Welcome to the latest issue of Paediatrics Research Review.

In this issue, a study in Puerto Rico examines the impact of prenatal Zika virus exposure on cognitive development in infants, a US cohort study reports the efficacy of a brief screening tool for suicide risk in youth, and a cluster randomised trial investigates the impact of the CEASE intervention on parental smoking. Children with recurrent febrile UTI are reported to be at increased risk for renal scarring, the prevalence of childhood overweight and obesity appears to have stabilised in most European countries, and Chinese investigators report the efficacy of propranolol for infantile hepatic haemangiomata.

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

Kind Regards,
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Cognitive development of infants exposed to the Zika virus in Puerto Rico
Authors: Valdes V et al.

Summary: This study evaluated cognitive development in infants exposed to the Zika virus in utero. 65 infants whose mothers underwent prenatal Zika virus testing were assessed using the Mullen Scales of Early Learning at a mean age of 9 months. General cognitive and domain-specific scores did not differ significantly between infants who were or were not exposed to Zika virus prenatally, except for receptive language score. After adjustment for key confounders, exposure to Zika virus and Hurricane Maria were independently and significantly associated with receptive language scores.

Comment: Zika virus is an arthropod-borne flavivirus transmitted by mosquitoes named after the Ugandan forest where it was first detected in 1947. Clinical manifestations of Zika virus infection occur in approximately 20% of patients and include acute onset of low-grade fever with maculopapular pruritic rash, arthralgia (notably small joints of hands and feet), and nonpurulent conjunctivitis. Outbreaks of Zika virus infection have occurred in Africa, Southeast Asia, and the Pacific Islands; currently, there is a Zika virus outbreak in the Americas, the Caribbean, and the Pacific. The range of Zika virus infection in children includes intrauterine infection (vertical transmission during pregnancy), intrapartum infection (vertical transmission at the time of delivery), and postnatal infection (transmission via mosquito bites). The principal clinical features of congenital Zika syndrome include microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures, irritability, arthrogryposis, ocular abnormalities, and sensorineural hearing loss. Intrapartum and postnatal infections usually have milder disease. This paper adds to the literature by describing subtle differences in cognitive development in the first year of life. There is no specific treatment for Zika virus infection and there is no vaccine for prevention. Management consists of symptomatic treatment. Preventive measures include personal protective measures to prevent mosquito bites and institution of measures to eliminate and control mosquito breeding sites.

Reference: JAMA Netw Open 2019;2(10):e1914061

Abstract
Assessment of selective and universal screening for suicide risk in a pediatric emergency department

Authors: DeVilder J et al.

Summary: This retrospective US cohort study examined the utility of the Ask Suicide-Screening Questions (ASQ) instrument for assessing suicide risk in a paediatric ED setting. The ASQ was administered to individuals aged 8–18 years with medical, behavioural, and psychiatric presenting problems (universal condition) and to individuals aged 8–18 years with medical, behavioural, and psychiatric presenting problems at an urban paediatric ED (selective condition), then to individuals aged 8–18 years with medical, behavioural, and psychiatric presenting problems (universal condition). The complete cohort comprised 15,003 individuals. In the selective condition, there were 275 suicide-related ED visits and 3 deaths by suicide during a mean 1133.7 days of follow-up. In the universal condition, there were 118 suicide-related ED visits and no deaths during a mean 366.2 days of follow-up. After adjustment for demographic characteristics and baseline presenting problem, positive ASQ screens were associated with greater risk of suicide-related outcomes among both the universal sample (hazard ratio, 6.8) and the selective sample (hazard ratio, 4.8).

Comment: In the ED a brief screening tool may have some value in identifying risk for suicidal behaviour in adolescents when they are assessed by non-mental health clinicians. The ASQ is a 4-item instrument that clinicians can administer to screen for risk of suicide in patients who present to paediatric EDs with psychiatric or general medical complaints. The four items are: 1) In the past few weeks, have you wished you were dead? 2) In the past few weeks, have you felt that you or your family would be better off if you were dead? 3) In the past week, have you been having thoughts about killing yourself? 4) Have you ever tried to kill yourself? Answering yes to at least one question constitutes a positive screen that should trigger a more extensive evaluation of the patient’s risk for suicide. A cross-sectional study in patients aged 10–21 years who presented to paediatric EDs with psychiatric or general medical problems found that the ASQ had good psychometric properties. In psychiatric patients, the positive and negative predictive values were 71% and 97%; in general medical patients, positive and negative predictive values were 59% and 100%. Although some paediatricians have the requisite training and experience to manage patients with suicidal ideation, most patients are referred to psychiatrists and other mental health clinicians if these specialists are available.

Reference: JAMA Netw Open 2019;2(10):e1914070

Treating parents for tobacco use in the pediatric setting

Authors: Nabi-Burza E et al.

Summary: This cluster randomised trial evaluated the impact of the CEASE intervention on parental smoking. 10 paediatric practices in 5 US states were randomised to either implement the CEASE protocol or maintain usual care. 8164 parents were included, of whom 961 (27.1%) in intervention practices and 1105 (23.9%) in control practices were current smokers. Change in smoking prevalence over the 2 years of intervention implementation favoured the intervention (−2.7% vs 1.1%), as did the quit rate (2.4% vs −3.2%).

Comment: Evidence of adverse respiratory effects of secondhand smoke (SHS) exposure for children was first reported in 1986 by the US Surgeon General and the National Research Council. Subsequent public health reports have identified additional health risks associated with SHS exposure in children including quality of life and costs, prematurity and perinatal mortality, fetal growth and development, sudden infant death syndrome, respiratory symptoms and illness, lower respiratory illnesses, chronic respiratory symptoms, asthma, reduced lung function, arterogenesis and middle ear disease. It is disappointing that in this study, the educational and pharmacological interventions only resulted in a 2.7% reduction in parental smoking. Psychological support in addition to pharmacological interventions have been shown to increase the rate of smoking cessation.

Reference: JAMA Pediatr 2019; published online Aug 12

Abstract
Association of renal scarring with number of febrile urinary tract infections in children

Authors: Shaikh N et al.

Summary: This post hoc analysis of the RIVUR and CUTIE trials investigated the risk of renal scarring in children with febrile UTIs. 345 children with vesicoureteral reflux (VUR) and 124 without VUR underwent a dimercaptosuccinic acid (DMSA) renal scan approximately 4 months after their last febrile UTI. The incidence of renal scarring was 2.8% after 1 febrile UTI, 25.7% after 2 febrile UTIs, and 28.6% after ≥3 febrile UTIs. The risk of renal scarring after a second febrile infection was 11.8 times higher than after a single febrile infection, and the risk of renal scarring after ≥3 febrile infections was 13.7 times higher than after a single febrile infection.

Comment: The role of renal scintigraphy in the management of children with an acute UTI is controversial. Scintigraphy at the time of an acute UTI provides information about the extent of renal parenchymal involvement. In addition, DMSA will identify most >70% children with moderate to severe VUR (grade II or higher). In spite of the radiation, this observation has prompted some experts to suggest that DMSA be used as the initial imaging test to identify children at higher risk for renal scarring (the “top down” approach). In a systematic review of 33 studies, approximately 60% of children with initial UTI had DMSA scans consistent with acute pyelonephritis in the acute phase of illness, but only 15% had renal scarring at follow-up. The AAP and NICE guidelines do not support the use of DMSA in the routine evaluation of children with first UTI. Careful clinical follow-up of all children with UTI and the use of ultrasound may obviate the need for routine DMSA scans.

Reference: JAMA Pediatr 2019; published online Aug 5

Efficacy of propranolol treatment in infantile hepatic haemangiomata

Authors: Yang K et al.

Summary: This retrospective Chinese study investigated the efficacy of propranolol for the treatment of children with multifocal and diffuse infantile hepatic haemangiomata. 13 patients were included; 2 had diffuse lesions and 11 had multifocal lesions. 11 (84.6%) patients had cutaneous infantile haemangiomata. Hepatomegaly was the predominant clinical presentation, and 3 patients had hypothyroidism. Age at diagnosis ranged from 1–26 (median 2) months and the duration of treatment ranged from 4–30 (median 24) months. For patients with hypothyroidism, the thyroid hormone level was normal after 4 weeks' treatment with propranolol and levothyroxine. All but 1 patient responded well to propranolol. No significant treatment-related adverse effects were observed during follow-up.

Comment: In 2008, the serendipitous observation that the use of propranolol to treat heart failure in two young children with infantile haemangiomata was associated with a change in colour, softening, and decrease in size of the haemangiomata led to the initiation of larger observational studies and randomised trials. All studies demonstrated improvement with propranolol. In 2014, propranolol hydrochloride oral solution was approved by the US Food and Drug Administration for the treatment of proliferating infantile haemangiomata requiring systemic therapy. Reports of successful treatment of haemangiomata with systemic propranolol led to the investigation of topical beta-blocker therapy for the treatment of infantile haemangiomata. Topical propranolol 1% or timolol 0.5% may be used for the treatment of thin, superficial haemangiomata (e.g. haemangiomata of minor cosmetic concern located on the face) as an alternative to observation, particularly if parents desire treatment. Topical beta-blockers may also have a role in the treatment of small, ulcerated haemangiomata and in preventing rebound growth in children who are being tapered off oral propranolol.


Prevalence and trends of overweight and obesity in European children from 1999 to 2016

Authors: Garrido-Miguel M et al.

Summary: This meta-analysis assessed trends in overweight and obesity among children across Europe from 1999 to 2016. A search of MEDLINE, Embase, CINAHL, and Web of Science identified 103 studies (477,020 children aged 2–13 years) in 28 countries that were suitable for inclusion. Combined prevalence of overweight and obesity decreased over time in the Belarusian region (from 30.3% to 25.6%) but increased in the Mediterranean region (from 22.9% to 25.0%). No significant changes were seen from 1999 to 2016 in the combined prevalence of overweight and obesity in Atlantic Europe (from 18.3% to 19.3%) or Central Europe (from 15.6% to 15.3%).

Comment: Obesity in children and adolescents is a significant public health problem in many societies. The comorbidities of obesity include abnormalities in cardiovascular, dermatologic, endocrine, gastrointestinal, neurologic, orthopaedic, psychosocial, and pulmonary health, as well as functional limitations. Body mass index (BMI) is widely used to classify overweight (BMI >25 kg/m²) and obesity (BMI >30 kg/m²) in adults as it is closely related to body fat and long term health hazard outcome. In children and adolescents, BMI is widely changed by age and sex, and thus these cutoff values cannot be considered for the definition of obesity in children. At least 3 different definitions for child and adolescent overweight and obesity have been proposed: 1) the World Health Organization uses BMI for adolescents and weight-for-height z-score for children; 2) the Center for Disease Control and prevention (CDC 2000) produced sets of percentiles of BMI by age and sex specific in the US for children and adolescents aged 2–18 years; 3) the International Obesity Task Force (IOTF) uses cutoff values of BMI by age and sex based on data from 6 countries fitter by the LMS method, linking BMI values (16, 17, 18.5, 25 and 30 kg/m²) at 18 years to child centiles, which are averaged across the countries. The CDC and IOTF criteria are the most commonly used in the diagnosis of obesity and overweight among children and adolescents.


Accuracy of autism screening in a large pediatric network

Authors: Guthrie W et al.

Summary: This study determined the accuracy of universal screening for autism spectrum disorder (ASD). 25,999 children in the US who had a well-child visit between 16 and 26 months underwent universal, primary care-based screening for ASD using the Modified Checklist for Autism in Toddlers with Follow-Up (M-CHAT/F). ASD prevalence was found to be 2.2%. The M-CHAT/F had a sensitivity of 58.8% and a positive predictive value (PPV) of 14.6%. Sensitivity was higher in older toddlers and those with repeated screenings, whereas PPV was lower in girls. Specificity and PPV were lower in children of colour and those from lower-income households.


Rotavirus epidemiology and monovalent rotavirus vaccine effectiveness in Australia: 2010–2017

Authors: Maguire J et al.

Summary: Rotavirus vaccine has been funded for infants under the Australian National Immunisation Program (NIP) since 2007, with the Rotarix® vaccine used in NSW since that time. This study examined the vaccine effectiveness (VE) of Rotarix® vaccine among children who presented with rotavirus gastroenteritis during a large outbreak in NSW in 2017. Rotavirus cases increased 3.1-fold from 2016 to 2017; the highest rate was among children younger than 2 years of age. For notified cases in 2017, estimates of 2-dose VE were 88.4%, 83.7%, and 78.7% in children aged 2, 4 and 6 months of age, respectively. Specificity was found to be 2.2%. The M-CHAT/F had a sensitivity of 38.8% and a positive predictive value (PPV) of 14.6%. Specificity was higher in older toddlers and those with repeated screenings, whereas PPV was lower in girls. Specificity and PPV were lower in children of colour and those from lower-income households.

Comment: ASD is a biologically-based neurodevelopmental disorder characterised by impairments in two major domains: 1) deficits in social communication and social interaction; and 2) restricted repetitive patterns of behaviour, interests, and activities. Screening for ASD is indicated in children with delayed language and communication milestones, in children with a regression in social or language skills, and in children whose parents raise concerns regarding ASD. The AAP recommends ASD-specific screening of all children at 18 and 24 months of age because these are critical times for early social and language development, and earlier intervention is more effective for ASD. Although population-based ASD screening is not universally recommended, this study demonstrates that it is possible, but the low sensitivity and PPV are of concern.


Comment: Rotavirus is the most common cause of severe, acute gastroenteritis in infants and children worldwide. In the pre-vaccine era, rotavirus was estimated to cause approximately 440,000 deaths, 2 million hospitalisations, and 25 million outpatient visits per year worldwide among children under 5 years of age. In Australia the vaccine was successfully incorporated into the NIP in July 2007 with a marked reduction in severe gastroenteritis cases particularly in children under 5 years of age. It is administered orally at 2 and 4 months of age (Rotarix®) or at 2, 4 and 6 months of age (Rotatad®). Adverse events were reported in 41.6 per 1000 doses. The events most commonly reported at a national level were vomiting, abdominal pain and diarrhea. Cases of Intussusception were reported to the Therapeutic Goods Administration at a rate of 2.8 per 100,000 doses of rotavirus vaccine with the majority (60%) of cases in infants 2–3 months of age after dose 1 of either vaccine. This is similar to the reporting rate observed in the US. If the increase in cases seen in 2017 is sustained, re-immunisation may need to be considered in children over 6 months of age.

Reference: Pediatrics 2019;144(3):e20191024
Predictors and outcomes of early intubation in infants born at 28-36 weeks of gestation receiving noninvasive respiratory support

Authors: Roberts C et al.

Summary: This study examined predictors and outcomes of early intubation in preterm infants with respiratory distress. 564 preterm infants born at 28–36 (mean 32) weeks' gestation were included; 13.5% received early intubation. Multivariable analysis found that lower gestational age and higher fraction of inspired oxygen (FiO₂) predicted the need for intubation within 72 hours. Intubation was associated with a prolonged duration of respiratory support and supplemental oxygen, and with pneumothorax and nasal trauma. In infants born at <32 weeks' gestation, intubation was also associated with bronchopulmonary dysplasia (BPD) and patent ductus arteriosus requiring treatment.

Comment: Although mechanical ventilation can be lifesaving, it may cause chronic lung injury resulting in BPD, a major complication of prematurity. As a result, continued efforts have been focused upon development of new technologies and ventilator strategies to minimise lung damage, including the use of early continuous positive nasal airway pressure (nCPAP) in preterm infants. More recently heated, humidified, high-flow nasal cannulae (HHFNC) delivery devices have been increasingly used at initial flow rates of 4–6 L/min up to a maximum of 8 L/min for neonesates in place of nCPAP devices. The theoretical benefit for HHFNC is based on the belief that the use of a higher flow rate washes out nasopharyngeal dead space and replaces the end-expiratory gas within the upper airway with fresh gas that is oxygenated, humidified, and heated and provides positive airway distending pressure.

Reference: J Pediatr 2019; published online Oct 11

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

Outcomes at 18 to 22 months of corrected age for infants born at 22 to 25 weeks of gestation in a center practicing active management

Authors: Watkins P et al.

Summary: This retrospective cohort study evaluated outcomes in extremely preterm infants after admission to a NICU. 255 infants born at 22–25 weeks’ gestation in 2006–2015 at a single institution were included (77 infants were born at 22–23 weeks’ gestation and 178 were born at 24–25 weeks’ gestation). Survival to hospital discharge in those surviving to NICU admission was 78% in those born at 22–23 weeks and 89% in those born at 24–25 weeks (p=0.02), 64% of surviving infants born at 22–23 weeks and 76% of those born at 24–25 weeks had no or mild neurodevelopmental impairment.

Comment: The survival of extremely low birthweight (ELBW; <1000g) infants continues to improve with most survivors having mild or no neurodevelopmental impairment. Interpretation of the neonatal outcomes literature is challenging because of differences in clinical practice (e.g. limits of viability), study design (study population, evaluation tools, and outcome definition), and changes in perinatal care over time. As a result, these factors need to be considered when comparing individual studies or attempting to apply results of the literature clinically. A report from the National Institute of Child Health and Human Development Neonatal Research Network that assessed neurodevelopmental outcome for 3785 ELBW infants demonstrated improved survival and neurodevelopmental outcome at 18–22 months adjusted age over 3 time periods (1993–1994, 1995–1996, and 1997–1998) and a reduction in the rate of severe cerebral palsy from 2011 to 2015 (18% vs 7%); however, the rate of moderate to severe cognitive impairment remained unchanged (21% in 2011 and 16% in 2015). A population-based Australian study of preterm infants with gestational age below 28 weeks reported infants born in 2005 compared with those born in the 1990s had lower rates of severe developmental delay (3.7% vs 14.8%) and severe disability (3.7% vs 15.4%) at 2 years of age. In contrast to other studies, survival rates between the two cohorts were not significantly different (6% vs 70%). In the UK EPICure study, survival of ELBW infants improved from 1995 to 2006 (30% vs 52%). At 3-year follow-up, there was a higher proportion of survivors without disability (8% vs 16%); however, there was no change in the proportion of survivors with severe disability (18% vs 19%). The risk of impairment increased with decreasing gestational age.

Reference: J Pediatr 2019; published online Oct 9