Welcome to the latest issue of Paediatrics Research Review.

In this issue, we report that integrating ACT into parental asthma education leads to an overall improvement in asthma control in children, a US study looks at paediatric antibiotic stewardship efforts in EDs throughout the country, and a pooled analysis of data from 5 studies shows that inactivated influenza vaccine is more effective than quadrivalent live attenuated vaccine for paediatric influenza vaccination. US researchers report that almost one-third of children with ASD do not receive behavioural or medication treatment, and that younger siblings of children with ASD or ADHD are at increased risk for both disorders, and the PRIME investigators suggest that intranasal ketamine may be a useful alternative to intranasal fentanyl for pain associated with acute extremity injuries in children.

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

Kind Regards,

Dr Katie Heathershaw
katie.heathershaw@researchreview.com.au

Acceptance and commitment therapy for parental management of childhood asthma

Authors: Chong Y et al.

Summary: This randomised controlled trial investigated the use of group-based ACT to improve parental management of childhood asthma. 168 parents and their children (aged 3–12 years) with asthma were recruited in a public hospital in Hong Kong and randomised to receive 4 sessions of group-based ACT plus asthma education (ACT group) or an asthma education talk plus 3 telephone follow-ups (control group). Compared with the control group, children whose parents received ACT made significantly fewer ED visits in the 6-month follow-up period due to asthma exacerbations (adjusted incidence rate ratio, 0.20; p=0.001). Parents in the ACT group also reported a significant decrease in psychological inflexibility, anxiety, and stress.

Comment: Asthma is one of the most common chronic health problems seen in paediatrics. Whilst there is much in the published literature about medical treatment of asthma, much less is known about effective management of the psychological difficulties in the parents of asthmatics, and the potential impact of such management on health service utilisation. This trial in a public hospital in Hong Kong compared parents randomised to a 4-session, group-based ACT plus asthma education or to a control group consisting of asthma education and phone follow-up. ACT is a well-accepted psychological treatment modality used by therapists in the management of anxiety, mood disorders and other mental health conditions. Children whose parents had the ACT intervention made significantly fewer ED visits at 6 months post-intervention, and their parents also reported a decrease in psychological inflexibility, anxiety, and stress. This study suggests that addressing psychological factors in parents can play an important role in the management of childhood asthma.


Abstract

Abbreviations used in this issue:

ACT = acceptance and commitment therapy;
ADHD = attention-deficit/hyperactivity disorder;
ASD = autism spectrum disorder; ED = emergency department.

YOU CAN CHANGE THEIR FUTURE

Authors: Poole N et al.

Summary: This cross-sectional retrospective study evaluated antibiotic prescribing for children in US hospital EDs. Of the mean 29 million annual ED visits by children, 14% occurred at paediatric EDs. Antibiotics were prescribed more frequently after non-paediatric than paediatric ED visits (24% vs 20%; p<0.01), and antibiotic prescribing frequencies were stable across the study period. 44% of all antibiotics prescribed were broad spectrum, and 32% (2.1 million per year) were generally not indicated. Non-paediatric EDs had a higher frequency of prescribing macrolides than paediatric EDs (18% vs 8%; p<0.0001) and a lower frequency of guideline-concordant prescribing for respiratory conditions (77% vs 87%; p<0.001).

Comment: Children who present to EDs are frequently prescribed antibiotics; however, it is not always the case that these prescriptions are clinically indicated or appropriate. This study used retrospective data from the 2009–2014 National Hospital Ambulatory Medical Care Survey to compare the patterns of antibiotic prescribing in paediatric EDs (>75% of patients under 18) vs non-paediatric EDs. The authors note that the overall frequency of antibiotic prescribing was significantly higher in non-paediatric EDs. Notably, non-paediatric EDs were also much more likely to prescribe macrolides, and much less likely to provide antibiotic prescriptions in accordance with clinical guidelines. These findings suggest that the efforts made in paediatric antimicrobial stewardship must be further extended in order to reach children presenting at non-paediatric EDs.

Reference: Pediatrics 2019;143(2):e20181056

Abstract

Independent commentary by Dr Katie Heathershaw MBBS, FRACP, MD

Katie is one of Melbourne’s most sought after developmental and behavioural paediatricians. Her clinical interests include child behaviour problems, developmental and learning disorders (including ASD and ADHD), sleep problems of infants and children, infant distress and general paediatric medicine. She graduated MBBS from University of Melbourne in 1990, and obtained her specialist qualification in paediatrics, FRACP, in 1998, then went on to obtain a post graduate degree in 2003. Katie developed her passion for working in paediatrics whilst working in the Centre for Community Child Health, Royal Children’s Hospital, and undertaking advanced training in Developmental and Behavioural Paediatrics.

Live attenuated and inactivated influenza vaccine effectiveness

Authors: Chung J et al.

Summary: This report combined data from 5 US studies to compare the vaccine effectiveness (VE) of quadrivalent live attenuated vaccine with that of inactivated influenza vaccine in children and adolescents. Of 17,173 patients aged 2–17 years in the 5 studies, 4579 received inactivated influenza vaccine, 1979 received quadrivalent live attenuated vaccine, and 10,615 were unvaccinated. Analysis of pooled individual patient-level data showed that VE against influenza A/H1N1pdm09 was 67% for inactivated influenza vaccine compared with 20% for quadrivalent live attenuated vaccine. Recipients of quadrivalent live attenuated vaccine were at higher risk for influenza A/H1N1pdm09 than recipients of inactivated influenza vaccine (odds ratio, 2.66). The vaccines had comparable efficacies against influenza A/H3N2 and B.

Comment: Influenza vaccination can be achieved using either quadrivalent live attenuated vaccine or inactivated influenza vaccine. Despite the fact that both vaccines are available in many countries, there is still little high-quality data on the comparative efficacy of these vaccine preparations in children and adolescents. This study incorporated data from five separate US trials comparing quadrivalent live attenuated vaccine and inactivated influenza vaccine VE in order to resolve this question. Analysis of data from 17,173 total participants revealed that although quadrivalent live attenuated vaccine and inactivated influenza vaccine had similar effectiveness in preventing infection with influenza A/H3N2 and influenza B, quadrivalent live attenuated vaccine was significantly less effective at preventing infection with influenza A/H1N1pdm09. This finding was consistently observed across two influenza seasons and across all age groups studied. This suggests that inactivated influenza vaccine is by far the better choice for paediatric influenza vaccination, supporting the current policy in Australia of vaccinating all age groups with inactivated influenza vaccine.

Reference: Pediatrics 2019;143(2):e20182094

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.

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**Bifidobacterium abundance in early infancy and vaccine response at 2 years of age**

Authors: Huda M et al.

Summary: This prospective observational study examined the association of Bifidobacterium levels in early infancy with memory responses to early vaccination measured at 2 years of age. Infants were vaccinated with Bacillus Calmette-Guérin (BCG) at birth, oral polio virus at birth and at 6, 10, and 14 weeks, tetanus toxoid (TT) at 6, 10, and 14 weeks, and hepatitis B virus at 6, 10, and 14 weeks. Bifidobacterium levels were measured in the infants' stools at 6–15 weeks of age (near the time of vaccination), and T-cell and antibody responses to the vaccines were measured at 6 weeks, 15 weeks, and 2 years. Mean Bifidobacterium abundance in early infancy was positively associated with CD4 T-cell responses to BCG, TT, and hepatitis B virus at 15 weeks, with CD4 responses to BCG and TT at 2 years, and with plasma TT-specific immunoglobulin G and stool polio-specific immunoglobulin A at 2 years.

Comment: Much research in recent years has highlighted the elaborate interplay between the intestinal microbiota and the immune system; however, there are few data on how this interaction affects paediatric vaccine responsiveness. This prospective study examined the association between intestinal levels of Bifidobacterium spp. in early infancy with the magnitude and quality of vaccine-induced responses present at 2 years of age. More specifically, the authors analysed CD4+ T-cell responses and antibody responses to the BCG vaccine, oral poliovirus vaccine, hepatitis B vaccine, and tetanus toxoid vaccine. The authors found that an increased abundance of intestinal Bifidobacterium in early infancy was associated with increased CD4+ T-cell responses to BCG and TT and increased antibody responses to TT and polio at 2 years of age. This finding highlights an opportunity for interventions in early infancy which could increase vaccine effectiveness, although further work is needed to determine which other bacterial species play an important role, and whether any other vaccine responses are modulated in a similar manner.


**Aetiological spectrum, clinical differentiation and efficacy of polyethylene glycol over lactulose in children with constipation**

Authors: Poddar U et al.

Summary: This observational study determined the clinical features that differentiate organic from functional constipation in children, and compared the efficacy of polyethylene glycol (PEG) and lactulose for the treatment of childhood constipation. 316 consecutive children with constipation (median age 44 months) were evaluated between January 2007 and December 2014. 77.5% of cases were found to have functional constipation, and the remainder had organic constipation. Multivariable analysis showed that delayed passage of meconium, growth failure, absence of retentive posturing and absent faecal impaction were associated with organic pathology. In children with functional constipation, both PEG and lactulose were equally effective at 3 months. However, more children who initially received lactulose had to be switched to PEG due to lack of efficacy.

Comment: Constipation is an extremely common paediatric presentation and the cause of considerable morbidity. This prospective study from India included 316 consecutive children with constipation enrolled between 2007 and 2014. Standard treatment of functional constipation (Rome III criteria) was disqualification with PEG followed by laxatives: lactulose in the first 4 years, PEG in the last 4 years. The majority of the children (77.5%) had functional constipation whilst the commonest organic cause was Hirschsprung’s (39.4%). Organic pathology was more likely with a history of delayed passage of meconium, growth failure, absence of retentive posturing and absent faecal impaction. Both treatments were successful at 3 months, however more children in the lactulose group had to be switched to PEG due to lack of efficacy (p=0.0002), meaning that treatment with PEG may be slightly superior.


**Continuous versus intermittent vancomycin infusions in infants**

Authors: Gwee A et al.

Summary: This multicentre randomised controlled trial compared the use of continuous versus intermittent vancomycin infusions in infants in 2 tertiary neonatal units. 111 infants aged 0–90 days who required vancomycin therapy for at least 48h were randomly assigned to receive continuous or intermittent vancomycin infusions. The proportion of infants achieving target concentrations at the first steady-state level was higher for those receiving a continuous infusion (85% vs 41%; p<0.001). Fewer dose adjustments were required in the continuous infusion group, and the mean daily dose required to achieve target vancomycin concentrations was lower with continuous infusion (40.6 vs 60.6 mg/kg/day; p<0.01).

Comment: Continuous vancomycin infusion in adults is known to be preferable to intermittent infusion, as it allows earlier attainment of target plasma drug levels with reduced incidence of drug-related adverse events. This study aimed to determine whether this is also the case in infants treated with vancomycin. The study was conducted as a multicentre randomised controlled trial wherein 111 infants requiring intravenous vancomycin therapy were randomised to receive either continuous or intermittent infusion. The results indicated that compared to intermittent vancomycin infusion, continuous infusion allowed more rapid attainment of the target plasma drug concentration with a lower total daily dose, as previously reported in adults. The authors did not observe adverse drug reactions in either group. These findings indicate that continuous infusion should be the standard of care for infants requiring treatment with intravenous vancomycin.

Reference: Pediatrics 2019;143(2):e20182179

**Sibling recurrence risk and cross-aggregation of attention-deficit/hyperactivity disorder and autism spectrum disorder**

Authors: Miller M et al.

Summary: This US study examined the risk of ADHD and autism in younger siblings of affected children. Data were extracted from medical records of 2 large health care systems in the US. 15,175 later-born siblings of children with ADHD, ASD, and no known diagnosis were included. Compared with younger siblings of children without ADHD or ASD, younger siblings of children with ASD were more likely to be diagnosed with ASD (odds ratio [OR], 30.38) or ADHD (OR, 3.70), and younger siblings of children with ADHD were more likely to be diagnosed with ADHD (OR, 13.05) or ASD (OR, 4.35).

Comment: As anyone in community or developmental/behavioural paediatrics is aware, ADHD and ASD seem to have common genetic factors and biological influences and frequently co-occur in the same child or within the same family. This study examined within-diagnosis sibling recurrence risk as well as sibling cross-aggregation of ADHD and ASD in younger siblings of children with either. Participants were over 15,000 later-born siblings of children with either ADHD, ASD or no known diagnosis who were classified either ADHD risk (n=730), ASD risk (n=138) or no known risk (n=14,287). When compared with siblings of children without a known diagnosis, later-born siblings of children with ASD were 30.4 times more likely to be diagnosed with ASD, and 3.7 times more likely to be diagnosed with ADHD in the absence of ASD. Siblings of children with ADHD were about 13 times more likely to be diagnosed with ADHD, and 4 times more likely to be diagnosed with ASD without ADHD. These findings further support the shared genetic factors for both disorders and emphasise the need for screening for both disorders in siblings of those with either condition. This study also provides useful data for counselling families about recurrence risk for subsequent children.


**Prevalence and treatment patterns of autism spectrum disorder in the United States, 2016**

Authors: Xu G et al.

Summary: This study estimated the prevalence and treatment patterns of ASD among US children. Data were extracted from the 2016 National Survey of Children’s Health for 43,032 children aged 3–17 years. The prevalence of ever-diagnosed ASD and current ASD were 2.79% and 2.50%, respectively. The state-level prevalence of ASD varied from 1.54% in Texas to 4.88% in Florida. 70.5% of children with current ASD were being treated for either ADHD risk (n=730), ASD risk (n=138) or no known risk (n=14,287). When compared with siblings of children without ASD, younger siblings of children with ASD were 30.4 times more likely to be diagnosed with ASD, and 3.7 times more likely to be diagnosed with ADHD in the absence of ASD. Siblings of children with ADHD were about 13 times more likely to be diagnosed with ADHD, and 4 times more likely to be diagnosed with ASD without ADHD. These findings further support the shared genetic factors for both disorders and emphasise the need for screening for both disorders in siblings of those with either condition. This study also provides useful data for counselling families about recurrence risk for subsequent children.

Effect of intranasal ketamine vs fentanyl on pain reduction for extremity injuries in children

Authors: Frey T et al.

Summary: The PRIME trial compared intranasal ketamine with intranasal fentanyl for pain reduction in children with acute extremity injuries. 90 children aged 8–17 years who presented to an ED in the US with moderate to severe pain due to traumatic limb injuries were randomised to receive intranasal ketamine (1.5 mg/kg) or intranasal fentanyl (2 μg/kg). 30 minutes after drug administration, the mean visual analog scale reduction was 30.6mm for ketamine and 31.9mm for fentanyl (p=NS). The risk of adverse events was higher in the ketamine group (relative risk, 2.5), but all events were minor and transient.

Comment: Although opiates are generally used as the standard of care for treatment of severe pain in children due to trauma, they can have problematic adverse effects. Furthermore, children presenting to emergency with traumatic injuries are often not given adequate analgesia in a timely manner. This study therefore aimed to determine whether intranasal ketamine could provide pain relief of similar efficacy to fentanyl (a commonly used intranasal opiate in children). 90 children presenting to emergency with trauma were randomised to receive ketamine or fentanyl intranasally. Although the analgesic effects of intranasal ketamine were found to be comparable to those of fentanyl, children treated with ketamine were more likely to experience transient drug-related adverse effects (though these were mild in nature). While this study does not provide any major evidence against or in favour of the use of ketamine for analgesia in children, it does suggest that ketamine may be an effective alternative to opiates in children if opiates are contraindicated.


Abstract


Authors: Prickett K et al.

Summary: This study examined changes in firearm ownership in the past 4 decades among US families with young children, and the impact of these changes on firearm-related mortality in young children. Individual-level data from the National Vital Statistics System were merged with household-level data from the General Social Survey to estimate firearm-related child mortality and family firearm ownership from 1976 to 2016. The proportion of families with young children who owned firearms declined from 50% to 45% in non-Hispanic white families and from 38% to 6% in non-Hispanic African American families, but the proportion of white families with young children who owned handguns increased from 25% to 32% over the same time. 72% of white firearm-owning families with young children owned a handgun in 2016. Increases in handgun ownership partially explained the recent growth in firearm-related mortality in white children.

Comment: In the US, firearm-related fatalities are a top three cause of death among children, whilst in Australia this cause is not in the top ten. This important study examined changes in firearm ownership among families of young children from 1976–2016 in an attempt to understand recent increases in firearm-related mortality in 1- to 5-year-olds. Data were collected and merged from the National Vital Statistics System with data from the General Social Survey to estimate national firearm-related child mortality and family firearm ownership. Firearm ownership decreased across the time period in non-Hispanic white families (50% to 45%) and non-Hispanic African American families (38% to 6%). The important statistic was the increased likelihood of white families to own a handgun (increased from 25% in 1976 to 32% in 2016, or 72% of firearm-owning families in this demographic). This change in the type of firearm may explain the recently rising firearm mortality among young white children. This study provides further evidence, if it were necessary, of the need for change in US gun legislation.


Abstract