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VITAMIN D FOR PREVENTING RICKETS IN HEALTHY, FULL TERM NEWBORNS. A SYSTEMATIC REVIEW

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Objectives: To determine with a systematic review (SR) if Vitamin D, compared to placebo or no treatment, reduces rickets in healthy, full term infants.

Methods: Types of studies: Randomized controlled trials (RCT) or quasi-randomized controlled trials assessing the efficacy of vitamin D in reducing rickets in newborn infants. Types of participants: Infants born at term (>=37 weeks gestational age). Types of interventions: Vitamin D given orally or i.m. given at least for 4 weeks versus placebo or no intervention. Types of outcome measures: Primary outcome measures include clinical sign of rickets; secondary outcome measures include any of the following: bone mineralization, linear growth, radiological signs of rickets. Search strategy: A search was done on MEDLINE using the highly sensitive strategy of Dickersin, modified to exclude studies on preterm and low birth weight newborn infants. Methods of the systematic review: Standard Cochrane systematic review methods were planned. A subgroup analysis was planned to evaluate effects in formula- and breast-fed infants. **Results and conclusions:** Only two RCT fulfilling the inclusion criteria were retrived. One study was excluded because comparison was made between different doses of vitamin D. No meta-analysis was therefore performed. The single RCT enrolled 18 healthy, full term, breast-fed infants (9 placebo, 9 vitamin D at 400 U/die); 13 infants were followed up to 52 weeks (7 placebo, 6 vitamin D). Bone mineral content was higher in supplemented infants at 12 weeks, but the difference was no longer significant at 26 and 52 weeks. No infant was reported to have rickets. Based on the results of this review it is concluded that current practice and guidelines are not based on data coming from consistent, well conducted RCTs, but from data coming from observational studies.

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EOSINOPHILS AND THEIR STATE OF ACTIVATION IN PRETERM INFANTS WITH RDS AND BPD

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Background: The study aimed at investigating the role of the eosinophils in the pathogenesis of Bronchopulmonary Dysplasia (BPD).

Methods: Thirteen preterm infants with Respiratory Distress Syndrome (RDS), 15 with BPD and 16 healthy were investigated. Venous blood samples were collected from all infants and serum was analyzed for the total amount of eosinophils, neutrophils, levels of ECP and CD9.

Results: The eosinophil count was significantly increased in infants with BPD compared to RDS and healthy infants (1414, 797 and 471 PBE/microliter respectively, p=0.03). Furthermore, significantly increased levels of ECP (p=0,002), decreased EG2 and lower levels of CD9 (p=0,01) point at activation of eosinophils. These differences cannot be explained by the differences in GA and BW between the three groups of infants. Moreover, the ECP levels at four weeks of age, were positively correlated with the duration of supplemental oxygen. The eosinophil count fell promptly when steroid treatment was started in the BPD group.

Conclusions: Our findings support the concept of an eosinophil contribution to the pathogenesis of BPD in infants. Table. Immunological expressions of eosinophilic activities at four weeks of postnatal age. Data depict median (min-max).

	RDS	BPD	Healthy	Significance level	Difference
Eosinophils PBE/μL	797 (269–3056)	1414 (383–4353)	471 (184–2020)	p=0.03	CLD*RDS=Healthy
ECP μg/L	12.8 (3,9–44)	34(7.1–89)	9.8(4.2–29)	p=0.002	CLD*RDS=Healthy
EG2 MFI	27.4(14.9–45.7)	22.9(19.7–35.4)	29.9(18.1–49)	p=0.09	ns
CD9 MFI	94(66.5–118.2)	74.5(64.3–99.6)	86.2(31–125.8)	p=0.01	CLD*RDS=Healthy

* depicts statistically significant difference

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ANTIMICROBIAL COMPONENTS OF VERNIX CASEOSA

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Background: In late pregnancy, the oily secretion sebum together with the shed peridermal cells makes up a lipid rich substance, called vernix caseosa. Vernix acts as a biofilm, covering the surface of newborn babies. Until now, it's function has mainly been thought to minimize excessive water loss. We have identified a number of antimicrobial components in vernix, such as antimicrobial peptides that act by disrupting cytoplasmic membranes, indicating an active protection against microbes by vernix. Antimicrobial peptides are of various origins and are considered to be significant in the first line of host defense among diverse groups of organisms, ranging from plants to mammals. The aim of this study was to identify novel antimicrobial components of vernix, e.g. peptides and lipids, that are active against group B streptococcus (GBS) and *E. coli*, and to study the relationship between surface protection of neonates and the antimicrobial activity found in vernix.

Methods: Vernix samples were collected from 82 newborns. Superficial skin cultures were analyzed from all neonates to evaluate bacterial colonization. Extracts from vernix samples were prepared and each extract was screened for activity against GBS and *E. coli*. Both active and inactive extracts were analysed by HPLC. Purification of the active extracts were carried out in order to identify the active component. Component of apparently pure HPLC fraction was characterized by MS/MS analysis.

Results: Fifteen groups of bacteria were found to colonize the surface of the 82 babies. One was not colonized by bacteria, 26 were colonized with one group of bacteria, 33 were colonized with two groups, 19 were colonized with three groups, and three were colonized with four groups. Sixtyfive extracts showed activity against GBS, and 21 extracts against *E. coli*. The quantity of the active component in each extract was shown to vary according to the activity of the extracts. One HPLC fraction was active against both GBS and *E. Coli*. The active component in this fraction has been purified and identified as a lipid.

Conclusion: Our results reveal an antimicrobial component found in vernix that is active against both Gram positive and Gram negative bacteria. In order to find a potential relationship between antimicrobial components of vernix and the colonization data further investigation is needed. This includes identification of more antimicrobial components, measurements of their expression levels, and studies of their synergistic interaction.

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THE EFFECTIVENESS OF NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION VS CONTINOUS POSITIVE AIRWAY PRESSURE TO REDUCE THE DURATION OF RESPIRATORY SUPPORT AND THE INCIDENCE OF BRONCHOPULMONARY DISPLASIA

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Aims: To compare the efficacy of nasal intermittent positive-pressure ventilation (NIPPV) with nasal continous positive airway pressure (NCPAP) in neonates with less 34 weeks of gestation in the early stages of moderate respiratory distress syndrome (RDS).

Methods: A prospective, randomized trial was performed. NCPAP was delivered at an end-expiratory pressure varying from 2 to 6 cm H2O, while peak pressure of 14–20 cm H2O and end-expiratory pressure of 2–6 cm H2O were used NIPPV at ventilatory rates of 40 breath per minute.

Results: Between January 2001 and January 2003, 128 infants with RDS (<34 weeks' GA) were admitted to the NICU; (all in-born). 66 of 128 were eligible for enrolment in this study; the other 62 infants were matched one of the exclusion criteria. 30 infants were randomised to NCPAP and 32 infants to NIPPV. Study infants also were similar in all characteristics. At time 4 hours, there was no difference in the paO2 values between the groups, but infants treated with NIPPV showed significantly lower pCO2 values at time 4 (36 + 2 vs 58 + 4). Also, the NIPPV group showed a lower incidence of apneic episodes (0.4 + 0.3 vs 0.9 + 02) and a shorter time of respiratory support with both differences reaching statistical significance (480 + 20 vs 740 +20).Two infants needed endotracheal intubation, one for each group. Side effects were similar for either groups. Bronchopulmonary dysplasia at 36 wekks (BPD 36-wk) was observed in 9 patients of NCPAP group and 3 of NIPPV group.

Conclusions: Our clinical trial has showed that NIPPV is an effective methodic for treatment of moderate RDS in preterm infants, it is efficacy in reducing apnea episodes, and it reduces the time of ventilatory support for the preterm with RDS. The reduction of the duration of ventilation was remarkable, reduced the hospital stay and costs of treatment; furthermore, it could a reduce the risk for developing bronchopulmonary dysplasia.We suggest that a trial of noninvasive ventilation using an alternative to initial intubation shoul be considered, so that to reducing neonatal morbidity speculating on a decreased ventilator-induced trauma and oxigen toxicity. We believe that the use of noninvasive ventilatory techniques will significantly reduce neonatal morbidity, and hope that our observations will stimulate additional prospective evaluations of these approaches. References: 1.Khalaf MN, et al Pediatrics 2001 ;108 :13–17; 2. De Paoli AG et al. Acta Paed 2003;92:70–75 3. M.Bisceglia et al.Ped Research 2003;54:571

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VIRULENCE FACTORS IN NEONATAL BLOOD ISOLATES OF STAPHYLOCOCCUS EPIDERMIDIS

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Background: *Staphylococcus epidermidis* is the predominating etiology of neonatal septicemia in industrilized countries, but specific virulence factors associated with *S. epidermidis* are incompletely described. The aim of the present study was to investigate possible virulence factors representing different pathogenetic steps in neonatal blood isolates of *S. epidermidis*: a) Up-regulation of inflammatory activity in endothelial cells b) the ability to express bacterial surface proteins and biofilm of importance for bacterial colonization and c) antibiotical resistance.

Methods: All blood isolates of *S. epidermidis* collected at the neonatal intensive care unit, Örebro University Hospital, Sweden 1990 - 97 were classified as representing sepsis (n=12) or contaminants (n=38) and compared according to endothelial activation and to the prevalence of genes encoding for biofilm-production (ica ABD), fibrinogen-binding protein (fbe) and meticillin resistance (mecA). Endothelial cells were prepared from umbilical veins (HUVEC) and challenged by the different bacterial strains. The endothelial release of Intracellular Adhesion Molecule 1 (ICAM-1), endothelial selectin (E-selectin), vascular cell adhesion molecule 1 (VCAM-1) and interleukin-8 (IL-8) was investigated by an ELISA-assay. Endothelial cell death was determined by light microcopy. The genes of ica ABD, fbe and mecA were detected by PCR and biofilm-production was investigated by trypan-blue-staining.

Results: The sepsis-strains of *S. epidermidis* induced a significantly higher endothelial release of ICAM-1 (p=0.021, Mann-Whitney-U), E-selectin (p=0.002) and IL-8 (p=0.010) compared to the contaminants. The sepsis-strains also turned out to be more cytotoxic to HUVEC; Nine out of twelve sepsis strains induced > 50% cytotoxicity to HUVEC compared to 15/38 contaminant strains (p=0.047, Fischer's exact test). The prevalence of the ica-operon, biofilm-production, fbe- or mecA-genes did not discriminate between sepsis- and contaminants strains. None of the investigated bacterial strains induced endothelial release of VCAM-1.

Conclusion: Sepsis strains of *S. epidermidis* induced a higher endothelial release compared to contaminants of inflammatory mediators involved in the recruitment of cirkulating neutrophils . This might reflect important steps in the pathogenesis of neonatal *S. epidermidis* sepsis. In neonatal infections biofilm-producing properties of *S. epidermidis* might be less important.

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SURFACTANT TREATMENT DURING CONTINUOUS POSITIVE AIRWAY PRESSURE - A SAFE ALTERNATIVE FOR MODERATELY PRETERM INFANTS

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Background: Mechanical ventilation (MV) is one of the cornerstones in the treatment of preterm infants with Respiratory Distress Syndrome (RDS). However, MV also contributes to lung injury and is one of the major risk factors for later development of Bronchopulmonary Dysplasia (BPD). A treatment strategy with surfactant administration during nasal Continuous Positive Airway Pressure (nCPAP) significantly reduces the number of preterm infants with RDS requiring MV. The objective was to follow-up on the effects after implementing surfactant treatment during a brief intubation, INSURE (i.e. INtubation SURfactant Extubation) in combination with nCPAP for moderately preterm infants with RDS.

Methods:A retrospective, descriptive study of 2 Swedish neonatal units (Karolinska and Huddinge) over a 10-year period (1993–2002), during which the INSURE-strategy was implemented in one unit (Huddinge, 1998). All infants with a gestational age of ≥27 to <34 weeks and RDS were included. Arterial to alveolar oxygen ratio (A/a ratio) at treatment start was used to assess severity of lung disease for infants treated with surfactant and/or MV. Outcome parameters such as BPD, air leaks, intracranial hemorrhage, retinopathy and mortality were compared.

Results:488 infants were included. During the first 5 years of the study period similar numbers of infants required MV at both units. After implementing the INSURE strategy at Huddinge in 1998 there was a 68% reduction in the number of infants treated with MV. At Karolinska the treatment strategy remained unchanged with approximately 64% of infants with RDS receiving MV, compared to 20% at Huddinge. This could not be explained by differences in the population, the mean gestational age was 29 weeks in both units, mean birth weight 1324 and 1397 g at Karolinska and Huddinge respectively. The a/A ratio was 0.15±0.07 versus 0.17±0.04 at treatment start indicating similar disease severity. There were no significant differences in the outcome parameters.

Conclusion: The study confirms the results of previous reports showing that surfactant treatment in combination with nCPAP effectively reduces the need for mechanical ventilation in preterm infants with RDS. We found no differences in morbidity and mortality indicating that the INSURE strategy is equally safe as MV. The procedure was quick and well tolerated by the infants, although experience in good CPAP care is a prerequisite. The theoretical benefits of avoiding unnecessary trauma to the lungs remains to be further investigated.