What might happen.

Richard Beasley and colleagues report a strong association between use of paracetamol in the first year of life and asthma at 6–7 years of age, and a dose-dependent association between current paracetamol use and symptoms of severe asthma. We believe Beasley and colleagues might have overstated their conclusions.

With this cross-sectional, retrospective study, Beasley and colleagues contend with the intrinsic difficulties of recall bias, misclassification bias, and confounding by indication. Paracetamol use has been found to be highly associated with an increased risk of all causes of death, highlighting the potential for drawing invalid conclusions about causal relations in observational studies of commonly used drugs.

The categorisation of paracetamol use seems somewhat arbitrary. It is hard to reconcile, for example, the finding that “medium” (at least once per year) use of paracetamol is strongly associated with asthma. We also question the use of “wheeze and whistling in the chest” as a surrogate for the diagnosis of asthma. A physician-based diagnosis would have been preferable. Although Beasley and colleagues state that wheeze and whistling in the chest is a reliable surrogate, we think it subjective.

We commend Beasley and colleagues for using the population-attributable risk proportion (PAR%) to estimate the fraction of population-level asthma attributable to paracetamol use. However, PAR% is population-specific. Assuming that the association between paracetamol use and asthma is truly causal, regions with a higher frequency of paracetamol use will have a higher proportion of paracetamol-induced asthma in the population (i.e., a larger PAR%). As indicated in Beasley and colleagues’ webtable 1, the prevalence of paracetamol use varies substantially from centre to centre. Thus, we question the appropriateness of calculating a combined PAR% for all 47 centres.

To conclude, we take issue with the statement that “paracetamol use in infancy and frequent use later in childhood strongly increases the risks of asthma”. Findings from this study are suggestive of such an association, but the findings should be interpreted with caution.
Oral sucrose for procedural pain in infants

Rebecca Slater and colleagues (Oct 9, p 1225) question the benefit of sucrose for alleviating procedural pain in infants. We believe that they might have overstated their conclusions and suggest a more cautious interpretation of the study findings.

In agreement with other studies, Slater and colleagues report a significant reduction in observed pain scores in infants given sucrose compared with placebo. An intriguing observation was the absence of any difference in nociceptive pathway activity in infants who received sucrose or placebo. On this basis, Slater and colleagues conclude that oral sucrose is ineffective for pain relief in infants, and discourage its routine use in infants.

We disagree that the documented cortical measures are a reliable surrogate of perceived pain in infants. The WHO definition of pain refers to the subjective and emotional experience being of primary importance. Our access to infants’ emotions is that sucrose has long-term negative effects. We agree with Slater and colleagues that every effort should be made to minimise nociceptive pathway activation in infants.

We declare that we have no conflicts of interest.

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4 Campbell D. Newborn babies should not be given sugar as pain relief, says study. The Guardian Sept 2, 2010.
Efficacy of hypertonic nebulized saline in bronchiolitis: Improved outcome measures needed

To the Editor:

The recent report by Al-Ansari et al. adds to recent studies investigating the use of nebulized hypertonic saline (HS) for the treatment of bronchiolitis. However, we believe that the authors might have overstated their conclusions, and we suggest a more cautious interpretation of their study findings.

Pooled data from 4 randomized controlled trials (RCTs) of nebulized 3% HS (coadministered predominantly with bronchodilators) have shown a potential benefit in bronchiolitis, albeit using different delivery methods and timing of administration. Reduced length of stay and lower clinical severity scores were seen in patients with mild to moderate bronchiolitis and were more marked in outpatients than in inpatients. A more recent RCT reported by Luo et al. also showed that 3% HS (administered without bronchodilator) was beneficial in patients with moderate to severe bronchiolitis.

Al-Ansari et al. show that regular administration of nebulized 5% saline compared with 0.9% saline reduced the mean severity score of 0.43 (95% confidence interval, 0.02-0.88) at 48 hours in mild bronchiolitis (mean severity score, 5.6 at baseline). We question the clinical significance of this reduction on a 12-point severity scale. Although the authors report a “consistent trend favoring 5% saline,” their Figure 1 of stay, and need for respiratory support, to truly define the potential role of this promising treatment.

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Susceptibility to respiratory syncytial virus bronchiolitis linked to vitamin D deficiency? Cautious interpretation of study findings required

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We read with interest the recent report by Belderbos and colleagues entitled 'Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis'[1]. We are concerned that the title may be misleading to readers, that the authors may have overstated their conclusions and therefore urge caution in interpretation of the study findings.

In the study Belderbos and colleagues provide preliminary data on a potential association between low cord vitamin D levels and subsequent risk of respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) in the first year of life. As a result, they suggest that 'vitamin D supplementation during pregnancy may be a useful strategy to prevent RSV LRTI'.

Before accepting the conclusion by Belderbos et al several points need to be taken into consideration. Figure 1 illustrates the somewhat unusual study design by the authors in relation to recruitment and consent. Of 1007 eligible infants, fewer than half had an initial cord blood sample taken. Of the remaining 481 infants, 465 (97%) had a second interview at one month, not when the 'infant was aged 1 to 3 weeks' as reported. Only at this point was informed consent obtained, with 65% refusing to be included in the study. The potential influence of this extraordinarily high number of excluded infants on overall study results is not discussed. Of the 156 infants that were included in analysis, only 18 (12%) subsequently developed an RSV LRTI.

Although the 18 infants that developed 'parent-reported RSV LRTI' had ‘1.3-fold lower' mean cord 25-OHD concentrations compared to infants that did not develop a RSV LRTI (65 nmol/L vs. 84 nmol/L, p=0.009), both groups had a 'normal' mean vitamin D levels. The authors do not actually define vitamin D deficiency in their manuscript, but we presume a level of < 50 nmol/L was deemed deficient given further analyses. Furthermore, the authors do not provide data on vitamin D levels in the 'cases' or 'controls' at any time during follow up. This is important as almost...
Is nebulised hypertonic saline useful as an adjunctive treatment for acute bronchiolitis in infants and children less than 24 months of age?

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Oral versus sequential IV/Oral antibiotics for acute pyelonephritis in infants and children: cautious interpretation of study findings required

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The use of potentially less intensive treatment regimens for acute pyelonephritis is topical in paediatrics(1). We read with interest the recent paper by Bocquet et al comparing oral to sequential IV/oral antibiotics for the treatment of acute pyelonephritis in infants and children (2). The authors should be commended for attempting a multi-centre randomized controlled trial (RCT) to complement existing evidence supporting less intensive treatment approaches in children(1). Nevertheless, we have significant concerns regarding the study methodology, analysis and interpretation and feel the authors have significantly overstated their conclusions. We therefore believe cautious interpretation of the study finding is warranted.

In this study, children with their first febrile urinary tract infection (UTI) with abnormalities on DMSA were randomised to receive 10 days of oral cefixime (PO) or sequential intravenous cefotaxime (4 days) followed by oral cefixime (6 days) (IV/PO arm). The primary endpoint in the study was the presence of renal scarring on follow-up DMSA testing up to eight months later. Based on the observation that the proportion of patients in each group with renal scarring was similar in both groups, the authors
RCT of Montelukast as Prophylaxis for Upper Respiratory Tract Infections in Children: No effect but a case of therapeutic creep?

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Letter in response to: Kozer et al. RCT of montelukast as prophylaxis for upper respiratory tract infections in children

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Dear Editor, Randomized controlled trials (RCTs) in children with asthma have shown that compared to placebo, the daily administration of montelukast in addition to regular inhaled glucocorticoid treatment improves FEV1 and decreases the requirement for rescue medications (1). Furthermore, the intermittent use of montelukast has been associated with modest reductions in health-care resource utilization of health care resources and asthma interval symptoms (2–3). Preceding upper respiratory tract infection (URTI) is the most common trigger for an acute exacerbation of asthma in children but there are currently no data on the use of montelukast in preventing URTIs in 'healthy' children. We therefore read with interest the recent manuscript by Kozer et al that investigated the use of montelukast as prophylaxis in preventing URTIs in healthy children (4). Although we commend Pediatrics for publishing the results of this industry–sponsored trial that reported negative results, we have several concerns regarding the study design and methodology, data
Imaging after a first febrile UTI in infants and children: less is more?

Although universally recommended by the American Academy of Paediatrics, the need for a voiding cystourethrogram (VCUG) following a first febrile UTI in infants continues to generate debate. The UK NICE guidelines recommend a more selective approach for imaging based on defined risk factors. In this study, Schroeder and colleagues assessed the impact of incorporating an algorithm adapted from the NICE guidelines into routine clinical care. Study endpoints included the use of imaging, detection of VUR, antibiotic use and UTI recurrence. Results were provocative. Although adherence to the algorithm was not universal, an 85% reduction in the proportion of children that had a VCUG ordered and a 70% reduction in the number of children prescribed antibiotic prophylaxis was observed post introduction of the algorithm. No increased risk for UTI recurrence was shown within six months. All cases of high grade VUR (Grade 4-5) were identified but not surprisingly likely cases of low-grade VUR (Grade 1-3), the clinical relevance of which is debatable, were missed. The authors acknowledge several limitations to their study including the criteria used for defining UTI, its retrospective nature, incomplete follow up data and lack of other imaging modalities including DMSA. Recent trend data within Australia suggest less VCUG scans are being ordered by paediatricians and the study by Schroeder et al is likely to provide a measure of reassurance in this regard.

Reference

HEADS UP
edited by Craig Mellis (craig.mellis@sydney.edu.au)

Is malodorous urine associated with urinary tract infection in children?

Although commonly reported by parents, the association of malodorous urine with confirmed urinary tract infection (UTI) in children remains controversial. In this two-year prospective study, the authors investigated whether parental reporting of malodorous urine was associated with confirmed UTI in children aged 1 to 36 months presenting with fever without focus. Of 331 children (median age 12 months), 51 (15%) had a confirmed UTI. The majority of urine specimens (88%) were obtained via catheter. Malodorous urine was reported in 57% (42-70) of children with confirmed UTI and 32% (42-70) of children without UTI. On regression analysis, children with malodorous urine were more likely to have a UTI (OR 2.83 (1.54-5.2)) compared to children without malodorous urine, even after adjustment for sex and the presence of reflux. Although malodorous urine is more likely in children with confirmed UTI results suggest that up to 40% of children with a UTI do not have malodorous urine and that as many as 30% of children with malodorous urine do not have a UTI. Therefore we cannot definitively rule in or out a diagnosis of UTI based on urinary odour alone, but it may a useful sign to aid clinical decision-making in routine clinical practice.

Reference

RCT of Lansoprazole for children with poorly controlled asthma: No effect, potentially harmful and a case of therapeutic creep?

Although regularly prescribed in children with poorly controlled asthma with or without symptoms of gastroesophageal reflux (GER), the benefit of PPIs in improving asthma control remains uncertain. In this study, 306 children with poorly controlled asthma were randomized to receive either lansoprazole or placebo for 24 weeks in addition to their regular asthma treatment. The primary outcome measure was the change in the Asthma Control Questionnaire (ACQ) score at 24 weeks. The groups were well matched at baseline in regard to ACQ scores, lung function and the presence of comorbid conditions including GER. Overall there were no differences in the ACQ score nor for any of the secondary outcome measures between the groups irrespective of GER status. There were more adverse events in terms of upper respiratory tract infection (p=0.02), sore throat (p=0.02), bronchitis (p=0.04) and activity related bone fractures (p=0.06) in the lansoprazole group compared to placebo. This study suggests lansoprazole is not effective and may potentially be harmful in children with poorly controlled asthma. Concerns has been raised about the exponential use of PPIs in children over the past decade and their potential to cause adverse effects and this study provides further evidence that we should exercise caution before reaching for the prescription pad.

Reference


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CORRESPONDENCE

Amoxicillin-clavulanate for chronic wet cough in children: cautious interpretation of study findings warranted

We read with interest the recent paper by Marchant et al comparing amoxicillin-clavulanate to placebo for the treatment of chronic wet cough in children. The authors should be commended for attempting a randomised controlled clinical trial in this group of patients that often present paediatricians with a management dilemma. Nevertheless, we have significant concerns regarding several aspects of the study methodology, analysis and interpretation and feel that the authors have overstated their conclusions. We therefore urge caution in interpretation of the study findings.

First, the definition of chronic cough used in the study (greater than 3 weeks) contradicts the authors' previously recommended definition of chronic cough based on a score from baseline. We question the use of a median (IQR) VCD score on a scale that contains six categories. We feel it would have been preferable to report the proportion of patients with cough resolution in each VCD score category within the two groups. In Table 1 of the manuscript, it can be seen that the baseline 75th centile VCD score in both groups was 3.0. This would indicate that children whose VCD score was greater than 0.5 at study endpoint, despite significant improvement in their symptoms, would still be classified as a failure based on the primary outcome. Fourth, given the relatively long period of time that elapsed between patient recruitment and subsequent publication, it would have been interesting to know the long-term outcomes of the children. Finally, although beyond the scope of the current study, the potential impact of prolonged antibiotic treatment in selecting out resistant organisms should not be discounted.

Despite the shortcoming to the study by Marchant et al that preclude definitive conclusions, we believe it represents a valuable contribution to the literature in...

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To the Editor

We read with interest the recent article by Ivarsson and colleagues(1). The study adds to several from this group investigating the association of various factors, including infant feeding and timing of introduction of gluten, with subsequent development of celiac disease(2– 4). The information provided is derived from a larger dataset and is not new but a novel aspect is the comparison between the prevalence of celiac disease in two birth cohorts. The authors contend, based on their findings, that early introduction of gluten from 4 months with concurrent breastfeeding can potentially prevent celiac disease. We have several concerns that question this conclusion.

The pre-specified null hypothesis is curious considering the cohorts selected for comparison ('Swedish epidemic' 1993 cohort and a 1997 cohort). Results (higher rates of celiac disease in the 1993 cohort) confirmed what the authors already thought a priori. The authors have previously published on the decreased risk for celiac disease in children in whom gluten was introduced while breastfeeding was continued(3, 4). The present study was unlikely to report contrary findings.

Given the main aim was to correlate infant feeding patterns with risk of celiac disease, the methodology was overly focused on the screening strategy. Limited information was provided regarding the questionnaire and the information obtained was not correlated with risk of developing celiac disease on an individual basis. No formal analyses were included to establish the relationship between infant feeding patterns with subsequent development of celiac disease, adjusted for cohort.

The authors’ conclusion regarding the timing of introducing gluten (4 months) is not supported by their data, as there was no difference between cohorts in the median age at which gluten was introduced. The authors are quick to ascribe this to recall bias but accept accurate recall of the duration of breastfeeding.

The discussion is lengthy and the authors provide multiple hypotheses as to why the timing of and the amount of gluten introduced may influence the risk of developing celiac. The most interesting finding, namely the high proportion of asymptomatic children that screened positive and the implications, if any, this may have on a population level is not discussed.

While the authors have shown a difference in the prevalence of celiac disease between two birth cohorts, we urge caution given the limited data provided, in accepting the conclusion that infant feeding patterns are primarily responsible.

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The term 'acid–reflux' is commonly used by parents that seek medical care for infants with feeding problems and irritability. This is often followed by a request for an acid–suppressing medication. Although long presumed safe, recent evidence now questions the safety of proton–pump inhibitors and has shown their potential to cause harm.1, 2

With this in mind, we read with interest the recent manuscript by Scherer and colleagues3 that investigated how different levels of information provided by a physician can influence parents' decisions regarding treatment. Specifically, in their study, four separate written vignettes were provided to parents to ascertain whether the provision of a disease label (Gastro Esophageal Reflux Disease (GERD)) and information on medication 'ineffectiveness' influenced parental interest in medicating their infant. We believe the way the vignettes were presented would inherently bias parents towards medicating their infants irrespective of a disease label. In our view the condition of the infant in the vignettes suggests underlying pathology and is not representative of the vast majority of infants that present with GER. Further, information provided regarding medication 'ineffectiveness' actually suggests the medication might be effective given the word 'probably' was used in the vignette. However, despite these reservations, the study is novel and highlights how clever marketing, personal experience and the way the information is provided by a physician can influence decisions regarding treatments.

Despite employing a complex study design, the study unfortunately lacks important information. There is no description of how randomisation was done and the number of parents in each group is not provided. Despite collecting the data, the demographic variation between subgroups is not described and there is no evidence that the distribution of potential confounding factors such as parental age have been considered. A
Lack of benefit of steroids for the prevention of Henoch–Schönlein purpura-associated nephritis

With a lack of evidence to support their use, the role of steroids in preventing Henoch–Schönlein purpura (HSP)-associated nephritis has remained controversial. In this well-conducted, multicentre, blinded, randomised placebo-controlled trial, Dudley et al. provide high-quality evidence for a lack of benefit of steroids in preventing HSP nephritis. In their study, 352 children with HSP were randomised to either prednisolone (2 mg/kg/day for 7 days; 1 mg/kg/day for 7 days) or placebo for 14 days. Follow-up assessments were done at 4 weeks, 3 months and 12 months. The primary outcome was the presence of proteinuria (urine protein : creatinine (UP : UC) of >20 mg/mmol) at 12 months. At 12 months, only 70% of patients had urine samples available for analysis for the primary outcome. However, despite this, there was no difference in the proportion of children that had a UP : UC > 20 mg/mmol, even after controlling for baseline proteinuria and medications that may affect the level of proteinuria (βdds ratio 1.29 (95% confidence interval 0.58–2.82)). The most common reason for unblinding was the presence of severe abdominal pain. The study by Dudley et al. provides paediatricians with the best available evidence to date and does not support a role for steroids in preventing HSP nephritis.

Reference


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