-0.84).
- After adjustment for variables that were clinically relevant or statistically significant, including BMI, race, tobacco use, marital status and education level, there was a significant reduction in spontaneous PTB <34 wks in the ASA group (aOR 0.46, 95% CI 0.23-0.89).
- These findings suggest that ASA for PTB prevention requires further study.

### DO USE DIURETICS?

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Acute responses to diuretic therapy in extremely low gestational age newborns: results from the prematurity and respiratory outcomes program cohort study. Blaisdell CJ, Troendle J, Zajicek A, et al. J Pediatr. June 2018

- This observational cohort study evaluated 835 premature infants, 23 0/7 to 28 6/7 weeks gestational age, at 13 tertiary care units in the United States.
- The study controlled for gestational age, birth weight, sex, and respiratory status before receiving diuretics.
- The author's **analysis did not support the ability of diuretics to substantially improve extremely premature infant's respiratory status.**

### GASTRIC RESIDUALS?

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**THE IMPACT OF ROUTINE EVALUATION OF GASTRIC RESIDUAL VOLUMES ON THE TIME TO ACHIEVE FULL ENTERAL FEEDING IN PRETERM INFANTS.** RISKIN A, ET AL. *J PEDIATR.* 2017 OCT;189:128-134.

- **STUDY DESIGN:** Data were collected on all gavage-fed infants born at  $\leq 34$  weeks gestational age (GA) for 2 years before ( $n = 239$ ) and 2 years after the change ( $n = 233$ ).
- **RESULTS:** The median GA was 32.0 (IQR: 29.7-33.0) weeks before and 32.4 (30.4-33.4) weeks after the change ( $P = .02$ ). Compared with historic controls, infants with selective evaluations of gastric residual volumes weaned from parenteral nutrition 1 day earlier ( $P < .001$ ) and achieved full enteral feedings (150 cc/kg/day) 1 day earlier ( $P = .002$ ). The rate of NEC (stage  $\geq 2$ ) was 1.7% in the selective gastric residual volume evaluation group compared with 3.3% in the historic control group ( $P = .4$ ). Multiple regression analyses showed that the strongest predictor of time to full enteral feedings was GA. Routine evaluation of gastric residual volume and increasing time on noninvasive ventilation both prolonged the attainment of full enteral feedings.
- **CONCLUSIONS:** *Avoiding routine evaluation of gastric residual volume before every feeding was associated with earlier attainment of full enteral feedings without increasing risk for NEC.*

## NEW DATA ON CAFFEINE

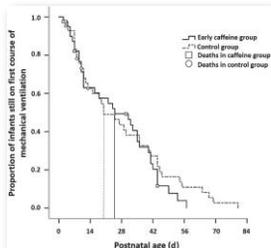
**ASSOCIATION BETWEEN EARLY CAFFEINE CITRATE ADMINISTRATION AND RISK OF ACUTE KIDNEY INJURY IN PRETERM NEONATES: RESULTS FROM THE AWAKEN STUDY.** HARER M, ET AL. *JAMA PEDIATR.* 2018 APR 2

- **RESULTS:** The study cohort ( $n = 675$ ) was 55.4% (DESIGN, SETTING, AND PARTICIPANTS: This study was a secondary analysis of the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study, a retrospective observational cohort that enrolled neonates born from January 1 to March 31, 2014. The dates of analysis were October 2016 to December 2017.
- $n = 374$  male, with a mean (SD) gestational age of 28.9 (2.8) weeks and a mean (SD) birth weight of 1285 (477) g. **Acute kidney injury occurred in 122 neonates (18.1%) in the first 7 days after birth. Acute kidney injury occurred less frequently among neonates who received caffeine than among those who did not (50 of 447 [11.2%] vs 72 of 228 [31.6%],  $P < .01$ ).** After multivariable adjustment, administration of caffeine remained associated with reduced odds of developing AKI (adjusted odds ratio, 0.20; 95% CI, 0.11-0.34), *indicating that for every 4.3 neonates exposed to caffeine one case of AKI was prevented. Among neonates with early AKI, those receiving caffeine were less likely to develop stage 2 or 3 AKI (adjusted odds ratio, 0.20; 95% CI, 0.12-0.34).*
- **CONCLUSIONS AND RELEVANCE:** *Caffeine administration in preterm neonates is associated with reduced incidence and severity of AKI.*

**AMARO CM, ET AL. EARLY CAFFEINE AND WEANING FROM MECHANICAL VENTILATION IN PRETERM INFANTS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL.** *J PEDIATR.* 2018.

- Preterm infants born at 23-30 weeks of gestation requiring mechanical ventilation in the first 5 postnatal days were randomized to receive a 20 mg/kg loading dose followed by 5 mg/kg/day of caffeine or placebo until considered ready for extubation.
- Infants were randomized to receive caffeine ( $n = 41$ ) or placebo ( $n = 42$ ). Age at first successful extubation did not differ between early caffeine (median, 24 days; IQR, 10-41 days) and control groups (median, 20 days; IQR, 9-43 days;  $P = .7$ ).
- An interim analysis at 75% enrollment showed a trend toward higher mortality in 1 of the groups and the data safety and *monitoring board recommended stopping the trial. Unblinded analysis revealed mortality did not differ significantly between the early caffeine (9 [22%]) and control groups (5 [12%];  $P = .22$ ).*

**AMARO CM, BELLO JA, JAIN D ET AL. EARLY CAFFEINE AND WEANING FROM MECHANICAL VENTILATION IN PRETERM INFANTS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL.** *J PEDIATR.* 2018.



Murner-Lavanchy IM, Doyle LW, Schmidt B et al. *Neurobehavioral Outcomes 11 Years After Neonatal Caffeine Therapy for Apnea of Prematurity.* Pediatrics 2018.

- Measures of general intelligence, attention, executive function, visuomotor integration and perception, and behavior were obtained in up to 370 children.
- Neurobehavioral outcomes were generally similar for both the caffeine and placebo group. The caffeine group performed better than the placebo group in fine motor coordination (mean difference [MD] = 2.9; 95% confidence interval [CI]: 0.7 to 5.1;  $P = .01$ ), visuomotor integration (MD = 1.8; 95% CI: 0.0 to 3.7;  $P < .05$ ), visual perception (MD = 2.0; 95% CI: 0.3 to 3.8;  $P = .02$ ), and visuospatial organization (MD = 1.2; 95% CI: 0.4 to 2.0;  $P = .003$ ).
- **CONCLUSIONS:** *Neonatal caffeine therapy for apnea of prematurity improved visuomotor, visuospatial, and visuospatial abilities at age 11 years. General intelligence, attention, and behavior were not adversely affected by caffeine, which highlights the long-term safety of caffeine therapy for apnea of prematurity in very low birth weight neonates.*

## IS THERE A PROBLEM WITH SCREENING FOR CCHD AT ALTITUDE?

PARANKA MS, BROWN JM, WHITE RD, PARK MV, KELLEHER AS, CLARK RH. **THE IMPACT OF ALTITUDE ON SCREENING FOR CRITICAL CONGENITAL HEART DISEASE.** J PERINATOL 2018. [EPUB AHEAD OF PRINT].

- We conducted a prospective clinical study of implementation of a newborn pulse oximetry screening for congenital heart disease in 34 independent hospitals. Infants were eligible for enrollment if their gestational age was 35-44 weeks.
- Of the 34 sites which enrolled infants into our study, 24 were located at or below 2000 feet; 5 were located between 4700 and 6000 feet and 5 were located above 6000 feet in altitude.
- We screened 6109 infants; 65 (1.1%) had a positive screen.
- *The frequency of a positive screen increased from 0.2% for infants born at sites at or less than 2000 feet to 6% for sites located above 6000 feet.*
- *We stopped enrollment at the site located at 8163 feet after enrolling 65 infants because 23 (35%) were positive.*

PARANKA MS, BROWN JM, WHITE RD, PARK MV, KELLEHER AS, CLARK RH. **THE IMPACT OF ALTITUDE ON SCREENING FOR CRITICAL CONGENITAL HEART DISEASE.** J PERINATOL 2018. [EPUB AHEAD OF PRINT].

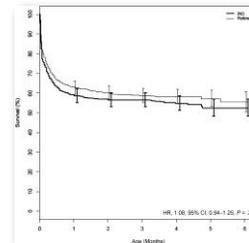
- Using an algorithm that increased the inspired oxygen content to correct for the altitude-related decrease in partial pressure of oxygen, most infants (93%) who had a positive screening test by the AAP algorithm passed the oxygen challenge test.
- As an alternate approach, one of our sites used a lower threshold of >93% for their screening algorithm.

## DOES iNO PROMOTE BETTER SURVIVAL IN INFANTS WITH RDS OR RDS WITH PULMONARY HYPERTENSION?

CAREY WA, WEAVER AL, MARA KC, CLARK RH. **INHALED NITRIC OXIDE IN EXTREMELY PREMATURE NEONATES WITH RESPIRATORY DISTRESS SYNDROME.** PEDIATRICS 2018. [EPUB AHEAD OF PRINT]

- We queried the Pediatrix Medical Group Clinical Data Warehouse to identify all neonates born at 22 to 29 weeks' gestation from 2004 to 2014.
- In our study sample, we included singletons who required mechanical ventilation for treatment of RDS and excluded those with anomalies. The primary outcome was death before discharge. Through a sequential risk set approach, each patient who received iNO during the first 7 days of life ("case patient") was matched by using propensity scores to a patient who had not received iNO at a chronological age before the case patient's iNO initiation age (defined as the index age for the matched pair).
- Among 37 909 neonates in our study sample, we identified 993 (2.6%) who received iNO. The 2 matched cohorts each contained 971 patients. We did not observe a significant association between iNO exposure and mortality (hazard ratio, 1.08; 95% confidence interval, 0.94-1.25; P = .29).

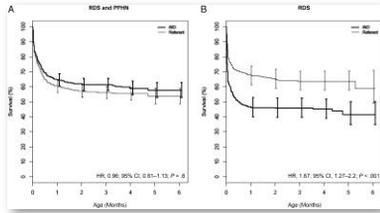
Overall survival by iNO status of patients in the matched cohort.



William A. Carey et al. Pediatrics 2018;141:e20173108  
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PEDIATRICS

**Overall survival by iNO status of (A) patients in the matched cohort with RDS and PPHN and (B) patients in the matched cohort with RDS.**



William A. Carvey et al. Pediatrics 2018;141:e20173108



SHOULD WE MYELOMENINGOCELE BE REPAIRED PRENATALLY?

**FARMER DL, ET AL. THE MANAGEMENT OF MYELOMENINGOCELE STUDY: FULL COHORT 30-MONTH PEDIATRIC OUTCOMES. AM J OBSTET GYNECOL 2018;218(2):256.E1-256.E13**

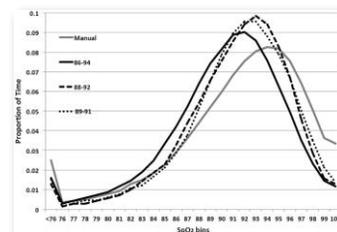
- The data for 183 patients corroborate the original findings of Management of Myelomeningocele Study, confirming that prenatal repair improves the primary outcome composite score of mental development and motor function (199.4 +/- 80.5 vs. 166.7 +/- 76.7, P = .004).
- Prenatal surgery also resulted in improvement in the secondary outcomes of independent ambulation (44.8% vs. 23.9%, P = .004), WeeFIM self-care score (20.8 vs 19.0, P = .006), functional level at least 2 better than anatomic level (26.4% vs 11.4%, P = .02), and mean Bayley Scales of Infant Development, Second Edition, psychomotor development index (17.3% vs 15.1%, P = .03), but does not affect cognitive development at 30 months.
- The full cohort data of 30-month cognitive development and motor function outcomes validate in utero surgical repair as an effective treatment for fetuses with myelomeningocele.*
- Current data suggest that outcomes related to the need for shunting should be counseled separately from the outcomes related to distal neurologic functioning.

OXYGEN DELIVERY AND MONITORING

**VAN DEN HEUVEL MEN, ET AL. OPTIMAL TARGET RANGE OF CLOSED-LOOP INSPIRED OXYGEN SUPPORT IN PRETERM INFANTS: A RANDOMIZED CROSS-OVER STUDY. J PEDIATR 2018.**

- Forty-one preterm infants (gestational age [median] 26 weeks, age [median] 21 days) on FIO2 >0.21 receiving noninvasive respiratory support were subjected to A-FIO2 using 3 SpO2 target ranges (86%-94%, 88%-92%, or 89%-91%) in random order for 24 hours each. Before switching to the next target range, SpO2 was manually controlled for 24 hours (washout period).
- The percent time within the 86%-94% SpO2 alarm range was similar for all 3 A-FIO2 target ranges (74%). Time spent in hyperoxemia was not significantly different between target ranges.
- However, the time spent in severe hypoxemia (SpO2 <80%) was significantly reduced during the narrowed target ranges of A-FIO2 (88%-92%; 1.9%, 89%-91%; 1.7%) compared with the wide target range (86%-94%; 3.4%, P < .001).
- CONCLUSIONS:** *Narrowing the target range of A-FIO2 to the desired median +/-2% is effective in reducing the time spent in hypoxemia, without increasing the risk of hyperoxemia.*

**VAN DEN HEUVEL MEN, VAN ZANTEN HA, BACHMAN TE, TE PAS AB, VAN KAAM AH, ONLAND W. OPTIMAL TARGET RANGE OF CLOSED-LOOP INSPIRED OXYGEN SUPPORT IN PRETERM INFANTS: A RANDOMIZED CROSS-OVER STUDY. J PEDIATR 2018.**



OUTCOMES OF OXYGEN SATURATION TARGETING DURING DELIVERY ROOM STABILISATION OF PRETERM INFANTS. JU LEE OEI ET AL. HTTP://DX.DOI.ORG/10.1136/ARCHDISCHILD-2016-31236

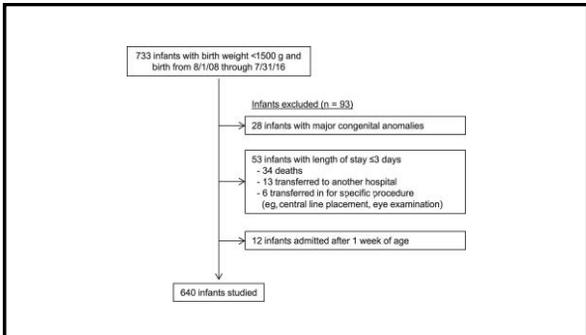
- Design: Data from 768 infants <32 weeks gestation from 8 randomised controlled trials (RCTs) of lower (±0.3) versus higher (±0.6) initial inspiratory fractions of oxygen (FIO2) for resuscitation, were examined.
- Interventions: Lower (±0.3) versus higher (±0.6) oxygen resuscitation strategies targeted to specific predefined SpO2 before 10 min of age.
- Results: 5 min SpO2 data were obtained from 706 (92%) infants. Only 159 (23%) infants met SpO2 study targets and 323 (46%) did not reach SpO2 80%. Pooled data showed decreased likelihood of reaching SpO2 80% if resuscitation was initiated with FIO2 <0.3 (OR 2.63, 95% CI 1.21 to 5.74, p<0.05). SpO2 <80% was associated with lower heart rates (mean difference -8.37, 95% CI -15.73 to -1.01, \*p<0.05) and after accounting for confounders, with IVH (OR 2.04, 95% CI 1.01 to 4.11, p<0.05). Bradycardia (heart rate <100 bpm) at 5 min increased risk of death (OR 4.57, 95% CI 1.62 to 13.98, p<0.05). Taking into account confounders including gestation, birth weight and 5 min bradycardia, risk of death was significantly increased with time taken to reach SpO2 80%.
- Conclusion: *Not reaching SpO2 of 80% at 5 min is associated with adverse outcomes, including IVH. Whether this is because of infant illness or the amount of oxygen that is administered during stabilization is uncertain and needs to be examined in randomized trials*



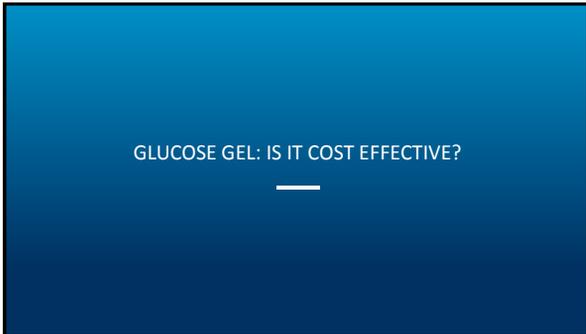
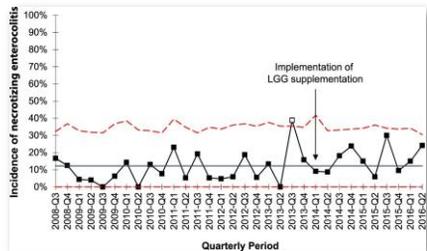
Routine Supplementation of Lactobacillus Rhamnosus GG and Risk of Necrotizing Enterocolitis in Very Low Birth Weight Infants

Andrea F. Kane, MD, Anisha D. Bhatia, MD, Patricia W. Denning, MD, Andi L. Shane, MD, MPH, MSc, Ravi Mangal Patel, MD, MSc

The Journal of Pediatrics  
Volume 195, Pages 73-79.e2 (April 2018)  
DOI: 10.1016/j.jpeds.2017.11.055



THE JOURNAL OF PEDIATRICS 2018;195:73-79.e2 DOI: 10.1016/j.jpeds.2017.11.055



GLASGOW MJ, HARDING JE, EDLIN R. **COST ANALYSIS OF TREATING NEONATAL HYPOGLYCEMIA WITH DEXTROSE GEL.** J PEDIATR 2018.

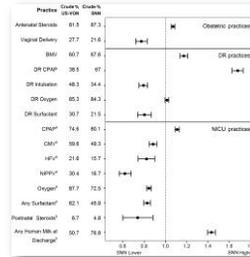
- A decision tree was used to model overall costs, including those specific to hypoglycemia monitoring and treatment and those related to the infant's length of stay in the postnatal ward or neonatal intensive care unit, comparing the use of dextrose gel for treatment of neonatal hypoglycemia with placebo, using data from the Sugar Babies randomized trial.
- In the primary analysis, treating neonatal hypoglycemia using dextrose gel had an overall cost of NZ\$6863.81 and standard care (placebo) cost NZ\$8178.25; a saving of NZ\$1314.44 per infant treated. Sensitivity analyses showed that dextrose gel remained cost saving with wide variations in dextrose gel costs, neonatal intensive care unit costs, cesarean delivery rates, and costs of monitoring.
- Because it is noninvasive, well tolerated, safe, and associated with improved breastfeeding, buccal dextrose gel should be routinely used for initial treatment of neonatal hypoglycemia.

VARIABILITY IN PRACTICE AND OUTCOME

ADAMS M, BASSLER D, BUCHER HU ET AL. **VARIABILITY OF VERY LOW BIRTH WEIGHT INFANT OUTCOME AND PRACTICE IN SWISS AND US NEONATAL UNITS.** PEDIATRICS 2018

- Retrospective observational study including all live-born infants with a birth weight between 501 and 1500 g as registered by SNN and US-VON between 2012 and 2014. A total of 123,689 infants were born alive in 696 US-VON units and 2209 infants were born alive in 13 SNN units.
- Adjusted risk ratios (aRRs) for the composite "death or major morbidity" (aRR: 0.56, 95% confidence interval: 0.51-0.62) and all other outcomes were either comparable or lower in SNN except for mortality, for which aRR was higher (aRR: 1.28, 95% confidence interval: 1.09-1.50). *Propensity score matching and restricting the analysis to infants for which we expect no survival bias, because both networks routinely initiate intensive care at birth, revealed comparable aRR.*
- *Variations in observed practices between SNN and US-VON were large.*

Obstetrical, DR, NICU, and nutritional practices as crude cumulative incidence proportions of both SNN and US-VON and indirectly standardized, case mix- adjusted observed to expected ratios.



Mark Adams et al. Pediatrics doi:10.1542/peds.2017-3436

WHAT NEW? ROP TREATMENT

WALLACE DK, ET. AL. **Assessment of Lower Doses of Intravitreal Bevacizumab For Retinopathy Of Prematurity: A Phase 1 Dosing Study.** JAMA Ophthalmol 2017;135(6):654-656. [HTTP://JAMANETWORK.COM/JOURNALS/JAMAOPHTHALMOLOGY/ARTICLE-ABSTRACT/2621875](http://jamanetwork.com/journals/jamaophthalmology/article-abstract/2621875)

- Between **May 2015 and September 2016**, 61 premature infants with type 1 ROP in 1 or both eyes were enrolled in a masked, multicenter, phase 1 dose de-escalation study. One eye of 10 to 14 infants received 0.25 mg of intravitreal bevacizumab. If successful, the dose was reduced for the next group of infants (to 0.125 mg, then 0.063 mg, and finally 0.031 mg).
- Outcome measure: Success was defined as **improvement in preinjection plus disease or zone 1 stage 3 ROP by 5 days after injection or sooner, and no recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks.**
- **Results:** Fifty-eight of 61 enrolled infants had 4-week outcomes completed; mean birth weight was 709 g and mean gestational age was 24.9 weeks. Success was achieved in 11 of 11 eyes at 0.25 mg, 14 of 14 eyes at 0.125 mg, 21 of 24 eyes at 0.063 mg, and 9 of 9 eyes at **0.031 mg. (0.625/0.31=20)**
- **Conclusions:** **A dose of bevacizumab as low as 0.031 mg was effective in 9 of 9 eyes in this phase 1 study and warrants further investigation.**

VANDERVEEN DK, ET AL. **ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR PRIMARY TREATMENT OF TYPE 1 RETINOPATHY OF PREMATURITY: A REPORT BY THE AMERICAN ACADEMY OF OPHTHALMOLOGY.** OPTHALMOLOGY 2017;124(5):619-633.

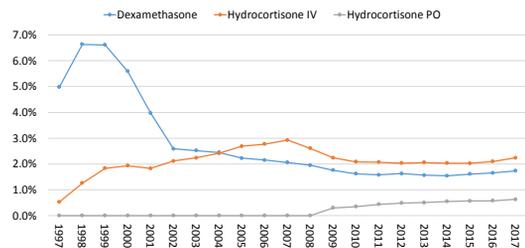
- Current level II and III evidence indicates that intravitreal anti-VEGF therapy is as effective as laser photocoagulation for achieving regression of acute ROP.
- *Although there are advantages to anti-VEGF pharmacotherapy for zone I disease or aggressive posterior ROP, the disadvantages are that the ROP recurrence rate is higher, and vigilant and extended follow-up is needed because retinal vascularization is usually incomplete.*
- *After intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks.*
- *The effects of lowering systemic VEGF levels on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment.*

STAHL ET AL. **COMPARING ALTERNATIVE RANIBIZUMAB DOSAGES FOR SAFETY AND EFFICACY IN RETINOPATHY OF PREMATURITY: A RANDOMIZED CLINICAL TRIAL.** JAMA PEDIATR. DOI:10.1001/JAMAPEDIATRICS.2017.4838

- *Pilot study (n=19 patients) demonstrates that ranibizumab is effective in controlling acute ROP and that 24% of the standard adult dose (0.12mg) appears equally effective as 40% (0.20mg).*
- Superior vascularization of the peripheral retina with 0.12mg of ranibizumab indicates that the *lower dose may be favorable.*
- Unchanged plasma VEGF levels point toward a limited systemic drug exposure after ranibizumab.

## WHAT ABOUT POSTNATAL STEROIDS?

### POSTNATAL STEROID USE IN THE NICU ALL ADMITS WITH NO FILTERS.



BAUD O, ET AL. **ASSOCIATION BETWEEN EARLY LOW-DOSE HYDROCORTISONE THERAPY IN EXTREMELY PRETERM NEONATES AND NEURODEVELOPMENTAL OUTCOMES AT 2 YEARS OF AGE.** JAMA 2017;317(13):1329-1337.

- After birth, patients were randomly assigned to receive placebo or hydrocortisone (*0.5 mg/kg twice per day for 7 days, followed by 0.5 mg/kg per day for 3 days*).
- Of 1072 neonates screened, 523 were assigned to hydrocortisone (n = 256) or placebo (n = 267) and 406 survived to 2 years of age.
- A total of 379 patients (93%; 46% female) were evaluated (194 in the hydrocortisone group and 185 in the placebo group) at a median corrected age of 22 months (interquartile range, 21-23 months).
- The distribution of patients without neurodevelopmental impairment (73% in the hydrocortisone group vs 70% in the placebo group), with mild neurodevelopmental impairment (20% in the hydrocortisone group vs 18% in the placebo group), or with moderate to severe neurodevelopmental impairment (7% in the hydrocortisone group vs 11% in the placebo group) was not statistically significantly different between groups (P = .33).
- The incidence of cerebral palsy or other major neurological impairments was not significantly different between groups.

BASSLER ET AL. **LONG-TERM EFFECTS OF INHALED BUDESONIDE FOR BRONCHOPULMONARY DYSPLASIA.** N ENGL J MED 378;2. JANUARY 11, 2018

- 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) randomly assigned to receive early (within 24 hours after birth) inhaled budesonide or placebo.
- Prespecified secondary long-term outcome was neurodevelopmental disability among survivors, defined as a composite of cerebral palsy, cognitive delay (a Mental Development Index score of <85 [1 SD below the mean of 100] on the Bayley Scales of Infant Development, Second Edition, with higher scores on the scale indicating better performance), deafness, or blindness at a corrected age of 18 to 22 months.
- Adequate data on the prespecified composite long-term outcome were available for 629 (73%) infants.
- 148 (48.1%) of 308 infants assigned to budesonide had neurodevelopmental disability, as compared with 165 (51.4%) of 321 infants assigned to placebo (relative risk, adjusted for gestational age, 0.93; 95% confidence interval [CI], 0.80 to 1.09; P = 0.40).
- *There were more deaths in the budesonide group than in the placebo group (82 [19.9%] of 413 infants vs. 58 [14.5%] of 400 infants for whom vital status was available; relative risk, 1.37; 95% CI, 1.01 to 1.86; P = 0.04).*

HALLIDAY H.L. **UPDATE ON POSTNATAL STEROIDS.** NEONATOLOGY 2017;111:415-422.

- Current recommendations are that postnatal steroid treatment should be reserved for preterm infants who are *ventilator-dependent after the first 7-14 days of life and any course should be low dose and of short duration* to facilitate endotracheal extubation.
- Budesonide/surfactant mixtures show some promise as a means of reducing chronic lung disease in preterm infants with severe respiratory distress syndrome, *but further larger studies with long-term follow-up are needed* before this treatment can be recommended as a routine intervention.

## NAS MANAGEMENT

KRAFT WK, ET AL. **BUPRENORPHINE FOR THE TREATMENT OF THE NEONATAL ABSTINENCE SYNDROME.** NEW ENGLAND JOURNAL OF MEDICINE 2017;376(24):2341-2348

- In this single-site, double-blind, double-dummy clinical trial, we randomly assigned **63 term infants (>37 weeks of gestation)** who had been exposed to opioids in utero and who had signs of the neonatal abstinence syndrome to receive either sublingual buprenorphine or oral morphine.
- Infants with symptoms that were not controlled with the maximum dose of opioid were treated with adjunctive phenobarbital.
- *The primary end point was the duration of treatment for symptoms of neonatal opioid withdrawal.*
- Secondary clinical end points were the length of hospital stay, the percentage of infants who required supplemental treatment with phenobarbital, and safety.

KRAFT WK, ET AL. **BUPRENORPHINE FOR THE TREATMENT OF THE NEONATAL ABSTINENCE SYNDROME.** NEW ENGLAND JOURNAL OF MEDICINE 2017;376(24):2341-2348

- The median duration of treatment was significantly shorter with buprenorphine than with morphine (15 days vs. **28 days**).
- The median length of hospital stay (21 days vs. **33 days**) ( $P < 0.001$  for both comparisons) was shorter.
- Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group ( $P = 0.36$ ).
- Rates of adverse events were similar in the two groups.

HALL ES, ET AL. **IMPLEMENTATION OF A NEONATAL ABSTINENCE SYNDROME WEANING PROTOCOL: A MULTICENTER COHORT STUDY.** PEDIATRICS. 2015;136:E803-E810

- 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%,  $P = .004$ ).
- Adoption of a stringent weaning protocol resulted in improved NAS outcomes, demonstrating generalizability of the protocol-driven weaning approach.

Davis JM, Shenberger J, Terrin N et al. Comparison of Safety and Efficacy of Methadone vs Morphine for Treatment of Neonatal Abstinence Syndrome: A Randomized Clinical Trial. JAMA Pediatr 2018;172(8):741-748

- Despite recommendations that opioids should be used for treatment of NAS, no universal evidence-based pharmacologic treatment strategy exists. In addition, no drug is approved for use in infants by the FDA.
- The differential response to the type of opioid used to treat NAS resides in the unique characteristics of each drug. The active R enantiomer of methadone possesses greater  $\mu$ -opioid receptor agonist activity than morphine but has lower receptor affinity.
- Metabolism of methadone by cytochrome P450 iso-enzymes can vary by as much as 30-fold in liver and 11-fold in gut. The higher fat solubility, protein binding, and volume of distribution of methadone prolongs the half-life and allows a longer dose interval

Davis JM, Shenberger J, Terrin N et al. Comparison of Safety and Efficacy of Methadone vs Morphine for Treatment of Neonatal Abstinence Syndrome: A Randomized Clinical Trial. *JAMA Pediatr* 2018;172(8):741-748

- Randomized, double-blind, intention-to-treat trial, term infants from 8 US newborn units whose mothers received buprenorphine, methadone, or opioids for pain control during pregnancy were eligible.
- A total of 117 infants were randomized to receive methadone or morphine from 2014 to 2017.
- **RESULTS** A total of 183 mothers consented to have their infants in the study; 117 (64%) infants required treatment. Demographic variables and risk factors were similar except for more prenatal cigarette exposure in infants who received methadone. Adjusting for study site and maternal opioid type, methadone was associated with decreased mean number of days for length of stay (LOS) by 14% (0.86; 95%CI, 0.7-1.0;  $P = .046$ ), corresponding to a difference of 2.9 days; and 16% reduction in length of treatment (LOT) (0.84; 95%CI, 0.73-0.97;  $P = .02$ ), corresponding to a difference of 2.3 days. Methadone was also associated with reduced median LOS (16 vs 20 days,  $P = .005$ ), LOS attributable to NAS (16 vs 19 days,  $P = .005$ ), and LOT (11.5 vs 15 days,  $P = .009$ ).
- *Study infants had better short-term outcomes than 170 nonrandomized infants treated with morphine per standard institutional protocols.*

**Table 4. Primary and Secondary Outcomes**

Outcome	Methadone (n = 58)	Morphine (n = 58)	Methadone-Morphine Comparison			
			Unadjusted Statistic <sup>a</sup> (95% CI)	P Value	Adjusted <sup>b</sup> Statistic <sup>a</sup> (95% CI)	P Value
<b>LOS</b>						
Mean (SD)	21.8 (15.0)	23.2 (8.8)	0.94 (0.80 to 1.11)	.48	0.86 (0.74 to 1.00)	.046
Median (IQR)	16 (14 to 22)	20 (16 to 27) <sup>c</sup>				
<b>LOS attributable to NAS</b>						
Mean (SD)	18.9 (7.5)	21.1 (6.9)	0.89 (0.79 to 1.02)	.09	0.86 (0.77 to 0.97)	.01
Median (IQR)	16 (14 to 22)	19 (16 to 25) <sup>c</sup>				
<b>LOT</b>						
Mean (SD)	14.7 (8.0)	16.6 (6.9)	0.89 (0.76 to 1.04)	.14	0.84 (0.73 to 0.97)	.02
Median (IQR) <sup>d</sup>	11.5 (10 to 17)	15 (12 to 19) <sup>e</sup>				
Phenobarbital, No. (%) <sup>f</sup>	10 (17.2)	17 (29.3)	0.45 (0.19 to 1.10)	.08	0.44 (0.18 to 1.09)	.07
Infants needing a dose increase, No. (%) <sup>g</sup>	22 (37.9)	28 (48.3)	0.57 (0.27 to 1.20)	.14	0.51 (0.23 to 1.14)	.10
Weight gain, mean (SD), g/d	8.4 (13.9)	11.2 (14.2)	-2.7 (-7.8 to 2.3)	.30	-3.2 (-8.0 to 1.7)	.20

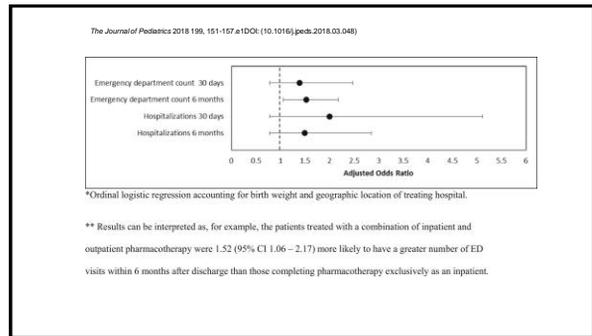
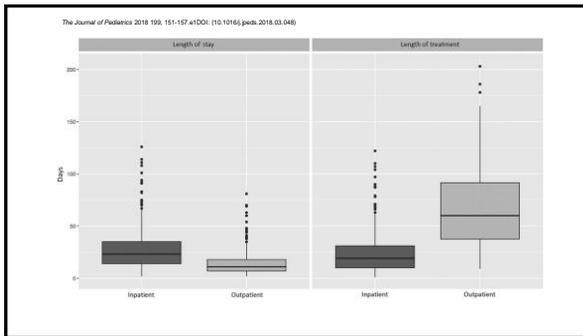
Abbreviations: IQR, interquartile range; LOS, length of hospital stay; LOT, length of drug treatment; NAS, neonatal abstinence syndrome.   
<sup>a</sup> Adjusted for site and type of maternal opioid (methadone, buprenorphine, or opioids for pain).   
<sup>b</sup> Difference in medians statistically significant ( $P = .009$ ).   
<sup>c</sup> Does not include 4 infants whose mothers were treated with opioids for pain because of sparse strata, leading to problems with model estimation.   
<sup>d</sup> Statistics are relative numbers of days for LOS, LOS attributable to NAS, and difference for weight gain.

### Most important limitation.

- Commercially available methadone contained 15% alcohol as a preservative.
- Because alcohol could affect short and longer-term outcomes, the US Food and Drug Administration (FDA) required that a preservative-free methadone solution be prepared using methadone powder (Mallinckrodt Inc).
- The FDA first required development of compounding procedures using Good Clinical Practice guidelines.

Maalouf FI et al. Outpatient Pharmacotherapy for Neonatal Abstinence Syndrome. *J Pediatr* 2018;199:151-157.

- Retrospective cohort study of infants enrolled in the Tennessee Medicaid program used administrative and vital records data from 2009 to 2011.
- Among a cohort of 736 patients with confirmed NAS, 72.3% were treated with pharmacotherapy of which approximately one-half (45.5%) were discharged home on outpatient medications.
- For infants discharged on outpatient pharmacotherapy, initial hospital length of stay was shorter (11 vs 23 days;  $P < .001$ ) and length of therapy was longer (60 vs 19 days; adjusted incidence rate ratio [aIRR] 2.84, 95%CI 2.31-3.52).
- *After adjusting for potential confounders, infants discharged on outpatient pharmacotherapy had a greater number of ED visits within 6 months of discharge (adjusted odds ratio [aOR] 1.52, 95% CI 1.06-2.17) compared with those treated as inpatients alone.*



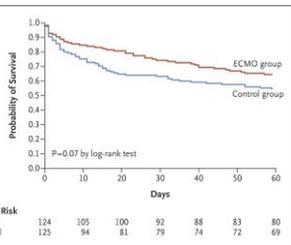
Original Article  
**Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome**

Alain Combes, M.D., Ph.D., David Hajage, M.D., Ph.D., Gilles Capellier, M.D., Ph.D., Alexandre Damouie, M.D., Ph.D., Sylvain Lavoie, M.D., Christophe Guerin, M.D., Daniel Da Silva, M.D., Lara Zefrani, M.D., Ph.D., Patricia Tricot, M.D., Benoit Veber, M.D., Ph.D., Eric Maury, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Yves Cohen, M.D., Ph.D., Christian Richard, M.D., Ph.D., Pierre Kalfon, M.D., Ph.D., Lila Bouadma, M.D., Ph.D., Hossain Mendejou, M.D., Gaëtan Brodeur, M.D., Ph.D., Guillaume Lebraton, M.D., Ph.D., Laurent Brochard, M.D., Ph.D., Niall D. Ferguson, M.D., Eddy Fan, M.D., Ph.D., Arthur S. Slutsky, M.D., Daniel Brodie, M.D., Alain Mercat, M.D., Ph.D., for the EOLIA Trial Group, REVA, and ECMONet

N Engl J Med  
 Volume 378(21):1965-1975  
 May 24, 2018

## Study Overview

- This trial compared extracorporeal membrane oxygenation with non-ECMO ventilator care in patients with severe ARDS.
- There was no significant between-group difference in 60-day mortality.
- Interpretation was made difficult by crossovers from control to ECMO treatment.



## Conclusions

- Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy.



Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns. A Randomized Clinical Trial. JAMA Pediatr. Published online May 14, 2018. doi:10.1001/jamapediatrics.2018.0623

- Among newborns receiving respiratory support, does treating pneumothoraces diagnosed on chest radiography with needle aspiration result in fewer infants having chest drains inserted within 6 hours of diagnosis?
- Treatment options for a symptomatic pneumothorax in newborns include needle aspiration (NA) and chest drain (CD) insertion. There is little consensus as to the preferred treatment, reflecting a lack of evidence from clinical trials.
- RCT conducted from October 7, 2013, to December 21, 2016. The setting was 5 tertiary European neonatal intensive care units. Infants receiving respiratory support (endotracheal ventilation, continuous positive airway pressure, or supplemental oxygen >40%) who had a pneumothorax on CX that clinicians deemed needed treatment were eligible for inclusion.
- Infants were randomly assigned (1:1) to drainage using NA or CD insertion, stratified by center and gestation at birth (<32 vs ≥32 weeks).
- 70 infants, 33 were assigned to NA and 37 to CD insertion. Their median gestational age was 31 (27-38) vs 31 (27-35) weeks, and their median birth weight was 1385 (1110-3365) vs 1690 (1060-2025) g, respectively.
- Fewer infants assigned to NA had a CD inserted within 6 hours (55% [18 of 33] vs 100% [37 of 37]; relative risk, 0.55, 95% CI, 0.40-0.75) and during hospitalization (70% [23 of 33] vs 100% [37 of 37]; relative risk, 0.70, 95% CI, 0.56-0.87).

## Initial Metabolic Profiles Are Associated with 7-Day Survival among Infants Born at 22-25 Weeks of Gestation

Scott P. Oltman, MS, Elizabeth E. Rogers, MD, Rebecca J. Baer, MPH, James G. Anderson, MD, Martina A. Steurer, MD, Matthew S. Pantel, MD, J. Colin Partridge, MD, Larry Rand, MD, Kelli K. Ryckman, PhD, Laura L. Jelliffe-Pawlowski, PhD

The Journal of Pediatrics  
 Volume 198, Pages 194-200.e3 (July 2018)

Use of metabolomics significantly strengthens the association with 7-day survival in infants born extremely premature. Physicians may be able to use metabolic profiles at birth to refine mortality risks and inform postnatal counseling for infants born at <26 weeks of gestation.

### What Parents Want to Know after Preterm Birth?

Jaworski et al. *J Pediatr* 2018;200:58-63; and Bell et al. <https://doi.org/10.1016/j.jpeds.2018.04.025>

- The main message is that many parents of infants born very preterm view their children as having a good personality, being happy, and making developmental progress.
- One-half or more of parents in all groups were concerned about their child's health and development.
- *Most important, there was no correlation between the parents' perception of their child's status and the degree of neurodevelopmental impairment as graded by standard testing.*