Chapter Three Citations

1. **A meta-analysis of the efficacy of ocular prophylactic agents used for the prevention of gonococcal and chlamydial ophthalmia neonatorum**

Abstract

"INTRODUCTION:

Neonatal eye prophylaxis has been routine in North America for more than a century. Contextual changes justify reexamining this practice, and prompted a systematic review of the efficacy of prophylactic agents.

METHODS:

We searched MEDLINE (1966-2008), EMBASE (1980-2008), CINAHL (1982-2008), and the Cochrane library (the first quarter of 2008) for relevant clinical trials and hand-searched the resulting reference lists. We independently evaluated eligibility and study quality. Meta-analyses were performed using a random effects model.

RESULTS:

Each of the eight included studies had substantial methodologic weaknesses. Data to estimate the efficacy of prophylaxis in the prevention of gonococcal ophthalmia neonatorum (GON) were not available. One study found no differences in rates of chlamydial ophthalmia neonatorum (CON) when three agents were compared to no prophylaxis: silver nitrate (relative risk [RR] = 1.06; 95% confidence interval [CI], 0.55-2.02; 2225 newborns), erythromycin (RR = 0.93; 95% CI, 0.48-1.79; 2306 newborns), and tetracycline (RR = 0.82; 95% CI, 0.42-1.63; 2299 newborns). No statistically significant differences were found between agents in the prevention of GON. Erythromycin and povidone-iodine both decrease the risk of CON when compared to silver nitrate (RR = 0.71; 95% CI, 0.52-0.97; 4514 newborns, and RR = 0.52; 95% CI, 0.38-0.71; 2005 newborns, respectively).

DISCUSSION:

Failure rates of universal eye prophylaxis support reexamination of this policy where the prevalence of maternal infection is low."

Link

http://www.ncbi.nlm.nih.gov/pubmed/20630358

Reference

Darling, Elizabeth K., and Helen Mcdonald. "A Meta-analysis of the Efficacy of Ocular Prophylactic Agents Used for the Prevention of Gonococcal and Chlamydial Ophthalmia Neonatorum." Journal of Midwifery & Women's Health 55.4 (2010): 319-27.

2. **Aluminum in pediatric parenteral nutrition products: measured versus labeled content.**

Abstract

"***OBJECTIVE:***

Aluminum is a contaminant in all parenteral nutrition solutions. Manufacturers currently label these products with the maximum aluminum content at the time of expiry, but there are no published data to establish the actual measured concentration of aluminum in parenteral nutrition solution products prior to being compounded in the clinical setting. This investigation assessed quantitative aluminum content of products commonly used in the formulation of parenteral nutrition solutions. The objective of this study is to determine the best products to be used when compounding parenteral nutrition solutions (i.e., those with the least amount of aluminum contamination).

METHODS*:*

All products available in the United States from all manufacturers used in the production of parenteral nutrition solutions were identified and collected. Three lots were collected for each identified product. Samples were quantitatively analyzed by Mayo Laboratories. These measured concentrations were then compared to the manufacturers' labeled concentration.

RESULTS:

Large lot-to-lot and manufacturer-to-manufacturer differences were noted for all products. Measured aluminum concentrations were less than manufacturer-labeled values for all products.

CONCLUSIONS:

The actual aluminum concentrations of all the parenteral nutrition solutions were significantly less than the aluminum content based on manufacturers' labels. These findings indicate that 1) the manufacturers should label their products with actual aluminum content at the time of product release rather than at the time of expiry, 2) that there are manufacturers whose products provide significantly less aluminum contamination than others, and 3) pharmacists can select products with the lowest amounts of aluminum contamination and reduce the aluminum exposure in their patients."

Link

http://www.ncbi.nlm.nih.gov/pubmed/22477831

Reference

Poole, Robert L., Linda Schiff, Susan R. Hintz, Allison Wong, Nicol Mackenzie, and John A. Kerner. "Aluminum Content of Parenteral Nutrition in Neonates: Measured Versus Calculated Levels." Journal of Pediatric Gastroenterology and Nutrition 50.2 (2010): 208-11.

3. Duration of Protection After Infant Hepatitis B Vaccination Series

Abstract

"**BACKGROUND:**

Little is known about duration of protection after the infant primary series of hepatitis B (HB) vaccine in settings of low HB endemicity. This study sought to determine the proportion of adolescents immunized as infants who had protective titers of antibody to hepatitis B surface antigen (anti-HBs) before and after a challenge dose of vaccine.

METHODS:

US-born 16- through 19-year-olds who received a recombinant HB vaccine 3-dose series initiated within 7 days of birth (group 1) or at ≥4 weeks of age (group 2) and completed by 12 months of age were enrolled. Participants had serologic testing before and 2 weeks after randomization to receive a challenge dose of 10 µg or 20 µg of Engerix-B. Baseline and postchallenge levels of anti-HBs were compared by group, challenge dosage, and demographic and behavioral characteristics.

RESULTS:

At baseline, 24% had protective anti-HBs levels of ≥10 IU/mL; 92% achieved protective levels after challenge dose. Although group 1 had a lower proportion of seroprotection at baseline, group and challenge dosage were not associated with postchallenge proportion of seroprotection. Being in group 2, higher test dosage, higher baseline geometric mean titer, and nonwhite race were associated with significantly higher geometric mean titer after challenge dose.

CONCLUSIONS:

More than 90% of study participants immunized against HB as infants exhibited a seroprotective response to a challenge dose of vaccine. Duration of protection from the primary infant HB vaccine series extended through the adolescent years in the setting of low HB endemicity."

Link

http://pediatrics.aappublications.org/content/133/6/e1500

Reference

"Duration of Protection After Infant Hepatitis B Vaccination Series." Pediatrics 133.6 (2014).

4. **Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age**

Abstract

"**Importance**

Prevention of iron deficiency in infancy may promote neurodevelopment. Delayed umbilical cord clamping (CC) prevents iron deficiency at 4 to 6 months of age, but long-term effects after 12 months of age have not been reported.

Objective

To investigate the effects of delayed CC compared with early CC on neurodevelopment at 4 years of age.

Design, Setting, and Participants

Follow-up of a randomized clinical trial conducted from April 16, 2008, through May 21, 2010, at a Swedish county hospital. Children who were included in the original study (n = 382) as full-term infants born after a low-risk pregnancy were invited to return for follow-up at 4 years of age. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and Movement Assessment Battery for Children (Movement ABC) scores (collected between April 18, 2012, and July 5, 2013) were assessed by a blinded psychologist. Between April 11, 2012, and August 13, 2013, parents recorded their child's development using the Ages and Stages Questionnaire, Third Edition (ASQ) and behavior using the Strengths and Difficulties Questionnaire. All data were analyzed by intention to treat.

Interventions

Randomization to delayed CC (≥180 seconds after delivery) or early CC (≤10 seconds after delivery).

Main Outcomes and Measures

The main outcome was full-scale IQ as assessed by the WPPSI-III. Secondary objectives were development as assessed by the scales from the WPPSI-III and Movement ABC, development as recorded using the ASQ, and behavior using the Strengths and Difficulties Questionnaire.

Results

We assessed 263 children (68.8%). No differences were found in WPPSI-III scores between groups. Delayed CC improved the adjusted mean differences (AMDs) in the ASQ personal-social (AMD, 2.8; 95% CI, 0.8-4.7) and fine-motor (AMD, 2.1; 95% CI, 0.2-4.0) domains and the Strengths and Difficulties Questionnaire prosocial subscale (AMD, 0.5; 95% CI, >0.0-0.9). Fewer children in the delayed-CC group had results below the cutoff in the ASQ fine-motor domain (11.0% vs 3.7%; $P = .02$) and the Movement ABC bicycle-trail task (12.9% vs 3.8%; $P = .02$). Boys who received delayed CC had significantly higher AMDs in the WPPSI-III processing-speed quotient (AMD, 4.2; 95% CI, 0.8-7.6; $P = .02$), Movement ABC bicycle-trail task (AMD, 0.8; 95% CI, 0.1-1.5; $P = .03$), and fine-motor (AMD, 4.7; 95% CI, 1.0-8.4; $P = .01$) and personal-social (AMD, 4.9; 95% CI, 1.6-8.3; $P = .004$) domains of the ASQ.

Conclusions and Relevance

Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country."

Link

http://archpedi.jamanetwork.com/article.aspx?articleid=2296145

Reference

Andersson, Ola, Barbro Lindquist, Magnus Lindgren, Karin Stjernqvist, Magnus Domellöf, and Lena Hellström-Westas. "Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age." JAMA Pediatrics JAMA Pediatr 169.7 (2015): 631.

5. Maternal status regulates cortical responses to the body odor of newborns

Abstract

“Studies in non-human mammals have identified olfactory signals as prime mediators of mother-infant bonding and they have been linked with maternal attitudes and behavior in our own species as well. However, although the neuronal network processing infant cues has been studied for visual and auditory signals; to date, no such information exists for chemosensory signals. We contrasted the cerebral activity underlying the processing of infant odor properties in 15 women newly given birth for the first time and 15 women not given birth while smelling the body odor of unfamiliar 2 day-old newborn infants. Maternal status-dependent activity was demonstrated in the thalamus when exposed to the body odor of a newly born infant. Subsequent regions of interest analyses indicated that dopaminergic neostriatal areas are active in maternal-dependent responses. Taken together, these data suggests that body odors from 2 day-old newborns elicit activation in reward-related cerebral areas in women, regardless of their maternal status. These tentative data suggests that certain body odors might act as a catalyst for bonding mechanisms and highlights the need for future research on odor-dependent mother-infant bonding using parametric designs controlling for biological saliency and general odor perception effects.”

Link

http://journal.frontiersin.org/article/10.3389/fpsyg.2013.00597/full

Reference

Lundström, Johan N., Annegret Mathe, Benoist Schaal, Johannes Frasnelli, Katharina Nitzsche, Johannes Gerber, and Thomas Hummel. "Maternal Status Regulates Cortical Responses to the Body Odor of Newborns." Frontiers in Psychology Front. Psychol. 4 (2013)

6. Mechanisms of acetaminophen-induced cell death in primary human hepatocytes.

Abstract

“Acetaminophen (APAP) overdose is the most prevalent cause of drug-induced liver injury in western countries. Numerous studies have been conducted to investigate the mechanisms of injury after APAP overdose in various animal models; however, the importance of these mechanisms for humans remains unclear. Here we investigated APAP hepatotoxicity using freshly isolated primary human hepatocytes (PHH) from either donor livers or liver resections. PHH were exposed to 5mM, 10mM or 20mM APAP over a period of 48 h and multiple parameters were assessed. APAP dose-dependently induced significant hepatocyte necrosis starting from 24h, which correlated with the clinical onset of human liver injury after APAP overdose. Interestingly, cellular glutathione was depleted rapidly during the first 3h. APAP also resulted in early formation of APAP-protein adducts (measured in whole cell lysate and in mitochondria) and mitochondrial dysfunction, indicated by the loss of mitochondrial membrane potential after 12h. Furthermore, APAP time-dependently triggered c-Jun N-terminal kinase (JNK) activation in the cytosol and translocation of phospho-JNK to the mitochondria. Both co-treatment and post-treatment (3h) with the JNK inhibitor SP600125 reduced JNK activation and significantly attenuated cell death at 24h and 48h after APAP. The clinical antidote N-acetylcysteine offered almost complete protection even if administered 6h after APAP and a partial protection when given at 15 h.

CONCLUSION:

These data highlight important mechanistic events in APAP toxicity in PHH and indicate a critical role of JNK in the progression of injury after APAP in humans. The JNK pathway may represent a therapeutic target in the clinic.”

Link

http://www.ncbi.nlm.nih.gov/pubmed/24905542

Reference

Xie, Yuchao, Mitchell R. Mcgill, Kenneth Dorko, Sean C. Kumer, Timothy M. Schmitt, Jameson Forster, and Hartmut Jaeschke. "Mechanisms of Acetaminophen-induced Cell Death in Primary Human Hepatocytes." Toxicology and Applied Pharmacology 279.3 (2014): 266-74.

7. **Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations.**

Abstract

“Immune challenges during early development, including those vaccine-induced, can lead to permanent detrimental alterations of the brain and immune function. Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of aluminum (Al) adjuvants through routine vaccinations. According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic. Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs. When assessing adjuvant toxicity in children, several key points ought to be considered: (i) infants and children should not be viewed as "small adults" with regard to toxicological risk as their unique physiology makes them much more vulnerable to toxic insults; (ii) in adult humans Al vaccine adjuvants have been linked to a variety of serious autoimmune and inflammatory conditions (i.e., "ASIA"), yet children are regularly exposed to much higher amounts of Al from vaccines than adults; (iii) it is often assumed that peripheral immune responses do not affect brain function. However, it is now clearly established that there is a bidirectional neuro-immune cross-talk that plays crucial roles in immunoregulation as well as brain function. In turn, perturbations of the neuro-immune axis have been demonstrated in many autoimmune diseases encompassed in "ASIA" and are thought to be driven by a hyperactive immune response; and (iv) the same components of the neuro-immune axis that play key roles in brain development and immune function are heavily targeted by Al adjuvants. In summary, research evidence shows that increasing concerns about current vaccination practices may indeed be warranted. Because children may be most at risk of vaccine-induced complications, a rigorous evaluation of the vaccine-related adverse health impacts in the pediatric population is urgently needed.”

Link

http://www.ncbi.nlm.nih.gov/pubmed/22235057

Reference

Tomljenovic, L., and C. Shaw. "Mechanisms of Aluminum Adjuvant Toxicity and Autoimmunity in Pediatric Populations." Lupus 21.2 (2012): 223-30.

8. Ritual circumcision and risk of autism spectrum disorder in 0- to 9-year-old boys: national cohort study in Denmark

Abstract

"**Objective**

Based on converging observations in animal, clinical and ecological studies, we hypothesised a possible impact of ritual circumcision on the subsequent risk of autism spectrum disorder (ASD) in young boys.

Design

National, register-based cohort study.

Setting

Denmark.

Participants

A total of 342,877 boys born between 1994 and 2003 and followed in the age span 0–9 years between 1994 and 2013.

Main outcome measures

Information about cohort members' ritual circumcisions, confounders and ASD outcomes, as well as two supplementary outcomes, hyperkinetic disorder and asthma, was obtained from national registers. Hazard ratios (HRs) with 95% confidence intervals (CIs) associated with foreskin status were obtained using Cox proportional hazards regression analyses.

Results

With a total of 4986 ASD cases, our study showed that regardless of cultural background circumcised boys were more likely than intact boys to develop ASD before age 10 years (HR = 1.46; 95% CI: 1.11–1.93). Risk was particularly high for infantile autism before age five years (HR = 2.06; 95% CI: 1.36–3.13). Circumcised boys in non-Muslim families were also more likely to develop hyperkinetic disorder (HR = 1.81; 95% CI: 1.11–2.96). Associations with asthma were consistently inconspicuous (HR = 0.96; 95% CI: 0.84–1.10).

Conclusions

We confirmed our hypothesis that boys who undergo ritual circumcision may run a greater risk of developing ASD. This finding, and the unexpected observation of an increased risk of hyperactivity disorder among circumcised boys in non-Muslim families, need attention, particularly because data limitations most likely rendered our HR estimates conservative. Considering the widespread practice of non-therapeutic circumcision in infancy and childhood around the world, confirmatory studies should be given priority."

Link

http://jrs.sagepub.com/content/early/2015/01/07/0141076814565942.full

Reference

Frisch, M., and J. Simonsen. "Ritual Circumcision and Risk of Autism Spectrum Disorder in 0- to 9-year-old Boys: National Cohort Study in Denmark." Journal of the Royal Society of Medicine 108.7 (2015): 266-79.

Abstract

Link

Reference

Abstract

Link

Reference