distinguish the early initiators of NEC from the later consequences of the disease pathology. To elucidate the mechanisms and identify clinical interventions, animal models showing spontaneous NEC development may help. In this review, we summarize some recent results from studies on preterm pigs during the early feeding-induced mucosal dysfunction and later NEC development. We show that introduction of suboptimal enteral formula diets, coupled with parenteral nutrition, predispose to disease, while advancing amounts of mother's milk from birth protects against disease. Hence, the transition from parenteral to enteral nutrition shortly after birth plays a pivotal role to secure gut growth, digestive maturation and an appropriate response to bacterial colonization in the sensitive gut of preterm neonates. Ongoing studies in preterm pigs aim to identify the optimal time, amount and diet of the first enteral milk that best secure both early gut adaptation and later body growth and health.

183 PREVENTION OF NECROTISING ENTEROCOLITIS

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Necrotising enterocolitis (NEC) is a potentially disastrous illness that occurs in 6–8% of preterm (gestation < 32 weeks) very low birth weight neonates. The mortality (~25%) and morbidity of ≥ Stage II NEC (e.g. need for surgery, survival with short bowel syndrome with protracted feed intolerance, complications of prolonged dependence on parenteral nutrition, recurrent infections, and prolonged hospital stay) is significant. The incidence (10–12%), mortality (40–45%), and morbidity including need for surgery, and risk of long-term neurodevelopmental impairment after surviving surgery for NEC is worse in extremely low birth weight neonates. The economic burden of NEC is substantial (~500 million to 1 billion dollars per year in the USA) considering the prolonged hospital stay due to the associated complications. NEC has become one of the common causes of death in preterm neonates surviving the first week of life. The pathogenesis of NEC remains poorly understood despite decades of research. Prevention of prematurity, the single most important risk factor for the illness, has proved to be a difficult task. The absolute number of preterm neonates at risk for the illness has increased with advances in neonatal intensive care. Prevention of NEC has thus become a priority. The well established (e.g. antenatal glucocorticoids, early preferential feeding with breast milk, standardised feeding protocols) as well as newer strategies (e.g. probiotics, prebiotics) for primary as well as potentially secondary (e.g. pentoxifylline, bosentan) prevention of NEC will be reviewed.

184 INTRAPERITONEAL CYTIDINE 5′-DIPHOSPHOCHOLINE (CDP-CHOLINE) ADMINISTRATION REDUCES THE SEVERITY OF INTESTINAL INJURY IN A NEONATAL RAT MODEL OF NECROTIZING ENTEROCOLITIS

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Background The aim of this study was to evaluate the possible cytoprotective effect of CDP-choline treatment on intestinal cell death and apoptosis in a neonatal rat model of NEC.
Methods A total of 30 newborn pups were divided equally into 3 groups as follows: Control, NEC, and NEC+CDP-choline groups. NEC was induced by enteral formula feeding, exposure to hypoxia-hyperoxia and cold stress. CDP-choline was administered intraperitoneally at a dose of 300 mg/kg/day for 3 days starting from the first day of life. Macroscopical, histopathological, ibflammatory markers, caspase-3 expression and apoptosis were evaluated on the gut samples. Activities of xanthine oxidase, superoxide dismutase, glutathione peroxidase, malondialdehyde and myeloperoxidase were determined.
Results Median clinical sickness score, macroscopic gut assessment score and intestinal injury score were significantly improved in pups in NEC+CDP-choline group. In contrast, median apoptosis score was significantly higher in NEC group compared with NEC+CDP-choline group. Proinflammatory cytokine concentrations (IL-1β, IL-6 and TNF-α) and caspase-3 expression in the intestinal tissue of the NEC+CDP-choline group were significantly lower. Moreover, tissue GSH-Px and SOD activities were preserved, whereas tissue MDA content, MPO and XO activities were significantly lower in NEC+CDP-choline group.
Conclusion This is the first study to report beneficial effects of CDP-choline treatment on intestinal injury in a neonatal rat model of NEC. Intraperitoneal CDP-choline administration significantly reduced clinical sickness score, ameliorated macroscopic and histopathological intestinal injury, reduced the inflammation and decreased apoptosis. These data suggest that, CDP-choline may be used as an effective therapeutic agent for prevention of NEC.

185 MESENTERIC ARTERY REACTIVITY AND SMALL INTESTINE MORPHOLOGY IN A CHICKEN MODEL OF HYPOXIA-INDUCED FETAL GROWTH RESTRICTION

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Background and aims Infants with intrauterine growth retardation are prone to intestinal dysfunction which is manifested by feeding intolerance and, in the most severe cases, necrotizing enterocolitis. The morphological and molecular mechanisms that lead to these complications are not completely understood and suitable experimental models are necessary. We aimed to characterize mesenteric artery (MA) reactivity, small intestine morphometry and intestinal expression of VEGF in a chicken model of hypoxia-induced fetal growth restriction.
Methods Chicken embryos (15 and 19 days) and hatchlings (< 3-h-old and 1-d-old) were incubated under hypoxic (15% O_2 from day 0 to day 19 of incubation) or normoxic conditions. Vascular reactivity was studied using wire miography. Intestinal morphometry was assessed in hematoxyline-eosine-stained sections. The expression of VEGF mRNA was determined by RT-PCR analysis.
Results Hypoxia altered the responsiveness of chicken embryo MAs to acetylcholine, the NO donor sodium nitroprusside and the constrictor polypeptide ET-1. However, the majority of these alterations, with the exception of the hyperresponsiveness to ET-1, were not present in the hypoxic hatchlings. When intestinal histology was analyzed, subtle hypoxia-induced changes were noted in the muscularis propia and the villi from the hatchlings. Hypoxic incubation also diminished the expression of VEGF mRNA in the terminal ileum of the hatchlings.
Conclusions Chronic moderate hypoxia during incubation results in subtle but significant alterations in chicken MA reactivity, small intestine morphology and VEGF expression. Whether these alterations may have a direct effect on the functional status of the intestine remains to be investigated.

186 PROTECTIVE EFFECTS OF COLCHICINE IN AN EXPERIMENTAL MODEL OF NECROTIZING ENTEROCOLITIS IN NEONATAL RAT

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Introduction The pathophysiology of necrotizing enterocolitis (NEC) includes massive production of endogenous cytokines with exaggerated activation of inflammatory pathways. Colchicine has been used as an anti-inflammatory agent. The aim of this study was to investigate the possible beneficial effects of colchicine in a neonatal rat model of NEC.
Methods Rats were randomly divided into 3 groups: control group; saline-treated NECgroup; colchicine-treated NEC group. NEC was induced by hyperosmolar enteral formula feeding and exposure to hypoxia/reoxygenation after cold stress. Intestinal samples were harvested for biochemical and histopathological analysis.
Results The grade of intestinal injury of pups in the saline-treated NEC group was found to be significantly higher than in the control or the colchicine-treated groups ($p<0.001$, $p=0.003$; respectively). Median level of intestinal malondialdehyde was significantly higher in the saline-treated NEC group compared to the control group ($p=0.006$) and the colchicine-treated group ($p=0.015$). Significantly higher activities of intestinal superoxide dismutase and glutathione peroxidase activities were observed in the colchicine-treated NEC group compared to the saline-treated group ($p=0.033$ and $p=0.030$; respectively). Tissue levels of tumor necrosis factor- α and interleukin 1β were significantly higher in the saline-treated NEC group compared to rats in the colchicine-treated group ($p<0.001$, $p=0.003$; respectively). A comparison of saline-treated and colchicine-treated NEC pups revealed that treatment with colchicine was associated with significantly lower tissue levels of TNF- α and IL-1β ($p<0.01$, both).
Conclusion We observed that; in this model of NEC**,** colchicine has favorable effects onintestinal histological and biochemical changes.

187 SYSTEMATIC REVIEW OF RANDOMIZED CONTROL TRIALS TO REVIEW THE ROLE OF PREBIOTICS IN PREVENTION OF NECROTIZING ENTEROCOLOITIS IN PRETERM NEWBORNS

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Background and aims Necrotizing enterocolitis (NEC) is an important cause of mortality and serious morbidity in preterm infants. Prebiotics are specific oligosaccharides which have been shown to promote proliferation of beneficial bacteria in gut. This systematic review aims to review the literature to investigate the role of prebiotics in the prevention of NEC in preterm infants.
Methods Electronic databases CSDR-DARE, MEDLINE, CINAHL, EMBASE, Scopus, Web of science were serached from the date of inception to March 27, 2012. Additional citations were retrieved from the bibliography of the selected articles, Google scholarand abstracts of conference proceedings. The eligible studies were RCTs or quasi-RCTs enrolling inpatient preterm infants that compared use of Prebiotics (any dose and duration) with control (placebo/no treatment) for the outcomes of NEC (stage >=2 Bell's classification, perforation and any stage), growth and any other potentially beneficial effect or serious side-effects. Two independent reviewers extracted the data and assessed the risk of bias in included studies. Descripencies were resolved with consensus.
Results 14 studies fulfilled the inclusion criteria. None reported on the primary outcome of stage>=2 NEC. Two RCT reported on NEC (any stage) and showed no significant difference between the groups. There was no difference noted in the growth parameters [(weight & length (3 studies); head growth (2 studies)]. There was a trend towards higher stool frequency (one study) and higher Bifidobacterium count in stool (2 studies) in the Prebiotic group.
Conclusion Current data is insufficient to recommend the use of Prebiotics in preterm infants for prevention of NEC.

188 ANALGESIA AND SEDATION IN CRITICALLY ILL CHILDREN; LOCAL RELIGION OR EVIDENCE BASED?

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Over the last decade increasingly RCT's have been published about optimal dosing of opioids and benzodiazepines in critically ill children of different age groups.

In this way progress is made about optimal dosing as well as combination of therapies against the background of the use of novel ways of trial design.

To this effect the application of population pharmacokinetics-pharmacodynamics (NON-MEM) using spare data have guided the design of trials preceded by in vitro simulation and prediction of dose effect responses.

Both in the premature infant as well as in the so-called surgical newborn, dosages have been adjusted based on solid observational and experimental data sets for which the results should be evaluated. Apart from short term pharmacodynamic parameters such as validated pain scores, and eventually pharmacokinetic data analysis potentially equally important is the evaluation of long term consequences both of neonatal pain and the use of opioids. Experimental data have revealed increased neuro apoptosis in the developing brain. The data of a number of RCT's conducted by our group will be combined with prospective longitudinal data recently acquired combining quantitative sensory testing (QST) under conditions of fMRI.

In this way the question whether neonatal pain and/or opioid use results in altered pain response and long term negative sequelae can be answered.

189 STILL HURTING NEWBORN BABIES EIGHT YEARS AFTER WE FOUND OUT!

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Objective To study whether new pharmacological and non-pharmacological guidelines lowered numbers of painful procedures in neonates and changed the amount and frequency of analgesic therapy as compared to the results of our previous study in 2001.
Design A prospective observational study.Setting: Level III NICU of the Erasmus MC-Sophia Children's Hospital, Rotterdam.
Participants Neonates admitted at postnatal ages less than 3 days with length of stay at least 72 hours.
Main outcome measures Number of all potentially painful procedures and analgesic therapy recorded at the bedside during the first 14 days of NICU stay.
Results A total number of 21076 procedures were performed in the 175 neonates studied during 1730 patient-days (mean 12.2). The mean number of painful procedures per neonate per day was 11.4 (SD 5.7), significantly lower than the number of 14.3 (SD 4.0) in 2001 ($p<0.001$). The use of analgesics was 36.6% compared to 60.3% in 2001. Failed procedures encompassed sixty-three percent of all peripheral arterial line insertions vs. 37.5% in 2001 and 9.1% venipunctures vs. 21% in 2001.