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POSTNATAL STEROID TREATMENT AND OCCURRENCE OF CEREBRAL PALSY AT THE AGE OF TWO YEARS AMONG NEONATES BELOW 32 WEEKS. THE EPIPAGE COHORT

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Background: The increasing survival of very low birthweight babies and the improvement of their management are not associated with a decreased incidence of cerebral palsy (CP). Among many risk factors, postnatal systemic steroids have been pointed out by clinical and experimental studies. The aim of this work is to explore the relationship between these treatments and CP at the age of two years in a population based cohort.

Methods: We conducted a population based study on the Epipage cohort, including 2358 premature infants of less than 32 weeks of gestation, and surviving at discharge, born in 1997 in 9 french areas. From this population 408 were lost to follow-up (17 %). The analyses have been performed on 1950 neonates followed up to the age of two years. We choosed the definition of cerebral palsy used by the SCPE. There was no data about the type of steroid used. All infants were evaluated from a medical form filled by a physician. We made an univariate analysis to identify risk factors of CP in this cohort , then a multivariate analysis by logistic regression . We also studied two subgroups of preterm neonates: below 28 weeks, and those free of cerebral lesions.

Results: mean gestational age was 30 weeks (± 0.1) and the average weight 1380 g (± 9.1). The incidence of cerebral palsy was 7.6 % and 14 % of infants treated by postnatal steroids (OR = 1.8 [1.1 - 2.8]). The other risk factors after multivariat analysis were cerebral hypoxia (OR = 5.5 [1.8 - 8.9]), and severe intraventricular haemorrhages (stage 3 or 4) (OR = 6.1 [1.6 – 6.3]). The decreasing gestational age was nearly significative (OR = 1.2 [1.0 – 1.3]). Protective factors were maternal hypertension (OR = 0.6 [0.3 – 1.0]), and fetal growth restriction (OR = 0.5 [0.2 – 0.9]). Although not significantly, the same trend was observed in the studied subgroups (neonates below 28 weeks (OR = 2.1 [0.9 – 4.8]) and neonates free of neonatal cerebral lesions (OR = 1.3 [0.6 - 2.4])).

Conclusion: These results are consistent with the data from randomized trials, and are supported by many physiopathological arguments. Analysis concerned a broader population than ventilated newborns included in these trials. Prescription of postnatal systemic steroids should be restricted, and only used in rescue for babies with severe respiratory distress.

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SUPERIORITY OF A NOVEL SURFACTANT, SURFAXIN (LUCINACTANT), OVER EXOSURF (COLFOSCERIL PALMITATE) IN PREVNTING RESPIRATORY DISTRESS SYNDROME IN VERY PRETERM INFANTS: A PIVOTAL , MULTINATIONAL, RANDOMIZED TRIAL

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Background: Animal-derived, protein-containing surfactants perform better vs. non–protein-containing surfactants for the prevention and treatment of Respiratory Distress Syndrome (RDS). A new generation, non–animal-derived surfactant, Surfaxin, containing a peptide that mimics human SP-B, appears effective in animals and in early studies of infants with RDS.1 Our objective was to compare the efficacy and safety of Surfaxin vs. Exosurf in the prevention of RDS.

Methods: This was a Phase 3, pivotal, masked, multinational, randomized trial comparing Surfaxin (5.8 mL/kg or 175 mg/kg) vs. Exosurf for preventing RDS. Survanta® served as a reference arm in a 2:2:1 randomization strategy. Exosurf and Survanta were dosed per package insert. Inclusion criteria were: birth weight (BW) 600-1250 g, gestational age (GA) <32 wk, and successful intubation. Dosing occurred within 30 min of birth. Primary outcomes (adjudicated by an independent masked committee) were the incidence of RDS at 24 hours and RDS-related mortality by Day 14. Secondary outcomes included the occurrence of air leaks, incidence of bronchopulmonary dysplasia at the postconceptional ages of 28 days and 36 weeks, and other complications of prematurity. The trial was event-driven; primary outcomes and overall safety were assessed by an independent Data Safety Monitoring Board.

Results: Over 22 months, 49 centers randomized 1294 infants in BW strata of 600–800 g, 801-1000 g, and 1001–1250 g. Overall BW and GA were 1001 g and 29.3 weeks, respectively. Primary outcome results are shown below: See table.

	Surfactant			
	Surfaxin	Exosurf	Survanta	P-value
Outcome	N=527	N=509	N=258	
RDS at 24 hours	206(39%)	240(47%)	86(33%)	0.005
RDS -related death by Day 14	25(4.7%)	49(9.6%)	27(10.5%)	0.001

*Surfaxin vs. Exosurf, based on logistic regression adjusting for center and BW strata.

Conclusion: Surfaxin is significantly more efficacious than Exosurf in the prevention of RDS and in reducing RDS-related mortality through 14 days after birth.

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COMPARISON OF INCIDENCES OF ALL-CAUSE MORTALITY BETWEEN THE NOVEL SURFACTANT, SURFAXIN (LUCINACTANT) AND THE ANIMAL DERIVED SURFACTANTS SURVANTA (BERACTANT) AND CUROSURF (PORACTANT ALFA)

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Background: Animal-derived, protein-containing surfactants perform better vs. non–protein-containing surfactants for prevention and treatment of Respiratory Distress Syndrome (RDS). A new generation, non–animal-derived surfactant, Surfaxin, containing a peptide that mimics the action of human SP-B, has been shown to be effective in animals, in studies of infants with RDS, I and in large, controlled studies in the prevention of RDS in preterm infants. Our objective was to compare the incidence of all-cause mortality at Days 14 and 28, and at 36 weeks postconceptional age of Surfaxin vs. Survanta and Surfaxin vs. Curosurf across two clinical trials measuring their respective safety and efficacy in the prevention of RDS.

Methods: A pooled analysis was performed across the only two Phase 3, masked, multinational, randomized trials comparing Surfaxin (5.8 mL/kg or 175 mg/kg) vs. Survanta (4.0 mL/kg or 100 mg/kg) and Curosurf (2.2 mL/kg or 175 mg/kg). All randomized patients were included. Endpoint definitions were the same for both trials. Adjustments were performed for birth weight (BW) strata and study centers. Inclusion criteria: BW 600-1250 g, gestational age <32 weeks, and successful intubation. Dosing and administration occurred within 30 min of birth. P values were calculated to assess treatment group differences using logistic regression adjusting for study center and BW strata.

Results: The pooled analysis of the two trials comparing Surfaxin with animal-derived surfactants is presented below: See table.

		Animal-derived	Surfaxin vs.	
All-cause mortality	Surfaxin	Surfactant	Animal-derived	surfactant
	(N=651)	(N=386)	p	value
By Day 14	99(15.2%)	66(17.1%)	0.245	
By Day 28	116(17.8%)	83(21.5%)	0.044	
By 26 weeks PCA*	132(20.3%)	93(24.1%)	0.045	

*Conceptual age as per last known menstruation. Analyses of further endpoints are in process and will be presented.

Conclusion: Combined data from these trials show lower all-cause mortality with Surfaxin than with the animal-derived surfactants (combined results of Survanta and Curosurf). Since Surfaxin has a higher concentration of surfactant apoprotein-equivalents—in the form of sinapultide—than any other commercially available surfactant, these results are consistent with the hypothesis that both the presence of, and a higher concentration of, surfactant protein amplify the benefits of surfactant therapy.

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RESUSCITATION WITH 100% O_2 INCREASES PULMONARY MMPS IN HYPOXIC PIGLETS

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Background: Respiration recovers faster in neonates resuscitated with ambient compared to 100% O_2. Matrix Metalloproteinase(MMPs) -9 and 2 play a role in pulmonary extracellular matrix remodelling and degradation after ischemia-reperfusion. **The objective:** Resuscitation of piglets with 100% oxygen is detrimental to pulmonary tissue compared to ambient air. We assessed MMP-9 and 2 in piglets after global hypoxia and subsequent resuscitation with ambient air or 100% O_2. **Material and Methods:** Sixty-nine piglets (12–36h of age) were resuscitated for 30min by ventilation with 21% or 100% O_2 after a hypoxic insult, and thereafter observed for 150min. In pulmonary tissue extracts and tracheal aspirate, MMPs were analysed by gelatine zymography and in situ zymography.

Results: In pulmonary tissue gelatin zymography pro-MMP-9 was increased in the resuscitated groups compared to baseline ($p<0.005$), pro- and active MMP-2 were increased in the group resuscitated with 100% oxygen compared to ambient air ($p<0.005$). In tracheal aspirate pro-MMP-9 and 2 were doubled in the ones resuscitated with 100% oxygen compared to ambient air. In situ zymography gave the same results.

Conclusion: 100% versus 21% oxygen for resuscitation of newborn piglets gives increased MMP-9 and 2 in pulmonary tissue and tracheal aspirate. Our data suggests that ambient air is less toxic to the lungs than 100% oxygen.

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IMPAIRED IL-4-ASSOCIATED GENERATION OF CCR4-EXPRESSING T CELLS IN NEONATES AT HEREDITARY ALLERGY RISK

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Background: Reduced microbial exposure in early life may be partly responsible for an increase in atopic diseases in 'westernised' societies but the underlying mechanisms remain elusive. Objective To examine how exposure to bacterial lipopolysaccharide (LPS) during the first antigen encounter might influence the maturation of neonatal lymphoid cells, and to analyse possible differences in this respect between neonates with a high risk of allergy due to family history (FH+) and controls with no apparent risk (FH-).

Methods: Cord blood mononuclear cells from the FH+ or FH- group were stimulated with pure LPS or â-lactoglobulin (â-LG) in its inherent LPS milieu. T-cell expression of chemokine receptors CCR4 and CXCR3 was determined by flow cytometry and RT-PCR. Cellular expression of IL-4 was analysed by quantitative RT-PCR, whereas IFN-ã was analysed by both quantitative RT-PCR and ELISA.

Results: Stimulation with LPS, or â-LG together with LPS, induced up-regulation of CCR4 ($P<0.05$) and CXCR3 ($P<0.05$). For CCR4 such up-regulation was related to the level of IL-4 produced by the same T cells ($rS=0.49$, $P=0.03$), whereas CXCR3 expression was negatively correlated with the IL-4 levels ($rS=-0.56$, $P=0.02$). Compared with the FH- group, the FH+ group showed a significantly lower capacity for induction of CCR4+ T cells (mean % of total T cells: FH+, 2.42% vs. FH-, 5.74%; $P<0.01$), and tended to express less IL-4 mRNA. Conversely, induction of CXCR3 and IFN-ã was not significantly different between the two groups. C

Conclusion: When the immune system in early life encounters antigen together with LPS, T-cell localization for further immune induction within lymphoid tissue is facilitated by CCR4 and CXCR3 expression. In neonates at hereditary risk of allergy this homeostatic mechanism is jeopardised due to poorly up-regulated CCR4. Conversely, Th1 responses to antigen in the presence of LPS is not reduced compared with controls.

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IMPAIRMENT OF PUTATIVE REGULATORY T CELLS IN CORD BLOOD FROM NEONATES WITH HEREDITARY ALLERGY RISK

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Background: The hygiene hypothesis suggests that the increasing prevalence of allergy in "westernised" countries is due to reduced bacterial exposure in early life, but the underlying mechanism remains elusive. **Objective:** To analyse the effect of the bacterial product lipopolysaccharide (LPS) on the generation of regulatory T (T_R) cells in neonates with allergy risk due to a family history of atopy (FH^+) and in controls without such hereditary risk (FH^-).

Methods: Cord blood mononuclear cells from the FH^+ and FH^- groups were stimulated with bovine â-lactoglobulin in an inherent LPS milieu. T-cell phenotypes indicative of T_R cells ($CD25^+$, $CD25^{high}$ and integrin $á_E^+$) and the proliferation antigen Ki-67 were quantified by flow cytometry. Release of TGF-â1 from its inactive complex was determined by ELISA.

Results: The FH^+ group showed reduced capacity for generation of $CD25^+$ T cells (FH^+, 16.2% vs. FH^-, 34.9%; $p<0.01$) and $á_E^+$ T cells (FH^+, 2.1% vs. FH^-, 3.9%; $p<0.05$). Moreover, the $CD25^{high}$ T cell subset tended to be impaired in the FH^+ group (FH^+, 5.1% vs. FH^-, 12.6%). The frequency of proliferating T cells was inversely related to the $CD25^{high}$ phenotype ($r=-0.54$, $p<0.05$), and also to the activation-induced release of TGF-â1 ($r=-0.80$, $p<0.001$).

Conclusions: This study suggested that early-life exposure to a dietary antigen in physiological LPS milieu may generate T_R cells, including the $CD25^{high}$ phenotype that was shown to be related to TGF-â activity and suppressed proliferation. This capacity was impaired in neonates with hereditary allergy risk, but clinical follow-up will be required to determine the effect on allergy emergence.