

A single dose of hydrocortisone and an albumin infusion were given initially. She was subsequently treated with warmed intravenous fluids for three days and antibiotics for 10 days. She recovered completely and continues to enjoy good health.

Profound hypothermia is extremely rare in children over 5 years of age. Results of investigations excluded infective and endocrine causes. A normal MRI brain scan showed there was no lesion of the hypothalamus or corpus callosum.

Ibuprofen is commonly prescribed for a raised temperature and is well tolerated in children. Side effects are not common, even in overdose.¹ Nevertheless we postulate that ibuprofen was responsible for hypothermia in this case. We are not aware of any published evidence documenting hypothermia after a single therapeutic dose of ibuprofen, but it has been recorded in a few cases of accidental and deliberate overdosage. Although patients may sometimes receive ibuprofen in toxic quantities, hypothermia is not a consistent feature.^{2,3} Hypothermia in overdosage is attributed to central nervous system depression.⁴

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Vagal overactivity: a risk factor of sudden infant death syndrome?

Since early 1990, the incidence of sudden infant death syndrome (SIDS) has dropped sharply because of public health campaigns decrying the dangers of the prone sleep position. The other known risk factors, such as preterm birth and young maternal age, are less susceptible to prevention campaigns.¹

Disordered autonomic function, including cardiorespiratory control, has been suggested to be involved in SIDS.^{2,3} Vagal overactivity (VO), characterised by breath holding spells and repeated syncope in specific circumstances, has been described as a manifestation of autonomic dysfunction.⁴ To investigate a possible relation between VO and SIDS, we investigated 65 children presenting documented VO; for example, clinical characteristics and a positive test for eyeball compression and/or electrocardiographic monitoring. Parents of these children were interviewed about their family history, especially with respect to the occurrence of SIDS among their other children.

Among their siblings, five of 126 had died of SIDS. All five children were full term infants. The average maternal age, birth weight, and age at death were respectively 27.4 (3.5) years, 3.3 (0.3) kg, and 3.5 (1.1) months. The rates of SIDS in siblings of children with VO were compared to those in the general population using the standardised incidence ratio (SIR), which is the ratio of the observed number to the expected number of cases of SIDS calculated by French incidence rates. The expected number of SIDS was 0.17 and hence the SIR was 29.4 (95% CI 9.5 to 68.6; $p < 0.00011$). Our result showed an overall significant excess of SIDS among siblings of children with VO. We verified that recruited children had not come to the centre because of a family history of SIDS. Since children with a positive family history of SIDS could be followed up more regularly than others, we estimated the SIR separately among siblings of children recruited during their follow up and those of children recruited during their first visit, and verified that there was no significant difference in SIR between these cases.

Despite the marked decline in SIDS, it is still the leading cause of postneonatal mortality. Better knowledge of other risk factors may allow identification of populations at high risk and a possible decline in infant mortality from SIDS through the implementation of appropriate prevention measures. Our findings suggest that VO may be involved in SIDS and that children with VO or a family history of VO may be a population at potential high risk of SIDS.

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Perforated duodenal ulcer disclosing medium chain acyl-CoA dehydrogenase deficiency

Medium chain acyl-CoA dehydrogenase deficiency (MCADD; McKusick 201450) typically presents in the first two years of life with recurrent episodes of hypoketotic hypoglycaemia, lethargy, coma, or sudden infant death. The trigger may be fasting, intercurrent infections, anaesthesia, or surgery. Incidence in the

UK is estimated at 0.45–1/10 000 live births.¹ We describe the case of a child who presented with marked encephalopathy unexplained by perforated duodenal ulcer, which led to the diagnosis of MCADD.

A 2 year old girl presented with a three week history of coryzal symptoms and three day history of frequent coffee ground vomiting. She was shocked, and had hepatomegaly and decreased conscious level. Blood glucose was 3.9 mmol/l (reference interval 3.3–5.5), plasma sodium 129 mmol/l (135–147), potassium 5.2 mmol/l (3.5–5.0), urea 17.8 mmol/l (3.3–6.6), creatinine 36 mmol/l (30–74), bicarbonate 15 mmol/l (21–28), base excess –5.4 mmol/l (–4 to +2) and C reactive protein 4 mg/l (0–5). Liver function tests and clotting were normal. She was resuscitated with a total of 50 ml/kg of colloid and crystalloid. The following day she relapsed with abdominal distension, shock, and deteriorating conscious level. Investigations showed glucose 14.2 mmol/l, amylase 20 IU/l (8–85), AST 186 IU/l (10–45), and ALT 129 IU/l (10–40). An x ray examination of the abdomen showed free air under the right hemidiaphragm. Emergency laparotomy revealed a single, 1 cm × 1 cm acute perforation in the second part of the duodenum. Histology and rapid urease test (CLO) of the duodenal biopsy for *Helicobacter pylori* were negative. Fasting blood gastrin was 20 mU/l (10–100). She was discharged home taking omeprazole. Upper gastrointestinal endoscopic biopsy (eight weeks later) for histopathology and CLO test from oesophagus, stomach, antrum, and duodenum were normal.

Analysis of urinary organic acids by gas chromatography and mass spectrometry, obtained a day after clinical presentation, revealed a marked increase in 5-hydroxyhexanoic acid (21% of total organic acids); a modest dicarboxylicaciduria (suberic accounted for 8% and adipic 6% of total organic acids); and a small but significant quantity of hexanoyl glycine (2% total organic acids) in the absence of ketonuria.

Blood obtained a week after clinical presentation, when analysed by tandem mass spectrometry, showed octanoylcarnitine 2.91 $\mu\text{mol/l}$ (≤ 0.19), hexanoylcarnitine 0.67 $\mu\text{mol/l}$ (≤ 0.29), and decenoylcarnitine 0.63 $\mu\text{mol/l}$ (≤ 0.10), with a subnormal concentration of acetylcarnitine 4.0 $\mu\text{mol/l}$ (6.2–27.5). This profile was consistent with MCADD. Polymerase chain reaction/restriction digests based method revealed two mutations in the MCAD gene.

The clinical details coupled with the absence of ketones and the increased 5-hydroxyhexanoic acid led us to look for an abnormality in the oxidation of fatty acids, and resulted in identification of the minor constituent, hexanoylglycine that is recognised as an indicative marker of MCADD. Increases in urinary hexanoylglycine and 5-hydroxyhexanoic acids in the absence of ketonuria have been reported previously in MCAD patients during clinical attack,² and also in a boy who died.³ Our case was unusual in that the amount of 5-hydroxyhexanoic acid was greater than even the sum of the individual dicarboxylic acids present, although high levels of 5-hydroxyhexanoic acids are reported in acute episodes.⁴ The increased concentration of octonoyl carnitine in blood was also consistent with a diagnosis of MCADD.

We believe that this is the first report of MCADD presenting with duodenal ulcer. It could be argued that the ulcer was the primary problem and that the decompensation was caused by the subsequent illness.

Thus, any child who has unexplained encephalopathy, regardless of its cause and clinical setting, should be screened for MCADD.

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Glucose metabolism in sleep disordered breathing

An association between sleep disordered breathing (SDB) and impaired glucose tolerance has been reported in adults.¹ Although SDB has been reported in diabetic children,² no data are available on glucose metabolism in children with SDB. We used glycated haemoglobin (HbA1c) for the preliminary assessment of glucose metabolism in paediatric SDB patients.

HbA1c was measured in 12 children aged 26-116 months (mean 63) with suspected SDB owing to adenotonsillar hypertrophy. Informed consent was obtained from the guardians of each patient, and consent was obtained from the child if older than 5 years of age. Overnight polysomnographic studies were performed once for each patient by the standard method described elsewhere.³ The desaturation time (percentage of total sleep time with oxygen saturation <90%), minimum oxygen saturation level, and apnoea-hypopnoea index (AHI) were calculated. Complete blood count, blood gases, and blood chemistry (glucose, total protein, albumin, urea nitrogen, creatinine, uric acid, sodium, chloride, potassium, calcium, phosphate, lactic dehydrogenase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, γ -glutamyl transpeptidase, alkaline phosphatase, total bilirubin, total cholesterol, and triglyceride) were also determined.

The patients had no respiratory failure, heart failure, or coma. None of their weights exceeded 120% of their ideal weight for their

heights. Desaturation time clearly divided the patients into two groups: six patients whose desaturation time was 0 or 0.1 (mild SDB group); and six whose desaturation time exceeded 4.0 (severe SDB group). The average HbA1c value for the severe SDB group (5.0, SE 0.07) was significantly higher than that for the mild SDB group (4.6, SE 0.10) ($p = 0.01$), although the actual HbA1c values were all within normal range. No other items showed significant differences between the two groups.

The severity of respiratory disturbances during sleep in diabetic children has been known to correlate with the duration of diabetes and with the HbA1c value.² Recently, SDB parameters were found to be associated with worsening insulin resistance independent of obesity in adults.⁴ The current study shows that serum HbA1c is increased in association with the degree of desaturation in non-obese paediatric SDB patients; HbA1c levels should, however, be monitored after treatment. SDB and glucose metabolism are hypothesised to be closely associated in children as well as adults.

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Short versus standard duration antibiotic treatment for UTIs: a comparison of two meta-analyses

Having recently published a meta-analysis on the same clinical question,¹ it was with great interest that we read Michael *et al*'s systematic review of short versus standard duration antibiotics for urinary tract infections (UTIs) in children.² Given the publication (in close succession) of two meta-analyses on the same question with (on the surface) strikingly different results, we thought a comment was in order.

First, we applaud the authors on their methodologically sound review. The literature search was explicitly described and exhaustive. In fact, the authors identified a few studies that we had missed.³⁻⁶ The study outcomes for meta-analysis (frequency of positive urine cultures at 0-7 days after treatment and at 10 days to 15 months after treatment, and development of resistant organisms and recurrent UTI) were relevant and clearly defined.

The authors provided appropriate and important meta-analysis measures including summary relative risks (RRs) and a quasi-NNT calculation with varying risk of treat-

ment failure in the standard treatment group and confidence intervals corresponding to "best" and "worst" case scenarios.

For their primary outcome, frequency of positive urine cultures 0-7 days after treatment, the authors found no significant difference between short (2-4 days) and standard (7-14 days) treatment (RR 1.06; 95% CI 0.64 to 1.76). This is in contrast to our finding of a 94% increased pooled risk of treatment failure with short course treatment (≤ 3 days) compared to standard treatment (7-14 days) (RR 1.94, 95% CI 1.19 to 3.15; NNT=13, 95% CI 100 to 7). Why the discrepancy? We postulate a few possible explanations and conclude that the two meta-analyses, on closer inspection, actually have very similar results.

Our omission of certain studies identified by Michael and colleagues may have biased our results. However, of the three studies³⁻⁵ that we missed and that they included in their analysis of treatment failure at 0-7 days after completion of treatment, two favoured standard duration treatment, which would have supported our pooled RR result. Another possible explanation for the divergent results was the use of different definitions of treatment failure. For our definition of treatment failure we pooled persistent infection (failure to eradicate the organism within 1 to 2 days of initiation of treatment) and relapse (recurrence of symptoms and reinfection within 2 weeks of cessation of treatment after initial bacteriologic cure), whereas Michael *et al* used frequency of positive cultures 0-7 days after cessation of treatment as their primary outcome measure of treatment failure. If reinfections later than 7 days after cessation of treatment occurred more often in recipients of short course treatment, then Michael *et al*'s definition of treatment failure could have failed to capture the therapeutic advantage of standard duration treatment.

However, the most likely explanation for the divergent results was the different ways in which the study question was framed and the resulting differences in studies included in the meta-analyses. We compared ≤ 3 days of treatment to 7-14 days of treatment, whereas Michael *et al* compared 2-4 days of treatment to 7-14 days of treatment and excluded 11 studies comparing single-dose or single-day treatment to standard duration treatment.⁷⁻¹⁷

The reasons for this exclusion are unclear, although we presume that they felt single-dose or single-day treatment was not a fair comparison with 7-14 day treatment. However, a number of randomised controlled trials (RCTs) made this comparison, suggesting that clinicians are, in fact, interested in the potential efficacy (and significantly increased ease and savings) of single-dose or single-day treatment. Inclusion of these studies in our analysis strongly influenced the pooled risk of treatment failure with short-course treatment. When we excluded these studies in a sub-group analysis of 3-day versus long course (7-14 day) treatment, the risk of treatment failure fell to 1.36 (95% CI 0.68 to 2.72) (NNT=50; 95% CI 33 - 13).

Thus, our meta-analysis demonstrates clearly that single dose or single day antibiotic treatment is not as effective as long-course treatment for UTIs in children. The two meta-analyses together suggest that:

- (1) "longer" short-course therapies may be as effective as 7-14 days of antibiotics and