

2006 PAS Annual Meeting

As you plan your meeting itinerary, be sure to include these late-breaking abstract presentations, selected for their high-quality and news-breaking research.

Late-Breaker Abstract Presentations

Sunday, April 30

8:00am-10:00am

3153 Late Breakers I:

Clinical Trials in Neonatology

PAS Platform Session ~ 3022-3024, Moscone West

Chairs: Lucky Jain and Robin H. Steinhorn

- 8:00** **Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure.** John P. Kinsella, Gary R. Cutter, William F. Walsh, Dale R. Gerstmann, Carl L. Bose, Claudia Hart, Kris C. Sekar, Richard L. Auten, Vinod K. Bhutani, Jeffrey S. Gerdes, Thomas N. George, W. Michael Southgate, Heather Carnedo, Robert J. Couser, Mark C. Mammel, David C. Hall, Mariann Pappagallo, Smeeta Sardesai, John D. Strain, Monika Baler, Steven H. Abman (Late-Breaker Abstract 1)
- 8:15** **Improved Outcome with Inhaled Nitric Oxide in Preterm Infants Mechanically Ventilated at 7-21 Days of Age.** Roberta A. Ballard, William E. Truog, Richard J. Martin, Philip L. Ballard, Avital Cnaan, Jeffrey D. Merrill, Michelle C. Walsh for the NO CLD Study Group (Late-Breaker Abstract 2)
- 8:30*** **The Natural Course of the Ductus Arteriosus in Very Low Birth Weight Infants.** S.L. Nemerofsky, E. Parravicini, C. Kleinman C, U. Sanocka, R.A. Polin, J.M. Lorenz (Late-Breaker Abstract 3)
- 8:45** **CO2 Inhalation as a New Treatment Modality for Apnea of Prematurity: A Randomized Double Blind Control Trial.** R.E. Alvaro, M. Klailil, S. Al-Saif, A. Al-Matary, M. Qurashi, A. Chiu, J. Minski, J. Manfreda, K Kwiatkowski, D. Cates, H. Rigatto. (Late-Breaker Abstract 4)
- 9:00** **A New Therapeutic Method for Entraining the Suck Central Pattern Generator in the Premature Infant.** Steven M. Barlow, Don S. Finan (Late-Breaker Abstract 5)
- 9:15** **EPIC Reduced Nosocomial Infection And Bronchopulmonary Dysplasia In A Cluster Randomized Controlled Trial of Canadian NICUs.** S.K. Lee, K. Aziz, N. Singhal, A. Ohlsson, J. Langley, R. Baker, B. Stevens, Y.C. McNab, Canadian Neonatal Network EPIC Study Group (Late-Breaker Abstract 6)
- 9:30** **Fluconazole Prophylaxis is Associated with Conjugated Hyperbilirubinemia in Extremely Low Birth Weight Infants.** Zubair H Aghai, Ronald Sutsko, Sushma Kaki, Manjula Mudduluru, Tarek Nakhla, Nicole Kemble, Judy Saslow, Gary Stahl (Late-Breaker Abstract 7)
- 9:45** **Antiretroviral Therapy (ART)-Associated Cardiotoxicity in Uninfected but ART-Exposed Infants Born to HIV-Infected Women: The Prospective NHLBI CHAART-I Study.** S.E. Lipshultz, W.T. Shearer, B. Thompson, K. Rich, I. Cheng, A. Milton, E.J. Orav, R.H. Pignatelli, L.I. Bezold, P. LaRussa, T.J. Starc, J. Glickstein, K. McIntosh, E.R. Cooper, S. O'Brien, S.D. Colan (Late-Breaker Abstract 8)

Monday, May 1

10:15am-12:15pm

4347 Late Breakers II:

Late Breaking Research in Pediatrics

PAS Platform Session ~ 2004, Moscone West

Chairs: Yvonne W. Wu and Paul Young

- 10:15*** **A Prospective, Longitudinal Study of Neurocognitive Deficits and Recovery Rates After Mild Traumatic Brain Injury Versus Isolated Extremity Injury in Children 10-17 Years of Age.** Nicole S. Sroufe, Joshua B. Kay, Bonita M. Singal, Seth A. Warschausky, Ronald F. Maio (Late-Breaker Abstract 9)
- 10:30** **Differences in Children's Development Across Australian Communities.** S. Goldfeld, M. Sayers, F. Oberklaid, S. Brinkman, and S. Silburn (Late-Breaker Abstract 10)
- 10:45** **Bedside Presentations in Outpatient Pediatrics: Visit Length and Parent, Preceptor and Resident Perceptions.** Raymond Baker, Melissa Klein, Zeina Samaan, William Brinkman (Late-Breaker Abstract 11)
- 11:00** **Preliminary Results from a 6-Month Study on the Safety and Efficacy of an Oral Insulin (Oral-lyn™) Administered at Lunch Time in Adolescent and Young Adult Type-1 DM Subjects Maintained on Basal s.c. Glargine Insulin and Pre-breakfast and Pre-dinner s.c. Regular Insulin.** Jaime Guevara-Aguirre, Marco Guevara-Aguirre, Jeannette Saavedra (Late-Breaker Abstract 12)
- 11:15** **Predictors of Prolonged Clinical Symptoms in Children with Acute Otitis Media Not Initially Treated with Antibiotics: An Individual Patient Data Meta-analysis.** Maroeska M. Rovers, Paul Glasziou, Cees L. Appelman, Peter Burke, David P. McCormick, Roger A. Damoiseaux, Nicole le Saux, Paul Little, Arno W. Hoes (Late-Breaker Abstract 13)
- 11:30*** **Decreased Immunogenicity of a Heptavalent Conjugate Pneumococcal Vaccine (7VCPnc) when Administered According to the Current UK Immunisation Schedule.** S.J. Moss, A.C. Fenton, J. Toomey, A. Grainger, R. Borrow, P. Balmer, J. Smith, A.R. Gennery (Late-Breaker Abstract 14)
- 11:45** **Comparison of the Efficacy and Safety of Cold-Adapted Influenza Vaccine, Trivalent with Trivalent Inactivated Influenza Vaccine in Children 6-59 Months of Age.** Robert Belshe, for the Influenza Vaccine Comparison Trial Group. (Late-Breaker Abstract 15)
- 12:00** **A Community Outbreak of Vaccine-Derived Poliovirus Infections, Minnesota, USA, 2005-2006.** Mark R. Schleiss, K. Scott Baker, Nadia Agudu, Paul Orchard, Neil Bratney, Richard Andersen, Paula Ackerman, Kristen Ehresmann, Gary Wax, Claudia Miller, Kathy Harriman, Jane Harper, Jean Rainbow, Ruth Lynfield, Susan Fuller, Elizabeth Cebeliniski, Jim Alexander, Jane Seward, Mark Pallansch, Olen Kew, Steve Oberste (Late-Breaker Abstract 16)

Monday, May 1

5:15pm-6:45pm

4822 Poster Session III: Genetics: Potpourri

PAS Poster Session ~ Level 1, Moscone West

- 83A*** **Balloon Occlusion Catheter-Based Delivery of HDAd into the Nonhuman Primate Liver Results in Stable, High Level Transgene Expression with Minimal Toxicity.** Gary Stapleton, Nicola Brunetti-Pierri, Donna Palmer, Yu Zuo, Arthur Beaudet, Charles Mullins, and Philip Ng (Late-Breaker Abstract 17)

* Indicates First Author is a Trainee (Student, Fellow, House

**Late Breakers I:
Clinical Trials in Neonatology Platform Session**

Sunday, April 30 8:00am-10:00am 3022-3024, Moscone West

1 Presentation Time: 8:00am

Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure

John P. Kinsella, Gary R. Cutter, William F. Walsh, Dale R. Gerstmann, Carl L. Bose, Claudia Hart, Kris C. Sekar, Richard L. Auten, Vinod K. Bhutani, Jeffrey S. Gerdes, Thomas N. George, W. Michael Southgate, Heather Carnedo, Robert J. Couser, Mark C. Mammel, David C. Hall, Mariann Pappagallo, Smeeta Sardesai, John D. Strain, Monika Baler, Steven H. Abman.

BACKGROUND: We conducted a multicenter, randomized, masked trial to determine the safety and efficacy of early, low-dose, prolonged inhaled nitric oxide (iNO) therapy in reducing BPD and death without increasing brain injury in premature newborns with respiratory failure requiring mechanical ventilation in the first 48 hours of life.

METHODS: We randomized 793 premature newborns of gestational age < 34 weeks with respiratory failure, and stratified by birth weight from 500-1250 g within 16 perinatal centers. 398 patients were treated with iNO (5 ppm) and 395 received placebo gas (controls). Treatment with study gas was continued for 21 days or until extubation. Primary outcome variables included the combined efficacy endpoints of death/BPD and safety endpoints of severe intracranial hemorrhage (ICH), periventricular leukomalacia (PVL), and ventriculomegaly. Baseline (pre-treatment) and follow-up cranial ultrasound examinations were performed.

RESULTS: At enrollment, there were no differences in gestational age, birth weight or disease severity between the iNO treatment and control groups. Overall, there was no difference in the incidence of death or BPD between groups, however, iNO therapy reduced the incidence of BPD for infants with birth weight ≥ 1000 g by 50% ($p=0.001$). Low-dose iNO therapy reduced the incidence of PVL ($p=0.048$), as well as the combined endpoints of ICH, PVL and ventriculomegaly ($p=0.032$) for the entire study population. iNO therapy did not increase the incidence of adverse events, including mortality, ICH, PVL, pulmonary hemorrhage, PDA, and others, in any birth weight subgroup.

CONCLUSIONS: We found that low-dose iNO reduced the incidence of BPD in infants with birth weights between 1000-1250 g, and prevented brain injury in premature newborns with respiratory failure.

2 Presentation Time: 8:15am

Improved Outcome with Inhaled Nitric Oxide in Preterm Infants Mechanically Ventilated at 7-21 Days of Age

Roberta A. Ballard, William E. Truog, Richard J. Martin, Philip L. Ballard, Avital Cnaan, Jeffrey D. Merrill, Michelle C. Walsh for the NO CLD Study Group. Dept of Pediatrics, University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia PA, University of Missouri-Kansas City and Children's Mercy Hospitals and Clinics, Kansas City MO, Rainbow Babies and Childrens Hospital, Case Western Reserve University Cleveland, OH.

Chronic lung disease (CLD) of premature infants is associated with prolonged hospitalization as well as abnormal pulmonary and neurodevelopmental outcome. In animal models, inhaled nitric oxide improves both gas exchange and lung structural development, however use of this therapy in infants at risk of CLD is controversial. To test the hypothesis that inhaled nitric oxide treatment of ventilated premature infants would safely increase survival without CLD, we conducted a randomized, stratified, double-blind, placebo-controlled trial at 21 centers with infants ≤ 1250 g birth weight who required ventilatory support at 7-21 days of age. Treated infants received decreasing concentrations of nitric oxide, beginning at 20 ppm, for a minimum exposure of 24 days. Infants receiving nitric oxide ($n=294$) and placebo ($n=288$) were comparable in birth weight (766 g vs 759 g), gestational age (26 weeks vs 26 weeks), age at entry (median 16 days) and other baseline characteristics. The rate of survival without CLD at 36 weeks postmenstrual age was 43.9% in treated infants and 36.8% in the placebo group ($p=0.042$), and there was a similar trend toward benefit for infants of 500-799 g and 800-1250 g. Severity of lung disease, based on hospitalization and requirement for ventilatory support, was less at 36 ($p=0.012$), 40 ($p=0.014$) and 44 ($p=0.033$) weeks. There were no differences between groups with regard to co-morbidities occurring after entry. In post hoc analyses, inhaled nitric oxide improved survival without CLD for infants enrolled at 7-14 days (49.1% vs 27.8%, $p=0.001$), but not for infants enrolled at 15-21 days (40.7% vs 42.8%), and benefit was restricted to infants with less severe lung disease at entry. We conclude that inhaled nitric oxide therapy in the second week of life improves the pulmonary outcome for premature infants at high risk for CLD without apparent short-term adverse effects.

3 Presentation Time: 8:30am Fellow in Training

The Natural Course of the Ductus Arteriosus (DA) in Very Low Birth Weight Infants (VLBW)

S. L. Nemerofsky, E. Parravicini, C. Kleinman, C. U. Sanoeka, R. A. Polin, J. M. Lorenz. Divisions of Neonatology and Pediatric Cardiology, Columbia University, Morgan Stanley Children's Hospital, New York, NY.

Spontaneous closure of the DA has been reported to occur in approximately 50% of VLBW infants. This population is often treated with indomethacin to avoid complications associated with a PDA. However, gentle ventilation strategies frequently employed are associated with fewer complications of respiratory disease. In this clinical setting, the rate of ductal closure and the clinical significance of ductal patency are unknown.

Our objective was to describe the natural course of the DA in VLBW infants managed with the Columbia approach to respiratory care: antenatal steroids, gentle resuscitation and early bubble CPAP via Hudson prongs for infants <33 weeks gestation with respiratory distress or who require positive pressure ventilation in the delivery room. Mechanical ventilation (\pm surfactant) is reserved for infants who require $FiO_2 \geq 0.60-0.80$ or pCO_2 persistently $>60-70$ mmHg with $pH < 7.2$.

This is a prospective observational study of 46 infants <1500g without congenital anomalies. Echocardiograms are performed on day of life 3, weekly for the first month and then bi-monthly until surgical ligation, discharge or death. In our NICU, PDAs are treated only in infants with heart failure, pre-renal failure, increased oxygen requirement on CPAP or who require increased ventilatory support.

The gestational age ranged from 23-31 weeks with a mean of 28 weeks. Birth weight ranged from 544-1450g with a mean of 1047g. Of the 33 (72%) infants who did not require ventilation during the first week of life, the DA closed spontaneously in 45%, 66% and 80%, by day of life 3, 1 week and 2 weeks of life, respectively. Of the 13 (28%) infants requiring ventilation during the 1st week of life, the DA closed spontaneously in 23%, 38% and 50%, by day of life 3, 1 week and 2 weeks of life, respectively. Four infants underwent surgical ligation and 4 received indomethacin. 10% (3) of the CPAP infants and 67% (6) of the ventilated infants had chronic lung disease at 36 weeks post menstrual age.

Most VLBW infants, managed with the Columbia approach to respiratory care, who did not require mechanical ventilation in the first week of life had spontaneous closure of the DA and a very low prevalence of chronic lung disease. Therefore, medical intervention for the PDA may not be indicated in this population.

4 Presentation Time: 8:45am

CO₂ Inhalation as a New Treatment Modality for Apnea of Prematurity: A Randomized Double Blind Control Trial

R. E. Alvaro, M. Klalil, S. Al-Saif, A. Al-Matary, M. Qurashi, A. Chiu, J. Minski, J. Manfreda, K. Kwiatkowski, D. Cates, H. Rigatto. Department of Pediatrics, University of Manitoba, Winnipeg, MB, Canada.

BACKGROUND: Methylxanthines have been considered the treatment of choice in apnea of prematurity, despite its side effects. Because CO₂ (1) is the physiological stimulus to breathe, and (2) seems to reduce apneas in low concentrations (0.5-1.0 %), we thought it could be an effective modality of treatment without significant side effects.

OBJECTIVE: To examine the merits of CO₂ inhalation in the treatment of apnea of prematurity. We hypothesized that inhalation of CO₂ decreases the rate and duration of apnea as effectively as theophylline with fewer side effects.

METHODS: We randomly assigned 79 preterm infants of gestational age between 27 and 32 weeks to receive theophylline (Theo; $n=41$) or CO₂ ($n=39$) [BW 1452 \pm 37 g (Mean \pm SEM); GA 29.9 \pm 0.2 wk; PNA 16 \pm 2 days]. After a control period (24 h), Theo plus nasal prongs at 0.5 l/min room air or placebo plus nasal prongs at 0.5 l/min with CO₂ (3% at the source, about 1% inhaled), were given for 3 days, followed by a recovery period (24 h).

RESULTS: Apnea time (primary endpoint) significantly decreased in the Theo group from 189 \pm 33 s/h (control) to 57 \pm 11 (day 1), 50 \pm 9 (day 2), and 61 \pm 13 (day 3) [$p=0.0001$] and in the CO₂ group from 183 \pm 44 to 101 \pm 26 (day 1), 105 \pm 29 (day 2), and 94 \pm 26 s/h (day 3) [$p=0.03$]. The number of apneas longer than 20 s also decreased significantly in the Theo group from 2.9 \pm 0.4 apneas/day (control) to 1.1 \pm 0.3 (day 1), 0.1 \pm 0.1 (day 2), and 0.4 \pm 0.2 (day 3) [$p=0.0001$] and in the CO₂ group from 3.3 \pm 0.7 to 1.3 \pm 0.4 (day 1), 0.8 \pm 0.3 (day 2), and 1.1 \pm 0.4 (day 3) [$p=0.0003$]. The number of desaturations (<85%) & bradycardias (80 beats/min) decreased significantly in both groups. Episodes of tachypnea (>70 breaths/min), tachycardia (>180 beats/min), emesis, & jitteriness were only increased in the Theo group. No significant differences were observed in the cerebral blood flow between control and the treatment period in any group. Seven infants in the CO₂ group failed to finish the study because of severe apneas; most of these infants required NCPAP after stopping the gas. No infants in the Theo group failed to complete the study.

CONCLUSIONS: Although both treatments were effective in reducing the number and severity of apneas in most infants, theophylline was more effective than CO₂. Some of this higher effectiveness may have been related to the distinct manner in which these agents were administered. While no significant side effects were found in the CO₂ group, infants in the theophylline group showed significantly more episodes of emesis, tachycardia, and jitteriness. These findings suggest that inhalation of low concentration of CO₂ could be a safer alternative to theophylline in the treatment of apnea of prematurity in preterm infants without any residual lung disease.

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Presentation Time: 9:00am

A New Therapeutic Method for Entraining the Suck Central Pattern Generator (CPG) in the Premature Infant

Steven M. Barlow and Don S. Finan, Neuroscience, University of Kansas, Lawrence, KS, and Neuroscience, University of Colorado, Boulder, CO.

BACKGROUND: Feeding competency is a challenging hurdle facing many premature babies with an extensive history of intubation due to respiratory distress syndrome (RDS). These preemies often lack a functional suck or manifest oromotor dyscoordination.

OBJECTIVE: This study, part of an ongoing NIH research trial, was designed to test a neural entrainment technique which provides patterned somatosensory input to the oral sensorium in RDS preemies.

DESIGN/METHODS: Twelve RDS preemies with no functional suck received suck entrainment therapy at 34 wks GA. The synthesized NNS pattern was delivered through a servo-motorized Soothie pacifier which delivered a series of pneumatic bursts (1.8 Hz pulse rate) followed by a 2-second pause period. A total of 34 NNS burst-pause trains were presented before feeding 4x/day over a two-week period. Repeated measures of non-nutritive suck (NNS) were during the 14-day suck entrainment schedule, including two pre-NTrainer baselines and up to 3 subsequent sessions using NEOSUCK RT. Treated RDS babies were compared statistically (GLM ANOVA) to a cohort of untreated RDS preemies (N=35) and healthy PRETERM controls (N=25) on several dependent measures, including NNS Bursts/min, Non-NNS Events/min, NNS Burst Cycles/min, Mean NNS Cycles/burst, and Total Mouthing Events/min.

RESULTS: Somatosensory entrainment of the oral sensorium was highly effective (p<0.001) in facilitating the emergence of suck CPG in RDS preemies who previously had no or severely limited suck. NNS performance dynamics for the RDS preemies surpassed the RDS controls on all dependent measures by more than 200%, and even outperformed the PRETERM controls for all measures. These remarkable effects were maintained during the training trial and led to competent oral feeds and shorter NICU stays.

CONCLUSIONS: The suck CPG can be entrained in preemies with RDS using a salient mechanosensory pattern to the oral sensorium which mimics the NNS.

Supported by: NIH R01 DC03311-04, NIH P30 HD02528, NIH P30 DC005803.

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Presentation Time: 9:15am

EPIC Reduced Nosocomial Infection And Bronchopulmonary Dysplasia In A Cluster Randomized Controlled Trial of Canadian NICUs

S. K. Lee, K. Aziz, N. Singhal, A. Ohlsson, J. Langley, R. Baker, B. Stevens, Y. C. McNab, and Canadian Neonatal Network EPIC Study Group, iCARE & Dept Pediatrics, U Alberta, Edmonton AB; Memorial U, St John's NF; U Calgary, AB; U Toronto, ON; Dalhousie U, Halifax NS; Dept HPEM & Nursing, U Toronto, ON; Dept HCE, UBC, Vancouver BC; Canada.

BACKGROUND: Current continuous quality improvement (CQI) methods employ a somewhat uncritical approach to practice change that may not be evidence-based or appropriate for individual institutions. We developed and tested a new objective Evidence-based Practice Identification and Change (EPIC) method for quality improvement that builds on existing evidence and uses data from individual institutions to target specific practices for change.

OBJECTIVE: To test whether EPIC reduces nosocomial infection (NI) and bronchopulmonary dysplasia (BPD) in NICUs.

METHOD: Using cluster randomization, 6 NICUs each were assigned to reduce NI (Group A) or BPD (Group B). Each group was blinded and acted as control for the other. Two NICUs not participating in the EPIC Study provided an additional control (Group C). We enrolled all infants ≤32 weeks gestation. BPD was defined as oxygen need at 28 days. NI was defined as positive blood and/or cerebrospinal fluid cultures. Baseline data were collected for 1 year to provide pre-intervention incidences of NI and BPD and to guide EPIC practice changes. EPIC training was provided to a multi-disciplinary team at each hospital, and EPIC interventions were implemented using quarterly practice change cycles (with control chart feedback) for 2 years. NICU groups (A and B) shared information within the group but not outside it.

RESULTS: There were 3564, 2813 and 1107 infants in Groups A, B and C respectively. Group A had more (33% vs 20%) outborn infants than Group B (p<0.05); other infant characteristics were similar. Nine months after EPIC interventions started, NI incidence in Group A decreased from 24.1% (baseline) to 12.5% (p<0.05) and the effect was sustained to 24 months; BPD incidence in Group A did not significantly change (from 32.7% to 32.2%). In Group B, BPD incidence decreased from 31.5% (baseline) to 21.7% (p<0.05); while NI incidence gradually decreased from 17.8% (baseline) to 7.1% (p<0.05) over 24 months. In Group C, there was no significant change in the incidence of NI or BPD.

CONCLUSIONS: EPIC is effective at reducing NI and BPD in the NICU. Interventions targeting one outcome may affect other outcomes. EPIC may be more effective and less expensive at improving quality of care than current CQI methods.

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Presentation Time: 9:30am

Fluconazole Prophylaxis is Associated with Conjugated Hyperbilirubinemia in Extremely Low Birth Weight Infants

Zubair H Aghai, Ronald Sutsko, Sushma Kaki, Manjula Mudduluru, Tarek Nakhla, Nicole Kemble, Judy Saslow and Gary Stahl, Pediatrics/Neonatology, Cooper University Hospital-RWJ Medical School, Camden, NJ.

BACKGROUND: Fluconazole is known to cause hepatotoxicity. Prophylactic fluconazole therapy in extremely low birth weight (ELBW) may be associated with conjugated hyperbilirubinemia (CH).

OBJECTIVES: To evaluate the effect of fluconazole prophylaxis on CH in ELBW infants. MATERIAL AND METHOD: ELBW infants (BW ≤ 1000 grams) born during pre-prophylaxis era (PPE, January 1998-February 2002) were compared with prophylaxis era (PE, March 2002-September 2005). ELBW infants born during PE received fluconazole prophylaxis for 6 weeks, as long as they had IV access. The two groups were compared for baseline demographics, risk factors for direct hyperbilirubinemia and the rate of CH. Infants with BW 1001-1500 G (BW 1001-1500) did not receive fluconazole prophylaxis in two eras. Risk factors and incidence of CH were also compared in BW 1001-1500 infants born in two eras.

RESULTS: Demographics and risk factors between groups are shown in table. During PPE, 22/137 (16%) ELBW infants developed CH, compared to 63/140 (45%) during PE (P<0.001). There was no significant difference in incidence of CH in BW 1001-1500.

CONCLUSION: Fluconazole prophylaxis significantly reduced fungal infections but was associated with an increased incidence of conjugated hyperbilirubinemia in ELBW infants.

	BW ≤ 1000 (n=277)			BW 1001-1500 (n=337)		
	PPE (n =137)	PE (n=140)	P	PPE (n =172)	PE (n=165)	P
BW (G)	681±169	749±133	0.67	1251±146	1249±136	0.9
GA (W)	24.9±2.29	25.7±1.8	0.27	29.6±2.0	29.6±2.1	0.9
Sex (M:F)	78:59	80:60	0.93	79:93	86:76	0.23
Duration of TPN	22.2±19.4	28.5±20.8	0.10	18.0±23	14.4±12.7	0.1
Bacterial infection	69	65	0.9	57	42	0.15
Invasive candidiasis	9 (6.7%)	0 (0%)	*0.006	1	1	NS
Incidence of CH	22(16%)	63(45%)	<0.001	17 (9.8%)	21(12.7%)	0.39
Duration of CH (median, range)	21(1-135)	47(7-102)	<0.001	14 (1-219)	32 (1-109)	0.44

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Presentation Time: 9:45am

Antiretroviral Therapy (ART)-Associated Cardiotoxicity in Uninfected but ART-Exposed Infants Born to HIV-Infected Women: The Prospective NHLBI CHAART-I Study

S. E. Lipshultz, W. T. Shearer, B. Thompson, K. Rich, I. Cheng, A. Milton I, E. J. Orav, R. H. Pignatelli, L. I. Bezold, P. LaRussa, T. J. Starc, J. Glickstein, K. McIntosh, E. R. Cooper, S. O'Brien, S. D. Colan, University of Miami, Miami, FL; Baylor College of Medicine and Texas Children's Hospital, Houston, TX; Clinical Trials and Survey Corporation, Baltimore, MD; University of Illinois, Chicago, IL; Brigham and Women's Hospital, Boston, MA; Children's Hospital, Boston, MA; Columbia University, New York, NY; Boston Medical Center, Boston, MA.

BACKGROUND: Treating pregnant HIV+ women with antiretroviral therapy (ART) has dramatically reduced maternal to child HIV transmission. However, long-term cardiotoxicity following in utero exposure to ART is a concern.

METHODS: To determine the cardiovascular effects of ART exposure on HIV- infants born to HIV+ mothers, echocardiograms at birth, 6 mo and 12 mo on infants enrolled in CHAART were compared to serial echos of HIV- infants in the P2C2 study, in which few received ART. All CHAART infants (N=91) were exposed to ART and 89% were exposed to highly active ART (HAART). No P2C2 infants (N=216) were exposed to ART or HAART. LV mass and septal wall thickness were normalized to BSA.

RESULTS: Mean LV mass ranged from 0.37 to 1.53 sd below normal in both cohorts, but the CHAART measurements for females progressively declined from the P2C2 measurements; at birth there was a 0.38 sd difference (p=0.03), and the difference increased to 0.98 sd and 0.85 sd at 6 mo and 12 mo respectively (p<0.001). The CHAART measurements for males were 0.49 sd and 0.35 sd lower than P2C2 measurements at 6 mo (p=0.01) and 12 mo (p=0.04). Septal wall thickness was slightly elevated in the P2C2 group but CHAART measurements were constantly lower than the P2C2 measurements by 1.2 sd at all ages (p<.001). LV afterload decreased slightly over time in the P2C2 group. The CHAART LV afterload measurements were 0.51 sd lower than the P2C2 measurements at birth (p=0.03) but moved in a positive direction until they were 0.48 sd higher than the P2C2 measurements by 12 mo (p=0.02).

CONCLUSION: ART exposure during fetal life is associated with progressive reductions in LV mass and septal wall thickness, and increases in LV afterload. We speculate that ART exposure results in reduced myocardial growth, increasing risk for higher LV afterload and impaired LV function. Long-term cardiac outcome studies are needed.

Late Breakers II: Late Breaking Research in Pediatrics Platform Session

Monday, May 1 10:15am–12:15am 2004, Moscone West

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Presentation Time: 10:15am

Fellow in Training

A Prospective, Longitudinal Study of Neurocognitive Deficits and Recovery Rates After Mild Traumatic Brain Injury Versus Isolated Extremity Injury in Children 10–17 Years of Age

Nicole S. Sroufe, Joshua B. Kay, Bonita M. Singal, Seth A. Warschausky, and Ronald F. Maio. Dept of Emergency Medicine, Dept of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI.

OBJECTIVES: The purpose of this study is to determine the nature and rate of recovery of neurocognitive deficits resulting from mild traumatic brain injury (MTBI) in children.

DESIGN/METHODS: Prospective, longitudinal, observational study using a convenience sample from a tertiary care pediatric emergency department (ED) of a Level 1 Trauma Center. Period: November 2004–February 2006. Subjects: Children ages 10–17 years treated in the ED and discharged. MTBI group: patients with blunt head trauma, GCS 13–15, no intracranial abnormalities, and any combination of: loss of consciousness \leq 30 minutes, post-traumatic amnesia \leq 24 hours, altered mental status, or focal neurological deficits. Control group: patients with isolated extremity injuries. Measures: Symbol Digit Modalities Test (SDMT), a measure of cognitive processing speed; and a 12 item Post Concussion Symptom Questionnaire. Assessments were completed in person at baseline and at 1 and 4–5 weeks post injury. Analysis: Fisher's exact tests and t-tests, repeated measures mixed models with random intercept, and Wilcoxon rank sum tests, with Bonferroni adjustment for multiple comparisons.

RESULTS: This analysis includes 29 MTBI patients and 45 controls. There were no differences between groups with regard to prior head injury or prior loss of consciousness; ADHD was more prevalent in the control group ($p=0.0128$). The recovery trajectory for the SDMT was not different between groups ($p=0.6078$), but there was a statistically significant difference within groups over time ($p<0.0001$). In both groups, a significant difference exists between time 0 and 1; scores peaked at 1 week and leveled off. Patients with MTBI had more post-concussive symptoms than injured controls at all time points ($p<0.009$); they returned to pre-injury status within 4–5 weeks.

CONCLUSIONS: Adolescents with MTBI experience significant neurocognitive changes that, on average, resolve within 5 weeks of injury. However, patients with extremity injuries also demonstrate neurocognitive deficits that recover over time. This suggests that some deficits observed after MTBI may not be due, exclusively, to brain injury and may occur following other types of trauma.

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Presentation Time: 10:30am

Differences in Children's Development Across Australian Communities

S. Goldfeld, M. Sayers, F. Oberklaid, S. Brinkman, and S. Silburn. Centre for Community Child Health, Melbourne, Victoria, Australia; North Metropolitan Area Health Service, Perth, West Australia, Australia; Telethon Institute for Child Health Research, Perth, West Australia, Australia.

BACKGROUND: There is increasing recognition that local community involvement and accountability are important factors in improving outcomes for young children. The Australian Early Development Index (AEDI) aims to measure and compare the health and development of populations of children across Australia to help communities assess how well they are doing in supporting young children and their families.

DESIGN/METHODS: The AEDI, originally developed in Canada and modified slightly for use in Australia, is a population measure of development based on a checklist completed by children's teachers during the first year of formal schooling. It consists of over 100 questions measuring five developmental domains: language and cognitive skills; emotional maturity; physical health and well-being; communication skills and general knowledge; and, social competence. Data on children in their first year of school are aggregated, analysed and reported for each suburb or postcode across each domain.

RESULTS: In 2004 and 2005 the AEDI was completed by 1,037 teachers for 18,619 children in 28 communities across Australia. The average age of the children was 6 years (SD 0.46). In the overall national sample there were 22.7% of children with one or more developmental vulnerabilities and 10.9% with two or more. Demographic markers such as socio-economic status, ethnic background and indigenous status were all powerful predictors of developmental vulnerability across each of the AEDI domains. However, these markers do not fully explain the observed variability between and within the participating communities. The proportion of children identified as developmentally vulnerable across each of the AEDI domains was observed to vary significantly between communities and was also evident within communities (i.e. between localities and suburbs within communities).

CONCLUSIONS: This is the largest single database of children's development in Australia. In this population significant proportions of children are developmentally at risk; however within communities the developmental variability suggests local risk and protective factors play an important role in making a difference to outcomes for children.

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Presentation Time: 10:45am

Bedside Presentations in Outpatient Pediatrics: Visit Length and Parent, Preceptor and Resident Perceptions

Raymond Baker, Melissa Klein, Zeina Samaan, and William Brinkman. Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

BACKGROUND: Teaching in the continuity setting requires teaching curriculum content efficiently and directly observing resident performance. Nationally, family-centered care to strengthen the physician-family trust has become a priority. Moving the teaching encounter to the bedside and away from the conference area is one method which may accomplish these educational goals and preserve family-centered care. In the adult literature, bedside presentations have been shown to be favored by patients and to positively impact teaching and learning.

OBJECTIVE: To compare family, preceptor (PRE), and resident (RES) perceptions, and length of visit, for bedside presentations (BP) versus conference area presentations (CAP) in an outpatient pediatric primary care setting.

DESIGN/METHODS: An 8-wk crossover study design was used in which PRE and first-year pediatric RES alternated weekly the location of patient presentations between the exam room and the conference area. After the visit, a research assistant surveyed parents and recorded the time elapsed since arrival at the clinic. At the end of the study, RES and PRE were surveyed on their experiences with both BP and CAP. Differences in ratings based on location of presentation were calculated. Data were analyzed using Chi square, signed-ranks, and t-tests as appropriate.

RESULTS: 348 RES encounters were studied (151 BP v. 189 CAP) involving 15 first yr RES and 15 PRE. Visit length was comparable (BP mean 1.6 hrs. v. CAP 1.58, $P=0.53$). Parent satisfaction was high in both locations. PRE favored BP for adding opportunities to evaluate RES competencies ($P=0.008$), provide legitimate feedback ($P=0.03$), and role-model ($P=0.008$). PRE felt that BP decreased RES comfort level when discussing sensitive topics ($P=0.02$). RES were less comfortable with BP for discussing sensitive topics ($P=0.03$), and felt more embarrassed when they didn't know the answer to a PRE question ($P=0.03$). RES reported that BP presentations permitted preceptors to demonstrate more physical exam skills ($P=0.03$) and to observe interactions more to provide feedback ($P=0.008$).

CONCLUSIONS: BP require the same amount of time and result in equally high parent satisfaction as CAP. Although RES are less comfortable with BP, PRE are better able to observe, evaluate, and give feedback on resident skills and to role model and teach using a hands-on approach.

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Presentation Time: 11:00am

Preliminary Results from a 6-Month Study on the Safety and Efficacy of an Oral Insulin (Oral-lyn™) Administered at Lunch Time in Adolescent and Young Adult Type-1 DM Subjects Maintained on Basal s.c. Glargine Insulin and Pre-breakfast and Pre-dinner s.c. Regular Insulin

Jaime Guevara-Aguirre, Marco Guevara-Aguirre, and Jeannette Saavedra. Institute of Endocrinology IEMYR, Quito, Ecuador.

The stabilization phase of this study is being reported elsewhere in this meeting (two additional subjects were included after this initial report). Participating subjects in this 6-month Phase are 24 adolescents (12M; 12F) and 5 young adults (2M; 3F) referred to us in various degrees of metabolic control as reflected by altered baseline measurements of glucose 236.6 (116.6) mg/dL; fructosamine 472.6 (126.6) μ mol/L; and glycosylated hemoglobin (HbA1c) 9.8 (2.3) g/dL. Baseline demographics of the 24 adolescents are: Age 14.7y (2.1); Bone age 14.1 (2.2); CA/BA 1.0 (0.1); Height 153.8cm (9.4); Weight 51.0kg (10.2); BMI 21.7 (3.2); Duration of DM 6.7 (2.8). Baseline demographics of the 5 young adults are: Age 20.6y (2.2); Bone age (BA) 18.8 (0.4); CA/BA 1.1 (0.1); Height 161.1cm (12.8); Weight 62.5kg (9.3); BMI 23.0 (1.8); Duration of DM 7.0 (1.7). Mean age for the entire group is 15.7y (3.0); BA 14.9 (2.7); CA/BA 1.1 (0.1); Duration of the DM is 6.8 (2.6). After stabilization with basal s.c. glargine insulin and 3 pre-prandial s.c. regular insulin injections, standard therapy continued for 4 weeks for comparison. Immediately thereafter, split doses of Oral-lyn™ immediately before and after lunch replaced lunch-time injection of regular insulin. Patient-collected glucose values, fructosamine and HbA1c were compared weekly (3–4 weeks per each treatment). Values are reported at the end of each phase.

PHASE	FRUCTOSAMINE		HbA1C		GLUCOSE (BASAL)	
	MEAN	SD	MEAN	SD	MEAN	SD
BASELINE	476.89	130.22	9.9	2.38	236.6*	116.5
REGULAR INSULIN	368.2	91	8.4	1.6	140.4	35.5
ORAL-LYN	379.1	133	8.5	2.1	143.3	39.9
COMPARED TO BASELINE	<.0001		<.0001		<.0005	
10-WEEK DATA	377.9	98	7.9	1.6		

(*Glucose values at baseline were determined by laboratory; other glucose values were determined by glucometer)

After comparison, a 6-month Phase of Oral-lyn™ treatment at lunch time was initiated. Fructosamine and HbA1c results between the 8th and 10th week of treatment demonstrated that fructosamine and HbA1c levels maintain the a trend towards normalization.

In summary, successful replacement of regular s.c. insulin for Oral-lyn™ during the initial 10 weeks of this 6-month trial was achieved as demonstrated by patient-collected glucose levels, fructosamine and HbA1c measurements.

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Presentation Time: 11:15am

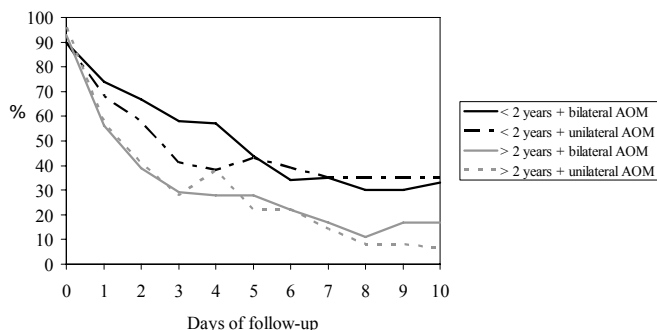
Predictors of Prolonged Clinical Symptoms in Children with Acute Otitis Media Not Initially Treated with Antibiotics: An Individual Patient Data Meta-analysis
 Maroeska M. Rovers, Paul Glasziou, Cees L. Appelman, Peter Burke, David P. McCormick, Roger A. Damoiseaux, Nicole le Saux, Paul Little, Arno W. Hoos. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Netherlands; Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Netherlands; Department of Otolaryngology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Netherlands; University of Oxford, Department of Primary Health Care, Institute of Health Sciences, Oxford, UK; Primary Medical Care, Community Clinical Sciences Division, Southampton University, Aldermoor Health Centre, Southampton, UK; Department of Pediatrics, University of Texas Medical Branch, Galveston, TX; Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada.

BACKGROUND: Acute otitis media (AOM) is one of the most common childhood infections, the leading cause of doctors' visits, and the most frequent reason children take antibiotics or undergo surgery. The high incidence and high rate of spontaneous recovery from AOM suggest that it is a natural phenomenon, inevitable like a common cold, and part of the gradual maturation of the child's anatomy and immune system. However, untreated AOM can occasionally lead to suppurative complications. Currently there are no tools to discriminate between children with mild, self-limiting episodes of AOM and those at risk of a prolonged course.

OBJECTIVE: To determine the independent predictors of a prolonged course in children with AOM not initially treated with antibiotics.

METHODS: In an individual patient data meta-analysis with the control groups of 6 randomised controlled trials (n=824 children with acute otitis media, aged 6 months to 12 years), we determined the predictors of poor short term outcome in children with AOM. The primary outcome was a prolonged course of AOM, which was defined as fever and/or pain at 3-7 days.

RESULTS: Of the 824 included children, 303 (37%) had pain and/or fever at 3-7 days. Independent predictors for fever and/or pain at 3-7 days were: age less than 2 years (OR 2.1; 95% CI 1.5-2.9), and bilateral AOM (OR 1.7; 95% CI 1.2-2.4). The prognostic model showed a good fit (goodness-of-fit test p=0.93), and the AUC was 0.63 (95% CI 0.59-0.68). Figure 1 shows the proportion of children experiencing fever and/or pain in the subgroups of the predicting variables during the follow-up period. The absolute risks of pain and/or fever at 3-7 days was highest in children aged less than 2 years with bilateral AOM, i.e. 55% (95% CI 47-63) (20% of all children). The risk in children aged 2 years or older with unilateral AOM was 25% (95% CI 20-30) (47% of all children). The difference regarding the absolute risks of pain and/or fever at 3-7 days was smaller when only age was studied, i.e., 47% (95% CI 43-51) in children aged less than 2 years and 31% (95% CI 25-37) in those aged 2 years or older.



CONCLUSIONS: The risk of a prolonged course was two times higher in children aged less than 2 years with bilateral AOM than in children aged 2 years or older with unilateral AOM. Clinicians can use these features to advise parents and to follow these children more actively.

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Presentation Time: 11:30am

Fellow in Training

Decreased Immunogenicity of a Heptavalent Conjugate Pneumococcal Vaccine (7VCPnc) when Administered According to the Current UK Immunisation Schedule

S. J. Moss, A. C. Fenton, J. Toomey, A. Grainger, R. Borrow, P. Balmer, J. Smith, and A. R. Gennery. Newcastle Neonatal Service, RVI, Newcastle Upon Tyne, Clinical Medical Sciences, University of Newcastle Upon Tyne, PHLS Meningococcal Reference Unit, Manchester.

BACKGROUND: 7VCPnc has been shown to be immunogenic and efficacious when administered in a 4 dose schedule at 2, 4, 6 and 12 months of age. The immunogenicity of 7VCPnc at 2, 3 and 4 months of age has been studied, but not when administered with the other vaccines currently in the UK immunisation schedule, particularly the meningococcal group C conjugate vaccine.

METHODS: 54 healthy term infants were immunised with 7VCPnc (Prevenar, Wyeth) Meningococcus C conjugate vaccine (Meningitec, Wyeth) and combined diphtheria, tetanus, polio, 5-component acellular pertussis, and HiB conjugate vaccine (Pediacef, sanofi Pasteur) in separate limbs. IgG against the 7 pneumococcal serotypes were measured by ELISA at the time of the first immunisation and 4 weeks after the 3rd immunisation. Protection was measured as post immunization levels of specific IgG \geq 0.35 μ g/ml and higher than pre-immunisation levels.

RESULTS: Of 38 infants analysed, most produced putative protective IgG levels for serotypes 4 [30/32], 18C [37/38], 19F [26/26], 9V [32/35], 14 [29/35] and 23F [29/34], less than half did so with type 6B [16/36]. However, a proportion of these infants failed to demonstrate a 4 fold increase in titres from pre-immunisation levels (type 4 [1/30], type 6B [2/16], type 9V[2/32] type 14[4/29], type 18C[6/37], and type 19F[1/26] and type 23F[3/29]).

Of the 24 infants that were tested against all 7 serotypes only 10 had putatively protective levels to all serotypes with 9 having these levels against 6 serotypes and 4 against 4 serotypes.

CONCLUSIONS: These results suggest that the majority of infants in our cohort are not adequately protected against invasive pneumococcal disease following a primary course of 7VCPnc when administered according to the current UK immunisation schedule. We would therefore reiterate the need for the recommended booster dose.

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Presentation Time: 11:45am

Comparison of the Efficacy and Safety of Cold-Adapted Influenza Vaccine, Trivalent (CAIV-T) with Trivalent Inactivated Influenza Vaccine (TIV) in Children 6-59 Months of Age

Robert Belshe, for the Influenza Vaccine Comparison Trial Group. St. Louis University Health Sciences Center, St. Louis, MO.

BACKGROUND: Influenza vaccination is recommended for all children 6-59 months of age. Reported efficacy of TIV is modest in young children. CAIV-T is an investigational live attenuated intranasal influenza vaccine.

OBJECTIVE: To evaluate the efficacy and safety of CAIV-T compared with TIV in preventing culture-confirmed influenza in children 6-59 months of age.

METHODS: Eligible children were randomized (1:1) to receive 1 dose (if previously vaccinated) or 2 doses 35 \pm 7 days apart (if previously unvaccinated) of CAIV-T or TIV before the 2004-2005 influenza season.

RESULTS: 7836 children (3893 CAIV-T; 3943 TIV) were included in the per protocol efficacy analysis. The incidence of culture-confirmed influenza illness was 55% lower ($P<0.001$) in the CAIV-T compared with the TIV group. All H1N1 and about half of B infections were caused by viruses antigenically matched to vaccine; all H3N2 infections were caused by non-vaccine-like strains. CAIV-T was superior to TIV in preventing culture-confirmed H1N1 influenza (89% reduction, $P<0.001$); in addition, there were 28% fewer cases of culture-confirmed matched influenza B in the CAIV-T group (P =not significant). CAIV-T was superior to TIV in preventing influenza caused by non-vaccine-like H3N2 virus (79% reduction, $P<0.001$). In children 6-23 months of age, greater relative efficacy for CAIV-T vs TIV was observed against all strains (56% reduction, $P<0.001$) and all non-vaccine-like strains (64% reduction, $P<0.001$). The overall incidence of adverse events and serious adverse events was similar in both groups except for a higher incidence of runny nose/nasal congestion in CAIV-T recipients (2.5%-5.6% increase) and a higher incidence of injection site reactions in TIV recipients (3.6%-7.6% increase). There were no significant differences through the whole study period for all reported wheezing or medically significant wheezing (MSW). Previously unvaccinated children 6-23 months had a small but statistically significant increase in MSW at 42 days post dose 1 but not thereafter.

CONCLUSIONS: CAIV-T was significantly more effective than TIV in preventing culture-confirmed influenza illness caused either by strains antigenically similar to those in the vaccine or non-vaccine-like strains in children 6-59 months of age.

Funding Source: This research was supported by MedImmune, Inc.

Off-label Disclaimer: The information concerns a use that has not been approved by the US Food and Drug Administration.

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Presentation Time: 12:00pm

A Community Outbreak of Vaccine-Derived Poliovirus Infections, Minnesota, USA, 2005–2006

Mark R. Schleiss, K. Scott Baker, Nadia Agudu, Paul Orchard, Neil Bratney, Richard Andersen, Paula Ackerman, Kristen Ehresmann, Gary Wax, Claudia Miller, Kathy Harriman, Jane Harper, Jean Rainbow, Ruth Lynfield, Susan Fuller, Elizabeth Ceblinski, Jim Alexander, Jane Seward, Mark Pallansch, Olen Kew, and Steve Oberste. University of Minnesota Children's Hospital, Minneapolis, MN; Minneapolis Children's Hospital; Minnesota Department of Health, St. Paul, MN; and Centers for Disease Control (CDC) and Prevention, Atlanta GA.

We describe a case of vaccine-derived poliovirus infection in an infant with severe combined immune deficiency (SCID) and an associated community outbreak of infection identified by epidemiologic investigation. The infant, a Minnesota native living in a largely unimmunized Amish community, presented with recurrent infections over the first six months of life, including non-healing ulcers, pneumonia, and gastroenteritis. An immunological evaluation revealed low immunoglobulin levels, significantly low T and absent B cell counts, and low numbers of NK cells, confirming the diagnosis of SCID. Additional workup revealed the diagnosis of Omenn's syndrome, with a point mutation (K991E) in the RAG-1 gene. Following referral to our institution for bone marrow transplantation (BMT), an evaluation for diarrhea resulted in identification of an enterovirus from a stool culture. This isolate was identified at the Minnesota Department of Health (MDH) as poliovirus type 1 associated with oral poliovirus vaccine. The infant had received no prior immunizations. Sequence analysis of the VP1 gene of the patient's isolate at the CDC identified the virus as a Sabin type 1 variant, 2.1% divergent from the vaccine strain. The child was not paralyzed. Sequence analysis also suggested that the vaccine-derived virus had originated from another chronically infected, immunodeficient individual (immunodeficiency-associated vaccine-derived polio virus; iVDPV). Sequencing data indicated that the source vaccination was administered approximately 16 months earlier, suggesting that virus had circulated in the community prior to acquisition by the index case. Epidemiological investigation found no source for the virus, and no paralytic disease, in the Amish community in which the child lived. Virological investigation demonstrated that the 3 unvaccinated siblings of the index case were anti-PV1 positive. Four additional healthy children from 2 other Amish families were excreting poliovirus in their stool. The index case remained hospitalized; there were no cases of transmission to health care providers or other patients. Weekly infusions of polio-specific immunoglobulin therapy, as well as oral IgG, had no impact on viral shedding. After 10 weeks of hospitalization, the patient underwent an unrelated-donor BMT. Successful engraftment was noted beginning the week of 2-12-06. Remarkably, bone marrow engraftment resulted in viral clearance. This outbreak demonstrates that iVDPVs can circulate in under-vaccinated communities. It also illustrates the difficulties associated with chronic enterovirus infections in immunocompromised patients, as well as the successful therapeutic utilization of BMT in this setting.

Poster Session III: Genetics: Potpourri

Monday, May 1

5:15pm–6:45pm

Level 1, Moscone West

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Presentation Board: 83A

Fellow in Training

Balloon Occlusion Catheter-Based Delivery of HDAd into the Nonhuman Primate Liver Results in Stable, High Level Transgene Expression with Minimal Toxicity
Gary Stapleton, Nicola Brunetti-Pierri, Donna Palmer, Yu Zuo, Arthur Beaudet, Charles Mullins, and Philip Ng. Departments of Molecular and Human Genetics and Pediatric Cardiology, Baylor College of Medicine, Houston, TX.

Helper-dependent adenoviral vectors (HDAd)s hold tremendous potential for liver-directed gene therapy as they can mediate long-term transgene expression without chronic toxicity. However, due to a nonlinear dose-response, high doses are required to achieve hepatic transduction resulting in dose-dependent acute toxicity. To overcome this important obstacle, we developed a minimally invasive method to preferentially deliver low dose HDAd into the liver of 30 kg baboons to achieve efficient hepatic transduction. Briefly, a single balloon occlusion catheter was percutaneously positioned in the inferior vena cava of baboon 1 to occlude hepatic venous outflow. 1×10^{11} vp/kg of a HDAd expressing the baboon α -fetoprotein (bAFP) marker was injected directly into the occluded liver via a percutaneously placed hepatic artery (HA) catheter and left to dwell in the liver for 15 min before balloon deflation. As controls, 1×10^{11} vp/kg was administered to baboon 2 by peripheral intravenous injection and baboon 3 by HA injection without balloon occlusion. All procedures were well tolerated, and all three animals returned to their normal pre-injection states with no clinical manifestations of toxicity. Mild transaminitis was seen in all animals, peaking at 24 to 48 h post-vector but returning towards baseline the next day: For ALT, a 2.3, 1.1, and 1.4-fold increase over baseline were observed for baboons 1, 2 and 3, respectively. For AST, a 4.8, 1.6 and 2.8-fold increase were seen for baboons 1, 2 and 3, respectively. Importantly, serum bAFP levels increased 425-fold over baseline for baboon 1 (from 4.5ng/ml at baseline to 1914ng/ml), while only a modest increase of 12-fold and 5.6-fold were observed for baboon 2 (from 9ng/ml to 109ng/ml) and 3 (from 18ng/ml to 103ng/ml), respectively. To date, bAFP levels have been sustained (≥ 56 days). These results suggest the therapeutic index of HDAd can be significantly improved by delivering the vector preferentially into the liver using a minimally invasive balloon occlusion catheter technique and may be a first step towards clinical application of HDAd for liver-directed gene therapy.

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