Paediatrics Research Review™

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In this issue:

- Rotavirus vaccines reduce inpatient and ED visits
- Rotavirus vaccination and risk of intussusception
- Prednisolone vs dexamethasone for croup
- Topical tacrolimus vs corticosteroids for children with atopic dermatitis
- Going-to-sleep position in late pregnancy can affect birth weight
- Offspring growth after metformin vs insulin treatment for gestational diabetes
- A pivotal response treatment package for children with ASD
- Testing for meningitis in febrile infants with positive urinalysis
- Early childhood vaccination status of preterm infants
- Adverse childhood experiences increase the future risk of obesity

Abbreviations used in this issue:

aOR = Adjusted odds ratio; **ASD** = autism spectrum disorder; **ED** = emergency department.

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Welcome to the latest issue of Paediatrics Research Review.

In this issue, a large post-licensure study reports that RotaTeq® and Rotarix® vaccines continue to perform well in preventing severe rotavirus-associated infections in children, and a meta-analysis reports that neonatal rotavirus vaccination does not increase the risk of intussusception. An Australian study shows that prednisolone and low-dose dexamethasone are equally effective for the treatment of croup, Finnish investigators find that children with moderate to severe atopic dermatitis and signs of early sensitisation appear to benefit more from topical tacrolimus than corticosteroid treatment, and the results of a meta-analysis support public health campaigns encouraging pregnant women to sleep on their side in the third trimester.

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

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Association of rotavirus vaccination with inpatient and emergency department visits among children seeking care for acute gastroenteritis, 2010-2016

Authors: Payne D et al.

Summary: This US study evaluated the impact of RotaTeq® (RV5) and Rotarix® (RV1) vaccines on inpatient and ED visits for childhood rotavirus infection. 10,813 children aged <5 years seeking medical care at 7 paediatric medical institutions for acute gastroenteritis in 2010–2016 were included. Among 1193 rotavirus-positive cases and 9620 rotavirus-negative controls, at least 1 dose of any rotavirus vaccine was 82% protective against rotavirus-associated inpatient visits and 75% protective against rotavirus-associated ED visits. No significant differences were observed between the 2 vaccines during the 7-year period. Vaccine effectiveness against inpatient and ED visits was 81% for RV5 (3 doses) and 78% for RV1 (2 doses). A mixed course of both vaccines provided 86% protection. Rotavirus patients who were not vaccinated had severe infections 4 times more often than those who were vaccinated.

Comment: Before the introduction of rotavirus vaccines, rotavirus infection was the most common cause of severe gastroenteritis in infants and young children. The rotavirus immunisation programme recommended all infants <6 months of age to receive a course of either Rotarix® (2 doses, at 2 and 4 months of age) or RotaTeq® (3 doses, at 2, 4 and 6 months of age). Since the introduction of the rotavirus vaccination programme into the national immunisation programmes in more than 80 countries worldwide, there have been dramatically reduced rates of acute gastroenteritis hospitalisation among children globally. Ongoing surveillance of disease prevalence and severity is important for continued monitoring of vaccine effectiveness. This large post-licensure study in the US was conducted across 7 institutions over 6.5 years between 2009 and 2016 and studied children <5 years of age seeking medical care for acute gastroenteritis. It found that vaccine effectiveness against hospital and ED visits was 81% for RV5 and 78% for RV1, especially among younger children and there was no statistically significant difference between the two vaccines. Even 1 dose of the vaccine was 82% protective against hospitalisation and 75% protective against ED visits with rotavirus infection, and unvaccinated patients were 4 times more likely to have a severe rotavirus infection than vaccinated patients. Overall, rotavirus vaccine continued to protect against rotavirus disease, particularly against severe infections and in younger children.

Reference: JAMA Netw Open 2019;2(9):e1912242

Abstract

Association between rotavirus vaccination and risk of intussusception among neonates and infants

Authors: Lu H et al.

Summary: This meta-analysis evaluated the association between rotavirus vaccination and risk of intussusception in neonates and infants. A search of PubMed, Web of Science, Cochrane library, and Embase databases identified 25 randomised placebo-controlled trials (n=200,594) that were suitable for inclusion. 20 cases of definite intussusception were diagnosed within 31 days after rotavirus or placebo vaccination, 74 cases were reported within 1 year, and 59 were reported within 2 years. The rates of intussusception reported at any of the time-points did not differ significantly between vaccine and placebo groups.

Comment: Since the introduction of the first licensed vaccine for rotavirus in North America in the 1990s there have been concerns about a possible association between the receipt of rotavirus vaccine and the occurrence of intussusception in young infants. However, it currently remains unclear whether this represents a true increase in overall risk of intussusception, or an early increased risk compensated by a subsequent decreased risk and reduction in cases of intussusception in older children. This systematic review and meta-analysis included 25 randomised clinical trials of neonates and infants that compared the risk of intussusception between vaccinated and placebo groups, and included 200,594 participants (104,647 receiving vaccine and 95,947 receiving placebo) in 33 countries from 4 continents. The results suggested that neonatal rotavirus vaccination was not associated with an increased risk of intussusception for up to 2 years after vaccination among neonates or infants.

Reference: JAMA Netw Open 2019;2(10):e1912458
Abstract

Prednisolone versus dexamethasone for croup

Authors: Parker C et al.

Summary: This randomised controlled trial in Australia compared the use of prednisolone and dexamethasone for childhood croup. 1252 children aged >6 months (maximum weight 20kg) who presented with croup to a tertiary paediatric ED or an urban district ED in Perth were randomised to receive a single dose of dexamethasone 0.6 mg/kg, low-dose dexamethasone 0.15 mg/kg, or prednisolone 1 mg/kg. Mean Westley Croup Score at baseline was 1.4 for dexamethasone, 1.5 for low-dose dexamethasone, and 1.5 for prednisolone. At 1 hour after treatment, the adjusted difference in scores was 0.03 for low-dose dexamethasone and 0.05 for prednisolone compared with dexamethasone. Re-attendance rates in the week after treatment were 17.8% for dexamethasone, 19.5% for low-dose dexamethasone, and 21.7% for prednisolone (p=NS).

Comment: Glucocorticoid therapy is a standard part of croup management. Dexamethasone 0.6 mg/kg is the gold standard treatment most commonly used for croup but is less easy to source outside a hospital setting. In this study, standard dose dexamethasone was compared with low-dose dexamethasone 0.15 mg/kg and prednisolone 1 mg/kg, the latter being much more accessible in a community setting. In this randomised trial involving 1252 children with croup, symptom improvement was similar in patients treated with a single dose of oral prednisolone or dexamethasone at the 1-hour mark and an increased risk of unscheduled medical re-attendance during the 7 days after treatment was not detected in the low-dose dexamethasone or prednisolone arms. Based on these findings, prednisolone and low-dose dexamethasone are both acceptable for treatment of croup in the community setting. However, it was also noted that children treated with prednisolone were more likely to require a repeat dose, and at the 3-hour mark, low-dose dexamethasone was less convincing than high-dose dexamethasone, suggesting that a subgroup with more severe disease benefitted from high-dose dexamethasone.

Reference: Pediatrics 2019;144(3):e20183772
Abstract

Young children with moderate-to-severe atopic dermatitis can be treated safely and effectively with either topical tacrolimus or mild corticosteroids

Authors: Perälä M et al.

Summary: This Finnish study compared the use of topical tacrolimus and topical corticosteroids in young children with atopic dermatitis (AD). 75 children aged 1–3 years with moderate to severe AD were randomised to open-label treatment with either topical tacrolimus or a topical corticosteroid for 3 years. The Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), transepidermal water loss (TEWL), eczema area, serum total immunoglobulin E (IgE) and blood eosinophil count improved in both groups during the first 12 months (interim analysis). However, patients with signs of early sensitisation at baseline had significantly lower TEWL at the eczema site and a smaller eczema area at 12 months in the tacrolimus group compared with the corticosteroid group.

Comment: Topical steroids are the standard of care in AD but infants with moderate to severe dermatitis are often under-treated due to concerns about adverse effects of topical steroids. The topical calcineurin inhibitors tacrolimus and pimecrolimus are an alternate treatment option and act by inhibiting the function of T lymphocytes and Langerhans cells and by suppressing cytokine-mediated responses. They repair the disturbed epidermal barrier, reduce the incidence of flares and do not cause skin atrophy, making them suitable for long-term treatment. Although the efficacy and safety of topical calcineurin inhibitors have been documented in adults and children, there is still little data on tacrolimus, especially the 0.1% formulation, in children under 2 years of age. This study was an interim analysis of 75 patients at 1 year in an ongoing 3-year randomised open-label comparative follow-up study of topical tacrolimus vs corticosteroid treatment among 1–3 year-old children with moderate to severe eczema. The patients were randomised 1:1 to treatment with 0.03% tacrolimus ointment (and if needed, 0.1% tacrolimus ointment) or 1% hydrocortisone acetate ointment, (and if needed, hydrocortisone butyrate 0.1% ointment). Early sensitisation to food or aeroallergen was assessed and defined as one or more of the following: elevated serum total IgE, elevated eosinophil count, positive skin prick tests or specific IgE ≥0.35 kU/L to aero or food allergens at baseline. The treatment response was evaluated with efficacy measures such as the Rajka & Langeland Severity Score, IGA, the EASI, TEWL, and the percentage of body surface area affected. Both groups in the study showed an improvement in serum total IgE and the blood eosinophil count. However, patients with signs of early sensitisation at baseline had statistically significantly lower TEWL at the eczema site and a smaller eczema area at 12 months in the tacrolimus group. No severe adverse effects were seen during the treatment. It was concluded that young children with AD and signs of early sensitisation, implying higher risk of allergic diseases, may benefit more from early tacrolimus than corticosteroid treatment. However, larger prospective trials are needed to confirm these findings.

Reference: Acta Paediatr 2019; published online Sep 4
Abstract

Association of supine going-to-sleep position in late pregnancy with reduced birth weight

Authors: Anderson N et al.

Summary: This secondary analysis of a meta-analysis investigated the association between the position in which pregnant women go to sleep and infant birth weight. Women with ongoing pregnancies at 28 weeks' gestation were interviewed about sleep position as part of 4 case-control studies investigating sleep and stillbirth in NZ, Australia, and the UK. Of 1760 women, 3.2% reported that they had usually fallen asleep in the supine position during the previous month. Adjusted mean birth weight was 3410g among women who reported supine position and 3554g among women who reported nonsupine position (adjusted mean difference, 144g; p=0.009). Going to sleep supine was associated with a 3-fold increase in small for gestational age birth weight by INTERGROWTH-21st standards and a nonsignificant increase in small for gestational age birth weight by customised standards.

Comment: Maternal supine position in late pregnancy is associated with significant haemodynamic changes that can lead to reduced uterine artery blood flow, reduced placental perfusion, and consequently reduced foetal blood flow. Repeated exposure to supine maternal position during sleep in late pregnancy therefore has the potential to adversely affect foetal growth and lead to foetal growth restriction. This study examined the association between maternal supine going-to-sleep position after 28 weeks of pregnancy and lower birth weight and birth weight centiles. Of the total 1760 study participants, only a small number of 57 (3.2%) reported they usually went to sleep supine during the previous 1–4 weeks. However, this study found that in this small group, there was a clinically relevant and independent reduction in mean birth weight of 144g, or an adjusted mean reduction of 10% in birth weight centile, adjusted for variables known to be associated with birth size. This study group was small and hence further larger scale studies will be needed to replicate these findings. Once validated, it could potentially lead to public health campaigns that encourage women in the third trimester of pregnancy to settle to sleep on their side instead of in the supine position, to optimise foetal birth growth and birth weight.

Reference: JAMA Netw Open 2019;2(10):e1912614
Abstract

Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes

Authors: Tarry-Adkins J et al.

Summary: This meta-analysis evaluated the impact of maternal metformin treatment on neonatal, infant, and childhood growth trajectories. A search of PubMed, Ovid Embase, Medline, Web of Science, ClinicalTrials.gov, and the Cochrane database identified 28 studies (n=3976) that evaluated outcomes of gestational diabetes mellitus (GDM)-affected pregnancies that were randomised to treatment with metformin or insulin. Neonates born to metformin-treated mothers had lower birth weights and lower ponderal indices than neonates born to insulin-treated mothers. The odds of macrosomia and large for gestational age were lower after maternal treatment with metformin. In contrast to the neonatal phase, metformin-exposed infants were significantly heavier than those in the insulin-exposed group. In mid-childhood, body mass index (BMI) was significantly higher after maternal metformin exposure than after insulin exposure.

Comment: There are several effective treatment strategies available for the treatment of GDM including the use of metformin and insulin. However, the impact of these treatments on long-term foetal, infant, and childhood growth is not fully understood. This paper reported a systematic review of 28 studies that included 3976 mothers who were randomised to receive either metformin or insulin for treatment of GDM and included all studies that reported the weight and growth of their babies in utero, at birth, or later in childhood. The results showed that babies whose mothers were treated with metformin weighed on average 108g less at birth than those whose mothers were treated with insulin, and had a lower risk of being born large for gestational age (>90th centile). However, metformin-exposed infants were 0.44kg heavier at 18–24 months and had higher BMI (by 0.8 kg/m^2) by mid-childhood (5–9 years) than insulin-exposed children. Despite lower average birth weight, metformin-exposed children appear to experience accelerated postnatal growth, resulting in heavier infants and higher BMI by mid-childhood compared to insulin-exposed children. This pattern of low birth weight and rapid postnatal catch-up growth is associated with increased risk of adverse long-term cardio-metabolic outcomes. These findings highlight the need for further studies examining the metabolic impact of intrauterine metformin exposure. One of the main limitations of the current study was the considerable variability in the dose of metformin used (ranging from 500–3000mg daily) and also the variability in the criteria used to diagnose GDM between the studies, with a total of 8 different diagnostic criteria being used.

Reference: PLoS Med 2019;16(8):e1002848
Abstract

A pivotal response treatment package for children with autism spectrum disorder

Authors: Gengoux G et al.

Summary: This Stanford University study evaluated the effects of a pivotal response treatment package (PRT-P) on the communication skills of children with ASD. 48 children aged 2–5 years with ASD and significant language delay were randomly assigned to PRT-P or a delayed treatment group for 24 weeks. PRT-P consisted of parent training and clinician-delivered in-home intervention. Analysis of child utterances during the structured laboratory observation showed that children receiving PRT-P had greater improvement in frequency of functional utterances compared with the delayed treatment group. Children receiving PRT-P also had greater improvements on the Brief Observation of Social Communication Change and the Clinical Global Impressions Improvement subscale, and in the number of words used.

Comment: This randomised controlled trial evaluated the effect of a PRT-P consisting of parent training and clinician-delivered in-home intervention, in comparison to stable community-based treatment, on the communication skills of children with ASD. 48 children with ASD and significant language delay between the ages of 2 and 5 years were randomly assigned to PRT-P or the community treatment group for 24 weeks. Children in PRT-P demonstrated greater improvement in frequency of functional utterances, greater improvement on the Brief Observation of Social Communication Change, on the Clinical Global Impressions Improvement subscale, and in the number of words used on a parent-report questionnaire. Additional research will be needed to understand the optimal combination of treatment settings, intensity, and duration, and to identify child and parent characteristics associated with improved treatment responses.

Reference: Pediatrics 2019;144(3):e20190178
Abstract

Testing for meningitis in febrile well-appearing young infants with a positive urinalysis

Authors: Wang M et al.

Summary: This retrospective cohort study determined factors associated with cerebrospinal fluid (CSF) testing in febrile young infants with a positive urinalysis. Data for 20,570 well-appearing febrile infants aged 7–60 days old who presented to 124 hospitals in 2015–2017 were reviewed. Overall, 3572 infants had a positive urinalysis, and 2511 (70.3%) underwent CSF testing. Factors associated with CSF testing included: age 7–30 days (aOR, 4.6), abnormal inflammatory markers (aOR, 2.2), and site volume >300 febrile infants per year (aOR, 1.8). There were no cases of delayed meningitis among 505 infants treated for urinary tract infection (UTI).

Comment: This study was a retrospective cohort study and collected data on 20,570 well-appearing febrile infants aged 7–60 days old presenting to 124 hospitals from 2015 to 2017. Overall, 3572 infants had a positive urinalysis and of these, 2511 (70.3%) underwent CSF testing. Factors that were associated with CSF testing included: younger age (7–30 days), abnormal inflammatory markers, and site volume >300 febrile infants per year. Among 505 infants treated for UTI without CSF testing, there were no cases of delayed meningitis within 7 days of discharge, suggesting that routine CSF testing of febrile well-appearing infants aged 31–60 days old with a positive urinalysis may not be necessary. It would have been interesting to know what proportion of infants who underwent CSF testing tested positive for meningitis and what factors were associated with a positive test, but this information was not provided in this paper.

Reference: Pediatrics 2019;144(3):e20183979
Abstract

Early childhood vaccination status of preterm infants

Authors: Hofstetter A et al.

Summary: This retrospective US study determined the early childhood vaccination status of preterm infants. Vaccination data were retrieved from the Washington State Immunization Information System for 10,367 infants born in 2008–2013. Completion of the recommended 7-vaccine series by 19 months of age was compared between preterm infants (born at <37 weeks) and term/post-term infants. Preterm infants had lower 7-vaccine series completion by 19 months (47.5% vs 54.0%; aOR, 0.77) and 36 months (63.6% vs 71.3%; aOR, 0.73) compared with term/post-term infants. Full influenza vaccination coverage by 19 months also differed between groups (early preterm: 47.7%; late preterm: 41.5%; term/post-term: 44.7%).

Comment: This retrospective cohort study of 10,367 infants in Washington State compared the early childhood vaccination status of preterm infants to their term and post-term counterparts. It explored the receipt of the 7 recommended early childhood vaccinations (diphtheria, pertussis, and tetanus [DTP]; hepatitis B; inactivated poliovirus; *Haemophilus influenzae* type B [Hib]; pneumococcal; measles, mumps and rubella [MMR]; and varicella) as well as rotavirus vaccine, hepatitis A vaccine and influenza vaccinations among infants in these two groups. The results showed that at age 19 and 36 months, a significantly lower proportion of preterm infants had completed the 7-vaccines and rotavirus vaccinations as compared to term and post-term infants. Stratifying the preterm infants into early (23–33 weeks' gestation) and late (34–36 weeks' gestation) also showed similar results when each preterm group was compared to term and post-term infants. There was no difference overall in influenza vaccination status between preterm and term/post-term infants, however, when the early and late preterm infants were compared separately, it was seen that the early preterm infants had higher influenza vaccination coverage and the late preterm infants had lower influenza vaccination coverage as compared to term/post-term infants. Preterm infants are at increased risk for vaccine-preventable infections and their associated complications, and therefore, strategies are needed to improve the timely receipt of vaccinations in the high-risk preterm population.

Reference: Pediatrics 2019;144(3):e20183520
Abstract

Independent commentary by Dr Suja Mary Mathew

Dr. Suja Mathew is a general paediatrician with 25 years of experience, who has worked in India and Australia. She currently works as a general paediatric in private practice in Adelaide Paediatrics and at Danny's Place, which is a multi-disciplinary obesity service for children and adolescents in Adelaide. She also works as the Research Fellow in the Vaccinology and Immunology Research Trials Unit (VIRTU) at Women's and Children's Hospital in Adelaide. She is interested in all aspects of paediatric medicine and has a special interest in endocrinology and obesity as well as in developmental and behavioural paediatrics.

Adverse childhood experiences are associated with an increased risk of obesity in early adolescence

Authors: Gardner R et al.

Summary: This analysis of the 'Growing Up in Ireland' cohort determined the impact of adverse childhood experiences on weight gain and obesity risk in adolescence. 6942 adolescents were assessed for 14 specific adverse childhood experiences, and overweight/obesity at 13 years. After adjusting for confounding, exposure to any adverse experience in childhood was associated with overweight/obesity in adolescence. There was a significant interaction between income and adverse childhood experiences for both incident overweight/obesity and weight gain.

Comment: Psychosocial factors including poverty and exposure to adverse experiences in childhood play an important role in adolescent health. This study sought to explore the impact of adverse childhood experiences on weight gain and the development of obesity in adolescence. Data from 6942 adolescents aged 9–13 years from the 'Growing Up in Ireland' cohort study were analysed. The main exposures studied were 14 specific adverse childhood experiences which included death and serious illness in the child, parent or close family member, parental incarceration, parental drug/alcohol abuse, parental conflict, separation, family displacement etc. More than 75% of the youth in the study had experienced an adverse experience and 17% experienced an adverse experience before age 9. The study found that exposure to adverse experiences before 9 years of age was associated with an elevated prevalence (aOR, 1.56) and incidence (incidence rate ratio, 2.15) of overweight/obesity at 13 years of age, independent of caregiver weight status and child physical activity level and dietary habits. The association between adverse experiences and obesity was more pronounced among children living in low-income households. These findings reinforce the concept that environmental stressors and social inequalities are important determinants of obesity risk in early adolescence, and support the need to consider social determinants of health when developing behavioural strategies to promote healthy weight status, particularly in early adolescence.

Reference: Pediatr Res 2019;86(4):522-8
Abstract

References: 1. Iascone D, *et al. F1000Prime Rep.* 2015;7:04. **2.** Lin CW, *et al. Pediatric Neurology* 2015;53:293–300. **3.** D'Amico A, *et al. Orphanet Journal of Rare Diseases.* 2011;6:71–81. **4.** SPINRAZA® (nusinersen) Approved Product Information, September 2018.