Do contextual factors moderate the effect of non-pharmacological pain relieving interventions in preterm infants? An observational-explorative study.

Gila Sellam, MNS, RN; Sandra Engberg, Prof., PhD, CRNP, FAAN\(^1\&2\); Eva Lucia Cignacco, PhD, RM\(^3\)

\(^1\)Institute of Nursing Science, University of Basel, Switzerland; \(^2\)Division of Neonatology, Children’s Hospital, University Hospital Bern, Switzerland; \(^3\)School of Nursing, University of Pittsburgh, Pennsylvania, USA

**Background**

- Enormous advances have been made in pain assessment of preterm infants over the past quarter century by developing valid tools for the evaluation of a pain status, however the challenges remain as assessors must rely on behavioral and physiological non-verbal cues of pain in this population.
- While there is evidence indicating that medical and demographic contextual factors (cFs) impact pain responses in preterm neonates, less is known about their impact on the effectiveness of non-pharmacological pain relieving interventions.

**Objective of the study**

To explore the effect of cFs on the impact of non-pharmacological interventions on pain during repeated routine heel stick procedures.

**Methods**

- An observational study as part of a randomized controlled trial examining pain reactivity to non-pharmacological interventions across repeated heel-sticks in preterms (see Cignacco et al., 2011).
- Seventy-one premature infants, 24-32 weeks of gestation, were randomized to 3 groups: sucrose facilitated tucking, or a combination of both.
- Five heelsticks across the first 14 days of life were videotaped. Pain response was rated with the “Bernese Pain Scale for Neonates” (BPSN) by 4 raters blinded to three phases (baseline, heel-stick, and recovery) of heel-stick.
- Demographic and medical cFs were extracted from medical charts.
- Mixed regression models were performed controlling for the intervention group and heelstick phase.

**Results**

- Gestational age (GA) at birth and post-natal age (PNA) had no significant effect on behavioral and physiological scores, but when combining them in the regression model PNA was negatively related to behavioral (p=0.005) and positively associated with physiological (p=0.012) pain scores, while GA at birth (p=0.012) was positively related to behavioral scores and negatively related to physiological scores (p=0.01).
- Number of painful procedures were negatively related to behavioral (p=0.02) pain scores, but positively associated with physiological scores (p=0.04).
- Gender (p=0.001) and ventilation at the time of heel-stick (p=0.01) were also negatively related to physiological scores.

**Table 1: Pain scores for all raters across all heelsticks measured by the BPSN**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std.Error</th>
<th>df</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.242</td>
<td>0.377</td>
<td>217</td>
<td>0.778</td>
<td>0.44</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-1.047</td>
<td>0.167</td>
<td>608</td>
<td>414</td>
<td>-9.261</td>
</tr>
<tr>
<td>2</td>
<td>0.982</td>
<td>0.167</td>
<td>608</td>
<td>414</td>
<td>5.872</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NPIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.134</td>
<td>0.178</td>
<td>294</td>
<td>149</td>
<td>0.873</td>
</tr>
<tr>
<td>2</td>
<td>0.231</td>
<td>0.176</td>
<td>319</td>
<td>276</td>
<td>1.301</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>0.231</td>
<td>0.999</td>
<td>63.1</td>
<td>3.266</td>
<td>2.126</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.002</td>
<td>0.153</td>
<td>6.034</td>
<td>0.043</td>
<td>0.056</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>0.096</td>
<td>0.082</td>
<td>0.786</td>
<td>0.034</td>
<td>0.659</td>
</tr>
<tr>
<td>Cardiovascular&amp; 0.150</td>
<td>0.198</td>
<td>0.796</td>
<td>0.009</td>
<td>0.843</td>
<td>0.328</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>0.003</td>
<td>0.014</td>
<td>0.390</td>
<td>0.034</td>
<td>0.569</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.184</td>
<td>0.198</td>
<td>30.6</td>
<td>0.094</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>0.121</td>
<td>0.123</td>
<td>71.6</td>
<td>320</td>
<td>0.983</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of HS procedure</td>
<td>0.009</td>
<td>0.131</td>
<td>0.577</td>
<td>0.706</td>
<td>0.48</td>
</tr>
<tr>
<td>Number of painful procedures</td>
<td>0.001</td>
<td>0.006</td>
<td>232.577</td>
<td>2.119</td>
<td>0.035*</td>
</tr>
</tbody>
</table>

No significance level set at 0.05*.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std.Error</th>
<th>df</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interception</td>
<td>0.242</td>
<td>0.377</td>
<td>217</td>
<td>0.778</td>
<td>0.44</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-1.047</td>
<td>0.167</td>
<td>608</td>
<td>414</td>
<td>-9.261</td>
</tr>
<tr>
<td>2</td>
<td>0.982</td>
<td>0.167</td>
<td>608</td>
<td>414</td>
<td>5.872</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NPIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.134</td>
<td>0.178</td>
<td>294</td>
<td>149</td>
<td>0.873</td>
</tr>
<tr>
<td>2</td>
<td>0.231</td>
<td>0.176</td>
<td>319</td>
<td>276</td>
<td>1.301</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>0.231</td>
<td>0.999</td>
<td>63.1</td>
<td>3.266</td>
<td>2.126</td>
</tr>
</tbody>
</table>

**Conclusions**

- These findings indicate that some contextual factors, mainly number of painful procedures and PNA, are associated with pain response in preterm infants treated with non-pharmacological interventions.
- However, the effects were not consistent for behavioral and physiological scores.

**References**

Comparative effectiveness of non-pharmacological pain relieving interventions in preterm infants. 
A pilot randomized trial.

Eva L Cignacco PhD, MSN, RM1; Gila Sellam MSN, RN1; Lillian Stoffel, BSN2, RN; Roland Gerull MD2; Mathias Nelle, MD2; 
K.J.S Anand Prof., MBBS, Dr.Phil3; Sandra Engberg Prof., PhD, CRNP, FAAN 1&4.
1Institute of Nursing Science, University of Basel, Switzerland; 2 Division of Neonatology, Children’s Hospital, University Hospital Bern, Switzerland; 3 Pediatric Critical Care Medicine, Le Bonheur Children’s Hospital, University of Tennessee Health Science Center, Memphis, Tennessee, USA. 4 School of Nursing, University of Pittsburgh, Pennsylvania, USA

Background
• Repeated and inadequately managed painful procedures preterm infants are exposed to during neonatal intensive care (NICU) can lead to alterations in pain response and impact quality of life of this population in terms of motor and cognitive disabilities during child- and adulthood.
• Some non-pharmacological pain relieving interventions are well established for the treatment of single painful procedures; however there is a lack of evidence regarding their effectiveness across time during NICU stay.

Objective of the study
To compare the effectiveness of two non-pharmacological pain relieving interventions across time after repeated heel-sticks in preterm infants.

Methods
• A multisite randomized control trial was conducted in three NICU’s in Switzerland comparing the effectiveness of:
  • 1) oral sucrose
  • 2) facilitated tucking (see figure 1)
  • 3) the combination of the two interventions.
• Study population: preterm infants between 24 0/7 and 32 0/7 weeks of gestation (stratified into 2 groups: 24 0/7-27 6/7 weeks and 28 0/7 - 32 0/7 weeks).
• Data were collected during the first 14 days of life.
• Three phases (baseline, heelstick, recovery) during 5 heel-sticks were videotaped for each infant.
• Four nurses blinded to the videotape phase rated 1055 video sequences in a random order with the “Bernese Pain Scale for Neonates” (BPSN).

Results
• Seventy-one infants were included in the study.
• Inter-rater reliability was high for the total BPSN scores (Cronbach’s alpha: 0.90-0.95).
• Facilitated tucking alone was significantly less effective to relief repeated procedural pain ($p<0.002$) than oral dose of sucrose (0.2ml/kg).
• Facilitated tucking in combination with sucrose seemed to have added value in the recovery phase, where this group deviated from the single-treatment groups with significantly lower pain scores ($p=0.003$).
• There were no significant differences in pain response between the two gestational age groups (24 0/7-27 6/7 weeks and 28 0/7 - 32 0/7 weeks).

Figure 2: Pain scores over the heel-sticks for phase 2 (heel-stick) measured by the Bernese Pain Scale for Neonates (BPSN)

Conclusions
• In this study oral sucrose and the combination of oral sucrose with facilitated tucking had a pain relieving effect even in very premature infants having the highest risk for repeated pain exposure, and these interventions remained effective during repeated procedural pain across time.
• Facilitated tucking alone was not as effective and cannot be recommended as a non-pharmacological pain relief for repeated pain exposure.

References

Supported by the Swiss National Foundation
Correspondence: eva.cignacco@unibas.ch
Antibody responses to natural influenza A/H1N1/09 disease or following immunization with adjuvanted vaccines, in immunocompetent and immunocompromised children

S. Meier1,2, M. Bel1, A. L’Huillier1,2, P.-A. Crisinel3, C. Combescure3, L. Kaiser4, S. Grillet5, K.M Pósfay-Barbe2, C.-A. Siegrist1, with the H1N1 Epidemiology Study Group of Geneva.

1 Center for Vaccinology and Neonatal Immunology, Department of Pediatrics and Pathology-Immunology 2 Pediatric Clinical Research Platform, Department of Pediatrics, 3 Clinical Research Center, 4 Laboratory of Virology and Swiss National Center for Influenza, Department of Genetics and Laboratory Medicine, University Hospitals of Geneva & Faculty of Medicine, University of Geneva, Switzerland

Background

In the context of the influenza A/H1N1/09 pandemic of autumn/winter 2009/2010, our aim was to compare antibody responses elicited by immunization with adjuvanted pandemic vaccines and by infection in immunocompetent and immunocompromised children.

Methods

We conducted a prospective parallel cohort study between November 2009 and February 2010, enrolling in one cohort children immunized with 1 dose (immunocompetent) or 2 doses (immunocompromised) of influenza A/H1N1/09 squalene-adjuvanted pandemic vaccines (Pandemrix®, GSK, adjuvant AS03 or Focetria®, Novartis, adjuvant MF59). The type of vaccine administered depended on current recommendations by the Swiss Office for Public Health (BAG/OFSP) as did the case definition for “immunosuppression”. The second cohort consisted of children having presented themselves at our emergency ward with flu-like symptoms, confirmed by PCR to be influenza A/H1N1/09 infection.

Antibody titers were measured by hemagglutination-inhibition (HAI) and microneutralisation (MN) assays at baseline (optional) and 4-6 weeks post-vaccination/infection in the Center for Vaccinology and Neonatal Immunology in Geneva. Vaccine adverse events were self-recorded during 7 days.

Results

The cohort of immunized children consisted of 48 immunocompetent (1 dose, 20 Pandemrix®, 28 Focetria®) and 27 immunocompromised children (2 doses, 6 Pandemrix®, 21 Focetria®) while 51 immunocompetent and 9 immunocompromised children were enrolled in the post-infection cohort.

The mean age was 10.5 years (interquartile range (IQR) 6.3-14.1) for the immunization cohort and 9 years (IQR 5.7 – 11.1) for the infection cohort. Ethnic background and gender proportions were comparable.

Conclusions:

1. Pre-vaccination titers were low (80% <40)
2. The curves of the vaccine- and influenza-induced titers are almost identical: the vaccine was as immunogenic as the infection

Conclusion/Discussion

In immunocompetent children, similarly high seroresponses may be expected after a single dose of adjuvanted vaccine as after infection. Two vaccine doses were sufficient for most (89%) immunocompromised children.
Determinants of Hepatitis A Vaccine Immunity in the Cohort of Human Immunodeficiency Virus-Infected Children Living in Switzerland

Cristina PA, Pfohl-Byar KA, Asio C, Checaux JJ, Kubler T, Rudd O, Nadel C, Segnitz CA, and the Swiss Mother and Child HIV Cohort Study of Switzerland (MoCoHiV)

1 University Hospitals of Geneva, Geneva; 2 University of Bern, Bern; 3 University Hospital CHUV, Lausanne; 4 Ochsneri Kinderklinik, St. Gallen; 5 University Children’s Hospital, Basel; 6 University Children’s Hospital of Zurich, Zurich

ABSTRACT

Introduction: Vaccination in HIV-positive children is often less effective. The goal of this study was to assess the efficacy of hepatitis A virus (HAV) vaccine in children infected with HIV.

Methods: Children, part of the Swiss Mother and Child Cohort Study, were enrolled prospectively. Vaccination recommendations for initial catch-up, or additional hepatitis A vaccination were based upon baseline antibody screening and seroconversion. HAV antibodies were assessed by ELISA and a protective cut-off value was 10 IU/mL.

Results: Eighty-two patients were included in the study (median age 11 years). Thirty-four derived from the MoCoHiV population and 48 from the Swiss Mother and Child Cohort. Forty-four (54.9%) patients were seronegative for HAV. Vaccine response was assessed after the primary dose in 2005 and seroconversion rates were 57.1% after 2 doses of vaccine. No factor influence significantly HAV vaccine priming response. However, baseline CD4 T cell counts > 750 cells/μL decreased significantly booster response (P=0.038).

Conclusion: Despite a high rate of seroconversion, patients with low CD4 counts had low antibody responses. However, the seroconversions observed in CD4 T cell counts > 750 cells/μL may be necessary to the efficacy of the vaccine.

BACKGROUND

Liver diseases are among the three primary causes of non-AIDS related deaths in patients with HIV through hepatotropic viral co-infection, liver toxicity of antiretroviral therapy, and emerging liver diseases such as nodular regenerative hyperplasia. It has been shown that HIV infection does not alter the clinical course of hepatitis A; however, this infection can have adverse effects in patients with liver disease. Thus, it seems apparent to offer the best protection against hepatitis A virus (HAV) in HIV-positive patients. Vaccination in HIV-positive children is often less effective. The goal of this study was to determine the parameters influencing the quality of the response to vaccination against HAV in children infected with HIV.

METHODS

Design: prospective cohort study.

Setting: recruitment, between June 6, 2006 and August 8, 2007, in 5 University Hospitals and one regional hospital that altogether follow most HIV-infected children in Switzerland.

Population: patients prospectively included in the Swiss Mother and Child HIV Cohort (MoCoHiV). Analysis of vaccine responders: first and/or second dose of HAV vaccine during the study period and available serologies.

Exposure: Demographic, ART treatment, viral load, CD4 cells at enrollment, CD4 cells nadir, intervention: baseline HAV serology, Vaccination (initial catch-up/additional) based upon baseline serology and vaccine history.

Outcome: Follow-up serology: ELISA (EnzygnostTM Anti-HAV, Dade Behring Marburg GmbH, Marburg, Germany), cut-off 2.0 IU/mL.

Data collection (MoCoHiV database): Clinical and biological data bioanamnecically.

DISCUSSION

Seroconversion: 97.9% compared to what has already been published in the literature for HAV-infected children (48.5-100%).

High rate of seroconversion: first and/or second dose of HAV vaccine during the study period and available serologies.

Unprimed (1 dose): 52 (62.2%) 59 (69.0%) 16 (18.8%) Primed (1 dose): 33 (37.8%) 37 (41.0%) 13 (14.2%).

CD4 T cells count < 750 cells/μL, 10% decrease in the primary antibody response (P<0.001).

VACCINE RESPONSE

Post-priming analysis: 29/35 naïve; Timing: 3 months (IQR 1.3); 2/29 non responders (14%); GMC 57 μIU/mL (95% CI 34–94).

Post-booster analysis: 33/36 boosted; Timing: 3.2 months (IQR 1.1); 1/33 non-responders (3%); GMC 962 μIU/mL (95% CI 503-1838).

DETERMINANTS OF RESPONSE

Post-priming analysis: no significant determinant (baseline CD4 T cell counts with P=0.06 on univariate analysis). Post-booster analysis: Baseline CD4 T cell count: P=0.005 on univariate analysis; Multivariate analysis with CD4 T cell counts, viral load (P=0.13 on univariate analysis) and nadir CD4 T cell counts (P=0.09), HAART treatment (P=0.16) → CD4 T cell counts (P<0.001)
Do Swiss physicians tell childhood cancer patients after completion of treatment that they are “cured”? 
A pilot study from the Swiss Childhood Cancer Registry

Stefan Essiga, Gisela Michel, Nicolas von Der Weid, Eva Bergsträsser, Claudia Kuehni

Definition of cure after childhood cancer remains controversial. Former patients have an excess risk of death even many decades into adulthood, due to second malignancies and treatment-related late effects. In the Erice statement, pediatric cancer experts recommended to use the term “cured” when discussing with cancer survivors. This pilot study is the first part of a mixed methods approach to see how the term “cure” is used in clinical practice.

We wanted to find out:
1) How many survivors were told that they were cured?
2) How long after diagnosis did this happen?
3) How do these survivors differ from others?

By April 2011, 192/449 survivors replied (43%, study ongoing). Their mean age was 24.0 years (SD=5.0, range 19-36), their age at diagnosis 8.5 years (SD=4.3, range 0-15). We excluded six who did not answer the questions and four who reported to have received the message of cure from their parents.

1) How many survivors were told that they were cured?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>74%</td>
<td>26%</td>
</tr>
</tbody>
</table>

2) How long after diagnosis did this happen?
The message, that they were cured, was given to survivors in average 6.4 years after diagnosis (range: 0-16 years). This differed between the two largest diagnostic groups (p=0.01).

3) How do these survivors differ from others?
The proportion of patients, who were told to be cured depended on the primary diagnosis (p<0.01), but not strongly on the presence of late effects of the cancer treatment (p=0.17).

Further information: www.childhoodcancerregistry.ch; Stefan Essig (sessig@ispm.unibe.ch)

S.E. was funded by a MD-PhD Fellowship: KFS 02606-06-2010 / SNF 323630-133897.
Introduction and Hypotheses

- The high prevalence of obesity in children warrants continuing public health attention. Besides the various health consequences of childhood obesity [1], many obese children suffer from behavioral problems or mental disorders [2, 3].
- The purpose of this study was to assess effectiveness of multidisciplinary group programs for obese children in Switzerland.
- Given the limited effectiveness of treatment, the identification of potentially modifiable risk factors may provide insights into new treatment approaches. Therefore tested the hypothesis that mental health status before treatment may predict improvements in physical health in obese children.

Methods

SUBJECTS AND DESIGN
- We present here data of 342 children (12.2 ± 2.2 years) of the ongoing national multi-center cohort study on the effects of multiprofessional therapy, collected between 03/2009 and 12/2010 in 22 certified programs in Switzerland.
- Initial data gathering was before treatment (T0); examinations at the end of the intensive treatment phase (T1) and 1 year after start (T2).
- The return of the questionnaires is not yet completed, therefore, a preliminary pre-protocol analysis is presented here.

OUTCOME VARIABLES

Primary outcome: BMI-SDS
- In compliance with national and international guidelines, BMI was adjusted for age and gender and expressed as z-score or standard deviation score (BMI-SDS) [4], in relation to WHO references.

Secondary outcome: Mental health problems
- To measure mental health problems, we used the Strengths and Difficulties Questionnaire (SDQ) [5], a commonly used instrument which discriminates well between children with and without psychopathology [6].

Results

Primary outcome
- A highly significant decrease in BMI-SDS was observed after treatment, with a mean change in BMI-SDS from baseline was -0.19 ± 0.36 (p<0.001) (Figure 1).
- We found significantly greater reductions of BMI-SDS in younger than in older patients at T1.

Results cont.

Secondary outcome
- Obese children had much higher rates of emotional and behavioral problems before treatment (T0) than a normative sample (Figure 2).
- Over 1 year, emotional and behavioral difficulties rates decreased by half (-20.6%) (Figure 3).
- Peer problems at T0 significantly predicted BMI-SDS change from T0 to T2 (T=-2.56; p<.05).
- Surprisingly, the direction of this effect was against our hypothesis: Children with peer problems above the clinical cut-off showed higher BMI-SDS reductions (Figure 4).

Conclusion
- Standardized family-based group therapy significantly improves the degree of adiposity and mental health in obese children.
- High levels of peer pressure may influence self-motivation of patients.
- Therefore peer problems at T0 may have positive effects on outcomes in obesity treatment.
- Health professionals, working with obese children, should attend not only to physical health but also to mental health status of their patients.

References


Correspondence

Dr. Margarete Bolten
University of Basel, Department of Child and Adolescent Psychiatry
Schenenstrasse 13, 4056 Basel, Switzerland
Phone: ++41(0) 61 265 89 71
Email: margarete.bolten@upkbs.ch

Prof. Dr. Dagmar l’Allemand
Children’s Hospital of Eastern Switzerland
Clinicaidstrasse 6, 9006 St. Gall, Switzerland
Phone: ++41(0) 71 243 1467
Email: dagmar.lallemand@kispisg.ch

*FOPH grant # 09.004211/204.0001/-629
Energy and protein requirements in ventilated critically ill children.

C Jotterand2, J Depeyre2, MH Perez1, J Cotting1

1Pediatric Intensive Care Unit, University Hospital, Lausanne,
2Department of Nutrition and Dietetics, University of Applied Sciences, Geneva, Switzerland.

Introduction

In critically ill children, under and overnutrition are associated with poor outcomes and must be avoided. Despite the importance of adequate nutritional support in this population, energy and protein requirements are still unclear. This study estimated energy and protein requirements in ventilated critically ill children by measuring daily energy expenditure (EE) and total urinary nitrogen excretion (TUN).

Method

Children with expected mechanical ventilation ≥ 72 hours and a FiO2 ≤ 60% were prospectively recruited. Nutritional status was assessed by the Waterloo Index. EE and TUN were measured daily until extubation by indirect calorimetry and chemoluminescence, respectively. Energy and protein intakes were obtained from total enteral and parenteral feeding, including intravenous solutions containing glucose for medication, using a computerized system (MetaVision of iMDsoft, Tel Aviv, Israel). Energy and protein intakes were recorded allowing the calculation of energy and nitrogen balances. The results were compared to the Recommended Dietary Allowances (RDA, 1989) for healthy children expressed by age groups. Protein requirement to achieve zero nitrogen balance was calculated for each age groups by linear regressions.

Results

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Median (IQ 25-75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (girls/boys)</td>
<td>74 (32/42)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>20.6 (4.2-34.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.9 (4.4-12.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>77.3 (59.5-93.3)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>10.6 (6.9-16.0)</td>
</tr>
<tr>
<td>PRISM score</td>
<td>6.0 (4.0-9.0)</td>
</tr>
<tr>
<td>Waterlow index</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Acute n (%)</td>
<td>31 (42)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy (kcal/kg/d)</th>
<th>Median (IQ 25-75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements (n)</td>
<td>407</td>
</tr>
<tr>
<td>EE</td>
<td>54 (47-62)</td>
</tr>
<tr>
<td>Energy intake</td>
<td>45 (34-59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nitrogen/Protein (g/kg/d)</th>
<th>Median (IQ 25-75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUN (equivalent in protein)</td>
<td>0.20 (0.16-0.25)</td>
</tr>
<tr>
<td>Protein intake</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>Nitrogen balance</td>
<td>-0.06 (-0.13-0.01)</td>
</tr>
</tbody>
</table>

Energy expenditure:
- Lower in children aged 4-8 years old 46.0±6.8 kcal/kg/d (p<0.05) compared to younger children
- Corresponded to only 55% of the RDA, with little differences among age groups
- No effect of diagnosis, sepsis, cardiopulmonary bypass, nutritional status
- Higher in children with a body temperature >37.5°C (p=0.003).
- Lower on days with neuromuscular blocking drugs (p=0.031).

Total urinary nitrogen:
- Higher in children 4-8 years (0.27±0.05 g/kg/d) than in younger children (p<0.05)
- No effect of diagnosis, sepsis, cardiopulmonary bypass, nutritional status, medication

Nitrogen balance and protein intake:
The amount of protein required to achieve zero nitrogen balance was:
- 1.4 g/kg/d in 0-6 months
- 1.6 g/kg/d in 7-12 months
- 1.5 g/kg/d in 1-3 years
- 2.2 g/kg/d in 4-8 years old

Conclusion

- These results suggest that while protein requirements in ventilated critically ill children are close to the recommendations for healthy children, energy requirements are significantly lower. Surprisingly, higher protein requirements (normalized for body weight) were observed in older children.
Effects of farming environments on atopy, wheeze, lung function, and exhaled nitric oxide in childhood

Oliver Fuchs1,2, Jon Genuneit3, Philipp Latzin4, Charlotte Braun-Fahrländer5, Erika von Mutius1, Urs Frey1,5

1Division of Paediatric Pulmonology, Department of Paediatrics, Inselspital and University of Bern, Switzerland,
2Institute of Epidemiology and Medical Biometry, Ulm University, Germany, 3Swiss Tropical and Public Health Institute and University of Basel, Switzerland, 4University Children’s Hospital, Ludwig-Maximilians-University, Munich, Germany, 5University Children’s Hospital (UKBB), University of Basel, Switzerland, both authors contributed equally

Introduction and Aims

Studies have consistently observed a protective farm effect on childhood atopy, however with a lesser role of microbial diversity in comparison to the effect on childhood asthma.2,3 Possible explanations include different protective mechanisms of farm exposures for these two entities. Thus, we studied the farm effect on childhood asthma and wheeze phenotypes together with objective markers like lung function and exhaled nitric oxide (FeNO) and their interrelation with atopy in participants of the GABRIEL Advanced (GABRIELA) Studies.

Study design

The GABRIELA Studies are cross-sectional multi-phase population-based surveys on the farm effect on asthma and allergic disease in childhood in rural areas of Austria, Southern Germany, and Switzerland (Figure 1).

Methods - Definitions

Atopy (Phase 3 disease stratum definition): Specific IgE ≥ 0.35 kU/l against ≥ one of: D. pteronyssinus, cat, birch, grass mix.

Asthma (Phase 3 disease stratum definition): Either wheeze in past 12 months, or asthma inhaler use ever or doctor’s diagnosis of asthma ≥ once or wheezy bronchitis > once.

Wheeze:

• Persistent and late-onset wheeze: according to European Respiratory Society (ERS) guidelines6, current wheeze: both groups combined.

• Transient wheeze: wheeze < 3 years of age but neither in Phase 1 nor in Phase 2

Methods – Measurements of objective markers, spirometry and FeNO

Performed by trained field-workers according to current guidelines by the ERS and the American Thoracic Society (ATS).4,5

Spirometry:

• Outcomes: forced expiratory volume during 1st second (FEV1), and ratio over forced vital capacity (FEV1/FVC), and midexpiratory flow (MEF25-75).

• EasyOne, EasyWare (ndd, Zurich, Switzerland).

• Bronchodilatation with 400 µg short-acting beta agonist (salbutamol).

• Positive bronchodilator response (BDR): relative FEV1 change of ≥12% from baseline.

Single-breath offline FeNO measurement (main outcome: FeNO in ppb):

• Offline sample kit and CLD 88 sp rapid chemoluminescence analyzer (Eco Medics AG, Duermten, Switzerland).

• Mylar coated bags (Quintron, Cedar Rapids, USA) in triplicates.

• Positive bronchodilator response (BDR): relative FEV1 change of ≥12% from baseline.

Methods – Statistical Analysis

(SAS 9.2, SAS Inst, Cary, NC, USA)

• Stratified weighted statistics, using Taylor series to estimate variances.

• Adjustment for confounders (resulting in change in estimate >10%), p-values < 0.05 were considered significant.

• Statistical interaction modeled between farm exposure categories and atopy, p-value was labeled as pinteraction.

Results

1. Farming is inversely associated with atopic sensitization.

2. Farming is inversely associated with all wheeze phenotypes.

3. Farm environments are not associated with a benefit for lung function before or after bronchodilator and FeNO levels in the general study population (data not shown).

4. Except for transient wheeze, all wheeze phenotypes were associated with atopy (data not shown). To discriminate between farm effect on atopy and wheeze, further analyses were stratified for atopy. Here, the farm effect on persistent, late-onset or current wheeze was only found for non-atopics (shown for current wheeze, pinteraction = 0.011).

Conclusions

Childhood exposure to farm environments not only protects from atopy, explaining effects on FeNO and lung function among atopic wheezers, but in addition from developing wheeze independent from atopy. This protective farm effect is not attributable to improved lung volume, airway size and lung mechanics among farm children. The underlying mechanisms are unknown, but farm exposures may impact on airway inflammation through anti-viral properties and alterations of the airway microbiome.

References

1. von Mutius, Verani, Nat Immunol 2010
2. Ege et al. New Eng J Med 2011
5. ESK8785, Am J Resp Crit Care Med 2005

Figure 1: Study design GABRIELA

Figure 2: Farm effect on current wheeze comparing non-atopics to atopics (Phase 2).

Figure 3: Farm effect on lung function and FeNO comparing non-atopics to atopics (Phase 3).
Comparison of online single-breath versus multiple-breath exhaled nitric oxide in children at school entry

Oliver Fuchs1,2, Philipp Latzin1, Florian Singer1, Elena Priietti1, Elisabeth Kieninger1, Carmen Casaulta1, Urs Frey1,2
Division of Paediatric Pulmonology, Department of Paediatrics, Inselspital and University of Bern, Switzerland, 2 University Children’s Hospital (UKBB), University of Basel, Switzerland

Introduction and Aims
Childhood asthma resembles a complex syndrome rather than a single disease.1 Exhaled nitric oxide (eNO) measurements are used to detect allergic airway inflammation and help distinguishing different childhood asthma and wheeze phenotypes. Table 1 displays the requirements by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) for the gold standard of eNO measurements, the online single-breath eNO (eNOsb) measurement, difficult to accomplish in young children.2

ERS/ATS requirements for online single-breath eNO measurements

- Inhalation to total lung capacity
- Inspiratory NO < 5 ppb
- Expiratory target flow 50 ml/s, duration of expiration ≥ 4 seconds
- Expiratory plateau at target flow of ≥ 2 seconds
- Expiratory pressure level at 5-20 cmH2O for velum closure
- Mean eNO from 2-3 manoeuvres, that agree within 10%, or 2 within 5%

Despite requiring less cooperation around school entry, there are no standards for online multiple-breath eNO measurements (eNOmb) with unrestricted flow rate. There are also no studies comparing eNOmb to eNOsb measurements. Within this study, we set out to close this gap of missing evidence for (i) feasibility and quality control, (ii) correlation and (iii) accuracy of eNOmb measurements in comparison to the current gold standard of eNOsb measurements.

Methods

Study population:
- Asthmatics attending the asthma clinic of the University Children’s Hospital of Bern, Switzerland.
- Healthy children during follow-up of an ongoing prospective birth cohort of unselected, healthy subjects, the BILD Cohort.3
- Study approved by the Cantonal and the Research Ethics Committee of the University Hospital Bern, Switzerland. All participants provided written informed consent for this study.

Exhaled nitric oxide measurements
- Rapid-response chemiluminescence analyzer (CLD 88 sp®; Eco Medics AG, Duermten, Switzerland).
- Flow recorded by ultrasonic flowmeter (Spironox®; Eco Medics AG, Duermten, Switzerland).
- Contamination of eNO by ambient NO avoided by using NO-free air for inspiration.
- Signal collection and analyses performed with software package (WBreath 3.28; ndd Medical Technologies, Switzerland).
- Main outcome parameters: eNO and NO output (eNO concentration multiplied with corresponding expiratory flow, V’NO, nl/min).

Analysis eNOsb
- According to ERS/ATS guidelines (see Table 1 above).2

Analysis eNOmb
- Breath-by-breath without flow restriction during 3rd quartile of expiration.3,4
- Results for eNOmb were extrapolated to target flow 50 ml/s (eNOmb50) according to standards.2
- Quality control criteria: further than (1) avoiding eNO contamination by ambient NO, we aimed (2) for 20 quiet tidal breathing manoeuvres, mean eNOmb per measurement calculated from (3) breaths within 10% volume deviation and (4) total mean eNOmb from 2-3 measurements, that agree within10%, or from 2 within 5%.

Statistical analyses (STATA 11 for Windows, STATA Corporation, College Station, TX, USA)
- Analysis by uni- and multivariable regression analyses, also performed for log-transformed data.
- Confounders were included in the final models if point estimates changed by at least 10% in univariable models, p-values<0.05 were considered significant.
- Accuracy of eNOmb compared to eNOsb was determined using the Bland and Altman method.

Results

(i) Feasibility and quality control of eNOmb compared to eNOsb measurements: eNOmb is slightly more feasible than eNOsb. Online eNOmb and eNOsb were measured in N=82 children, these were n=75 healthy children (mean±SD age 6.1±0.2 years, 43.5% males) and n=7 asthmatics (mean±SD age 12.0±4.0 years, 83.3% males).
- Measurements were acceptable according to quality control criteria for eNOmb in n=83 (76.8%) and for eNOsb in n=59 (72.0%) children, respectively.
- Paired data with both acceptable eNOmb and eNOsb measurements were available for n=52 children.

(ii) Results from eNOmb measurements are correlated with results from eNOsb measurements. Online eNOsb measurement results were correlated with results from eNOsb measurements (mean±SD 10.3±9.6 ppb) after extrapolation to eNOmb50 (mean±SD 10.6±9.3 ppb). Figure 1a, non-normally distributed) or when comparing V’NOmb to V’NOsb (Figure 1b, non-normally distributed) also on a log-log scale (Figures 2a and 2b, normal distributions).

Conclusions

Despite being correlated with the gold standard of single-breath eNO measurements at school entry, the wide range of limits of agreement with systematically slightly lower values hampers use of multiple-breath eNO in research, where exact values across the whole range are warranted. Being less dependent on cooperation in young children, it might be a promising tool for the clinical setting to discriminate between disease groups.

References
(De-)Medicalized Decision-Making in Paediatric Clinical Research

Jürg C. Streuli¹, Yvonne Cavicchia², Effy Vayena¹
Institute of Biomedical Ethics, University of Zurich¹ and Zurich University of Applied Sciences (ZHAW), School of Applied Psychology²

Background and aims

- Good clinical research requires respect of participants’ welfare, values and autonomy.
- Meeting these requirements may be compromised when the informed consent process is dictated by a set of values specific only to medicine.
- The study explores how medicalised versus information impacts on the research participants’ decision-making process in paediatric trials.

Conclusions

- Participants’ values and decisions were highly manipulable by different ways of informing them.
- Interdisciplinary teams should be aware of differing values and their influence on participants.
- The shown effects of medicalized vs. de-medicalized information can raise significant ethical questions in paediatric clinical research.

Methods

Phase I: Focus Group

- Focus group participants talked about how health care professionals should inform parents about their child’s intersex condition (disorder of sex development or DSD).
- The discussion (duration 120 minutes) was recorded and transcribed.
- The transcript was coded focusing on medicalized and demedicalized information.

<table>
<thead>
<tr>
<th>Medicalized Perspective</th>
<th>Demedicalized Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder as state</td>
<td>Condition as process</td>
</tr>
<tr>
<td>Focus on child’s problem</td>
<td>Focus on child’s development</td>
</tr>
<tr>
<td>Child as more vulnerable person</td>
<td>Child as active participant with evolving capacities</td>
</tr>
<tr>
<td>Prepared treatment-regime</td>
<td>Observing individual reaction over time</td>
</tr>
<tr>
<td>Producing/preparing function</td>
<td>Supporting interests and abilities</td>
</tr>
<tr>
<td>Therapy outside of usual living space</td>
<td>Therapy inside of usual living space</td>
</tr>
</tbody>
</table>

Table 1. Tendencies in giving medicalized versus demedicalized information to parents

Phase II: Video Consent

- Out of the focus-group transcript we created two videos (each 6 minutes) of medicalized and demedicalized information for parents.
- The videos did not give an explicit therapy recommendation pro/contra surgery.
- The videos were shown to potential parents, asking them consecutively about their tendency to decide for or against surgical intervention by a questionnaire.
- Participants: N=89, 3rd year medical students, m=39 (mean age 27.6 years); w=50 (mean age 23.4 years)

Results

- Videos showed significant influence on potential parent’s decision (p<0.001)
- Both, medicalized and demedicalized group felt as if their decision were based on their own attitude/values (table 2)
- Participants did not feel significantly influenced by the informing person

Table 2. Self-reported aspects influencing participants most
Creation of an International Data and Tissue Repository for pediatric ARDS

**Pediatric ARDS**
- Low incidence, high mortality: a rare disorder
- Diagnosed in the PICU: no known risk factors
- A Syndrome, not a Disease!
- Patient management supercedes risk analysis
- Clinical Trials: Failure by Heterogeneity!
- VPS (virtual pediatric ICU): 110 PICU’s, 400,000 patients

**NAF Data/Tissue Repository and Analysis System**

**Value Proposition**
- For Physicians and Patients
  - Early Identification and Impact of ARDS
  - Improve clinical trial results (patient stratification)
  - Improve patient management and outcomes
  - Establish dynamic recovery interface
  - Support development of clinical decision support tools
- For NAF
  - Establish basis for developing collaborative research common to clinical trial development
  - Use sub-individual diagnoses to improve potential for identifying factors, e.g., genetics, comorbidities, therapies, patient profile

**Data Source:** 5085 patients records from VPS Project

**Future:**
- Expand Collaboration in Europe
- Analyze N. Disease/Disaster Support Platform
- HP 3D and NPE applications

**Collaborators:**
- NAF International (USA)
- Genomics Institute (USA)
- Virtual Pediatric ICU (VPS)
- N. Disease/Disaster Support Platform
- HP 3D and NPE applications
Why PONTE?
Global crisis — ↓↓↓ funding for research
New drug development is hampered by:
- ↑↑↑ Costs = 2 x in 10 y
- ↓↓↓ ROI by 50% in 10 y
- Long duration of development >10 y
- Risk of post marketing drug failure
- Risk of failure of clinical applicability

Drug Repositioning
In a timely strategy
Offers faster, cheaper and safer solutions
PONTE
Aims to optimize drug repositioning
Has a strategic place in the current pharmaceutical market environment

PONTE Platform Objectives
PONTE aims at developing a set of intelligent procedures linking descriptive semantic representations of data involved in the clinical trial lifecycle to:
- Enable the development of a research question into a clinical trial through the comprehensive testing of the hypothesis across the clinical, molecular and commercial domains
- Efficiently guide clinical researchers through clinical trial protocol preparation through advanced decision support at multiple steps, intelligent queries to distributed heterogeneous data sources and advanced navigation through the clinical trial protocol
- Enable effective automatic identification of eligible individuals while focusing on patient safety, clinical trial efficacy and cost
- Support adaptive clinical trials

Expected Impact
Mitigation of patient safety risks
Improvement of study efficacy
Reduction of study costs

Stakeholders
Pharmaceutical companies
Research Institutions
Clinicians
Patients
Society

Technical Outcomes
- Highly descriptive, consistent models leading to a rich PONTE ontology capturing a wide variety of important concepts and various steps in clinical trial design, including tests of hypothesis validation, protocol design and patient selection.
- A set of novel mechanisms and tools for enabling semantic interoperability between the clinical research and the health care domains based on the PONTE Ontology and a wide set of available codings, terminologies, vocabularies on drugs, diseases and lab tests including SNOMED-CT, UMLS, ATC, ICD10, LOINC among others as well as health messaging standards such as HL7.
- An innovative Ontology Based Search Engine able to mine information based on the PONTE ontology which will incorporate the Linked Data Approach and allow the querying of and the navigation through a great variety of heterogeneous (in terms of syntax, structure, type, content, semantics, interfaces) data sources incl. EHRs, drug and disease information sources and clinical research findings;
- A set of intelligent decision support services covering the clinical trial protocol design and the patient selection phases with a clear focus on increasing clinical trial efficacy, strengthening patient safety and reducing trial costs;

PONTE Pilot Study
C.N.R. INSTITUTE of CLINICAL PHYSIOLOGY
Gabriele Monasterio Foundation
Pisa - Italy

Acute and long term effects of Thyroid Hormone Replacement therapy in patients with ST-Elevation Myocardial Infarction (STEMI) and borderline/reduced triiodothyronine levels.

Ponte’s SOA will be designed to be attractive for collaboration with major international data providers for strategic interfacing and integration of their data with its platform in order to ensure commercial success

Grant Agreement No. FP7-247001

This project is partially funded by the European Community under the 7th Framework Programme
Adapting the Zurich Clinical Trials Center’s Good Clinical Practice Standards for the Children’s Research Center of the University Children’s Hospital of Zurich

Manuela Felder, M.Sc, Emanuela Valsangiaccomo, MD, Oskar Jenni, MD, Claudia Hermann, PhD, Lustenberger Jürg, PhD, David Nadal, MD, Gabriela Senti, MD

Methods and Results

The process of establishing a GCP-conforming Quality Management System at the CRC was performed with the support and expertise of the Clinical Trials Center at the Medical Faculty of the University of Zurich.

The CTC and CRC set out to perform a gap-analysis for clinical research. In close collaboration the responsible persons on site gave their input on internal processes and helped to build a library of descriptive documents available on the intranet.

The development of QM Documents took place in two sub-processes. The first process included the creation of all WIs specific to the Children’s Hospital, and in a second process all generally applicable SOPs, WIs and the specifically paediatrics WIs was created.

Children’s Hospital specific WIs should primarily improve the internal research processes, whereas the focus of the universal and paediatrics specific quality documents is on the conduct of GCP-compliant research projects. While the universal and the paediatrics specific quality documents were largely created in-house, the development of hospital-specific WIs needed a very close collaboration with the staff and the researchers of the Children’s Hospital of Zurich.

Conclusion

The first feedback of local physicians involved in the implementation process expressed their conviction that working instructions and the use of corresponding forms and templates will greatly facilitate a clinical trial routine compliant with regulations and GCP standards. The chosen approach of profiting from established resources of elaborated structures generating high quality standards for clinical studies is an efficient means to significantly improve the management of clinical trials with paediatric patients.