Welcome to the latest issue of Paediatrics Research Review.

In this issue, we report an interesting intervention for promoting parent-child interactions and language development in children, the MORDOR II trial evaluates the benefits of mass azithromycin administration on childhood mortality in Niger, and a US simulation study demonstrates that DTaP vaccines confer imperfect but long-lived protection. An intriguing study shows how Google Glass® technology can improve social behaviour in children with ASD, a randomised controlled trial supports the use of early subthreshold aerobic exercise for adolescents with sport-related concussion, and US data confirm the importance of smoking cessation before pregnancy.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,
Prof Nicholas Freezer
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Assessment of a parent–child interaction intervention for language development in children

Authors: Christakis D et al.

Summary: This study evaluated the impact of a clinic-based ‘Talk It Up’ intervention on home language environment and language development in children. 61 English- or Spanish-speaking families participated in the 6-month multifaceted programme, and underwent Language Environment Analysis word counts with clinician feedback, coaching, and watched twice-weekly brief instructional videos via a smartphone app. Mean age of the children was 5.9 months. English was the primary language spoken in home for most (89%) families. At follow-up, the intervention was associated with significant improvements in adult word counts, parent-child conversational turns, and Developmental Snapshot score, but there were no improvements in child vocalisations.

Comment: Language development in children is very important in developing communication and socialisation. As this study demonstrates, there are a number of things that parents can do to promote their child’s early language and literacy development. These include speaking slowly and succinctly, asking open-ended questions, expanding on the child’s conversation, telling stories to each other, limiting television time, visiting the library, telling the child what they are doing, and reading every day. The American Academy of Pediatrics has developed a Literacy Toolkit that includes information for parents about selecting books and sharing books with children of various ages and a policy statement for literacy promotion. In a systematic review of 59 randomised and 17 non-randomised clinical trials in 5848 children aged <6 years who had or were at risk for language impairment, parent-implemented interventions were moderately associated with improved child communication, engagement, and language outcomes.

Reference: JAMA Netw Open 2019;2(6):e195738

Abstract

Abbreviations used in this issue:
ASD = autism spectrum disorder; DTaP = diphtheria, tetanus, acellular pertussis.
Longer-term assessment of azithromycin for reducing childhood mortality in Africa

Authors: Keenan J et al.

Summary: The MORDOR II trial investigated the long-term impact of mass azithromycin administration on childhood mortality in Africa. In the original MORDOR I trial, 594 communities in Niger were randomised to receive 4 twice-yearly mass distributions of either azithromycin or placebo to children aged 1–59 months. In MORDOR II, the same communities then received two additional open-label azithromycin distributions over 1 year. Mortality rates after the additional 2 doses in MORDOR II were 24.0 per 1000 person-years in communities that had originally received placebo and 23.3 per 1000 person-years in those that had originally received azithromycin (p=NS). Mortality rates after the additional azithromycin doses decreased by 13.3% in communities that originally received placebo and 23.3 per 1000 person-years in those that had originally received azithromycin (p=NS).

Comment: Azithromycin has activity against a number of childhood infections, and randomised trials from sub-Saharan Africa have demonstrated that mass azithromycin administration reduces childhood mortality compared with placebo. In a follow-up study of one of these trials, which had included over 190,000 children in Malawi, Niger, and Tanzania and reported a mortality reduction with twice-yearly azithromycin, continuation of azithromycin over a 3-year period was associated with a persistent mortality benefit. However, a subsequent randomised trial including more than 19,000 children in Burkina Faso and Mali failed to demonstrate a mortality benefit with azithromycin versus placebo, each given in conjunction with seasonal malaria prophylaxis over 3 years. The significance of these findings and the discrepancy between trials, as well as the longer-term effects and implications for health programmes, require clarification. Thus far, data are insufficient to support routine mass azithromycin administration for reduction of childhood mortality.


Association of rhinovirus C bronchiolitis and immunoglobulin E sensitization during infancy with development of recurrent wheeze

Authors: Hasegawa K et al.

Summary: This US multicentre cohort study evaluated between-virus differences in the risk of developing recurrent wheeze in childhood after hospitalisation for bronchiolitis in infancy. 716 infants aged <1 year who were hospitalised for respiratory syncytial virus (RSV)-only or rhinovirus bronchiolitis in 2011–2014 were assessed for development of recurrent wheeze at age 3 years. Multivariable Cox models found that, compared with infants with RSV-only infection, the risk of recurrent wheeze was not significantly different in those with rhinovirus A or B. However, infants with rhinovirus C were at significantly higher risk (hazard ratio [HR], 1.58), and those with both rhinovirus C infection and immunoglobulin E sensitisation to food or aeroallergens during infancy were at an even higher risk (HR, 3.03).

Comment: Viral respiratory infections, particularly with RSV and rhinovirus, are the most common causes of wheezing in infants and young children, and they have important influences on the development of asthma. In addition, viral infections, most often with rhinovirus, are the most common causes of wheezing and asthma exacerbations in children and adults with pre-existing asthma. Respiratory viruses interact with allergic sensitisation and other microbes to promote recurrent virus-induced wheezing and the development of asthma via a number of mechanisms including increased recruitment of inflammatory cells, promotion of cytokine production, enhancement of allergic inflammation, and augmented airways hyper-responsiveness. Wheezing with viral respiratory infections, particularly with RSV and rhinovirus, are important predictors of the subsequent development of asthma. However, it is unclear whether certain viral respiratory infections play a role in asthma inception or if wheezing with these infections is a predictor of childhood asthma.


Abstract

LET’S TAKE ON SMA
THE NO.1 GENETIC CAUSE OF DEATH IN YOUNG CHILDREN†

†In children under two years of age. For references and acronym definitions, please see primary advertisement.
Children receiving the intervention showed significant improvements on sessions with the intervention at home 4 times per week for 6 weeks. Applied Behavioural Analysis therapy, or Applied Behavioural Analysis, randomised to use the Superpower Glass®. 71 children aged 6–12 years with a formal ASD diagnosis who were randomly assigned to the intervention pairs Google Glass® intervention in addition to supportive care, display significant signs of NAS as defined by predetermined criteria based on the abstinence scoring system. This study examines the relative benefits of different pharmacological therapies and questions the use of morphine as standard care. Mature smoking before and during pregnancy and the risk of sudden unexpected infant death. Authors: Anderson T et al. Summary: This analysis of the Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Data Set (2007–2011) evaluated the effects of maternal smoking before and during pregnancy on sudden unexpected infant death (SUID) rates. SUID risk increased ≥2-fold with any maternal smoking during pregnancy (adjusted odds ratio [aOR], 2.44), and increased 2-fold between no smoking and smoking 1 cigarette daily throughout pregnancy. The probability of SUID increased linearly with each additional cigarette smoked per day, and plateaued at 20 cigarettes. Mothers who quit (aOR, 0.77) or reduced (aOR, 0.88) their smoking decreased their odds compared with those who continued smoking during pregnancy. It was calculated that 22% of SUIDs in the US could be directly attributed to maternal smoking during pregnancy. Duration of immunity and effectiveness of diphtheria-tetanus–acellular pertussis vaccines in children. Authors: Domenech de Cellès M et al. Summary: This simulation study evaluated the duration of immunity and the effectiveness of DTaP vaccine in US children. A mathematical, age-structured model of pertussis transmission was used to assess the duration of DTaP immunity after vaccination in children immunised according to the US immunisation schedule. It was estimated that vaccine effectiveness was >75% in children aged 5–9 years, and that >65% of children remained immune to pertussis 5 years after their last DTaP dose. Pharmacological treatments for neonatal abstinence syndrome. Authors: Disher T et al. Summary: This systematic review and meta-analysis compared pharmacological therapies for neonatal abstinence syndrome (NAS). A search of Medline, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov identified 18 randomised clinical trials of pharmacological treatments for NAS (alone or in combination with adjuvant treatments) that were suitable for inclusion. Treatments included buprenorphine, clonidine, dimethyl tincture of opium and clonidine, dimethyl tincture of opium, morphine, methadone, and phenoxybenzamine. Sublingual buprenorphine was found to be the optimal treatment for reducing the length of treatment and length of stay. The protection provided by diphtheria and tetanus toxoids decreases over time, necessitating booster doses in childhood, adolescence, and adulthood. The protection provided by acellular pertussis vaccine also decreases over time. The effectiveness of acellular pertussis vaccines was evaluated in several case-control studies during a recent pertussis outbreak in the US. In the largest study (682 cases), receipt of 5 doses of DTaP vaccine was associated with decreased risk of pertussis (odds ratio 0.11; 95% CI 0.006–0.21); the estimated vaccine effectiveness was 89% (95% CI 79–94%). However, vaccine effectiveness decreased with increasing interval since the last dose of DTaP (from 98% in the first 12 months to 71% by ≥60 months). These findings are consistent with those of other observational studies and national surveillance. Despite waning immunity, vaccination continues to be the most effective strategy to reduce pertussis morbidity and mortality. In another outbreak, children who received any doses of acellular pertussis vaccine were less likely to have severe illness or require hospitalisation than unvaccinated children, and children fully vaccinated with acellular pertussis vaccine had more rapid resolution of coughing.

Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder. Authors: Voss C et al. Summary: The Superpower Glass® intervention pairs Google Glass® with a face-identifying artificial intelligence app that tells wearers what emotions they’re seeing. This study evaluated the efficacy of Superpower Glass® for improving social outcomes in children with ASD. 71 children aged 6–12 years with a formal ASD diagnosis who were currently receiving applied behavioural analysis therapy were randomised to use the Superpower Glass® intervention in addition to applied behavioural analysis therapy, or applied behavioural analysis therapy only (control). Families were asked to conduct 20-minute sessions with the intervention at home 4 times per week for 6 weeks. Children receiving the intervention showed significant improvements on the Vineland Adaptive Behavior Scale socialisation subscale compared with controls (mean treatment impact, 4.58; p = 0.005). Positive (but not statistically significant) treatment effects were also seen for 3 other primary measures.

Early subthreshold aerobic exercise for sport-related concussion. Authors: Leddy J et al. Summary: This randomised controlled trial assessed the effectiveness of early subsymptom threshold aerobic exercise compared with a placebo-like stretching programme in adolescents recovering from sport-related concussion. 103 male and female adolescent athletes (aged 13–18 years) who presented to university concussion centres within 10 days of sport-related concussion were randomised to progressive subsymptom threshold aerobic exercise or a progressive placebo-like stretching programme. Both forms of exercise were performed for about 20 min/day, and participants reported daily symptoms and exercise compliance via a website. Participants in the aerobic exercise group recovered from concussion faster than those in the stretching group (median recovery time 13 vs 17 days; p = 0.009). Delayed recovery (>30 days) was reported in 4% of individuals in the aerobic group compared with 14% in the placebo group (p = 0.08).

Pharmaceutical treatments for neonatal abstinence syndrome. Authors: Disher T et al. Summary: This systematic review and meta-analysis compared pharmacological therapies for neonatal abstinence syndrome (NAS). A search of Medline, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov identified 18 randomised clinical trials of pharmacological treatments for NAS (alone or in combination with adjuvant treatments) that were suitable for inclusion. Treatments included buprenorphine, clonidine, dimethyl tincture of opium and clonidine, dimethyl tincture of opium, morphine, methadone, and phenoxybenzamine. Sublingual buprenorphine was found to be the optimal treatment for reducing the length of treatment and length of stay. A minority of patients have symptoms that persist or are permanent. Observational studies have suggested that strict physical rest for more than a few days after a concussion may prolong symptoms. In this randomised trial of over 100 adolescents with a sport-related concussion, daily aerobic exercise (e.g. stationary bicycle or treadmill) for up to 20 minutes, with duration and intensity adjusted to avoid worsening of symptoms and initiated within 10 days of the concussion, decreased the time to recovery compared with gentle stretching (median recovery time 13 vs 17 days). These findings support the recommendation that children and adolescents adhere to a brief period of rest for 24–48h after a concussion followed by a gradual and progressive return to non-contact physical activity individualised to avoid exacerbation of symptoms.

Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. Authors: Anderson T et al. Summary: This analysis of the Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Data Set (2007–2011) evaluated the effects of maternal smoking before and during pregnancy on sudden unexpected infant death (SUID) rates. SUID risk increased ≥2-fold with any maternal smoking during pregnancy (adjusted odds ratio [aOR], 2.44), and increased 2-fold between no smoking and smoking 1 cigarette daily throughout pregnancy. The probability of SUID increased linearly with each additional cigarette smoked per day, and plateaued at 20 cigarettes. Mothers who quit (aOR, 0.77) or reduced (aOR, 0.88) their smoking decreased their odds compared with those who continued smoking during pregnancy. It was calculated that 22% of SUIDs in the US could be directly attributed to maternal smoking during pregnancy.

Comment: A newborn infant born to a mother taking, using, or misusing opioids and/or other substances is at risk for withdrawal. Opioids to which infants are exposed prenatally include licit and illicit opioids or medications used to treat maternal opioid use disorder. The signs of NAS include a high-pitched cry, irritability, sleep/wake disturbances, alterations in tone or movement, feeding difficulties, gastrointestinal and autonomic disturbances, respiratory problems, and failure to thrive. The mainstay of care for the infant affected by NAS is non-pharmacological care, which is initiated prenatally with maternal teaching, continued at birth and throughout the infant’s hospitalisation. Pharmacological therapy is initiated for infants who, despite adequate supportive care, display significant signs of NAS as defined by predetermined criteria based on the abstinence scoring system. This study examines the relative benefits of different pharmacological therapies and questions the use of morphine as standard care.

Comment: A number of risk factors for sudden infant death syndrome (SIDS) have been identified. These include exposure to cigarette smoke, maternal age <20 years, prematurity, prone sleeping position, soft bedding, and overheating. Apnoea of prematurity, although a marker for prematurity, is not a risk factor for SIDS. Exposure of an infant to secondhand smoke after delivery also probably increases the risk of SIDS. This study supports the recommendation that expectant mothers should avoid smoking during pregnancy because of increased risk of SIDS, and other adverse effects such as small-for-gestational-age babies and the increased risk of respiratory infections later in life.

Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. Authors: Anderson T et al. Summary: This analysis of the Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Data Set (2007–2011) evaluated the effects of maternal smoking before and during pregnancy on sudden unexpected infant death (SUID) rates. SUID risk increased ≥2-fold with any maternal smoking during pregnancy (adjusted odds ratio [aOR], 2.44), and increased 2-fold between no smoking and smoking 1 cigarette daily throughout pregnancy. The probability of SUID increased linearly with each additional cigarette smoked per day, and plateaued at 20 cigarettes. Mothers who quit (aOR, 0.77) or reduced (aOR, 0.88) their smoking decreased their odds compared with those who continued smoking during pregnancy. It was calculated that 22% of SUIDs in the US could be directly attributed to maternal smoking during pregnancy.

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Nebulised surfactant to reduce severity of respiratory distress

Authors: Minocchieri S et al., on behalf of the CureNeb Study Team

Summary: This Australian study investigated whether nebulised surfactant reduces intubation requirements in preterm infants with respiratory distress treated with nasal continuous positive airway pressure (nCPAP). 64 preterm infants (<4h of age) at a tertiary neonatal unit in West Australia who required 22–30% supplemental oxygen were randomised to receive nCPAP or bubble nCPAP plus nebulised surfactant using a customised vibrating membrane nebuliser. Surfactant nebulisation was repeated after 12h if needed. Surfactant nebulisation was found to reduce intubation requirements: 34.3% of infants receiving nCPAP + nebulised surfactant were intubated within 72h compared with 68.7% of infants receiving nCPAP alone (relative risk, 0.526). The reduced requirement for intubation was limited to infants born at 32–33 weeks’ gestation.

Comment: Endotracheal intubation has been the standard technique of surfactant administration. However, intubation may be complicated by transient airway obstruction, pulmonary injury (volutrauma and barotrauma), pulmonary air leak, and airway injury. As a consequence, minimal or less invasive administrative techniques have been developed and appear promising. These interventions include aerosolised/nebulised surfactant preparations, laryngeal mask airway-aided delivery of surfactant, pharyngeal instillation, and the use of thin intratracheal catheters. This study is encouraging for the use of nebulised surfactant to reduce the incidence of intubation in preterm infants.


Abstract

Virtual reality for pediatric needle procedural pain

Authors: Chan E et al.

Summary: These 2 randomised clinical trials investigated the use of a virtual reality distraction for needle pain in children aged 4–11 years in the emergency department (ED) or an outpatient laboratory. The first trial enrolled 129 children requiring intravenous cannulation or venipuncture in the ED; the second study enrolled 129 children requiring venipuncture in an outpatient laboratory. Children in both trials were randomised to either virtual reality distraction or standard of care. In the ED, virtual reality distraction significantly reduced pain compared with standard of care (p=0.016). In the outpatient lab, both groups experienced an increase in pain from baseline, but this was less marked in the virtual reality group (p=0.034).

Comment: Pain is a complex experience comprising sensory, cognitive, behavioural, and psychological components, which can cause fear and greatly affect compliance with care for future procedures. Common paediatric pharmacological analgesia includes opioid therapy, which is known to have high tolerance and dependence, and side effects ranging from nausea and constipation to cognitive impairment and respiratory depression. Distraction is a common non-pharmacological technique used by health care professionals to manage and attenuate anxiety, and possibly pain, during painful procedures in paediatric patients. Both passive distraction (e.g. watching television, listening to a book) and active distraction (e.g. interactive toys, electronic games) have been extensively studied and cause a decrease in pain and anxiety. Immersive virtual reality allows the user to become an active participant in a virtual world as it captures the visual, auditory and tactile senses, as well as the limbic sense of emotion. It could well be a game changer for children and their families.


Abstract

If you see a child with normal cognitive function and profound hypotonia, this may be a sign of Spinal Muscular Atrophy (SMA). Treatment is available, so refer immediately for an urgent appointment with a paediatric neurologist to ensure optimal early intervention and access to treatment for children with SMA.2–4


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