Welcome to the latest issue of Child Health Research Review.

Highlights include a report of NZ’s excellent screening programme for congenital adrenal hyperplasia, evidence that long bone fractures in young children don’t all happen randomly and should be taken seriously, and a reminder that steroids should be used sparingly in children, be they intranasal, topical or otherwise. We also have a report of advances in the prevention of perinatal hepatitis B transmission, and evidence that antibiotic exposure in infancy may increase the risk of being an overweight toddler. Selection and comments for this issue have been provided by Paediatric Endocrinologist Dr Craig Jefferies and members of the Paediatric Infectious Diseases team (Dr Elizabeth Wilson, Dr Rachel Webb, Dr Lesley Voss) at Starship Children’s Hospital.

We hope you find the selected studies interesting and useful in your clinical practice.

Kind regards,
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Newborn screening for congenital adrenal hyperplasia in New Zealand, 1994–2013
Authors: Heather H et al.
Summary: This study evaluated the efficacy of national newborn screening for severe congenital adrenal hyperplasia (CAH) in New Zealand over the past 20 years. CAH cases diagnosed in the newborn period were identified from Newborn Metabolic Screening Programme records. Between 1994 and 2013, 44 neonates were diagnosed with CAH (1 in 26,727). Almost half of them were detected solely via screening (not clinically suspected), including 21% of all affected females. Among the group solely detected by screening, 17-hydroxyprogesterone sampling occurred at a mean age of 3.3 days, and treatment was initiated at 12 days. Symptoms were mild at diagnosis and there were no adrenal crises.

Comment (CJ): This is a conflict of interest for me but I’ve included it to highlight the excellent screening programme that NZ has had for more than 2 decades now. To date this is one of the more long standing ones in the world, and has benefited from the strong leadership at the national testing centre. In comparison, no such national programme for CAH is present in Australia. Children here are diagnosed early and prevented from having adrenal crisis and potentially death. Despite this screening, many are becoming unwell and symptomatic at or around the time the results are coming through, so if there are any concerns they should be referred in for treatment straight away, don’t wait for the newborn screen result.

Reference: J Clin Endocrinol Metab 2015;100(3):1002-8
Abstract

Risk factors for long-bone fractures in children up to 5 years of age
Authors: Baker R et al.
Summary: This nested case-control study investigated risk factors for first long-bone fractures in children up to the age of 5 years. Maternal, household and child risk factors for injury were assessed among 2456 children with long-bone fractures (cases) identified from the Health Improvement Network, a UK primary care research database, 1988–2004. 23,661 controls were matched to cases by general practice. Children who were the fourth-born in the family, or later, had a 3-fold greater risk of fracture than first-born children. In addition, compared with children aged <1 year, those aged 13–24 months had a 4-fold increased risk of first long-bone fracture and those aged >37 months had a 5-fold increased risk. Children in families with a history of maternal alcohol misuse had an increased risk of long-bone fracture (adjusted OR 2.33) compared to those with no documented history.

Comment (CJ): This article highlights that long bone fractures in young children (less than 5 years old) don’t all happen randomly and should be taken seriously. Although not indicative of non-accidental trauma, they are avoidable and children with lower levels of attention/supervision are at increased risk. Accidents do happen, but can be avoided (see http://www.safekids.org/), and consider at-risk young mothers, large family numbers and alcohol.

Reference: Arch Dis Child 2015;100:432-437
Abstract

Abbreviations used in this issue
CAH = congenital adrenal hyperplasia
ICU = intensive care unit
OR = odds ratio
Incidence of short stature at 3 years of age in late preterm infants

Authors: Nagasaka M et al.

Summary: This Japanese study investigated the incidence of short stature at 3 years of age in late preterm infants. 26,970 neonates who were born between 34 and 41 weeks’ gestation in 2006–2008 were included; 1414 of them were late preterm infants (34–36 weeks’ gestation) and 25,556 were term infants. The incidence of short stature at 3 years of age was 2.9% in the late preterm group compared with 1.4% in the term group. Of the late preterm infants, those who were born small-for-gestational-age (SGA) were more likely to be short at 3 years compared with those who were considered appropriate-for-gestation-age at birth (9.4% vs 2.1%).

Comment (CJ): This study from Japan is a further examination of the effects or causes of being born premature. There is good local and international evidence of the effect on growth of extreme prematurity; however this report further highlights the influence even being born late-prem has. Although the percentages are relatively small the clinical impact on numbers is relatively large, due to the large numbers of babies being born premature. However all is not doom and gloom, older and longer cohorts such as the POP Dutch cohort followed from 1983 until final height showed that catch up growth occurred throughout childhood and even into adolescence; however those born both preterm and growth restricted (SGA) do have higher rates of short stature. The key message would be that preterm and especially SGA preterm infants should be monitored appropriately for their growth and referred if signs of early puberty occur.

Reference: Arch Dis Child 2015;100(3):250-4

GPR30 gene polymorphisms are associated with gynecomastia risk in adolescents

Authors: Korkmaz H et al.

Summary: The G protein-coupled receptor, GPR30, is an estrogen receptor that has been shown to mediate estrogenic effects of human breast cancer cells. This study evaluated the association between GPR30 gene polymorphisms and gynecomastia in adolescent males. 109 male adolescents with gynecomastia and 104 controls had various hormone levels measured. DNA was extracted from whole blood for assessment of GPR30 genotypes (rs3808350, rs3808351 and rs11544331). Median estradiol levels (16.86 vs 11.80 IU/L; p<0.001) and dehydroepiandrosterone sulfate levels (146.5 vs 116.8 μg/dL; p=0.044) were higher in the gynecomastia group than the control group. The G allele of rs3808350 and the A allele of rs3808351 were common in patients with gynecomastia. Gynecomastia was more frequently seen in patients with the GG genotype of rs3808350 and in patients with gynecomastia. Gynecomastia was more frequently seen in patients with the GG genotype of rs3808350 and in patients with the AA genotype of rs3808351.

Comment (CJ): The G protein-coupled receptor GPR30 is a third and likely little known estrogen receptor (after estrogen receptor alpha and beta). In this report there is some evidence that polymorphisms of this third estrogen receptor are associated with adolescent gynecomastia. Gynecomastia is usually a results of an imbalance of estrogen and androgen (from a variety of causes including certain medications, drugs and adiposity), resulting in for example a relative increase in estrogen. Studies to date using tamoxifen or other estrogen receptor modulators are mixed in their results; however anecdotally some cases do very well, which makes one consider whether these types of polymorphisms may be clinically relevant.

Reference: Horm Res Paediatr 2015;83(3):177-82

Independent commentary by Dr Craig Jefferies

BHB, MBCHB, Dip Paeds, FRACP, MD.

Craig has been a Paediatric Endocrinologist based at the Starship Children’s Hospital since 2005, where he is the current Clinical Director of the Paediatric Endocrinology Service. He attended medical school at Auckland, and received the majority of his Paediatric training in Starship before completing a fellowship in Paediatric Endocrinology at the Hospital for Sick Children, Toronto, Canada. His current roles include: inpatient and outpatient care for Endocrinology and Diabetes at the Starship, as well as visiting outreach clinics in the North Island including Taranaki, Tauranga, Rotorua and Gisborne. He is an honorary senior lecturer at the Liggins Institute.

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Intranasal triamcinolone and growth velocity

Authors: Skoner D et al.

Summary: This study evaluated the effect of triamcinolone acetonide aqueous nasal spray on growth in children with perennial allergic rhinitis (PAR). 299 children aged 3–9 years with PAR were randomised in a double-blind design to receive triamcinolone nasal spray (110mg per dose) or placebo once daily for 12 months. Mean growth velocity during treatment was lower in the triamcinolone group than the placebo group (5.65 vs. 6.09 cm/year; p=0.01). The difference was evident within 2 months of treatment and stabilised thereafter. At follow-up (2 months after stopping treatment), growth velocity approached baseline velocity in the triamcinolone group and decreased slightly in the placebo group. No hypothalamus-pituitary-adrenal axis suppression was observed.

Comment (CJ): Pardon the pun, but the perennial problem of how much steroid is too much is well examined here. Although this exact nasal steroid is not widely used in NZ, there is evidence of steroid-induced growth reduction initially, however this normalises and there is no clinically significant effect of growth long term. The strength of this study is the design (randomised controlled trial). One weakness is no estimate of bone age maturity. However although safe it still enforces the logic to use steroids sparingly be they intranasal, topical or otherwise.

Reference: Pediatrics 2015; published online Jan 26

Abstract

Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus

Authors: Greenup A et al.

Summary: This Australian study investigated outcomes after administration of antiviral therapy during the third trimester in pregnant women with hepatitis B virus. 58 women received tenofovir, 52 received lamivudine and 20 received no antiviral treatment. Virologic response was better with tenofovir than with lamivudine: mean viral load fell from 7.98 log copies at baseline to 4.49 log copies at birth in the tenofovir group and 5.6 log copies at birth in the lamivudine group (p=0.01). Four tenofovir recipients did not tolerate the drug due to gastrointestinal adverse events, whereas lamivudine was well-tolerated by all recipients. Follow-up data were available for 95 infants. One of 44 in the tenofovir group acquired hepatitis B but none of 43 in the lamivudine group was infected. Two babies of 8 untreated mothers were infected.

Comment (RW): This study highlights a significant advance in the prevention of perinatal hepatitis B transmission, and is a timely reminder for lead maternity carers and general practitioners to refer all hepatitis B infected. E antigen positive, pregnant women to their local obstetric medicine or hepatology service for consideration of antiviral treatment. Whilst both tenofovir and lamivudine in the third trimester reduced perinatal hepatitis B transmission compared to no maternal antiviral treatment, tenofovir is favoured due to its potency and high resistance barrier, and appears to be safe for both mother and baby. Gastrointestinal side effects may be problematic. This is an area of evolving knowledge and infants who have been exposed to tenofovir in utero should be clinically monitored, in addition to having serology at 9 months of age following completion of their primary course of hepatitis B vaccination.

Reference: J Hepatol 2014;61(3):502-7

Abstract

Azithromycin in early infancy and pyloric stenosis

Authors: Eberly M et al.

Summary: This US study evaluated the association between oral azithromycin and erythromycin exposure in infancy and the subsequent development of infantile hypertrophic pyloric stenosis (IHPS). A retrospective cohort study of 1,074,236 children born in 2001–2012 was performed using the military health system database. Infants prescribed either oral erythromycin or azithromycin in the first 90 days of life were evaluated for development of IHPS. 2466 (0.2%) of the children in the study developed IHPS. Azithromycin exposure in the first 14 days of life was associated with an increased risk of IHPS (adjusted OR, 8.26); and exposure between 15 and 42 days had an adjusted OR of 13.3 and exposure between 2466 (0.2%) of the children in the study developed IHPS. Azithromycin exposure in the first 14 days of life was associated with an increased risk of IHPS (adjusted OR, 8.26); and exposure between 15 and 42 days had an adjusted OR of 13.3 and exposure between 15 and 42 days had an adjusted OR of 4.10. There was no association with either macrolide when used between 14 and 90 days of life.

Comment (CJ): Whilst azithromycin use should still be recommended for pertussis prophylaxis, a potentially fatal disease for infants) so it is fortunate the risk for IHPS seems lower than that with erythromycin. As azithromycin has a similar stimulatory action on gastrointestinal motility as erythromycin it is not surprising that it carries a risk of IHPS, but this is the first population based study to show it. Azithromycin use in infants has increased (for pertussis prophylaxis, a potentially fatal disease for infants) so it is fortunate the risk for IHPS seems lower than that with erythromycin. Whilst azithromycin use should still be recommended for pertussis prophylaxis, physicians and parents should be aware of the pyloric stenosis risk. The study finding supports vaccinating pregnant women and all those in contact with young infants against pertussis to minimise the need for prophylaxis.


Abstract

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

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Predictors of disease severity in children hospitalized for pertussis during an epidemic

Authors: Marshall H et al.

Summary: This Australian study determined predictors of severe pertussis in children hospitalised during an epidemic. 120 children hospitalised with laboratory confirmed pertussis during a 12-month period (May 2009–April 2010) were included. Cases were scored using objective clinical findings and were classified using a pertussis severity score (PSS) as either severe (PSS >5) or not severe (PSS ≤5). 61.7% of the children were classified as not severe and 38.3% were classified as severe. Most of the severe cases (54.3%) were aged <2 months. Presence of co-infection, <2 months old, fever >37.5°C and history of prematurity were independent predictors of severe disease. 23 of 70 cases aged ≥2 months of age had not received pertussis vaccine.

Comment (RW): A challenge for clinicians who manage infants with pertussis is deciding which babies will go on to develop severe disease requiring prolonged hospital care. The authors of this study developed a clinical scoring system to predict pertussis disease severity, the first of its kind intended for use outside the developed world. Of 120 hospitalised cases, 34% were admitted for over 7 days and 17% needed high dependency unit or ICU care. 50% of infants <2 months old had the highest pertussis severity score 5. On univariate analysis, risk factors for severity included prematurity, age <2 months, co-infection with another respiratory pathogen, apnoea and fever. On multivariable analysis only fever remained as an independent risk factor. The clinical utility of this scoring system is yet to be determined, however the study’s findings reinforce current guidelines that very young infants with pertussis should be managed cautiously, with a low threshold for hospitalisation. We need better protection for young infants who have not yet been vaccinated. Currently, the most effective strategy is by promoting pertussis immunisation (Boostrix®) for all pregnant women at 28–38 weeks’ gestation.


Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life

Authors: Saara A Et al.

Summary: This Finnish study evaluated the impact of antibiotic exposure during infancy on weight and height in healthy children. The population-based cohort comprised 12,062 healthy boys and girls who had weight and height measurements and drug purchase data available from birth to 24 months. Body mass index (BMI) and height, expressed as z-scores at the median age of 24 months were compared between children exposed and unexposed to antibiotics. Exposed children were on average heavier than unexposed children (p<0.001 for boys and p<0.05 for girls). The effect was most pronounced after exposure to macrolides before 6 months of age, or in those children who had >1 exposure.

Comment (RW): Antibiotics have been used as growth promoters in agriculture for many years, but little is known about the impact of antibiotics on human infant growth. In this Finnish population of over 12,000 healthy children, the risk of being overweight increased after antibiotics at less than 6 months of age, multiple antibiotic courses and macrolides. These findings warrant further consideration in light of the global obesity epidemic and present another reason to be judicious when prescribing antibiotics to infants and young children. Further research addressing potential confounders such as infant feeding practices and parental obesity is needed, along with long-term follow-up of growth and metabolism. What is the underlying mechanism for these observations and why is the timing of antibiotic exposure in infancy so important? It would be interesting to undertake a similar study in New Zealand, where there are high rates of both childhood obesity and community antibiotic prescribing.


Authors: Schapbach L et al., for the for the ANZICS Paediatric Study Group

Summary: This study evaluated temporal trends in the incidence and mortality of severe infections in critically ill children in Australia and NZ. 97,127 children aged <16 years who required ICU care in Australia and NZ in 2002–2013 for invasive infection, sepsis, or septic shock were included. Two time periods were compared: 2002–07 and 2008–13. The age-standardised incidence increased each year by an average of 0.56 cases per 100,000 children for invasive infection, sepsis, or septic shock in critically ill children in Australia and New Zealand, 2002–13. The age-standardised incidence increased each year by an average of 0.56 cases per 100,000 children for invasive infections, 0.09 cases per 100,000 children for sepsis, and 0.08 cases per 100,000 children for septic shock. Mortality rates were 3.9%, 5.6% and 17.0% for invasive infection, sepsis, and septic shock, respectively (compared with 3.0% of all paediatric ICU admissions). Children admitted with invasive infections, sepsis, and septic shock accounted for 26.4% of paediatric deaths in ICUs. Comparing 2008–13 with 2002–07, risk-adjusted mortality decreased significantly for invasive infections (OR 0.72; p=0.016) and sepsis (OR 0.66; p=0.016), but not for septic shock (OR 0.79; p=NS).

Comment (LU): Prevention strategies such as the introduction of Haemophilus influenzae type B vaccine and pneumococcal vaccine along with the meningococcal B vaccination campaign have helped reduce severe septic episodes in children. This study evaluating Australian and NZ incidence and mortality data for sepsis events requiring admission to intensive care, found a rising incidence over the decade evaluated. Many of these episodes are related to comorbidities and the increasing intensity of health care and development of new technologies. However, nearly 50% of children did not have a major comorbidity and one third of deaths occurred in this group. Bacteria were the commonest group of organisms, with Staphylococcus aureus (10% of episodes) being the most common organism in the years from 2008–2013. This study identifies a continuing need to develop and promote prevention programmes e.g. influenza/group A streptococcal vaccination, as well as initiation of early diagnostic and treatment strategies to prevent progression to severe sepsis.

Reference: Lancet Infect Dis 2015;15:46-54

Commentary provided by members of the Paediatric Infectious Diseases Team at Starship Children’s Hospital.

The Starship Paediatric Infectious Diseases Service provides care for children with complex, severe or chronic infectious diseases. The service has an important liaison role with Public Health, Microbiology and Infection Control services. It also provides management and co-ordination for regional children’s tuberculosis, HIV and rheumatic fever services. A national consultation service is provided for paediatricians, other specialist paediatric services, hospitals and policy makers.

Right: Paediatric Infectious disease consultants from left clockwise: Diana Lennon, Emma Best, Lesley Voss and Elizabeth Wilson. Not pictured Rachel Webb.