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ANTENATAL STEROIDS AND RISK OF BRONCHOPULMONARY DYSPLASIA: A LACK OF EFFECT OR A STATISTICAL ARTIFACT?

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Objectives: To test the hypothesis that the lack of protective effect of antenatal steroids (ANS) on bronchopulmonary dysplasia (BPD) could derive from overadjustment during analysis, caused by controlling for factors that are intermediate in the causal pathway between treatment and outcome.

Methods. A cohort of infants 23 to 32 weeks of gestation, admitted to 10 tertiary-level neonatal units in Lombardy (Northern Italy) in 1999–2002, was prospectively studied; 1118 neonates out of 1314 survived to 36 weeks; 15.9% developed BPD (oxygen requirement at 36 weeks); 82% were treated with ANS.

Results. In univariate analysis, ANS were not significantly protective against BPD; some intermediate factors (mechanical ventilation, greater severity of illness as measured by CRIB score, patent ductus arteriosus) were positively associated with (i.e. were risk factors for) BPD (OR=11.0, 1.46, 4.42 respectively, all P<0.001), and negatively associated with (i.e. prevented by) ANS (OR=0.58, 0.92, and 0.58 respectively, all P<0.001). In multiple logistic regression models without the above-mentioned intermediate risk factors, ANS-treated infants had a lower risk of BPD (OR 0.59; 95% CI 0.36, 0.95, P=0.03); other factors significantly associated to BPD were male sex (OR=2.07), late-onset sepsis (OR= 4.31), and birthweight (OR=0.62 for 100 g increase), all P<0.001. When also intermediate risk factors for BPD, which are prevented by ANS, were added to the model, ANS effect disappeared, thus demonstrating the existence of overadjustment.

Conclusions. These results support the hypothesis that incorrect methods of analysis can obscure ANS protection against BPD. Using proper adjustment, ANS appeared to decrease the risk of BPD in this cohort.

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BRADYCARDIA/DESATURATION/APNEA AFTER VACCINATION IN THE VERY LOW BIRTH WEIGHT NEWBORNS. A PROSPECTIVE STUDY

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Severe adverse reactions, i.e. apnea, bradycardia and desaturation, have been reported after DTP-Hib immunization in very preterm infants. The aim of this study was to evaluate the safety of a hexavalent vaccine (DTPa+IPV+Hib+HBV). All newborns < 30 week GA or < 1250g BW were prospectively enrolled to have their first dose of vaccine at 6–8 weeks of life, while being in our NICU. They were on continuous monitoring for 3 days before and 3 days after the vaccination, and all episodes of bradycardia/desaturation/apnea and related interventions were recorded. Between November 2003 and March 2005, 40 newborns were studied. BW was 924g (range 475-1445g) and GA was 27.5 wks (range 24 - 30 wks). Four severe adverse events were recorded. In detail: 1 case of apnea the day following the vaccination resolved with manual ventilation. A similar episode of apnea was recorded also before the vaccination. 1 case of desaturation the day following the vaccination concomitant with the meal and spontaneously resolved. An episode of desaturation in concomitance with the meal was recorded during the preceding monitoring. 1 case of desaturation the day preceding the administration of the vaccine. After the vaccination, two more episodes of spontaneously resolved desaturation were recorded. The examinations revealed a CMV infection. 1 case of bradycardia and desaturation the first day after the vaccination that required manual ventilation and an increased oxygen flow for some days. The examinations revealed a Rotavirus infection. In previous studies every new bradycardia/desaturation/apnea event or a 50% increase of these events after the vaccine administration was considered related to it. According to these criteria, two out of 40 infants (5%) had severe adverse reactions related to the vaccine, but the concomitant infections from CMV and Rotavirus respectively may have played a major role.

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THE NONIMPACT OF POST-1994 NEONATAL TECHNOLOGY ON IUGR PRETERM NEWBORNS

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Background: Widespread use of steroids and surfactant since the mid-1990s has improved survival for premature newborns (PN). Survival and neurodevelopmental outcomes are less favorable in the intrauterine growth restricted (IUGR) subset of premature newborns. Since 1983 our institution has cared for 398 IUGR PN with birth weights (BW) </= 900g including the worlds two smallest surviving newborns (280g female,1989; 260g female, 2004). We sought to compare survival among these IUGR PN before and after the advent of widespread use of steroids and surfactant.

Methods: Our retrospective study included newborns with gestational age (GA) >/= 22 wks, BW </=900g and weight </=10th %ile for GA. Statistical analysis: survival to discharge:z-ratio; BW and GA: student t-test.

Results: Newborns enrolled: 1983–94 (n=214) 1995–2004 (n=184) Survival to discharge: 1983–94 (61.2%) 1995–2004 (67.9%) p=0.16 Mean GA (wks): 1983–94 (27.5) 1995–2004 (27.1) p=0.17 BW (g): 1983–94 (662) 1995–2004 (639) p=0.14

Conclusions: Despite widespread use of antenatal/postnatal steroids and surfactant after 1994, we failed to find a significant increase in survival among the IUGR PN. We hypothesize that the stresses associated with IUGR may preclude an additional benefit from antenatal steroid therapy. We will examine possible benefits of management strategies often employed in our NICU while caring for IUGR PN. These strategies include: Ventilator management: set physiologic rates of 40–60 breaths per minute, wean inspiratory pressures as tolerated, keep oxygen saturations 86%–89%, use HFOV as rescue only, no elective extubation <700g; Pulmonary: 3–5 day steroid burst if requiring FiO2>/= 0.50 at 7 days of life; Sedation/analgesia: scheduled around-the-clock sedation for first week of life; Hematology: maintain hematocrit >/= 40 if FiO2 >/= 0.50 for a duration >72 hours.

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VISUAL FINDINGS IN INFANTS WITH PERIVENTRICULAR LEUKOMALACIA

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Aims. The aim of the study was to assess cortical visual function in infants with cystic periventricular leukomalacia (PVL).

Methods. Patients with type 3 PVL were assessed at 12 months corrected age using a battery of tests specifically designed to assess various aspects of visual function, including ocular movements, visual acuity (Keeler cards), visual fields and fixation shift. Infants with moderate or severe retinopathy (>stage 1) were excluded.

Results. Thirteen infants (5 m, 8 f) with GA 30.6 + 3.7 weeks and BW 1573 + 583 grams were included in the study. All had some abnormalities of visual function but the spectrum of severity observed was very wide, ranging from isolated abnormal ocular movements to severe abnormalities on all the aspects of visual function assessed. Ocular movements abnormalities were frequent (11/13) often associated to inability to follow an object for a complete arc. Acuity was reduced in 9/13, fixation shift was abnormal in 11/13 and visual fields were reduced in 10/13. Brain MRI was available in 12 of the 13 infants and all had abnormal optic radiations. The infants who also had obvious signs of atrophy of the thalami had a higher risk of developing more severe visual abnormalities.

Conclusions. Our results suggest that visual abnormalities are frequent in infants with cystic PVL and that a detailed assessment of various aspects of visual functions should be performed in order to identify the severity of cortical visual impairment.

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PREVENTING RESPIRATORY DISTRESS SYNDROME: A COMPARATIVE PHARMACOECONOMIC ANALYSIS OF LUCINACTANT (SURFAXIN) VERSUS POOLED ANIMAL-DERIVED SURFACTANTS

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Background: Lucinactant (Surfaxin®) is the first available synthetic surfactant containing a peptide (sinapultide; KL4) that mimics human SP-B. There are currently no published pharmacoeconomic analyses comparing lucinactant to the animal-derived surfactants in the prevention of respiratory distress syndrome (RDS) in very low birth weight (VLBW) pre-term infants.

Objectives: To estimate the clinical consequences and economic impact of lucinactant and pooled animal-derived surfactants (beractant [Survanta®] and poractant alfa [Curosurf®]) in the prevention of RDS among surviving pre-term infants weighing 600 to 1,250 grams.

Methods: A decision-analytic model was constructed using a hospital perspective to assess the pharmacoeconomics of surfactant replacement therapy. Data sources: a) epidemiologic data regarding low birth weight and VLBW infants is from the U.S. National Centers for Health Statistics (2003), and the Vermont Oxford Network (2004); b) clinical outcomes are from two randomized, controlled clinical trials of surfactant therapy (SELECT and STAR); and c) cost data is from an assessment of daily neonatal intensive care unit (NICU) costs for 244 pre-term infants with severe RDS (2004). Cost variables: Average cost of a day in the NICU on mechanical ventilation (MV) was U.S. $2,386 and was U.S. $1,565 off MV; surfactant pharmacy costs were included at price parity from the Red Book (2005).

Results: Surviving infants who received lucinactant compared to pooled animal-derived surfactants had 4.14 fewer NICU days (mean 75.68 days vs. 79.82 days, respectively). Fewer NICU days convert into a total cost savings per infant who survived of U.S. $5,841 in the lucinactant group compared to the pooled animal-derived cohort. Conclusions: When compared to pooled animal-derived surfactants, the synthetic surfactant lucinactant may reduce total initial NICU hospital costs in surviving infants who receive surfactant therapy.

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NEUROPROTECTIVE EFFECT OF ERYTHROPOIETIN IN OXYGEN-INDUCED CELL DEATH IN THE IMMATURE BRAIN

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Extremely premature infants often display signs of cognitive and motor dysfunction in later life. Previous studies have shown that neurological deficits may correlate with a loss of brain cells. Until now, hypoxia and inflammation and infection were viewed as the sources of tissue damage. In recent studies, oxygen therapy has been identified as a cause of widespread apoptotic neurodegeneration in the developing brain. These findings were associated with downregulation of neurotrophic factors. The present study investigated whether systemically administered erythropoietin, a hematopoietic growth factor with neuroprotective properties, may ameliorate brain damage induced by hyperoxia in infant rats. 6-day old Wistar rats were subjected to 80% oxygen for 24 hours and EPO was co-administered at several doses, 10.000 - 20.000 I.E. at the beginning of exposure. Pups receiving either no treatment, EPO-treatment, or hyperoxia in combination with vehicle treatment served as controls. Pups were sacrificed at 24 hours of exposure to oxygen, transcardially perfused and brains were subjected to De Olmos silver and Fluoro-Jade staining. Morphometric analysis of 10 different brain regions to determine the extent of damage revealed that hyperoxia-induced neurodegeneration was significantly attenuated in EPO treated animals. The maximum neuroprotective effect was achieved with a single dose of 20000 IE/kg, p<0.001, primarily in the cortex and the thalamus nucleii. These findings suggest EPO as a potential neuroprotective agent in hyperoxia-induced cell death in the immature brain.