

# PAEDIATRIC GUIDELINES 2006

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## **National guidelines against which the Paediatric Guidelines have been checked**

Advanced Paediatric Life Support

<http://www.resus.org.uk/pages/pals.pdf>

Breathing

<http://www.nottingham.ac.uk/paediatric-guideline/breathingguideline.pdf>

Diabetes

<http://www.sign.ac.uk/guidelines/fulltext/55/index.html>

Diabetic Ketoacidosis

<http://www.bsped.org.uk/professional/guidelines/docs/BSPEDDKAApr04.pdf>

Diarrhoea and vomiting

<http://www.nottingham.ac.uk/paediatric-guideline/diarrhoeaguideline.pdf>

<http://www.nottingham.ac.uk/paediatric-guideline/diarrhoeaguideline.pdf>

Kawasaki Disease

<http://circ.ahajournals.org/cgi/reprint/110/17/2747>

Epilepsy

<http://www.nice.org.uk/page.aspx?o=113360>

Idiopathic Thrombocytopenic Purpura

<http://www.bcshguidelines.com/pdf/BJH574.pdf>

Meningitis

[http://www.hpa.org.uk/infections/topics\\_az/schools/guideline\\_info/meningococcal\\_disease.htm](http://www.hpa.org.uk/infections/topics_az/schools/guideline_info/meningococcal_disease.htm)

Pleural effusion

<http://www.brit-thoracic.org.uk/c2/uploads/PaediatricPleural.pdf>

Pneumonia

<http://www.brit-thoracic.org.uk/c2/uploads/paediatriccap.pdf>

Protection

<http://www.rpsgb.org.uk/pdfs/childprotectguid.pdf>

[http://www.rcpch.ac.uk/publications/recent\\_publications/PaediatricForensicExaminations.pdf](http://www.rcpch.ac.uk/publications/recent_publications/PaediatricForensicExaminations.pdf)

Renal Failure

[http://www.renal.org/Standards/RenalStandards\\_2002b.pdf](http://www.renal.org/Standards/RenalStandards_2002b.pdf)

Urinary Tract Infection

[http://www.rcpch.ac.uk/publications/clinical\\_docs/UTI\\_in\\_children.pdf](http://www.rcpch.ac.uk/publications/clinical_docs/UTI_in_children.pdf)

# ABDOMINAL PAIN IN CHILDHOOD

## Supporting information

### What is the value of the abdominal x-ray in the diagnosis of acute abdominal pain?

Ultrasonography has been recommended by US sources as the most useful diagnostic tool in this situation for some years, principally for its precision and avoidance of the use of ionising radiation (Sivit, 2004; Sivit, 1997). Abdominal x-ray is advised primarily when small bowel obstruction or perforation is suspected (Sivit, 1997).

European sources have tended to be more conservative, advocating that ultrasonography (and to a lesser extent CT) be reserved for equivocal cases (van den Broek, 2004). Others, however, agree with the US view that that ultrasonography is more likely to reveal the underlying cause of pain than plain film radiography (Hayes, 2004; Rosendahl, 2004).

It has been suggested that chest x-ray should always be performed before abdominal x-ray, as pneumonia is frequently the cause of abdominal pain and vomiting in children with less than obvious signs of pulmonary disease (John, 1999).

A study in 2,427 children with suspected acute appendicitis (Even-Bendahan, 2003) found that ultrasound diagnosis halved the misdiagnosis rate from 13.2% to 6.5%, saving unnecessary surgery and identifying other conditions that mimic appendicitis. Abdominal x-ray was not advised in this study.

A retrospective review of 449 patient records of children having abdominal radiography (Rovira, 2005) found that the results were helpful in the diagnosis of less than half the cases that needed surgical intervention. The authors concluded that "Plain abdominal radiograph is of little value in the diagnosis of acute abdominal pain in children".

Even-Bendahan G, Lazar I, Erez I, et al. Role of imaging in the diagnosis of acute appendicitis in children. *Clin Pediatr* 2003;42:23-7

Hayes R. Abdominal pain: general imaging strategies. *Eur Radiol* 2004;14(Suppl 4):L123-37

John SD. Trends in pediatric emergency imaging. *Radiol Clin N Am* 1999;37:995-1034

Rosendahl K, Aukland SM, Fosse K. Imaging strategies in children with suspected appendicitis. *Eur Radiol* 2004;14(Suppl 4):L138-45

Rovira N, Curcoy AI, Trenchs V, et al. Value of plain abdominal radiography in the emergency department. *Pediatr Catalana* 2005;65:61-4

Sivit CJ. Imaging children with acute right lower quadrant pain. *Pediatr Clin North Am* 1997;44:575-89

Sivit CJ. Imaging the child with right lower quadrant pain and suspected appendicitis: current concepts. *Pediatr Radiol* 2004;34:447-53

Van den Broek WT, van der Ende ED, Bijnen AB, et al. Which children could benefit from additional diagnostic tools in case of suspected appendicitis? *J Pediatr Surg* 2004;39:570-4

### Evidence Level: V

### How specific is abdominal pain in the diagnosis of appendicitis?

A number of scoring systems have been developed in an attempt to improve the diagnosis of appendicitis (Kharbanda, 2005; Samuel, 2002; Alvarado, 1986). Common to all of them is the

localisation of tenderness to the right lower quadrant, migration of pain, and rebound tenderness/pain with percussion (all  $P < 0.001$ ).

Inclusion of these three pain-related signs resulted in a specificity of 0.72-0.92.

Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* 1986;15:557-64

Kharbanda AB, Taylor GA, Fishman SJ, et al. A clinical decision rule to identify children at low risk for appendicitis. *Pediatrics* 2005;116:709-16

Samuel M. Pediatric appendicitis score. *J Pediatr Surg* 2002;37:877-81

**Evidence Level: V**

**February 2006**

## ACUTE ASTHMA IN CHILDHOOD

### Supporting information

#### **Routine arterial blood gas (ABG) testing does not alter the initial management and thus is inappropriate?**

A prospective study in 89 acute severe asthma patients (Carruthers, 1995) found that when oxygen saturation was  $\geq 92\%$  (72 patients), 3 (4.2%) had respiratory failure. In the 82 patients with a saturation of  $\geq 90\%$ , 6 (7.3%) had respiratory failure. The authors concluded that an oxygen saturation of  $> 92\%$  gave sufficient indication that respiratory failure was unlikely and that ABG measurement was therefore unnecessary.

BTS/SIGN guidelines also acknowledge that ABG measurement is only necessary in those patients with oxygen saturation  $< 92\%$ .

Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? *Thorax* 1995;50:186-8

British Thoracic Society, Scottish Intercollegiate Guidelines Network. British Guideline on the management of asthma: a national clinical guideline. Revised edition November 2005  
[http://www.brit-thoracic.org.uk/iqs/sid.02750940697412684403511/Guidelinessince%201997\\_asthma\\_html](http://www.brit-thoracic.org.uk/iqs/sid.02750940697412684403511/Guidelinessince%201997_asthma_html)

**Evidence Level: IV**

#### **Nebulised treatment should not be given routinely if the child is breathless, without trying inhalers first?**

A comparative study (Boyd, 2005) looked at two sequential three-month periods. During the first period, nebulised therapy was given routinely and in the second period, treatment was with pressurised metered dose inhalers with spacers. Admission rates fell significantly from 31% to 20.6% during the second period, although no significant change in total hospital or emergency department times were recorded.

Boyd R, Stuart P. Pressurised metered dose inhalers with spacers versus nebulisers for beta-agonist delivery in acute asthma in children in the emergency department. *Emerg Med J* 2005;22:641-2

**Evidence Level: IV**

**Last amended May 2006**

# **BELL'S PALSY IN CHILDHOOD**

## **Supporting information**

### **Steroids are not a useful treatment in Bell's Palsy?**

A Cochrane review of 4 trials in 179 patients (Salinas, 2004) concluded that there was insufficient evidence with which to answer this question, and called for more and larger randomised controlled trials to be carried out.

Salinas RA, Alvarez G, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD001942

**Evidence Level: I (for no conclusive effect)**

**May 2006**

# BRONCHIOLITIS

## Supporting information

### **Drug treatments and physiotherapy are ineffective (in the acute phase) in immunocompetent patients and should not be used?**

A Cochrane review (Perrotta, 2005) of 3 RCTs found that chest physiotherapy using vibration and percussion techniques did not reduce length of hospital stay or oxygen requirement, or improve the severity clinical score. Chest physiotherapy using forced expiratory techniques remains to be evaluated by clinical research.

A Cochrane review of 8 trials in 394 children (Kellner, 1999) found that bronchodilators produced no improvement in measures of oxygenation, rate of hospitalisation (18% vs 26%, OR 0.70, 95% CI 0.36-1.35) or duration of hospitalisation (weighted mean difference 0.12, 95% CI -0.3 - 0.5).

A Cochrane review on the usefulness of antibiotics for bronchiolitis is currently in progress (Fonseka, 2005). A prospective randomised study in 136 children (Friis, 1984) found no benefit from antibiotic treatment.

A Cochrane review on 13 RCTs in 1198 children (Patel, 2004) found no benefits in terms of length of stay or clinical score in patients treated with glucocorticoids compared with placebo.

Fonseka K, Doust J, Spurling GKP, et al. Antibiotics for bronchiolitis in children. (Protocol) The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD005189

Friis B, Andersen P, Brenoe E, et al. Antibiotic treatment of pneumonia and bronchiolitis: a prospective randomised study. Arch Dis Child 1984;59:1038-45

Kellner JD, Ohlsson A, Gadomski AM, et al. Bronchodilators for bronchiolitis. The Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001266

Patel H, Platt R, Lozano JM, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004878

Perrotta C, Ortiz Z, Roque M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004873

**Evidence Level: I (for no effect of treatment)**

**Last amended May 2006**

## COELIAC DISEASE IN CHILDHOOD

### Supporting information

#### **Should a gluten-free diet be followed for life? What are the risks of non-compliance? What is the effect on bone density and what pharmacological interventions may be necessary if this is low?**

Only one longitudinal study of gluten-free diet (GFD) in young patients with coeliac disease has been published to date (Mora, 2001). 19 patients (mean age 14.2 +/-2.6 years) were studied after 4.3 +/- 0.6 years on a GFD and compared to 211 healthy children as a control group. Whole body bone mineral density (BMD) was significantly lower in the patient group compared to controls (0.022 g/cm<sup>2</sup>; P = .04) initially. Measurements were repeated in the patient group after 1.1 +/- years of GFD and after 4.3 +/- years of GFD and were identical to the control subjects on both occasions.

An earlier study by the same team comparing 30 patients with 240 controls found similar results (Mora, 1999).

Another study comparing 99 patients on GFD with 44 healthy controls (Pedrera, 2001) found no difference in bone mass determined by ultrasound between the groups, even when the GFD had not been strictly followed. BMD is higher after 24 months of GFD than after 12 months of GFD (Kalayci, 2001; Scotta, 1997).

A follow-up study of 15 patients re-investigated 15-18 years after diagnosis in infancy and early childhood (Thornquist, 1993) showed that gluten challenge followed by proximal jejunal biopsy demonstrated changes consistent with coeliac disease in every case. Re-introduction of GFD induced clinical recovery and was thus recommended as a life-long commitment. The gluten challenge may be as little as 0.2 g/day and still produce signs of relapse (Laurin, 2002). Despite suggestions that 10% - 20% of children may become tolerant to gluten during adolescence (Schmitz, 1996), life-long GFD is regarded as "the safest advice" for child patients (Farrell, 2002; McNeish, 1980).

A follow-up study in 210 patients (Holmes, 1989) found that coeliac patients on a GFD did not demonstrate increased risk of malignancy. In those on a reduced gluten, or a normal diet, however, there was an increased risk of cancers of the mouth, pharynx, or oesophagus (RR=22.7, p<0.001), and also of lymphoma (RR=77.8, p<0.001).

Vitamin status may be poor in up to half of adults who have followed a gluten-free diet for 10 years (Hallert, 2002).

Compliance to GFD can be problematical, particularly in adolescents (Fabiani, 2000), but is important as small amounts of gluten in the diet can activate mucosal cell-mediated immunity even if they cause no clinical symptoms (Auricchio, 1991).

A study of 91 patients with interrupted GFD (Shmerling, 1986) found that 71 (81.4%) had a flat proximal small bowel mucosa after 0.25-14.67 years off diet. In 11 patients (12%) deterioration of the mucosa occurred (without becoming flat) after 0.5-6.67 years off diet. 6 patients (6.6%) had a normal mucosa after 2.24-6.92 years off diet. The remaining 3 patients were not included, having been off diet for under 2 years. The authors concluded that the vast majority of patients were likely to relapse if GFD were discontinued. One study of adults with coeliac disease (McFarlane, 1996) suggests that fractures may be more common in patients than in controls (21% vs 3% of 75 patients and 75 matched controls). Fractures are more likely during periods of non-compliance with GFD (Vasquez, 2000).

No studies have been identified that deal with pharmacological treatment of coeliac disease in children. A daily intake (in adults) of 1500 mg of calcium (diet supplemented by tablets if necessary) has been recommended to guard against osteoporosis (Scott, 2000). Adults treated with calcium (1.0 g/day) and vitamin d supplements (32,000 IU/wk) in addition to GFD showed

no greater remineralisation than those treated with GFD alone in a small randomised study with 7 patients in each group (Mautalen, 1997). Magnesium deficiency may also be a treatable factor contributing to osteoporosis (Rude, 1996).

Auricchio S, Troncone R. Effects of small amounts of gluten in the diet of coeliac patients. *Panminerva Med* 1991;33:83-5

Fabiani E, Taccari LM, Ratsch IM, et al. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. *J Pediatr* 2000;136:841-3

Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180-8

Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther* 2002;16:1333-9

Holmes GK, Prior P, Lane MR, et al. Malignancy in coeliac disease: effect of a gluten free diet. *Gut* 1989;30:333-8

Kalayci AG, Kansu A, Girgin N, et al. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. *Pediatrics* 2001;108:E89

Laurin P, Wolving M, Falth-Magnusson K. Even small amounts of gluten cause relapse in children with celiac disease. *J Pediatr Gastroenterol Nutr* 2002;34:26-30

McFarlane XA, Dixey J, Dumfrey J, et al. Increased risk of bone fractures in coeliac disease. *Gastroenterology* 1996;110:A821

McNeish AS. Coeliac disease: duration of gluten-free diet. *Arch Dis Child* 1980;55:110-11

Mautalen C, Gonzalez D, Mazure R, et al. Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. *Am J Gastroenterol* 1997;92:313-8

Mora S, Barera G, Beccio S, et al. A prospective longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. *J Pediatr* 2001;139:516-21

Mora S, Barera G, Beccio S, et al. Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. *Am J Gastroenterol* 1999;94:398-403

Pedreira JD, Lopez MJ, Canal ML, et al. Quantitative phalangeal bone ultrasound is normal after long-term gluten-free diet in young coeliac patients. *Eur J Gastroenterol Hepatol* 2001;13:1169-73

Rude RK, Olerich M. Magnesium deficiency: possible role in osteoporosis associated with gluten-sensitive enteropathy. *Osteoporos Int* 1996;6:453-61

Schmitz J. Is celiac disease a lifelong disorder? *Clin Invest Med* 1996;19:352-6

Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. *Gut* 2000;46(Suppl I):i1-i8

Scotta MS, Salvatore S, Salvatoni A, et al. Bone mineralization and body composition in young patients with celiac disease. *Am J Gastroenterol* 1997;92:1331-4

Shmerling DH, Franckx J. Childhood celiac disease: a long-term analysis of relapses in 91 patients. *J Pediatr Gastroenterol Nutr* 1986;5:565-9

Thornquist H, Jacobsen GS, Dahl LB, et al. Coeliac disease and gluten-free diet: a following-up study of fifteen young adults. *Ann Nutr Metab* 1993;37:295-301

Vasquez H, Mazure R, Gonzalez D, et al. Risk of fractures in celiac disease patients: a cross-sectional, case-control study. *Am J Gastroenterol* 2000;95:183-9

### **Evidence Level: IV**

### **In asymptomatic siblings of children with coeliac disease, should screening for antiendomysial (EMA) antibodies be carried out, and if so, should a negative screen be repeated?**

There is an increased prevalence of coeliac disease among first-degree relatives of 10%, and a concordance rate of 30-40% in HLA-matched siblings, rising to approximately 70% in monozygotic twins (Hill, 2002). Antibody testing has demonstrated that some individuals remain asymptomatic despite having typical changes on small intestinal biopsy and these may be 7 times more numerous than those with symptoms (Hill, 2002). The largest study to date (Vitoria, 1994) discovered 18 new cases of coeliac disease in 642 first-degree relatives (2.8%). The EMA has a sensitivity and specificity approaching 100% (Ferreira, 1992) but will always be negative in those coeliac disease patients with selective IgA deficiency (approximately 3%) (Hill, 2002). Because the test employs immunofluorescence, it is vulnerable to subjective interpretation and may also be less reliable in children younger than 2 years of age (Hill, 2002). For these reasons, EMA may eventually be replaced by measurement of tissue transglutaminase (tTG) as the test of choice. The tTG test is recommended in current US guidelines (Hill, 2005). As a negative result does not completely exclude the diagnosis, it may be found necessary to repeat the test. This is particularly so in females, who have a higher risk of developing the disease (Vitoria, 1994).

Ferreira M, Davies SL, Butler M, et al. Endomysial antibody: is it the best screening test for coeliac disease? *Gut* 1992;33:1633-7

Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35:S78-S88

Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:1-19

Vitoria JC, Arrieta A, Astigarraga I, et al. Use of serological markers as a screening test in family members of patients with celiac disease. *J Pediatr Gastroenterol Nutr* 1994;19:304-9

### **Evidence Level: IV**

### **What is the optimal age at gluten challenge?**

Gluten challenge should only be necessary when doubt exists about the initial diagnosis and the adequacy of response to a gluten-free diet (Anon, 1990), and should be avoided before the age of 6 in order to minimise the risk for dental enamel defects (Hill, 2002; Anon, 1990). Other authors, however, are of the opinion that children over the age of 2 may be challenged with "little risk of

serious dental damage” (O’Halloran, 1998). In a study of 67 children under 2 years of age (Danielsson, 1990), 95.5% relapsed on gluten challenge, leading the authors to question whether the procedure was necessary at all, given such a low rate of non-relapse. Gluten challenge should not be undertaken during periods of rapid growth such as puberty (Hill, 2002).

Anon. Revised criteria for diagnosis of coeliac disease: report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;65:909-11

Danielsson L, Stenhammar L, Astrom E. Is gluten challenge necessary for the diagnosis of coeliac disease in young children? *Scand J Gastroenterol* 1990;25:957-60

Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35:S78-S88

O’Halloran ET, Read M, Barry RG, et al. The management of coeliac disease. *Irish Med J* 1998;91:199-202

### **Evidence Level: IV**

#### **What is the optimal duration of the gluten challenge and timing of biopsies?**

Although a 2-year challenge is sufficient in most circumstances, there are individual cases of children taking as long as 5-7 years to relapse (Anon, 1990), or, in one exceptional case (Hogberg, 1993), 14 years.

In one study in 24 patients (Laurin, 2002) however, 90% reacted to small (mean 1.7 g/d) intakes of gluten within 2 months.

Biopsy should be repeated at the onset of clinical relapse, or between 6 and 12 months in the absence of symptoms (Hill, 2002).

A compromise position may be that a normal biopsy after a 3-month gluten challenge excludes coeliac disease in the great majority of cases (Packer, 1978).

Anon. Revised criteria for diagnosis of coeliac disease: report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;65:909-11

Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35:S78-S88

Hogberg L, Stenhammar L, Wagermark J. Very late mucosal relapse in a girl with coeliac disease. *Acta Paediatr* 1993;82:887-9

Laurin P, Wolving M, Falth-Magnusson K. Even small amounts of gluten cause relapse in children with celiac disease. *J Pediatr Gastroenterol Nutr* 2002;34:26-30

Packer SM, Charlton V, Keeling JW, et al. Gluten challenge in treated coeliac disease. *Arch Dis Child* 1978;53:449-55

### **Evidence Level: IV**

## **Should gluten challenge be with a normal (gluten-containing) diet, or with gluten powder added to diet?**

As an adequate (10g/d) gluten intake is normally necessary for a valid gluten challenge, this can be achieved either with the use of measured amounts of gluten powder or by dietetic monitoring of intake (equivalent to a minimum of 2 slices of white bread daily for older children) (Anon, 1990).

Anon. Revised criteria for diagnosis of coeliac disease: report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;65:909-11

### **Evidence Level: V**

## **What other conditions may mimic the histopathological findings of coeliac disease?**

In infants, cows' milk sensitive enteropathy, postenteritis enteropathy, and giardiasis can all produce histologic features similar to coeliac disease; additional biopsies are thus necessary in this age group (Hill, 2002; Trier, 1998).

Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35:S78-S88

Trier JS. Diagnosis of celiac sprue. *Gastroenterology* 1998;115:211-6

### **Evidence Level: V**

## **Are bone density scans of use in the follow-up of children with coeliac disease?**

Bone mineral density in adult coeliac patients treated with GFD from childhood is normal compared to controls (Molteni, 1990). A study in 19 children with coeliac disease (Mora, 2001) found reduced bone density on diagnosis, but complete recovery occurred after one year of GFD. A study of bone mineral content and density in 91 treated, asymptomatic children with coeliac disease (Szathmari, 2001) found that density values were normal or higher than controls, but that bone size remained reduced. In contrast, a study comparing 32 coeliac patients with 82 healthy controls (Kalayci, 2001) found that at least 4 years of GFD were necessary for complete recovery of bone density, that osteopaenia could be observed among patients with sub-clinical or asymptomatic disease, and that bone density scanning was therefore worthwhile.

Kalayci AG, Kansu A, Girgin N, et al. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. *Pediatrics* 2001;108:e89

Molteni N, Caraceni MP, Bardella MT, et al. Bone mineral density in adult celiac patients and the effect of gluten-free diet from childhood. *Am J Gastroenterol* 1990;85:51-3

Mora S, Barera G, Beccio S, et al. A prospective longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. *J Pediatr* 2001;139:516-21

Szathmari M, Tulassay T, Arato A, et al. Bone mineral content and density in asymptomatic children with coeliac disease on a gluten-free diet. *Eur J Gastroenterol Hepatol* 2001;13:419-24

### **Evidence Level: IV**

## **Should small intestinal barium studies be performed in children with coeliac disease?**

The two-film barium meal has been described as “a reasonably reliable test for the exclusion of untreated coeliac disease in children” (Smith, 1977). A more recent review (Farrell, 2002) states that “small bowel barium studies are usually unnecessary” and recommends a plain x-ray film, CT scan, or both, if a complication such as lymphoma, carcinoma or ulcerative jejunoileitis is suspected.

Small bowel barium studies showing a significant reduction in the average number of jejunal folds and an increase in the number of ileal folds (i.e. a reversal of the normal pattern) have been used as a way of identifying non-responders to GFD in adult patients (Mike, 1990).

Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180-8

Mike N, Udeshi U, Asquith P, et al. Small bowel enema in non-responsive coeliac disease. *Gut* 1990;31:883-5

Smith SE, Littlewood JM. The two-film barium meal in the exclusion of coeliac disease. *Clin Radiol* 1977;28:629-34

### **Evidence Level: V**

## **Can calcium supplementation prevent the long-term risk of osteoporosis?**

Calcium absorption appears to be normal in patients on a GFD started in childhood (Kalayci, 2002), so that a calcium-rich GFD should be sufficient to prevent problems amongst those patients who strictly adhere to it.

Kalayci AG, Kansu A, Girgin N, et al. Bone mineral density and importance of a gluten-free diet in patients with celiac disease in childhood. *Pediatrics* 2001;108:e89

### **Evidence Level: IV**

## **What is the evidence for the use of tissue transglutaminase (tTG) as a diagnostic tool for coeliac disease?**

tTG was identified as a potential diagnostic test for coeliac disease in 1997 (Dieterich, 1997). Whilst the endomysium (EMA) antibody test is subjective and thus liable to observer and laboratory variability, tTG is an objective test and not laboratory dependent (Hill, 2002). It is cheaper, easier to perform, and more sensitive but less specific than the EMA test (Farrell, 2002). A study in 365 patients (208 coeliac patients and 157 controls) (Burgin-Wolff, 2002) compared EMA and tTG testing. Only 4 patients (1%) presented discordant tTG and EMA results, leading the authors to conclude that tTG was an accurate and observer-independent alternative to EMA. Other studies (Trevisiol, 2002; Chan, 2001) have found similar equivalency.

Burgin-Wolff A, Dahlbom I, Hadziselimovic F, et al. Antibodies against human tissue transglutaminase and endomysium in diagnosing and monitoring coeliac disease. *Scand J Gastroenterol* 2002;37:685-91

Chan AW, Butzner JD, McKenna R, et al. Tissue transglutaminase enzyme-linked immunosorbent assay as a screening test for celiac disease in pediatric patients. *Pediatrics* 2001;107:e8

Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med* 1997;3:797-801

Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002;346:180-8

Hill ID, Bhatnagar S, Cameron DJ, et al. Celiac disease: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35:S78-S88

Trevisiol C, Ventura A, Baldas V, et al. A reliable screening procedure for coeliac disease in clinical practice. *Scand J Gastroenterol* 2002;37:679-84

**Evidence Level: III**

**Last amended June 2006**

# CONSTIPATION IN THE CHILD

## *Supporting Information*

### **Abdominal x-rays are of use as a diagnostic tool in constipation?**

Radiographic assessment of 33 constipated and 67 control children (Leech, 1999) using a scoring system from 0 (no stool) to 5 (gross faecal loading with bowel dilatation) found that assessment of faecal loading was subjective and varied considerably between observers. Consistency was good if a single observer scored all radiographs, however. The authors concluded that, to limit exposure to radiation, radiography should not be routine, but should be reserved for the investigation of intractable constipation and that the same observer should score all radiographs. This accords with advice from the Royal College of Radiologists (RCR, 1998). Of the two earlier studies (Blethyn, 1995; Barr, 1979) using this technique in children, the former found more inter- and intra-observer correlation than did the latter, although both commended its usefulness. A study in adults, using a similar scoring system (Starreveld, 1990), found “significant correlation” between the radiograph scores and frequency of defaecation, faecal consistency and stool weight.

Abdominal x-ray may also be used in conjunction with radio-opaque markers to identify segments of colon with impaired motility (Fotter, 1998; Zaslavsky, 1998).

Barr RG, Levine MD, Wilkinson RH, et al. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. *Clin Pediatr* 1979;18:674-9

Blethyn AJ, Jones KV, Newcombe R, et al. Radiological assessment of constipation. *Arch Dis Child* 1995;73:532-3

Fotter R. Imaging of constipation in infants and children. *Europ Radiol* 1998;8:248-58

Leech SC, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. *Pediatr Radiol* 1999;29:255-8

Royal College of Radiologists. Making the best use of a department of clinical radiology, 4<sup>th</sup> edition. London: Royal College of Radiologists, 1998.

Starreveld JS, Pols MA, Van Wijk HJ, et al. The plain abdominal radiograph in the assessment of constipation. *Z Gastroenterol* 1990;28:335-8

Zaslavsky C, da Silveira TR, Maguilnik I. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998;27:138-42

### **Evidence Level: IV**

### **Studies of transit times are useful in the management of constipation?**

In a study of physiologic testing for constipation in 104 patients (Halverson, 1998), the test results “added significant information” in half the cases, leading to a specific diagnosis. Transit times and defaecography were found to be the most useful, the others being manometry, balloon compliance, pudendal nerve latency and electromyography.

Measuring total and segmental colonic transit times allows constipation caused by colonic dysfunction to be distinguished from that caused by distal obstruction (Zaslavsky, 1998). It may also provide evidence for the existence of slow-transit constipation in children as in adults (Benninga, 1996).

A study comparing transit times with Barr-scores (derived from abdominal radiographs) in 211 constipated children (Benninga, 1995) found transit times far more accurately distinguished children with constipation due to colonic inertia from those with encopresis/soiling or recurrent abdominal pain.

A study in 169 consecutive patients (de Lorijn, 2004) found that a colonic transit time of >100 hours to be associated with a poor outcome at one year, whilst transit times of < 100 hours were not predictive of outcome.

Other studies have also found transit times to be useful in the diagnosis and management of constipation (Benninga, 2004; Papadopoulou, 1994; Vattimo, 1993; Bautista, 1991; Vajro, 1988).

Bautista CA, Varela CR, Villanueva JA, et al. Measurement of colonic transit time in children. *J Pediatr Gastroenterol Nutr* 1991;13:42-5

Benninga MA, Voskujil WP, Akkerhuis GW, et al. Colonic transit times and behavior profiles in children with defecation disorders. *Arch Dis Child* 2004;89:13-16

Benninga MA, Buller HA, Tytgat GN, et al. Colonic transit time in constipated children: does pediatric slow-transit constipation exist? *J Pediatr Gastroenterol Nutr* 1996;23:241-51

Benninga MA, Buller HA, Staalman CR, et al. Defaecation disorders in children: colonic transit time versus the Barr-score. *Europ J Pediatr* 1995;154:277-84

De Lorijn F, van Wijk MP, Reitsma JB, et al. Prognosis of constipation: clinical factors and colonic transit time. *Arch Dis Child* 2004;89:723-7

Halverson AL, Orkin BA. Which physiologic tests are useful in patients with constipation? *Dis Colon Rectum* 1998;41:735-9

Papadopoulou A, Clayden GS, Booth IW. The clinical value of solid marker transit studies in childhood constipation and soiling. *Europ J Pediatr* 1994;153:560-4

Vajro P, Silano G, Longo D, et al. Orocoecal transit time in healthy and constipated children. *Acta Paediatr Scand* 1988;77:583-6

Vattimo A, Burrioni L, Bertelli P, et al. Total and segmental colon transit time in constipated children assessed by scintigraphy with <sup>111</sup>In-DTPA given orally. *J Nucl Biol Med* 1993;37:218-22

Zaslavsky C, da Silveira TR, Maguilnik I. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998;27:138-42

**Evidence Level: IV**

## **Osmotic or stimulant laxatives, Movicol, bowel cleansing preparations (eg Klean Prep), rectal enemas, combination therapy or prokinetic agents are of use in the management of constipation?**

No studies have compared the relative efficacy of different laxatives or clean-out procedures (Brooks, 2000). Nor have any randomised trials on laxatives and enemas been conducted without the inclusion of a behavioural component (Brooks, 2000). If dietary interventions fail to relieve constipation, a stool softening or osmotic laxative such as lactulose should be tried first, and a stimulant laxative such as senna, bisacodyl or sodium picosulfate syrup next, if necessary (Anon, 2000; Baker, 1999).

Movicol and Klean Prep are both polyethylene glycol preparations that are not recommended for use in children, in the case of the former, or not licensed for that use in the case of the latter (Anon, 2000). Both may be used if laxatives fail, however (Anon, 2000; Baker, 1999). A study in 74 children (Pashankar, 2003) treated for longer than 3 months (mean 8.4 months, range 3-30) with polyethylene glycol 3350 (PEG) found that symptoms improved significantly in all. In 31 children with encopresis, soiling ceased completely in 16 patients and decreased in all the others. Two evidence-based reviews (Arora, 2005; Kinservik, 2004) found that low-dose (3350) PEG, with or without added electrolytes, was safe and effective both in the short and long term management of constipation in children.

A double blind, randomised trial in 100 patients aged between 6 months and 15 years (Voskuil, 2004) compared PEG 3350 with lactulose. A significantly higher success rate (56% vs 29%) was found in the PEG group, which also reported fewer side effects.

A small study in 28 patients younger than 18 months of age (Michail, 2004) found that an initial dose of 0.88 g/kg/day, followed by a maintenance dose of 0.78 g/kg/day relieved constipation in 97.6% of them.

Small-volume sodium citrate enemas (micro-enemas) may also be tried (in preference to larger-volume phosphate enemas) (Anon, 2000).

If individual laxatives have failed, a combination (e.g. lactulose and senna) may be effective (Anon, 2000).

The prokinetic agent that has been most studied is cisapride. A small, double-blind, placebo-controlled study in 40 children (Nurko, 2000) found that cisapride produced a significant improvement in the number of spontaneous bowel movements per week (from 0.9 +/- 0.1 to 4.1 +/- 1.1) and a significant decrease in the number of soiling episodes per day (from 1.8 +/- 0.5 to 0.08 +/- 0.4). The number of patients using laxatives was also reduced from 77% to 24%.

Placebo, in comparison, had no effect. Similar results were obtained in 69 children taking part in another double-blind, placebo-controlled study (Halabi, 1999) and in further, non-blinded studies (Staiano, 1991; Murray, 1990). Cardiac arrhythmia can be a possible side-effect if cisapride is given with medications that interact with cytochrome P450 3A4, and the North American Society for Pediatric Gastroenterology and Nutrition advises caution in its use (Shulman, 1999).

Anon. Managing constipation in children. *Drug Ther Bull* 2000;38:57-60

Arora R, Srinivasan R. Is polyethylene glycol safe and effective for chronic constipation in children? *Arch Dis Child* 2005;90:643-6

Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. *J Pediatr Gastroenterol Nutr* 1999;29:612-26

Brooks RC, Copen RM, Cox DJ, et al. Review of the treatment literature for encopresis, functional constipation, and stool-toileting refusal. *Ann Behav Med* 2000;22:260-7

Halabi IM. Cisapride in management of chronic pediatric constipation. *J Pediatr Gastroenterol Nutr* 1999;28:199-202

Kinservik MA, Friedhoff MM. The efficacy and safety of polyethylene glycol 3350 in the treatment of constipation in children. *Pediatr Nurs* 2004;30:232-7

Michail S, Gendy E, Preud'Homme D, et al. Polyethylene glycol for constipation in children younger than eighteen months old. *J Pediatr Gastroenterol Nutr* 2004;39:197-9

Murray RD, Li, BU, McClung HJ, et al. Cisapride for intractable constipation in children: observations from an open trial. *J Pediatr Gastroenterol Nutr* 1990;11:503-8

Nurko S, Garcia-Aranda JA, Worona LB, et al. Cisapride for the treatment of constipation in children: a double-blind study. *J Pediatr* 2000;136:35-40

Pashankar DS, Bishop WP, Loening-Baucke V. Long-term efficacy of polyethylene glycol 3350 for the treatment of chronic constipation in children with and without encopresis. *Clin Pediatr* 2003;42:815-9

Shulman RJ, Boyle JT, Colletti RB, et al. The use of cisapride in children. *J Pediatr Gastroenterol Nutr* 1999;28:529-33

Staiano A, Cucchiara S, Andreotti MR, et al. Effect of cisapride on chronic idiopathic constipation in children. *Dig Dis Sci* 1991;36:733-6

Voskuijl W, de Lorijn F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut* 2004;53:1590-4

Evidence Level: V (II for cisapride)

n.b. Cisapride was withdrawn from the market in July 2000, but is available for specialist consultant use on a "named patient" basis.

### **What are the options for the management of faecal impaction?**

A randomised prospective study comparing mineral oil and oral lavage solution in 26 patients with faecal impaction (Tolia, 1993) found that patients in the lavage group had more frequent bowel movements and better clearance of impacted faeces. Compliance was, however, poorer than with mineral oil, probably due to the larger volume of solution required (20 ml/kg/h for 4 hours on two consecutive days versus 2-8 tablespoons of mineral oil twice a day for two days).

If laxatives, alone or in combination, bowel-cleansing preparations and enemas have all failed, manual evacuation under general anaesthetic may be the only option (Anon, 2000). This procedure may, however, be the cause of iatrogenic structural injury to the anal sphincters, leading to faecal incontinence (Gattuso, 1996).

Pulsed-irrigation enhanced-evacuation has been found simple, safe and effective in the management of faecal impaction (Gilger, 1994; Kokoszka, 1994) and removes the necessity for general anaesthesia.

Anon. Managing constipation in children. *Drug Ther Bull* 2000;38:57-60

Gattuso JM, Kamm MA, Halligan SM, et al. The anal sphincter in idiopathic megarectum: effects of manual disimpaction under general anaesthetic. *Dis Colon Rectum* 1996;39:435-9

Gilger MA, Wagner ML, Barrish JO, et al. New treatment for rectal impaction in children: an efficacy, comfort, and safety trial of the pulsed-irrigation enhanced-evacuation procedure. *J Pediatr Gastroenterol* 1994;18:92-5

Kokoszka J, Nelson R, Falconio M, et al. Treatment of fecal impaction with pulsed irrigation enhanced evacuation. *Dis Colon Rectum* 1994;37:161-4

Tolia V, Lin CH, Elitsur Y. A prospective randomized study with mineral oil and oral lavage solution for treatment of faecal impaction in children. *Aliment Pharmacol Ther* 1993;7:523-9

**Evidence Level: III (lavage solution); V (Pulsed-irrigation enhanced evacuation)**

### **What is the value of behavioural therapy/biofeedback in the treatment of constipation?**

A randomised controlled trial in 192 children (van der Plas, 1996) compared 94 patients who received conventional treatment (laxatives and advice) with 98 who received the same treatment plus 5 biofeedback training sessions. After 6 weeks, 86% of the biofeedback group had achieved normal defaecation dynamics, compared with 52% of controls. This did not, however, affect the clinical outcome, follow-up after one year revealing that 59% of the control group had a defaecation frequency of 3 times a week or more with no laxatives, compared to 50% of the biofeedback group.

Very similar results were obtained in further trials in 49 (Sunic-Omejc, 2002), 29 (Nolan, 1998) and 253 children (Loening-Baucke, 1995). Despite the absence of proven long-term benefit, biofeedback could be used initially to achieve a faster response to other therapy (Nurko, 2000). Further research in this area is indicated (Bassotti, 2004). A small randomised study in 36 patients (Croffie, 2005) compared 24 patients given biofeedback in the laboratory to 12 who were also given home biofeedback. There were no significant differences between the two groups at 2 and 4 months follow-up. A Cochrane review of data from 8 studies (Brazzelli, 2005) found higher rates or persisting (up to 12 months) defecation problems when biofeedback training was added to conventional treatment. The authors concluded that biofeedback could not be recommended for children with functional constipation.

Behavioural therapy has been shown to be a rapidly-effective and long lasting treatment (Howe, 1992). Of 58 encopretic children placed on a regimen based on attempting to defaecate after a specific meal, 60% were completely continent after 5 months and a further 23% had only staining (Lowery, 1885). A prospective study of behavioural therapy in 27 children with Hirschsprung's disease (van Kuyk, 2001) found that all outcome variables were significantly better in the 14 children of the treatment group compared to the 13 controls. The effect persisted at follow-up (mean 7 months).

Bassotti G, Chistolini F, Sietchiping-Nzepa F, et al. Biofeedback for pelvic floor dysfunction in constipation. *BMJ* 2004;328:393-6

Brazzelli M, Griffiths P. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *The Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD002240

Croffie JM, Ammar MS, Pfefferkorn MD, et al. Assessment of the effectiveness of biofeedback in children with dyssynergic defecation and recalcitrant constipation/encopresis: does home biofeedback improve long-term outcomes. *Clin Pediatr* 2005;44:63-71

Howe AC, Walker CE. Behavioral management of toilet training, enuresis, and encopresis. *Pediatr Clin N Am* 1992;39:413-32

Loening-Baucke V. Biofeedback treatment for chronic constipation and encopresis in childhood: long-term outcome. *Pediatrics* 1995;96:105-10

Lowery SP, Srouf JW, Whitehead WE, et al. Habit training as treatment of encopresis secondary to chronic constipation. *J Pediatr Gastroenterol Nutr* 1985;4:397-401

Nolan T, Catto-Smith T, Coffey C, et al. Randomised controlled trial of biofeedback training in persistent encopresis with anismus. *Arch Dis Child* 1998;79:131-5

Nurko S. Advances in the management of pediatric constipation. *Curr Gastroenterol Rep* 2000;2:234-40

Sunic-Omejc M, Mihanovic M, Bilic A, et al. Efficiency of biofeedback therapy for chronic constipation in children. *Coll Antropol* 2002;26(Suppl):93-101

van der Plas RN, Benninga MA, Buller HA, et al. Biofeedback training in treatment of childhood constipation: a randomised controlled study. *Lancet* 1996;348:776-80

van Kuyk EM, Brugman-Boezeman AT, Wissink-Essink M, et al. Defecation problems in children with Hirschsprung's disease: a prospective controlled study of a multidisciplinary behavioural treatment. *Acta Paediatr* 2001;90:1153-9

**Evidence Level: I (for lack of long-term benefit from biofeedback); IV (for behavioural therapy)**

### **What practice guidelines exist for constipation in childhood?**

The only evidence-based guidelines appear to be those from the North American Society for Pediatric Gastroenterology and Nutrition (Baker, 1999).

Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. *J Pediatr Gastroenterol Nutr* 1999;29:612-26

### **Is rectal biopsy of use?**

Rectal biopsy is generally requested to exclude the potentially fatal disorder, Hirschsprung's disease and is the only test that can do so reliably (Baker, 1999). A retrospective review of 186 rectal biopsies from 141 children (Ghosh, 1998) compared the age at onset of symptoms with the diagnosis of Hirschsprung's disease. 17 children (12%) had Hirschsprung's disease and all of these experienced the first onset of constipation within the neonatal period. The authors concluded that, if the age at onset of constipation was after the neonatal period, rectal biopsy was unnecessary. The only other previous study to address this question (Landman, 1987) also found that the age of onset of constipation correlated with a positive diagnosis.

A 5-year retrospective review of 70 patients referred for deep transanal rectal biopsy for intractable constipation (Simpson, 1996) found that a diagnosis was established in 30 of these, 17 of whom had subsequent surgical procedures to relieve the condition. The authors concluded that the investigation was justified in constipation refractory to medical management.

Retrospective analysis in 100 patients (Lewis, 2003) found that a history of delayed passage of meconium, abdominal distension, vomiting or the results of a contrast enema identified all patients with Hirschsprung's and excluded the condition in approximately 36% of patients with idiopathic constipation. The authors concluded that it was not necessary to perform a rectal biopsy in children with constipation who displayed none of the key features.

Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. *J Pediatr Gastroenterol Nutr* 1999;29:612-26

Ghosh A, Griffiths DM. Rectal biopsy in the investigation of constipation. *Arch Dis Child* 1998;79:266-8

Landman GB. A five-year chart review of children biopsied to rule out Hirschsprung's disease. *Clin Pediatr* 1987;26:288-91

Lewis NA, Levitt MA, Zallen GS, et al. Diagnosing Hirschsprung's disease: increasing the odds of a positive rectal biopsy result. *J Pediatr Surg* 2003;38:412-6

Simpson BB, Ryan DP, Schnitzer JJ, et al. Surgical evaluation and management of refractory constipation in older children. *J Pediatr Surg* 1996;31:1040-2

**Evidence Level: IV**

**Last Amended June 2006**

## **CYANOTIC CONGENITAL HEART DISEASE**

### **Supporting information**

**Cyanosis with mild or no respiratory distress indicates the likelihood of cardiac disease?**

“Cyanosis in association with pulmonary or cardiac disease may be only mild or moderate in degree. Severe cyanosis usually indicates the presence of a cardiac problem” (Sahn, 1973).

Sahn DJ, Friedman WF. Difficulties in distinguishing cardiac from pulmonary disease in the neonate. *Pediatr Clin N Am* 1973;20:293-301

**Evidence Level: V**

**Last amended June 2006**

## **CYSTIC FIBROSIS IN CHILDHOOD**

### **Supporting information**

#### **Pancreatic enzyme supplements in doses > 10,000 units lipase/kg/day have the potential to cause colonic strictures?**

A case-control study (FitzSimmons, 1997), looking at 29 patients with fibrosing colonopathy (FC) and 105 controls, found a RR of 10.9 (95% CI 1.6-71.8) of developing FC associated with a dose of pancreatic enzyme of 24,001-50,000 units of lipase/kg/day, as compared to a dose of < 24,001 units of lipase/kg/day. The RR associated with a dose of > 50,000 units/kg/day was 199.5 (95% CI 9.9 – 4026.0). The authors recommended that the daily dose of pancreatic enzymes should be < 10,000 units/kg/day for most patients.

Similar results have been reported from other studies (Freiman, 1996; Lancellotti, 1996; Smyth, 1995).

Fitzsimmons SC, Burkhardt GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1997;336:1283-9

Freiman JP, FitzSimmons SC. Colonic strictures in patients with cystic fibrosis: results of a survey of 114 cystic fibrosis care centers in the United States. *J Pediatr Gastroenterol Nutr* 1996;22:153-6

Lancelotti L, Cabrini G, Zanolla L, et al. High- versus low-lipase acid-resistant enzyme preparations in cystic fibrosis: a crossover randomized clinical trial. *J Pediatr Gastroenterol Nutr* 1996;22:73-8

Smyth RL, Ashby D, O'Hea U, et al. *Lancet* 1995;346:1247-51

**Evidence Level: IV**

**Last amended May 2006**

# DIABETIC KETOACIDOSIS IN CHILDHOOD

## Supporting information

**Fatalities are uncommon and are usually associated with cerebral oedema, hypokalaemia causing cardiac dysrhythmias, or coexisting infection, such as meningitis?**

Of 55 deaths in a cohort of children diagnosed between 1950 and 1980 (Scibilia, 1986), DKA was the cause in 17 (85%) of the 20 deaths at disease onset, and 18 (54%) of those occurring 2 months to 11 years after diagnosis.

In a report of 33 deaths in 4919 children with type I diabetes in Sweden (Sartor, 1995), 7 (21%) were DKA-related.

In a UK report of 83 diabetes-related deaths in patients <20 years of age (Edge, 1999), DKA was implicated in 69 (83%).

A multicentre study of 6977 hospitalisations for DKA (Glaser, 2001) recorded 61 (0.8%) episodes of cerebral oedema. Of these 61 children, 13 (21%) died. Two more children died during the episode of DKA, but not from cerebral oedema, bringing the overall mortality rate from DKA to 0.21%. This was similar to the rate of 0.25% previously reported from US paediatric institutions (Levitsky, 1991).

Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes, 1990-96. *Arch Dis Child* 1999;81:318-23

Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med* 2001;344:264-9

Levitsky LL, Ekwo E, Goselink CA, et al. Deaths from diabetes in hospitalized children (1970-1988). *Pediatr Res* 1991;29(Suppl):A195

Sartor G, Dahlquist G. Short-term mortality in childhood onset insulin-dependent diabetes mellitus: a high frequency of unexpected deaths in bed. *Diabet Med* 1995;12:607-11

Scibilia J, Finegold D, Dorman J, et al. Why do children with diabetes die? *Acta Endocrinol Suppl* 1986;279:326-33

**Evidence Level: IV**

**Last amended May 2006**

## **DIARRHOEA & VOMITING (D&V) IN CHILDHOOD**

### **Supporting information**

#### **D&V in infants may be a sign of sepsis?**

The online Merck Manual of Diagnosis and Therapy lists D&V as two of the possible symptoms of neonatal sepsis.

Vomiting was one of 31 clinical signs used to predict 43 sepsis deaths amongst 3567 neonates in an Indian study (Bang, 2005).

Bang AT, Bang RA, Reddy MH, et al. Simple clinical criteria to identify sepsis or pneumonia in neonates in the community needing treatment or referral. *Pediatr Infect Dis J* 2005;24:335-41

<http://www.merck.com/mrkshared/mmanual/section19/chapter260/260m.jsp>

**Evidence Level: V**

**Last amended May 2006**

# ENDOCRINE EMERGENCIES IN CHILDHOOD

## Supporting information

### Calcium

#### Hypercalcaemia

##### What is the definition of hypercalcaemia?

The normal physiologic range for serum calcium is 2.2 – 2.6 mmol/l (Heath, 2001). Consensus opinion on the cut-off point above which hypercalcaemia is diagnosed rests at 2.75 mmol/l (Hume, 1998). The ionised calcium (rather than the total serum calcium) level may be a more accurate indicator for hypercalcaemia, in which case the upper limit of normal is 1.35 mmol/l (Rodd, 1999).

Heath DA, Shaw NJ. Calcium and bone metabolism. In: Brook CG, Hindmarsh PC (eds). *Clinical pediatric endocrinology*, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p377

Hume R. Neonatal metabolic disorders. In: Campbell AG, McIntosh N (eds). *Forfar and Arneil's Textbook of pediatrics*, 5<sup>th</sup> ed. New York: Churchill Livingstone, 1998. p300

Rodd C, Goodyer P. Hypercalcemia of the newborn: etiology, evaluation, and management. *Pediatr Nephrol* 1999;13:542-7

##### Evidence Level: V

##### What are the appropriate initial investigations for hypercalcaemia?

The single key investigation is the concentration of intact parathyroid hormone in serum. This will usually be suppressed in most cases of hypercalcaemia other than primary or tertiary hyperparathyroidism and familial hypocalciuric hypercalcaemia. Assessment of urinary calcium excretion is also important as there will often be accompanying hypercalciuria with its attendant risk of nephrocalcinosis and renal impairment. If hypercalciuria is present, ultrasound will identify renal calcification (Heath, 2001).

Heath DA, Shaw NJ. Disorders of calcium and bone metabolism. In: Brook CG, Hindmarsh PC (eds). *Clinical pediatric endocrinology*, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p401

##### Evidence Level: V

##### Is treatment with furosemide appropriate?

Loop diuretics such as furosemide enhance the calciuric effects of volume expansion by inhibiting calcium reabsorption in the thick ascending limb of the loop of Henle, thus facilitating urinary excretion of calcium (Bilezikian, 1992). They must be used with care to avoid dehydration, which, by reducing the glomerular filtration rate, can actually worsen hypercalcaemia (Hsu, 2004)

Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992;326:1196-1203

Hsu SC, Levine MA. Perinatal calcium metabolism: physiology and pathophysiology. *Semin Neonatol* 2004;9:23-36

**Evidence Level: V**

**Are bisphosphonates also indicated as treatment for hypercalcaemia?**

Intravenous pamidronate has been proven to be efficacious in a number of cases of hypercalcaemia resistant to conventional treatment, normalising serum calcium levels in 2-5 days (Srivastava, 1999). Associated conditions have included liver or bone marrow transplantation (Attard, 1998; Profumo 1994; Rawlinson, 1991), leukaemia (Boudailliez, 1990), immobilisation from quadriplegia (Varache, 1991), and renal disease (Sellers, 1998). Pamidronate (Khan, 2001) and etidronate (Rice, 1999) have recently been used successfully in hypercalcaemia resulting from subcutaneous fat necrosis.

Attard TM, Dhawan A, Kaufman SS, et al. Use of disodium pamidronate in children with hypercalcemia awaiting liver transplantation. *Pediatr Transplant* 1998;2:157-9

Boudailliez BR, Pautard BJ, Sebert JL, et al. Leukaemia-associated hypercalcaemia in a 10-year-old boy: effectiveness of aminohydroxypropylidene bisphosphonate. *Pediatr Nephrol* 1990;4:510-11

Khan N, Licata A, Rogers D. Intravenous bisphosphonate for hypercalcemia accompanying subcutaneous fat necrosis: a novel treatment approach. *Clin Pediatr* 2001;40:217-9

Profumo RJ, Reese JC, Foy TM, et al. Severe immobilization-induced hypercalcemia in a child after liver transplantation successfully treated with pamidronate. *Transplantation* 1994;57:301-3

Rawlinson PS, Green RH, Coggins AM, et al. Malignant osteoporosis: hypercalcaemia after bone marrow transplantation. *Arch Dis Child* 1991;66:638-9

Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatrics* 1999;134:349-51

Sellers E, Sharma A, Rodd C. The use of pamidronate in three children with renal disease. *Pediatr Nephrol* 1998;12:778-81

Srivastava T, Alon US. Bisphosphonates: from grandparents to grandchildren. *Clin Pediatr* 1999;38:687-702

Varache N, Audran M, Clochon P, et al. Aminohydroxypropylidene bisphosphonate (AHPPrBP) treatment of severe immobilization hypercalcaemia in a young patient. *Clin Rheumatol* 1991;10:328-32

**Evidence Level: V**

## **Hypocalcaemia**

### **What is the definition of hypocalcaemia?**

The normal range for total serum calcium is approximately 2.10 – 2.55 mmol/l (2.2 – 2.6 mmol/l according to Heath, 2001) and most hypocalcaemic patients will be in the range 1.25 – 2.09 mmol/l (Guise, 1995). The cut-off point for treatment of neonatal hypocalcaemia has been defined as <1.75 mmol/l (Specker, 1992), or an ionised calcium <0.625 mmol/l (Hume, 1998).

Guise TA, Mundy GR. Evaluation of hypocalcemia in children and adults. *J Clin Endocrinol Metab* 1995;80:1473-8

Heath DA, Shaw NJ. Calcium and bone metabolism. In: Brook CG, Hindmarsh PC (eds). *Clinical pediatric endocrinology*, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p377

Hume R. Neonatal metabolic disorders. In: Campbell AG, McIntosh N (eds). *Forfar and Arneil's Textbook of pediatrics*, 5<sup>th</sup> ed. New York: Churchill Livingstone, 1998. p300

Specker BL, DeMarini S, Tsang RC. Vitamin and mineral supplementation. In: Sinclair JC, Bracken MB (eds). *Effective care of the newborn infant*. Oxford: Oxford University Press, 1992. p171

### **Evidence Level: V**

### **What are the appropriate initial investigations for hypocalcaemia?**

Initial diagnostic testing should include measurement of serum concentrations of intact PTH, magnesium, and vitamin D metabolites, 25OH<sub>D</sub> and 1,25-(OH)<sub>2</sub>D<sub>3</sub> (Heath, 2001; Guise, 1995). Two-site immunoradiometric and immunochemiluminometric assays for intact PTH are now sensitive enough to distinguish between hypoparathyroidism and nonparathyroid causes of hypocalcaemia (Endres. 1991).

Endres DB, Villanueva R, Sharp CF, et al. Immunoradiometric and immunochemiluminometric determinations of intact and total immunoreactive parathyrin: performance in the differential diagnosis of hypercalcemia and hypoparathyroidism. *Clin Chem* 1991;37:162-8

Guise TA, Mundy GR. Evaluation of hypocalcemia in children and adults. *J Clin Endocrinol Metab* 1995;80:1473-8

Heath DA, Shaw NJ. Calcium and bone metabolism. In: Brook CG, Hindmarsh PC (eds). *Clinical pediatric endocrinology*, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p390

### **Evidence Level: V**

### **Is treatment with alfacalcidol to be preferred to vitamin D?**

Vitamins D<sub>2</sub> and D<sub>3</sub>, although cheaper than alfacalcidol, require hepatic and renal transformation for full activation (Reber, 1995). If the cause of the hypocalcaemia is hypoparathyroidism, the hypocalciuric action of parathyroid hormone cannot take place and raising serum calcium may cause hypercalciuria, nephrolithiasis or renal damage

(Marx, 2000). Alfacalcidol, which does not require hepatic and renal transformation, is therefore indicated in hypoparathyroidism-induced hypocalcaemia (Heath, 2001). Vitamin D, in a dose of 5000 IU/day orally, is an alternative to calcium in the treatment of late neonatal hypocalcaemia (neonatal tetany) (Hume, 1998).

Heath DA, Shaw NJ. Disorders of calcium and bone metabolism. In: Brook CG, Hindmarsh PC (eds). Clinical pediatric endocrinology, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p391

Hume R. Neonatal metabolic disorders. In: Campbell AG, McIntosh N (eds). Forfar and Arneil's Textbook of pediatrics, 5<sup>th</sup> ed. New York: Churchill Livingstone, 1998. p298-300

Marx SJ. Hyperparathyroid and hypoparathyroid disorders. N Engl J Med 2000;343:1863-75

Reber PM, Heath H. Hypocalcemic emergencies. Med Clin N Am 1995;79:93-106

**Evidence Level: V**

**Last amended September 2004**

# ENDOCRINE EMERGENCIES IN CHILDHOOD

## Supporting information

### Carbohydrate

#### What is the appropriate dose of glucose with which to correct hypoglycaemia?

Textbooks and reviews alike recommend 2-4 ml/kg of 25% glucose at a rate of 1 ml/min (Sperling, 2000; McCabe, 1994; Shah, 1992; Schwartz, 1991) without quoting a source of reference. In a small study of 22 neonates (Lilien, 1977), hypoglycaemia was corrected within 10 minutes in 18 of them by a constant infusion of 8 mg/kg/min. A further 3 normalised within 30-50 minutes. The remaining patient had hyperinsulinaemia and responded only to diazoxide. A later study of 23 hypoglycaemic infants by the same team (Lilien, 1980) used a 200 mg/kg bolus over 1 minute, followed by a constant infusion of 8 mg/kg/min. All patients were normoglycaemic after 1 minute, with 1 patient developing transient hyperglycaemia.

Lilien LD, Grajwer LA, Pildes RS. Treatment of neonatal hypoglycemia with continuous intravenous glucose infusion. *J Pediatr* 1977;91:779-82

Lilien LD, Pildes RS, Srinivasan G, et al. Treatment of neonatal hypoglycemia with minibolus and intravenous glucose infusion. *J Pediatr* 1980;97:295-8

McCabe ER. Metabolic encephalopathies. In: McMillan JA, DeAngelis CD, Feigin RD, et al (eds). *Oski's Pediatrics: principles and practice*, 3<sup>rd</sup> ed. Philadelphia: Lippincott Williams & Wilkins, 1994. p1998

Schwartz R. Neonatal hypoglycemia: back to basics in diagnosis and treatment. *Diabetes* 1991;40(Suppl 2):71-3

Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. *BMJ* 1992;304:173-4

Sperling MA. Hypoglycemia. In: Behrman RE, Kliegman RM, Jenson HB (eds). *Nelson Textbook of pediatrics*, 16<sup>th</sup> ed. Philadelphia, Saunders, 2000. p449

#### Evidence Level: V

#### What is the basis for the definition of hyperinsulinism?

Considerable controversy surrounds the definition of hyperinsulinism (Aynsley-Green, 2000; Cornblath, 1990; Koh, 1988), although European Network for Research into Hyperinsulinism consensus favours the following criteria (Aynsley-Green, 2000):

Glucose requirements > 6-8 mg/kg/min to maintain blood glucose above 2.6 – 3 mmol/litre

Laboratory blood glucose < 2.6 mmol/litre

Detectable insulin at the point of hypoglycaemia with raised C peptide

Inappropriately low blood free fatty acid and ketone body concentrations at the time of hypoglycaemia

Glycaemic response after the administration of glucagon when hypoglycaemic

Absence of ketonuria

Aynsley-Green A, Hussain K, Hall J, et al. Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F98-F107

Cornblath M, Schwartz R, Aynsley-Green A, et al. Hypoglycemia in infancy: the need for a rational definition: a Ciba Foundation discussion meeting. *Pediatrics* 1990;85:834-7

Koh TH, Eyre JA, Aynsley-Green A. Neonatal hypoglycaemia: the controversy regarding definition. *Arch Dis Child* 1988;63:1386-98

## **Evidence Level: V**

### **Should blood glucose of 2.6 mmol/l be the cut-off point for investigating neonatal hypoglycaemia?**

The definition of hypoglycaemia in the newborn has remained controversial because of lack of significant correlation between plasma glucose concentration, clinical symptoms, and long-term sequelae (Kalhan, 2000). The authors of this review consider that, in clinically symptomatic infants, the cut-off point for investigation should be 2.5 mmol/l or less. In those who are asymptomatic or who are considered to be at risk for hypoglycaemia (e.g. preterm), 2.0 mmol/L should be the threshold level.

A study on blood glucose concentration in 17 children (Koh, 1988) found abnormal evoked potentials in 10 of 11 children who recorded levels below 2.6 mmol/L. Thus a cut-off point of 2.6 mmol/L for investigation was suggested. Only 5 infants in this study, however, were less than 1 month old, and there was no indication of how many infants were studied in the first few days of life (Eidelman, 2001).

Pointing out that glucose requirements in the neonatal brain are at least equal to those in adults, and that healthy adults show adverse reactions to blood glucose concentrations of 2.8-3.3 mmol/L, another authority recommends a minimum level of 2.8 mmol/L for infants (Schwartz, 1997).

A questionnaire sent to 420 neonatal paediatricians in the UK and 88 in Australia in 1992 (Koh, 1996) revealed a wide range in their definition of hypoglycaemia (<1(-4) mmol/L). Compared with a similar survey conducted in 1986 (Koh, 1988), there was a significant increase in the number of paediatricians defining safe blood glucose concentrations as being at least 2 mmol/L (78% vs 34% for term babies, 87% vs 22% for preterm babies). The number preferring to maintain levels of  $\geq 2.6$  mmol/L trebled as compared to 1986. This change was also noted in textbooks over the same 6-year period.

Eidelman AI. Hypoglycemia and the breastfed neonate. *Pediatr Clin N Am* 2001;48:377-87

Kalhan S, Peter-Wohl S. Hypoglycemia: what is it for the neonate? *Am J Perinatol* 2000;17:11-8

Koh TH, Vong SK. Definition of neonatal hypoglycaemia: is there a change? *J Paediatr Child Health* 1996;32:302-5

Koh TH, Aynsley-Green A, Tarbit M, et al. Neural dysfunction during hypoglycaemia. *Arch Dis Child* 1988;63:1353-8

Koh TH, Eyre JA, Aynsley-Green A. Neonatal hypoglycaemia: the controversy regarding definition. *Arch Dis Child Fetal Neonatal Ed* 1988;79:1386-8

Schwartz RP. Neonatal hypoglycemia: how low is too low? *J Pediatr* 1997;131:171-3

## **Evidence Level: V**

### **Are lower blood sugars acceptable in breastfed babies, due to their use of ketone bodies as a fuel source?**

A cross-sectional study of 156 term and 62 preterm infants (Hawdon, 1992) found that blood glucose concentrations were significantly lower in breastfed as compared to formula fed babies (mean, 3.6 mmol/L; range, 1.5-5.3 mmol/L vs mean, 4.0 mmol/L; range, 2.5 – 6.2 mmol/L).

Absolute concentrations also varied more for preterm than for term infants (1.5 –12.2 mmol/L vs

1.5- 6.2 mmol/L). None of the breastfed infants were symptomatic, despite 12% having blood glucose concentrations < 2.6 mmol/L. Breastfed infants were shown to respond to low blood glucose concentrations by increased production of ketone bodies, although the preterm infants did not have this ability.

Glucose concentration in symptomatic infants should be maintained at > 2.6 mmol/L.

Asymptomatic infants with documented hypoglycaemia should continue breastfeeding and have the blood glucose concentration rechecked within 2 hours, starting iv glucose treatment if the hypoglycaemia persists (Eidelman, 2001).

Eidelman AI. Hypoglycemia and the breastfed neonate. *Pediatr Clin N Am* 2001;48:377-87

Hawdon JM, Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *Arch Dis Child* 1992;67:357-65

### **Evidence Level: IV**

### **What are the minimum blood requirements for investigation of persistent hypoglycaemia?**

In a series of 26 patients diagnosed between 1975 and 1995 (Cresto, 1998), diagnosis was obtained by blood testing following a fasting tolerance test discontinued when symptoms appeared or blood sugar concentration reached 2.2 mmol/L or below. Blood was tested to measure insulin, glucose, C-peptide, free fatty acid and 3-hydroxybutyrate. The insulin:glucose ratio was calculated as pmol/L insulin:mmol/L glucose. A ratio less than 40 was considered normal and > 100 diagnostic of hyperinsulinism. Values between 40 and 100 were considered suggestive of persistent hyperinsulinaemic hypoglycaemia of infancy. Hyperinsulinism also inhibits the normal response to hypoglycaemia, preventing the increase of free fatty acids (normal values 478 +/- 14.3) and 3-hydroxybutyrate (normal values 58-170); low values for these will therefore reinforce the diagnosis (Landau, 1982). Elevated serum C-peptide concentration is also a useful tool in diagnosing hyperinsulinism. Normal values are 150 – 350 pmol/L (Bommen, 1984).

Bommen M, Stanhope R, Kurtz AB, et al. Plasma C peptide in hyperinsulinaemic hypoglycaemia. *Arch Dis Child* 1984;59:1096-8

Cresto JC, Abdenur JP, Bergada I, et al. Long term follow up of persistent hyperinsulinaemic hypoglycaemia of infancy. *Arch Dis Child* 1998;79:440-4

Landau H, Perlman M, Meyer S, et al. Persistent neonatal hypoglycemia due to hyperinsulinism: medical aspects. *Pediatrics* 1982;70:440-6

### **Evidence Level: V**

### **N.B. No protocols or policies from other units have been identified**

January 2002

# ENDOCRINE EMERGENCIES IN CHILDHOOD

## Supporting information

### Pituitary Axis

#### Panhypopituitarism

##### Cortisol

#### Should the maintenance dose of hydrocortisone be 12mg/m<sup>2</sup>?

The physiologic replacement dose of hydrocortisone (extrapolated mainly from adult studies) has been estimated at 10-15 mg/m<sup>2</sup> (Hoffman, 2002). In a study involving 50 children and adolescents aged 3-20 years, 44 of whom were ACTH deficient (DeVile, 1997), the mean total daily replacement dose of hydrocortisone was 12.3 mg/m<sup>2</sup>/day (range 5.5-18.5). This study demonstrated that a twice daily dose regimen resulted in low cortisol levels in the early hours of the morning, particularly in younger patients. This was avoided by administering the same total dose of hydrocortisone in three equal fractions.

A study in 33 normal children and adolescents aged 8-17 years (Linder, 1990) found the mean cortisol production rate to be 9.5 +/- 2.5 mg/day (6.8 +/- 1.9 mg/m<sup>2</sup>/day), suggesting that previous estimates have been too high.

Another study in 18 normal adolescent males (Kerrigan, 1993) found very similar results, with the younger subjects (Tanner I or II) recording 6.1 +/- 0.4 mg/m<sup>2</sup>/day and the older subjects (Tanner IV or V) recording 5.3 +/- 0.5 mg/m<sup>2</sup>/day.

The evidence suggests that the previously accepted maintenance dose for hydrocortisone may be too high at 12mg/m<sup>2</sup> and that symptoms of glucocorticoid excess may appear at this level. No studies have, however, been conducted in children under the age of 8.

DeVile CJ, Stanhope R. Hydrocortisone replacement therapy in children and adolescents with hypopituitarism. *Clin Endocrinol* 1997;47:37-41

Hoffman R. Panhypopituitarism. *eMed J* 2002;3:1-14

Kerrigan JR, Veldhuis JD, Leyo SA, et al. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. *J Clin Endocrinol Metab* 1993;76:1505-10

Linder BL, Esteban NV, Yergey AL, et al. Cortisol production rate in childhood and adolescence. *J Pediatr* 1990;117:892-6

#### Evidence Level: IV

#### Should the dose of hydrocortisone be doubled in the event of stress caused by surgery or illness?

The administration of stress doses of glucocorticoids is an inexact science and is not based on solid evidence (Miller, 2001). Most advice is to err on the side of overdosage, and doses of from 3 times replacement for febrile illness or minor surgery up to 10 times replacement for major accident or surgery have been recommended (Hoffman, 2002). More moderately, specific advice for surgery has been intramuscular administration of twice the day's physiological requirement at 18 hours before surgery, repeated at 8 hours before (Miller, 2001).

Hoffman R. Panhypopituitarism. *eMed J* 2002;3:1-14

Miller WL. The adrenal cortex and its disorders. In: Brook CG, Hindmarsh PC (eds). Clinical pediatric endocrinology, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p363

## **Evidence Level: V**

### **Diabetes insipidus**

#### **What is the optimum dosage regime and the preferred route of administration?**

Desmopressin, a synthetic analogue of vasopressin, is the treatment of choice for diabetes insipidus, as it has a longer duration of action than vasopressin, may be administered orally, intranasally or parenterally, and has no significant side-effects (Robertson, 2001; Baylis, 1998; Robinson, 1976; Edwards, 1973). There are wide individual variations in the dose required to control diuresis, from 100-1000 mcg orally (in 3 divided doses), 2-40 mcg intranasally, and 0.1-1 mcg parenterally (Baylis, 1998). The appropriate dose has to be found empirically, but is usually in the range 10-20 mcg intranasally or 100-400 mcg orally (Robertson, 2001). Although the intranasal route is most appropriate for infants, oral administration is usually preferred by older children and is equally efficacious (Boulgourdjian, 1997; Fjellestad, 1986; Westgren, 1986).

Baylis PH, Cheetham T. Diabetes insipidus. Arch Dis Child 1998;79:84-9

Boulgourdjian EM, Martinez AS, Ropelato MG, et al. Oral desmopressin treatment of central diabetes insipidus in children. Acta Paediatr 1997;86:1261-2

Edwards CR, Kitau MJ, Chard T, et al. Vasopressin analogue DDAVP in diabetes insipidus: clinical and laboratory studies. BMJ 1973;iii:375-8

Fjellestad A, Czernichow P. Central diabetes insipidus in children. V. Oral treatment with a vasopressin hormone analogue (DDAVP). Acta Paediatr Scand 1986;75:605-10

Robertson GL. Disorders of water balance. In: Brook CG, Hindmarsh PC (eds). Clinical pediatric endocrinology, 4<sup>th</sup> ed. Oxford: Blackwell Science, 2001. p208

Robinson AG. DDAVP in the treatment of central diabetes insipidus. N Engl J Med 1976;294:507-11

Westgren U, Wittstrom C, Harris AS. Oral desmopressin in central diabetes insipidus. Arch Dis Child 1986;61:247-50

## **Evidence Level: IV**

#### **Is the conversion factor between different administration routes valid?**

The validity of the conversion factor of 1:20 between intranasal and oral administration of desmopressin was confirmed in a study of 10 children with diabetes insipidus (Fjellestad-Paulsen, 1987). This compared the effect of 10-20 mcg of intranasal with 200-400 mcg of oral desmopressin. At 12 hours after administration, the ratio urine osmolality/plasma osmolality was above 1 only after 20 mcg intranasally (IN) and 400 mcg perorally (PO). Bio-equivalence was established between 10 mcg IN and 200 mcg PO and between 20 mcg IN and 400 mcg PO.

Fjellestad-Paulsen A, Tubiana-Rufi N, Harris A, et al. Central diabetes insipidus in children: antidiuretic effect and pharmacokinetics of intranasal and peroral 1-deamino-8-D-arginine vasopressin. Acta Endocrinol 1987;115:307-12

## **Evidence Level: IV**

## **Congenital adrenal hyperplasia**

### **What is the optimum dose of hydrocortisone?**

The usual maintenance dose of hydrocortisone is 15-18 mg/m<sup>2</sup> (New, 1998). A prospective randomised crossover trial in 26 children (Silva, 1997) compared hydrocortisone doses of 15 or 25 mg/m<sup>2</sup>. The higher dose was associated with significantly decreased height velocity over a 12 month period, indicating corticosteroid excess and leading the authors to conclude that full suppression, or even normalisation of plasma 17-hydroxyprogesterone and androgen levels should not be a target of treatment. A study of different dosing patterns in 8 patients (Winterer, 1985) found no difference in mean 24-hour plasma levels of 17-hydroxyprogesterone in patients given hydrocortisone 12.5 mg/m<sup>2</sup> spread between 3, 2, or 1 doses per day. The optimum daily dose of hydrocortisone must be adjusted to achieve a normal rate of growth and bone age advancement in each patient (Winterer, 1985).

Critically ill patients require a single iv hydrocortisone bolus followed by a constant rate infusion of hydrocortisone (Charmandari, 2001).

Charmandari E, Lichtarowicz-Krynska EJ, Hindmarsh PC, et al. Congenital adrenal hyperplasia: management during critical illness. *Arch Dis Child* 2001;85:26-8

New MI. Diagnosis and management of congenital adrenal hyperplasia. *Ann Rev Med* 1998;49:311-28

Silva IN, Kater CE, Cunha CF, et al. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. *Arch Dis Child* 1997;77:214-8

Winterer J, Chrousos GP, Loriaux L, et al. Effect of hydrocortisone dose schedule on adrenal steroid secretion in congenital adrenal hyperplasia. *J Pediatr* 1985;106:137-42

### **Evidence Level: V**

### **What is the usefulness of 17-OHP?**

17-hydroxyprogesterone (17-OHP) measurements offer a convenient supplement to measurements of height velocity and bone age maturation in the monitoring of steroid replacement therapy in congenital adrenal hyperplasia (Pincus, 1993). In 6 patients followed over a 4 year period, a strong correlation was noted between 17-OHP and height velocity (Pincus, 1993). 17-OHP levels vary throughout the day, and home-monitoring before each dose of hydrocortisone has been suggested in order to provide a more accurate reflection of adrenal activity (Bode, 1999). A basal 17-OHP value of >15 mmol/l (or ACTH-stimulated 17-OHP >30 mmol/l) may also be used to diagnose the non-classical form of 21-hydroxylase (NC-21OH) deficiency (Bachega, 2000).

Bachega TA, Billerbeck AE, Marcondes JA, et al. Influence of different genotypes on 17-hydroxyprogesterone levels in patients with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Clin Endocrinol* 2000;52:601-7

Bode HH, Rivkees SA, Cowley DM, et al. Home monitoring of 17 hydroxyprogesterone levels in congenital adrenal hyperplasia with filter paper blood samples. *J Pediatr* 1999;134:185-9

Pincus DR, Kelnar CJ, Wallace AM. 17-Hydroxyprogesterone rhythms and growth velocity in congenital adrenal hyperplasia. *J Pediatr Child Health* 1993;29:302-4

### **Evidence Level: IV**

## **What is the appropriate dose of synacthen (tetracosactrin) for the short synacthen test?**

The short synacthen test is available in high dose (HDT, 250 mcg) and low dose (LDT, 1 mcg) forms. Several researchers have considered that the HDT uses a supraphysiological dose and is not sensitive enough to detect mild degrees of secondary adrenal insufficiency. They report that the HDT underdiagnoses clinically significant adrenal insufficiency, with potentially serious consequences (Ammari, 1996; Soule, 1996; Streeten, 1996; Tsatsoulis, 1988).

Several studies have demonstrated that the plasma cortisol response to 1 mcg is equivalent to that obtained with 250 mcg in normal subjects (Talwar, 1998; Rasmuson, 1996; Daidoh, 1995; Crowley, 1991) and that the test is thus able to detect mild adrenal insufficiency.

A study (Gonzalbez, 2000) comparing both short synacthen tests with the insulin tolerance test (ITT) found no differences in the plasma cortisol response so long as different cut-off points were used for each test (500 nmol/l for LDT, 650 nmol/l for HDT, and 540 nmol/l for the ITT).

Other studies (Abdu, 1999; Bangar, 1998) have suggested an arbitrary cut-off point of 600 nmol/l in order to increase the sensitivity of both LDT and HDT. Gonzalbez and colleagues (2000) however, found that this produced a high number (up to 30%) of falsely subnormal responses that would have meant many patients receiving unnecessary chronic treatment with hydrocortisone.

Abdu TA, Elhadd TA, Neary R, et al. Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for the assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. *J Clin Endocrinol Metab* 1999;84:838-43

Ammari F, Issa BG, Millward E, et al. A comparison between short ACTH and insulin stress tests for assessing hypothalamo-pituitary-adrenal function. *Clin Endocrinol* 1996;44:473-6

Bangar V, Clayton RN. How reliable is the short synacthen test for the investigation of the hypothalamic-pituitary-adrenal axis? *Eur J Endocrinol* 1998;139:580-3

Crowley S, Hindmarsh PC, Holownia P, et al. The use of low doses of ACTH in the investigation of adrenal function in man. *J Endocrinol* 1991;130:475-9

Daidoh H, Morita H, Mune T, et al. Responses of plasma adrenocortical steroids to low dose ACTH in normal subjects. *Clin Endocrinol* 1995;43:311-5

Gonzalbez J, Villabona C, Ramon J, et al. Establishment of reference values for standard dose short synacthen test (250 g), low dose short synacthen test (1 g) and insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in normal subjects. *Clin Endocrinol* 2000;53:199-204

Rasmuson S, Olsson T, Hagg E. A low dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. *Clin Endocrinol* 1996;44:151-6

Soule SG, Fahie-Wilson M, Tomlinson S. Failure of the short ACTH test to unequivocally diagnose long-standing symptomatic secondary hypoadrenalism. *Clin Endocrinol* 1996;44:137-40

Streeten DH, Anderson GH, Bonaventura MM. The potential for serious consequences from misinterpreting normal responses to the rapid adrenocorticotropin test. *J Clin Endocrinol Metab* 1996;81:285-90

Talwar V, Lodha S, Dash RJ. Assessing the hypothalamo-pituitary-adrenocortical axis using physiological doses of adrenocorticotrophic hormone. *QJM* 1998;91:285-90

Tsatsoulis A, Shalet SM, Harrison J, et al. Adrenocorticotrophin (ACTH) deficiency undetected by standard dynamic tests of the hypothalamo-pituitary-adrenal axis. *Clin Endocrinol* 1988;28:225-32

**Evidence Level: IV**

**February 2002**

# ENDOCRINE EMERGENCIES IN CHILDHOOD

## Supporting information

### Thyroid Axis

#### What is the appropriate treatment for thyrotoxic crisis (thyroid storm)?

Thyroid storm is a life-threatening emergency that is very rare in childhood, with the literature confined to a handful of case reports (Kadmon, 2001; Ureta-Raroque, 1997; Lawless, 1992; Aiello, 1989; Christensen, 1987; Hayek, 1978; Galaburda, 1974). Treatment generally consists of 4 components (Wartofsky, 2000): a thionamide antithyroid drug (either propylthiouracil or methimazole) to block T<sub>4</sub> and T<sub>3</sub> synthesis; control of fever and hypovolaemia; administration of a  $\beta$ -blocker to relieve the tissue effects of high serum T<sub>3</sub> and T<sub>4</sub> concentrations; treatment of any underlying precipitating illness or injury. After initial treatment with propylthiouracil, sodium iodide may be given to block further hormone release, and hydrocortisone as supportive therapy (Tietgens, 1995; Gavin, 1991). No controlled trials of treatment for thyroid storm have been identified. The authors (Robuschi, 1986) of one study of sodium ipodate and iodide treatment in adult Graves' disease patients, showing rapid reduction of serum free thyroid hormone concentrations, suggest the applicability of these drugs in thyroid storm.

Aiello DP, DuPlessis AJ, Pattishall EG, et al. Thyroid storm presenting with coma and seizures in a 3-year-old girl. *Clin Pediatr* 1989;28:571-4

Christensen PA, Nissen LR. Treatment of thyroid storm in a child with dantrolene. *Br J Anaesth* 1987;59:523

Galaburda M, Rosman NP, Haddow JE. Thyroid storm in an 11-year-old boy managed by propranolol. *Pediatrics* 1974;53:920-2

Gavin LA. Thyroid crises. *Med Clin N Am* 1991;75:179-93

Hayek A. Thyroid storm following radioiodine for thyrotoxicosis. *J Pediatr* 1978;93:978-80

Kadmon PM, Noto RB, Boney CM, et al. Thyroid storm in a child following radioactive iodine (RAI) therapy: a consequence of RAI versus withdrawal of antithyroid medication. *J Clin Endocrinol Metab* 2001;86:1865-7

Lawless ST, Reeves G, Bowen JR. The development of thyroid storm in a child with McCune-Albright syndrome after orthopedic surgery. *Am J Dis Child* 1992;146:1099-102

Robuschi G, Manfredi A, Salvi M, et al. Effect of sodium ipodate and iodide on free T<sub>4</sub> and free T<sub>3</sub> concentrations in patients with Graves' disease. *J Endocrinol Invest* 1986;9:287-91

Tietgens ST, Leinung MC. Thyroid storm. *Med Clin N Am* 1995;79:169-84

Ureta-Raroque SS, Abramo TJ. Adolescent female patient with shock unresponsive to usual resuscitative therapy. *Pediatr Emerg Care* 1997;13:274-6

Wartofsky L. Thyrotoxic storm. In: Braverman LE, Utiger RD (eds). *Werner & Ingbar's The thyroid: a fundamental and clinical text*, 8<sup>th</sup> ed. Philadelphia: Lippincott Williams & Wilkins, 2000. p681

**Evidence Level: V**

**March 2002**

## **FEBRILE NEUTROPENIA IN CHILDREN**

### **Supporting information**

#### **What is the evidence for the appropriate pre-dose trough for gentamicin in febrile neutropenia beyond the neonatal period?**

Gentamicin administration carries the danger of ototoxicity or nephrotoxicity if the serum concentration of the drug is at any point too high. The BNF for Children recommends that the pre-dose trough concentration should be < 2 mg/L in multiple daily dose regimens, and < 1 mg/L for once-daily dosing.

A number of studies suggest that once-daily dosing achieves more stable trough levels than twice or three-times daily dosing. A review of 13 comparison studies (Miron, 2001) found that steady state trough concentrations > 2mg/L occurred in 5-55% of those on multiple doses, vs 0-24% of those on single doses.

A meta-analysis of 24 studies published between 1991 and 2003 (Contopoulos-Ionnidis, 2004) found that 22 of the 23 RCTs that had performed pharmacokinetic analyses showed that once-daily dosing achieved higher peak and lower trough levels, compared with multiple daily dosing.

Consensus opinion, based on clinical observation, appears to follow the advice given in BNF for Children.

Contopoulos-Ionnidis DG, Giotis ND, Baliatsa DV, et al. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-8

Miron D. Once daily dosing of gentamicin in infants and children. *Pediatr Infect Dis J* 2001;20:1169-73

**Evidence Level: V (Consensus opinion)**

**Last amended May 2006**

# HENOCH-SCHOENLEIN PURPURA

## Supporting information

### Are corticosteroids of use in HSP?

In a small retrospective study in 12 patients with HSP nephritis (Flynn, 2001), treatment was given for 12 weeks with either iv pulse methylprednisolone (10 mg/kg/dose up to a maximum of 1 g/day) or oral prednisolone in high doses (2mg/kg/day up to a maximum of 80 mg/day) followed by oral cyclophosphamide (2 mg/kg/day). Daily or alternate-day oral prednisolone was also given. Proteinuria (a risk factor for the development of renal insufficiency in HSP) was reduced, in terms of serial protein-to-creatinine ratios, from 6.3 +/- 4.4 to 0.8 +/- 0.8 (p = 0.002). Proteinuria was also reduced in 19 of 21 patients given prednisone in combination with azathioprine (Bergstein, 1998). 13 patients received oral prednisone and 8 were treated with iv methylprednisolone. Proteinuria decreased from 8.8 +/- 7.5 to 0.47 +/- 0.39 g/24 h (p < 0.01). Methylprednisolone pulse therapy was also found to be effective in a prospective study in 38 patients (Niaudet, 1998). At follow up (1-16 years after treatment), 27 children had clinically recovered. Renal biopsy in 18 of these patients showed a significant decrease of the activity index from 5.1 +/- 1.1 to 0.4 +/- 0.8 with a decrease in (or in some cases, disappearance of) IgA deposits.

In another retrospective analysis in 101 children with HSP (Reinehr, 2000), 57 with severe abdominal pain (n=34) or GI bleeding with abdominal pain (n=23) as features of their disease were treated with steroids. Treatment with prednisone (2 mg/kg, rising to 3-5 mg/kg if symptoms persisted for more than 24 hours) resulted in a 100% cure rate within 48 hours (77% within 24 hours). A further 43 children who were not given steroids had abdominal pain for a median of 5 days (range 1-28 days). The 26 patients who had received  $\geq$  1 week of prednisone treatment within the first 3 weeks of their disease had renal involvement in 2 (8%) of cases. This compared with 39 (52%) of the other 75 patients in the study.

In a report of 100 cases with a review of the literature (Saulsbury, 1999), 57 patients received corticosteroids. Patients were given oral or intravenous prednisone (mean dose 1.6 +/- 0.4 mg/kg per day) for 5 – 28 days (mean 8.9 +/- 3.7 days). Corticosteroids “seemed to be beneficial in hastening the resolution of abdominal pain and arthritis” but as neither randomisation nor a control group was used, the authors felt that no conclusions could be inferred from this observation. Corticosteroids in normal doses had no effect on rash, recurrence of symptoms, or acute or delayed nephritis.

A retrospective study of 69 children by the same author (Saulsbury, 1993) also found that steroids had no effect on preventing nephritis.

In contrast, the only randomised, controlled prospective study to date on this subject (Mollica, 1992) did find a “highly significant (P < 0.001) benefit for steroid therapy in preventing nephritis. 84 patients received oral delta-prednisone (1 mg/kg/d for 2 weeks) and 84 did not. None of the steroid group vs 10 (11.9%) of the controls developed nephropathy 2-6 weeks after the acute episode.

A retrospective analysis of 17 HSP patients with nephritis (Foster, 2000), treated with prednisone (1-2 mg/kg/d) and azathioprine in a similar dose, compared outcomes with a control group of 59. 15 of 17 (88%) in the treatment group vs 32 of 59 (54%) controls had a favourable outcome. Relative risk of an unfavourable outcome in controls was 6.3.

It appears that corticosteroid treatment does not shorten the duration of HSP, but does decrease morbidity (Rosenblum, 1987), including that associated with cutaneous vasculitis and fibrinolysis (Prandota, 2001).

Foster BJ, Bernard C, Drummond KN, et al. Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. *J Pediatr* 2000;136:370-5

Flynn JT, Smoyer WE, Bunchman TE, et al. Treatment of Henoch-Schonlein Purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001;21:128-33

Mollica F, Li Volti S, Garozzo R, et al. Effectiveness of early prednisone treatment in preventing the development of nephropathy in anaphylactoid purpura. *Eur J Paediatr* 1992;151:140-4

Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms of Schonlein-Henoch purpura nephritis. *Pediatr Nephrol* 1998;12:238-43

Prandota J, Pankow-Prandota L, Kotecki L. Impaired activation of the fibrinolytic system in children with Henoch-Schonlein purpura: beneficial effect of hydrocortisone plus Sigma-aminocaproic acid therapy on disappearance rate of cutaneous vasculitis and fibrinolysis. *Am J Ther* 2001;8:11-9

Reinehr T, Burk G, Andler W. Does steroid treatment of abdominal pain prevent renal involvement in Henoch-Schonlein Purpura? *J Pediatr Gastroenterol Nutr* 2000;31:323-4

Rosenblum ND, Winter HS. Steroid effects on the course of abdominal pain in children with Henoch-Schonlein purpura. *Pediatrics* 1987;79:1018-21

Saulsbury FT. Henoch-Schonlein purpura in children: report of 100 patients and review of the literature. *Medicine* 1999;78:395-409

Saulsbury FT. Corticosteroid therapy does not prevent nephritis in Henoch-Schonlein Purpura. *Pediatr Nephrol* 1993;7:69-71

### **Evidence Level: III**

### **What is the most appropriate analgesic/anti-inflammatory in HSP?**

Non-steroidal anti-inflammatory drugs are commonly used to treat arthritic pain in HSP (Cron, 1999) although no particular NSAID is recommended. There are a number of anecdotal reports of dapsone being efficacious in HSP, including paediatric patients (Ramelli, 1997; Sarma, 1994; Hoffbrand, 1991; Ledermann, 1983).

Cron RQ, Sharma S, Sherry DD. Current treatment by United States and Canadian rheumatologists. *J Rheumatol* 1999;26:2036-8

Hoffbrand BI. Dapsone in Henoch-Schonlein purpura: worth a trial. *Postgrad Med J* 1991;67:961-2

Ledermann JA, Hoffbrand BI. Dapsone in allergic vasculitis: its use in Henoch-Schonlein disease following vaccination. *J Roy Soc Med* 1983;76:613-4

Ramelli GP, Bianchetti MG. Dapsone in cutaneous Henoch-Schonlein syndrome: worth a trial. *Acta Paediatr* 1997;86:337

Sarma PS. Dapsone in Henoch-Schonlein purpura. *Postgrad Med J* 1994;70:464-5

### **Evidence Level: V**

**December 2002**

# PROLONGED NEONATAL JAUNDICE

## Supporting Information

### **What is the incidence of prolonged neonatal jaundice in term and preterm newborns?**

Jaundice persisting beyond 14 days of age (prolonged jaundice) can (rarely) be a sign of serious underlying liver disease (Hussein, 1991). Jaundice persists beyond 14 days in 15-40% of breastfed infants, depending on the series studied (Hannam, 2000). A prospective study of all 7139 term infants born at King's College Hospital (London) between January 1997 and June 1998 (Hannam, 2000) found 154 with prolonged jaundice, one of which had conjugated hyperbilirubinaemia (0.14 per 1000 live births).

Another study of 3661 babies in Sheffield (Crofts, 1999) found 127 who were jaundiced at 28 days, of which 125 were breastfed (9.2%).

Although preterm infants, whose livers are more immature, have prolonged jaundice more commonly than term infants (Fenton, 1998) there appear to be no studies of incidence in this group (Lucas, 1986).

Crofts DJ, Michel VJ, Rigby AS, et al. Assessment of stool colour in community management of prolonged jaundice in infancy. *Acta Paediatr* 1999;88:969-74

Fenton TR, Gastrointestinal problems and jaundice of the newborn. In: Campbell AG, McIntosh N, (eds). Forfar and Arneil's Textbook of pediatrics, 5<sup>th</sup> ed. New York: Churchill Livingstone, 1998. p219

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. *Acta Paediatr* 2000;89:694-7

Hussein M, Howard ER, Mieli-Vergani G, et al. Jaundice at 14 days of age: exclude biliary atresia. *Arch Dis Child* 1991;66:1177-9

Lucas A, Baker BA. Breast milk jaundice in premature infants. *Arch Dis Child* 1986;61:1063-7

### **Evidence Level: V**

### **When does serum bilirubin level of a neonate fall to adult level?**

High serum bilirubin levels in the first days of life "decline during the next several weeks to the values commonly found in adults" (Dennery, 2001). This time period is inexact, although 14 days is commonly accepted as a cut-off point for investigation of sustained jaundice (Fenton, 1998).

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001;344:581-90

Fenton TR, Gastrointestinal problems and jaundice of the newborn. In: Campbell AG, McIntosh N, (eds). Forfar and Arneil's Textbook of pediatrics, 5<sup>th</sup> ed. New York: Churchill Livingstone, 1998. p214

### **Evidence Level: V**

### **What is the incidence of glucose-6PD deficiency in British white children?**

Glucose-6PD deficiency is most common amongst Greek, Sardinian, Chinese, Jamaican and South East Asian populations (Beutler, 1994;Valaes, 1994; Singh, 1986; Doxiadis, 1961). There appear to be no epidemiological studies in British white children. The prevalence amongst white northern European populations has been estimated as less than 1 in 1,000 (Beutler, 1995).

Beutler E. Glucose-6-phosphate dehydrogenase deficiency and other enzyme abnormalities. In: Beutler E, Lichtman MA, Coller BS, et al (eds). Williams Hematology, 5<sup>th</sup> ed. New York, McGraw-Hill, 1995. p572

Beutler E. G6PD deficiency. Blood 1994;84:3613-36

Doxiadis SA, Fessas P, Valaes T. Glucose-6-phosphate dehydrogenase deficiency: a new aetiological factor of severe neonatal jaundice. Lancet 1961;i:297-301

Singh H. Glucose-6-phosphate dehydrogenase deficiency: a preventable cause of mental retardation. BMJ 1986;292:397-8

Valaes T. Severe neonatal jaundice associated with glucose-6-phosphate dehydrogenase deficiency: pathogenesis and global epidemiology. Acta Paediatr Suppl 1994;394:58-76

### **Evidence Level: V**

#### **What is the incidence of hereditary spherocytosis presenting with prolonged neonatal jaundice only?**

The incidence of hereditary spherocytosis in Northern Europeans has been estimated at 1:5,000 (Morton, 1962), although milder forms may be asymptomatic and therefore the true incidence may be higher. A recent review (Delhommeau, 2000) has taken this into consideration and suggested an incidence of 1:2,000. This condition has received little attention in the neonatal period (Delhommeau, 2000) and consequently no information can be identified concerning prolonged jaundice as the sole presenting symptom.

Delhommeau F, Cynober T, Schischmanoff PO, et al. Natural history of hereditary spherocytosis during the first year of life. Blood 2000;95:393-7

Morton NE, MacKinney AA, Kosower N, et al. Genetics of spherocytosis. Am J Hum Genet 1962;14:170

### **Evidence Level: V**

#### **What is the incidence of sickle cell anaemia in the British white population?**

The first evidence-based rates for sickle-cell in the UK (Hickman, 1999) give a zero incidence in the white population. The evidence level for this is “D” which equates to “Expert advice based on unpublished data”.

Hickman M, Modell B, Greengross P, et al. Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. Br J Haematol 1999;104:860-7

### **Evidence Level: V**

#### **What percentage of congenital hypothyroidism is missed in the Guthrie test?**

The first screening programme (Dussault, 1975) used a T4 assay alone, which had the potential for missing some babies with ectopic glands in whom T4 concentrations could be in the low-to-normal range. Later programs used TSH assay, which, although unable to detect secondary (pituitary or hypothalamic) hypothyroidism, proved extremely effective in identifying even mild cases of primary hypothyroidism (Hulse, 1980).

A report of the first 3 years of the UK national screening programme (Grant, 1988) recorded 493 cases in a total of 1,941,146 live births (incidence 1:3937). 4 cases were missed (0.8%), which was similar to the North American experience (Holtzman, 1986) of 2 missed cases for every 1 million infants screened.

Dussault JH, Coulombe P, Laberge C, et al. Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr* 1975;86:670-4

Grant DB, Smith I. Survey of neonatal screening for primary hypothyroidism in England, Wales, and Northern Ireland 1982-4. *BMJ* 1988;296:1355-8

Holtzman C, Slazyk WE, Cordero JF, et al. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. *Pediatrics* 1986;78:553-8

Hulse JA, Grant DB, Clayton BE, et al. Population screening for congenital hypothyroidism. *BMJ* 1980;280:675-8

## **Evidence Level: V**

### **What percentage of urinary tract infection in newborns presents with jaundice only?**

The association of urinary tract infection with neonatal jaundice has been well-recognised (Anon, 1971; Arthur, 1967), but no percentages can be identified for newborns presenting with jaundice alone. Most infants in published series have anaemia and/or septicaemia in addition to their jaundice (Hannam, 2000). Jaundice as the main presenting symptom of UTI appears to predominate in male infants at a ratio of 3:1 (Seeler, 1969), unlike the female preponderance generally found in paediatric UTI.

Anon. Urinary tract infection presenting as jaundice. *BMJ* 1971;iii:546-7

Arthur AB, Wilson BD. Urinary infection presenting with jaundice. *BMJ* 1967;i:539-40

Hannam S, McDonnell M, Rennie JM. Investigation of prolonged neonatal jaundice. *Acta Paediatr* 2000;89:694-7

Seeler RA, Hahn K. Jaundice in urinary tract infection in infancy. *Am J Dis Child* 1969;118:553-8

## **Evidence Level: V**

### **At what level of total serum bilirubin (TSB) does kernicterus occur in a) the term baby b) the preterm baby of 32 weeks? At what level should phototherapy be started in the term baby?**

The American Academy of Pediatrics (Anon, 1994) states that "It is not known at what bilirubin concentration...significant risk of brain damage occurs or when the risk of damage exceeds the risk of treatment". Cases of kernicterus have occurred at TSB levels below 200  $\mu\text{mol/l}$  (Gustafson, 1995).

One authority (Ives, 1999) suggests that the threshold lies "somewhere between 400 and 650  $\mu\text{mol/l}$ ". The AAP (Anon, 1994) recommends exchange transfusion and intensive phototherapy when serum bilirubin is  $\geq 430 \mu\text{mol/l}$  if age 25-48 hours or  $\geq 510 \mu\text{mol/l}$  if  $>48$  hours. Standard phototherapy should begin at 257  $\mu\text{mol/l}$  or 308  $\mu\text{mol/l}$  for the same age bands, in the term or near term infant.

Although the AAP document is under review (Anon, 2001), no updated guidance is as yet available.

Data from the Pilot Kernicterus Registry (Johnson, 2002) showed that the median total serum bilirubin (TSB) concentration of infants on readmission to hospital with kernicterus was 600  $\mu\text{mol/l}$  (350 mg/l).

The most recent information on this subject (Bhutani, 2004) indicates that TSB concentrations of  $>342 \mu\text{mol/l}$  ( $>200 \text{mg/l}$ ) should be a cause for concern and that values  $\geq 513 \mu\text{mol/l}$  ( $\geq 300 \text{mg/l}$ ) should be considered "dangerous".

TSB concentrations are, however, poor predictors of bilirubin toxicity in the sick or preterm infant (Bhutani, 2004). Although “free” or unbound bilirubin may provide a more accurate measure, no tests for this have been validated to date (Bhutani, 2004).

A sliding scale has been suggested, based on infant weight, to indicate when intensive phototherapy should be started, but exchange transfusion is recommended when TSB >190 mL/kg (Bhutani, 2004).

Anon. Practice parameter: Management of hyperbilirubinemia in the healthy term newborn. *Pediatrics* 1994;94:558-65

Anon. Neonatal jaundice and kernicterus. *Pediatrics* 2001;108:763-5

Bhutani VK, Johnson LH. Urgent clinical need for accurate and precise bilirubin measurements in the United States to prevent kernicterus. *Clin Chem* 2004;50:477-80

Gustafson PA, Boyle DW. Bilirubin index: a new standard for intervention? *Med Hypotheses* 1995;45:409-16

Ives NK. Neonatal jaundice. In: Rennie JM, Robertson NR, eds. *Textbook of neonatology*, 3<sup>rd</sup> ed. Edinburgh, Churchill Livingstone, 1999. p721

Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr* 2002;140:396-403

### **Evidence Level: V**

### **Can gamma-glutamyl transpeptidase (GGTP) be useful in distinguishing neonatal hepatitis (NH) from extrahepatic biliary atresia (EHBA)?**

A study in 132 patients (Arora, 1992) found that serum GGTP at a cut-off level maintaining 100% sensitivity for EHBA (< 150 IU L(-1)), used in conjunction with non-excreting 99mTc-mebrofenin IDA scans, reduced the false positivity of individual tests. In this series, operative cholangiograms would have been avoided in 21 patients having both tests, vs 9 when only IDA scan was performed.

A study in 47 infants with EHBA, 10 with NH and 130 age-matched healthy controls (Yamagiwa, 1996), noted significant differences in GGTP levels between the EHBA and NH infants at 6 weeks of age (314 +/- 232 IU/L vs 69 +/- 58 IU/L).

A much earlier study in 17 infants aged 5-16 weeks (Wright, 1960) found that the mean maximal GGTP level in NH patients (183 +/- 54 IU/L) was significantly lower than that found in EHBA patients (760 +/- 492 IU/L).

Arora NK, Kohli R, Gupta DK, et al. Hepatic technetium-99m-mebrofenin iminodiacetate scans and serum gamma-glutamyl transpeptidase levels interpreted in series to differentiate between extrahepatic biliary atresia and neonatal hepatitis. *Acta Paediatr* 2001;90:975-81

Wright K, Christie DL. Use of gamma-glutamyl transpeptidase in the diagnosis of biliary atresia. *Am J Dis Child* 1960;135:134-6

Yamagiwa I, Iwafuchi M, Obata K, et al. Pre-operative time course changes in liver function tests in biliary atresia: its usefulness in the discrimination of biliary atresia in early infancy. *Acta Paediatr Jpn* 1996;38:506-12

### **Evidence Level: IV**

### **What is the optimal dose and duration of treatment in total parenteral nutrition (TPN) related cholestasis?**

“To date, there is no universally accepted treatment for intractable TPN-associated cholestasis” (Al-Hathlol, 2006).

BNF for Children advises ursodeoxycholic acid (UDCA), 10 mg/kg 3 times a day.

Most studies have included very small numbers of patients. A pilot study in 7 children (Spagnuolo, 1996) found that UDCA took 4-8 weeks to normalise biochemical markers of cholestasis. Another, in 13 infants (Al-Hathlol, 2006) used a dose of 15-20 mg/kg/day and found that although patients responded from the second week of therapy, about four months of treatment were needed before normalisation occurred.

An alternative treatment is cholecystokinin, which needs to be administered intravenously for 3-5 days in a dose of 2-4 IDU/kg (Teitelbaum, 1997; Teitelbaum, 1995; Rintala, 1995).

Al-Hathlol K, Al-Madani A, Al-Saif S, et al. Ursodeoxycholic acid therapy for intractable total parenteral nutrition-associated cholestasis in surgical very low birth weight infants. *Singapore Med J* 2006;47:147-51

Rintala RJ, Lindahl H, Pohjavuori M. Total parenteral nutrition-associated cholestasis in surgical neonates may be reversed by intravenous cholecystokinin: a preliminary report. *J Pediatr Surg* 1995;30:827-30

Spagnuolo MI, Iorio R, Vegnente A, et al. Ursodeoxycholic acid for treatment of cholestasis in children on long-term parenteral nutrition: a pilot study. *Gastroenterology* 1996;111:716-9

Teitelbaum DH. Parenteral nutrition-associated cholestasis. *Curr Opin Pediatr* 1997;9:270-5

Teitelbaum DH, Han-Markey T, Schumacher RE. Treatment of parenteral nutrition-associated cholestasis with cholecystokinin-octapeptide. *J Pediatr Surg* 1995;30:1082-5

#### **Evidence Level: IV**

#### **What is the threshold for home phototherapy in patients with crigler najjar?**

No firm evidence has been identified with which to answer this question, but case reports mention a threshold serum bilirubin concentration of 15 mg/dL (0.833 mmol/L) (O'Reilly, 1988; Shevell, 1987). Home phototherapy is a relatively recent service in the UK, the first such service being reported in 2004 (Walls, 2004).

O'Reilly C, Dixon R. Crigler-Najjar syndrome: treatment at home with phototherapy. *Scott Med J* 1988;33:335-6

Shevell MI, Bernard B, Adelson JW, et al. Crigler-Najjar syndrome type I: Treatment by home phototherapy followed by orthotopic hepatic transplantation. *J Pediatr* 1987;110:429-31

Walls M, Wright A, Fowlie P, et al. Home phototherapy in the United Kingdom. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F282

#### **Evidence Level: V**

**Last amended May 2006**

# KAWASAKI DISEASE

## Supporting Information

### How frequently are the classic diagnostic criteria seen?

The cause of Kawasaki disease is still unknown and thus no diagnostic tests exist (Rowley, 1999). Diagnosis is therefore by clinical criteria (Dajani, 1993). This is defined as fever of at least 5 days' duration, plus the presence of four of the following:

changes in extremities

polymorphous exanthem

bilateral conjunctival injection

changes in the lips and oral cavity

cervical lymphadenopathy

and no evidence of another disease with similar clinical features.

Prompt diagnosis is vital in reducing the risk of cardiac complications (Rowley, 1999). The incidence of these complications can be reduced from 20-25% to <5% by early treatment with intravenous immune globulin and this, coupled with the increased appearance of atypical cases, has meant that more children are being treated for the condition without meeting diagnostic criteria.

In a retrospective review of 127 patients diagnosed with Kawasaki disease (Witt, 1999), 81 (64%) met the diagnostic criteria and 46 (36%) did not. Of the 15 patients who were found to have coronary artery abnormalities, 9 were from the 46 not meeting the criteria and 6 were from the 81 who did. The authors concluded that the criteria were an insensitive predictor of coronary artery abnormalities and that the treatment of patients not fully meeting the criteria had been justified. In another retrospective review of 132 Kawasaki patients (Hsieh, 2002), 20 (15%) did not meet the diagnostic criteria, but 5 of these (25%) had coronary artery lesions.

Similar conclusions were reached by another retrospective review of 44 cases (Joffe, 1995) in which 9 (20%) were atypical, 5 of which (56%) were in infants, one in 56 patients in which 8 (14%) were atypical (Stapp, 2000) and a small case series of 4 patients (Rowley, 1987).

Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80

Hsieh YC, Wu MH, Wang JK, et al. Clinical features of atypical Kawasaki disease. *J Microbiol Immunol Infect* 2002;35:57-60

Joffe A, Kabani A, Jadavji T. Atypical and complicated Kawasaki disease in infants: do we need criteria? *West J Med* 1995;162:322-7

Rowley AH, Shulman ST. Kawasaki syndrome. *Pediatr Clin N Am* 1999;46:313-29

Rowley AH, Gonzalez-Crussi F, Gidding SS, et al. Incomplete Kawasaki disease with coronary artery involvement. *J Pediatr* 1987;110:409-13

Stapp J, Marshall GS. Fulfillment of diagnostic criteria in Kawasaki disease. *South Med J* 2000;93:44-7

Witt MT, Minich L, Bohnsack JF, et al. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. *Pediatrics* 1999;104:e10-14

### Evidence Level: IV

### Is echocardiography of value in Kawasaki disease?

American Heart Association guidelines (Dajani, 1993) state that patients with fever and fewer than four principal clinical features can be diagnosed as having Kawasaki disease when coronary

artery disease is detected by two-dimensional echocardiography (or coronary angiography). Echocardiography also detects pericardial effusion in approximately 30% of patients with Kawasaki disease (Dajani, 1993). AHA guidelines for long-term management (Dajani, 1994) recommend echocardiography at presentation and at 6-8 weeks and 6-12 months following the onset of symptoms.

The necessity of performing the second follow-up (at 6-12 months) has been questioned by retrospective reviews of 50 patients (Scott, 1999) and 536 patients in a multi-centre study (Tuohy, 2001). Both of these found that no patient having a normal echocardiogram result at 2 weeks – 2 months after onset of symptoms had shown coronary abnormalities at the later follow-up.

Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80

Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease: report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;89:916-22

Scott JS, Ettetdgui JA, Neches WH. Cost-effective use of echocardiography in children with Kawasaki disease. *Pediatrics* 1999;104:e57-9

Tuohy AM, Tani, LY, Cetta F, et al. How many echocardiograms are necessary for follow-up evaluation of patients with Kawasaki disease? *Am J Cardiol* 2001;88:328-30

## **Evidence Level: IV**

### **What is the optimum dose and timing for intravenous immune globulin? Is a second dose required if fever persists?**

The optimal dose of IVIG remains controversial (Sato, 1999). American Heart Association guidelines (Dajani, 1993) recommend a dose of 2 g/kg as a single infusion over 12 hours. This advice has been reinforced in a meta-analysis of 7 RCTs comparing different doses of IVIG (Terai, 1997). Of 1629 patients, those given IVIG at 2 g/kg had a prevalence of coronary abnormalities (at day 30 of the illness) of 5.3%. This compared with 18.1% at doses of < 1 g/kg, and 17.3% at doses of 1.0 - 1.2 g/kg.

A study of 8,751 Japanese patients (Muta, 2004) found no evidence that IVIG treatment on day 4 or earlier (n=4731) was better at preventing cardiac sequelae than later treatment on days 5-9 (n=4020).

A Cochrane review (Oates, 2004) of 16 trials concluded that optimum treatment and timing was 2g/kg within 10 days of onset of symptoms.

Fever persisted for more than 3 days after treatment in 20%-30% of children in a randomised controlled trial in 549 patients comparing single to multiple infusions of IVIG (Newburger, 1991).

In a retrospective report on 13 patients (Sundel, 1993) whose fever did not respond to initial treatment with IVIG, 10 responded to a second dose within 36 hours. In the remaining 3, one responded to a further dose; the other 2 had eventually to be given iv methylprednisolone at 30 mg/kg before resolution of fever was achieved.

A retrospective, multicentre study of 378 patients (Burns, 1998) found that persistent fever was associated with an increased risk of treatment failure (P=0.002) and called for randomised trials to establish the efficacy of re-treatment.

Children with a C-reactive protein level >10 mg/dL, LDH level >590 IU/L and/or haemoglobin value <10 g/dL can be considered non-responsive to IVIG and should be considered for additional treatment at an early stage (Fukunishi, 2000).

Burns JC, Capparelli EV, Brown JA, et al. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998;17:1144-8

Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80

Fukunishi M, Kikkawa M, Hamana K, et al. Prediction of non-responsiveness to intravenous high-dose gamma-globulin therapy in patients with Kawasaki disease at onset. *J Pediatr* 2000;137:172-6

Muta H, Ishii M, Egami K, et al. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. *J Pediatr* 2004;144:496-9

Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-9

Oates WR, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children (Cochrane Review) In: *The Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Sato N, Sugimura T, Akagi T, et al. Selective high dose gamma-globulin treatment in Kawasaki disease: assessment of clinical aspects and cost effectiveness. *Pediatr Int* 1999;41:1-7

Sundel RP, Burns JC, Baker A, et al. Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993;123:657-9

Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997;131:888-93

### **Evidence Level: I (for initial treatment at 2 g/kg) IV (for re-treatment)**

### **Is aspirin efficacious in the treatment of Kawasaki disease?**

Aspirin is administered to patients with Kawasaki disease for its anti-inflammatory and anti-thrombotic effects (Rowley, 1999). In a multicentre, randomised controlled trial involving 549 children (Newburger, 1991) aspirin 80-100 mg/kg/d, with IVIG 2 g/kg reduced the prevalence of coronary abnormalities from 20%-25% to 2%-4%. An American Heart Association consensus statement (Dajani, 1993) recommends the same regime. After fever resolves, aspirin is continued at a lower dose (3-5 mg/kg/d) to decrease platelet adhesiveness (Chung, 1998; Dajani, 1993). A retrospective case review of 70 patients (Saulsbury, 2002), treated with either high-dose (80-100 mg/kg/d, n=24) or low-dose (3-5 mg/kg/d, n=46) aspirin as an adjunct to IVIG, found no benefit in the high-dose group. None of the 60 patients without coronary abnormalities at the start of treatment had developed them by the end. Mean duration of fever after initiation of therapy was 47 +/- 8 hours in the high-dose group vs 34 +/- 5 hours in the low-dose group. When the groups were differentiated by IVIG dose, the figures were 44 +/- 6 hours in patients given IVIG 400 mg/kg/dose on 4 consecutive days and 35 +/- 5 hours in patients given 2 g/kg as a single infusion. These findings accord with those of a meta-analysis of 7 RCTs (Terai, 1997) and indicate that IVIG, rather than aspirin, determines the duration of fever. A UK evidence-based guideline (Brogan, 2002) suggests medium dose (30-50 mg/kg/day in 4 divided doses) aspirin as a compromise.

Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002;86:286-90

Chung CJ, Stein L. Kawasaki disease: a review. *Radiology* 1998;208:25-33

Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80

Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-9

Rowley AH, Shulman ST. Kawasaki syndrome. *Pediatr Clin N Am* 1999;46:313-29

Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. *Clin Pediatr* 2002;41:597-601

Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997;131:888-93

## **Evidence Level: II**

### **Should physical activity be restricted in post-acute patients?**

An American Heart Association consensus statement (Dajani, 1994) links permitted physical activity with risk levels I-V as follows:

I (no coronary artery changes at any stage of illness): No restrictions beyond initial 6-8 weeks  
II (transient coronary artery ectasia that disappears during acute illness): No restrictions beyond initial 6–8 weeks

III (small to medium solitary coronary artery aneurysm): Patients in 1<sup>st</sup> decade of life – no restriction beyond initial 6-8 weeks; Patients in 2<sup>nd</sup> decade – Physical activity guided by stress testing every other year. Competitive contact athletics with endurance training discouraged

IV (one or more giant coronary artery aneurysms, or multiple small to medium aneurysms, without obstruction): Patients in 1<sup>st</sup> decade of life – no restriction beyond initial 6-8 weeks; Patients in 2<sup>nd</sup> decade – Annual stress testing guides recommendations. Strenuous athletics strongly discouraged. If stress test rules out ischaemia, non-contact recreational sports allowed

V (coronary artery obstruction): Contact sports, isometrics, and weight training should be avoided. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan

These risk levels are based on clinical experience and further evidence with which to update the recommendations has not yet been forthcoming (Rowley, 1999).

Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease: report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;89:916-22

Rowley AH, Shulman ST. Kawasaki syndrome. *Pediatr Clin N Am* 1999;46:313-29

## **Evidence Level: V**

### **What follow-up investigations are indicated in Kawasaki disease?**

These are again guided by initial risk level, related to the degree of coronary arterial involvement (Dajani, 1994), as follows:

I: None beyond the first year unless cardiac disease suspected

II: None beyond the first year unless cardiac disease suspected; Physician may choose to see patient at 3- to 5-year intervals

III: Annual follow-up with echocardiogram +/- electrocardiogram in first decade of life

IV: Annual follow-up with echocardiogram +/- electrocardiogram +/- chest x-ray +/- additional electrocardiogram at 6-month intervals. For patients in the first decade of life, pharmacologic stress testing should be considered

V: Echocardiogram and electrocardiogram at 6-month intervals and annual Holter and stress testing

In a survey of 308 US paediatric cardiologists on their management of Kawasaki disease patients (Kahwaji, 2002), replies were received from 97 (32%). Despite 1994 guidelines (Dajani, 1994),

61% of respondents provided follow-up for Risk Level I patients and a similar number would prefer to do so for Level II patients.

Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease: report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;89:916-22

Kahwaji IY, Connuck DM, Tafari N, et al. A national survey on the pediatric cardiologist's clinical approach for patients with Kawasaki disease. *Pediatr Cardiol* 2002;23:639-46

**Evidence Level: V**

**Last amended May 2003**

# LUMBAR PUNCTURE IN SUSPECTED MENINGITIS IN CHILDHOOD

## Supporting information

### **What is the risk of cerebral herniation (coning) associated with lumbar puncture to diagnose bacterial meningitis? Is the age of the patient a factor?**

Herniation or coning of the brain, the result of markedly raised intracranial pressure, is a common post-mortem finding in acute bacterial meningitis and may be the direct cause of death in up to 30% of child cases (Addy, 1987). Symptoms and signs of herniation occur in about 5% of cases of bacterial meningitis (Horwitz, 1980).

No consensus exists on the subject of whether lumbar puncture should or should not be routine in all cases of suspected bacterial meningitis. Coning can happen with or without lumbar puncture and also may occur in patients with a normal CT scan (Shetty, 1999; Stephenson, 1998; Rennick, 1993).

A retrospective review of 445 children over 30 days old (Rennick, 1993) identified herniation in 14 (45%) of the 31 children who died. 19 episodes of herniation occurred in the 17 children who had a lumbar puncture; 12 episodes occurred in the first 12 hours following lumbar puncture. CT results were normal in 5 (36%) of the 14 episodes in which scanning was performed around the time of the herniation.

A retrospective review of 252 cases in west Gloucestershire (Wylie, 1997) recorded 17 deaths (6.7%), of which 4 were “directly or indirectly associated with lumbar puncture”.

In a study of 123 children between 6 weeks and 15 years old seen consecutively at a university teaching hospital in Nigeria (Akpede, 2000), 18 (15%) showed evidence of herniation. Patients were divided into low or high risk groups according to a scoring system recording the presence or otherwise of convulsions, fever >3 days, age  $\leq$  12 months, shock, coma and temperature  $<36.6^{\circ}$  C. RR of herniation in high vs low risk groups was 66.6 (95% CI 9.3 – 477.1) and of death or neurological sequelae, 2.6 (95% CI 1.8 – 3.7). The authors concluded that lumbar puncture should not be performed in patients categorised as high risk.

Lumbar puncture is still performed in up to a third of patients with contraindications in some units (Winrow, 1998).

A Dutch team (Oostenbrink, 2001) have designed a clinical prediction rule that successfully identified 99 of 286 patients (aged 1 month to 15 years) with suspected bacterial meningitis that did not in fact have the disease. No cases were missed, and the authors suggest that the rule could be used to identify those patients not needing lumbar puncture.

A similar study from an Israeli team (Brik, 1997) proposed that lumbar puncture need not be routine in infants under 3 months of age not meeting the proposed criteria for being at high risk. Other investigators (Wiswell, 1995) have claimed that the diagnosis of neonatal bacterial meningitis “occasionally will be delayed or missed completely” if lumbar puncture is omitted. It is unclear whether older children are at higher risk of coning. The 19 children who suffered 21 episodes of coning in the Rennick series (1993) ranged in age from 4 months to 15 years, with an average age of 41 months.

Addy DP. When not to do a lumbar puncture. *Arch Dis Child* 1987;62:873-5

Akpede GO, Ambe JP. Cerebral herniation in pyogenic meningitis: prevalence and related dilemmas in emergency room populations in developing countries. *Dev Med Child Neurol* 2000;42:462-9

Brik R, Hamissah R, Shehada N, et al. Evaluation of febrile infants under 3 months of age: is routine lumbar puncture warranted? *Isr J Med Sci* 1997;33:93-7

Horwitz SJ, Boxerbaum B, O' Bell L. Cerebral herniation in bacterial meningitis in childhood. *Ann Neurol* 1980;7:524-8

Oostenbrink R, Moons KG, Donders AR, et al. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. *Acta Paediatr* 2001;90:611-7

Rennick G, Shann F, de Campo J. Cerebral herniation during bacterial meningitis in children. *BMJ* 1993;306:953-5

Shetty AK, Desselle BC, Craver RD, et al. Fatal cerebral herniation after lumbar puncture in a patient with a normal computed tomography scan. *Pediatrics* 1999;103:1284-7

Stephenson T. Coning may occur without lumbar puncture being done. *BMJ* 198;316:1015

Winrow AP. Lumbar puncture is still performed in patients with contraindications. *BMJ* 1998;316:1015

Wiswell TE, Baumgart S, Gannon CM, et al. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed? *Pediatrics* 1995;95:803-6

Wylie PA, Stevens D, Drake W, et al. Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study. *BMJ* 1997;315:774-9

**Evidence Level: IV (but no consensus)**

**July 2002**

# NEPHROTIC SYNDROME IN CHILDHOOD

## Supporting information

### **Femoral blood sampling is contraindicated due to the risk of thrombosis?**

The association between nephrotic syndrome and femoral arterial thrombosis is well recognised in a number of case reports in both children and adults (Holt, 2000; Nitatori, 1987; Sullivan, 1983; Patel, 1978; Harrison, 1972; Cameron 1971; Goldbloom, 1967).

Cameron JS, Ogg CS, Ellis FG, et al. Femoral arterial thrombosis in nephrotic syndrome. *Arch Dis Child* 1971;46:215-6

Goldbloom RB, Hillman DA, Santulli TV. Arterial thrombosis following femoral venipuncture in edematous nephrotic children. *Pediatrics* 1967;40:450-1

Harrison BM, Wood CB. Spontaneous femoral artery thrombosis and intermittent claudication in childhood nephrotic syndrome. *Arch Dis Child* 1972;47:836-7

Holt P, Swinnen J. Bilateral femoral artery thrombosis in nephrotic syndrome. *N Z Ned J* 2000;113:521

Nitatori T, Niitu K, Kudoh S, et al. Femoral arterial thrombosis in nephrotic syndrome. Steroid and long term heparin therapy. *J Cardiovasc Surg Torino* 1987;28:189-92

Patel R, Mandal AK. Arterial thrombosis associated with the nephrotic syndrome. *J Cardiovasc Surg Torino* 1978;19:129-34

Sullivan MJ, Hough DR, Agodoa LC. Peripheral arterial thrombosis due to the nephrotic syndrome: the clinical spectrum. *South Med J* 1983;76:1011-6

**Evidence Level: V**

**Last amended May 2006**

# NEPHROTIC SYNDROME: ANTIBIOTIC PROPHYLAXIS

## Supporting information

### **Is antibiotic prophylaxis to prevent peritonitis caused by *S Pneumoniae* indicated in children with nephrotic syndrome?**

An American Academy of Pediatrics report (Overturf, 2000) on children at increased risk of pneumococcal infection states: "Reduction of infection risk, compliance with prophylaxis, and effects on nasopharyngeal colonization with pneumococci have not been studied in nephrotic syndrome."

A review on the subject (McIntyre, 1998) concludes that although "penicillin prophylaxis...is not of proven benefit for nephrotic syndrome", the following subgroups of patients are most likely to benefit: Children under 2 years of age, with unresponsive or frequently relapsing disease, or who have had a previous episode of pneumococcal infection.

A retrospective review of 214 children with nephrotic syndrome (Gorensek, 1988) advises treatment with penicillin for suspected peritonitis but does not mention prophylaxis.

Serious infections may occur with the increase in penicillin-resistant pneumococci. A case report of two infants with penicillin resistant pneumococcal peritonitis whilst receiving penicillin prophylaxis (Milner, 1987) recommends pneumococcal vaccination at 2 years of age and no prophylaxis for under 2 years. Similar cases have been reported more recently (Ilyas, 1996).

Gorensek MJ, Lebel MH, Nelson JD. Peritonitis in children with nephrotic syndrome. *Pediatrics* 1988;81:849-56

Ilyas M, Roy S, Abbasi S, et al. Serious infections due to penicillin-resistant *Streptococcus pneumoniae* in two children with nephrotic syndrome. *Pediatr Nephrol* 1996;10:639-41

McIntyre P, Craig JC. Prevention of serious bacterial infection in children with nephrotic syndrome. *J Paediatr Child Health* 1998;34:314-7

Milner LS, Berkowitz FE, Ngwenya E, et al. Penicillin resistant pneumococcal peritonitis in nephrotic syndrome. *Arch Dis Child* 1987;62:964-5

Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics* 2000;106:367-76

### **Evidence Level: V**

### **Is influenza vaccination safe and effective in children with nephrotic syndrome?**

A case-control study in 19 children with nephrotic syndrome and 10 healthy controls (Poyrazoglu, 2004) found that influenza vaccine (0.25 ml for under 6 yrs of age and 0.5 ml for over 6 yrs of age) raised the percentage of children with protective antibody titres in the NS group from 10.5% before vaccination to 78.9% at 1 month and 87.5% at 6 months following vaccination. The mean concentration of specific IgG antibodies to influenza A increased 6-fold at 1 month and approximately 14-fold at 6 months. No adverse effects were recorded.

Similar results have been obtained in other studies (Brydak, 1998; Sheth, 1979; Sheth, 1978).

Adverse effects have been uncommon and limited to transient rises in protein levels or mild cold-like illnesses, other than one child who had exacerbation of nephrotic syndrome (Sheth 1979).

Brydak LB, Rajowski T, Machala M, et al. Humoral antibody response following influenza vaccination in patients with nephrotic syndrome. *Antiinfect Drugs Chemother* 1998;16:151-5

Poyrazoglu HM, Dusunsel R, Gunduz Z, et al. Antibody response to influenza A vaccination in children with nephrotic syndrome. *Pediatr Nephrol* 2004;19:57-60

Sheth KJ, Sedmak GV, Freeman ME, et al. Hemagglutination-inhibiting antibodies in vaccinated children with renal disease. *JAMA* 1979;242:1752-4

Sheth KJ, Freeman ME, Eisenberg C, et al. Influenza virus immunization. Antibody response and adverse effects in children with renal disease. *JAMA* 1978;239:2559-61

**Evidence level IV**

**Last amended March 2006**

Anon. Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. Report of a Workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. Arch Dis Child 1994;70:151-7

Baxter Healthcare Corporation. Albumin therapy.  
<http://www.albumintherapy.com/albumin/us/en/ask.isp#>

Department of Health. Immunisation against infectious diseases. London: Stationery Office, 1996

Department of Health. Update on immunisation issues: (iii) Pneumococcal conjugate vaccine for children under two years of age. PL/CMO/2002/4, PL/CNO/2002/4, PL/CPHO/2002/2. London: Department of Health, 2002

Evans JH. Current management of nephrotic syndrome. Curr Paediatr 1997;7:32-5

Hodson EM, Knight JF, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software

Holt RC, Webb NJ. Management of nephrotic syndrome in childhood. Curr Paediatr 2002;12:551-60

Royal Children's Hospital. Clinical practice guidelines: Nephrotic syndrome. Melbourne: Royal Children's Hospital, 2003

Royal College of Paediatrics and Child Health, Neonatal Paediatric Pharmacists Group. Medicines for children. London: RCPCH/NPPG, 1999

University Hospitals Leicester NHS Trust. Guideline 13: Nephrotic syndrome. Leicester: Leicester Royal Infirmary, 1999

## **PARACETAMOL POISONING IN CHILDHOOD**

### **Supporting information**

#### **Gastic lavage/emesis is not indicated?**

Both of these treatments are now considered potentially hazardous and have largely given way to the use of activated charcoal or supportive treatment only. A retrospective review carried out at Christchurch Hospital in New Zealand (Dillon, 2002) found that in 1994, 36% of children were treated with syrup of ipecac. By 1996, only 9% were given ipecac, whilst 49% were treated with activated charcoal. By 1999, 12% were treated with activated charcoal and 88% received no decontamination treatment at all.

Dillon C, Gee P. Gastrointestinal decontamination in paediatric exploratory ingestions. N Z Med J 2002;115:260-2

**Evidence Level: V**

**Last amended May 2006**

# PETECHIAL/PURPURIC RASHES IN THE CHILD

## Supporting information

### What is the predictive value of a) Clinical features b) Laboratory investigation in petechial/purpuric rashes in children?

Children presenting with petechial/purpuric rashes need prompt treatment if they have a meningococcal infection, but 90% or more of them do not and may suffer more from receiving unnecessary antibiotics (Nielsen, 2001). There are currently no guidelines on the management of these patients (Brogan, 2000).

A prospective study involving 264 infants and children hospitalised with fever and skin haemorrhage (Nielsen, 2001) identified five clinical variables that distinguished between meningococcal disease and other conditions on admission:

1. Skin haemorrhages of characteristic appearance
2. Universal distribution of skin haemorrhages
3. Maximum diameter of one or more skin haemorrhages greater than 2 mm
4. Poor general condition (based on a scoring system by McCarthy et al, 1982)
5. Nuchal rigidity

If any two or more of these were present, the probability of identifying a patient with meningococcal disease was 97%, with a false positive rate of 12%. The only laboratory tests found useful in this study were absolute band count ( $p=0.002$ , adjusted OR 38.3, 95% CI 3.8 to 385.1) and C reactive protein ( $p=0.0001$ , adjusted OR 12.4, 95% CI 4.7 to 32.7).

Another prospective study, involving 233 infants and children (Wells, 2001) also found the C reactive protein test helpful in that no child with a normal result ( $< 6\text{mg/l}$ ) had meningococcal infection. Again, however, clinical features were found to be of most use; children with meningococcal infection were found to be:

1. More likely to be ill (OR 16.7, 95% CI 5.8 to 47.6)
2. To have an axillary temperature  $>38.5^\circ\text{C}$  (OR 8.0, 95% CI 2.7 to 23.8)
3. To have extensive purpura (OR 37.2, 95% CI 11.7 to 118.3)
4. To have a capillary refill time of  $> 2$  secs (OR 29.4, 95% CI 9.4 to 92.6)

No child with a rash confined to the distribution of the superior vena cava (head, neck, and chest above the nipple line) had meningococcal infection. This study was the only one identified that looked at the significance of rash alone, without accompanying fever.

The authors of a prospective and retrospective audit of 55 children presenting with fever and a petechial rash (Brogan, 2000) propose using the "ILL criteria" (Irritability, Lethargy, Low capillary refill). These criteria were combined with total peripheral white blood cell count outside the range  $5-15 \times 10^9/\text{l}$ , and a C reactive protein  $> 5\text{mg/l}$  to provide a screening test for significant bacterial sepsis. This had a sensitivity (in those patients who had blood cultures performed ( $n=33$ )) of 100% (95% CI 48 to 100); specificity 57% (95% CI 37 to 76); positive predictive value 29% (95% CI 14 to 45); negative predictive value 100% (95% CI 79 to 100); pretest number needed to treat (NNT) 6.7; post-positive test NNT 3.3.

The findings of these three papers substantially confirm those of three earlier studies (in 411 (Mandl, 1997), 190 (Baker, 1989) and 129 (Van Nguyen, 1984) patients respectively), i.e. that the general appearance of the child and the extent of the rash were better indications of meningococcal infection than were the findings of laboratory tests.

Baker RC, Seguin JH, Leslie N, et al. Fever and petechiae in children. *Pediatrics* 1989;84:1051-5

Brogan PA, Raffles A. The management of fever and petechiae: making sense of rash decisions. *Arch Dis Child* 2000;83:506-7

McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics* 1982;70:802-9

Mandl KD, Stack AM, Fleisher GR. Incidence of bacteremia in infants and children with fever and petechiae. *J Pediatr* 1997;131:398-404

Nielsen HE. Diagnostic assessment of haemorrhagic rash and fever. *Arch Dis Child* 2001;85:160-5

Van Nguyen Q, Nguyen EA, Weiner LB. Incidence of invasive bacterial disease in children with fever and petechiae. *Pediatrics* 1984;74:77-80

Wells LC, Smith JC, Weston VC, et al. The child with a non-blanching rash: how likely is meningococcal disease? *Arch Dis Child* 2001;85:218-22

**Evidence Level: IV**

**April 2002**

## **PLEURAL EFFUSION IN CHILDHOOD**

### **Supporting information**

**It is not necessary to send a pleural fluid culture routinely before chest drain insertion if the cause is likely to be infective?**

BTS guidelines (Balfour-Lynn, 2005) state that cytological analysis of pleural fluid is only necessary "If there is any indication the effusion is not secondary to infection".

Balfour-Lynn IM, Abrahamson E, Cohen G, et al. BTS guidelines for the management of pleural infection in children. *Thorax* 2005;60(Suppl 1):i1-i21

**Evidence Level: V (Expert consensus guideline)**

**May 2006**

## PNEUMONIA IN CHILDHOOD (Tests)

### Supporting Information

**Do any of the following tests help differentiate bacterial from viral chest infections: chest x-ray, CRP, ESR, white cell count, blood cultures?**

A systematic review of the literature on chest x-rays for distinguishing between viral and bacterial chest infections (Swingler, 2000) found “no clinically useful degree of accuracy” demonstrated in the 5 studies meeting the author’s inclusion criteria. This was largely due to the poor design of most of the 13 studies identified in the literature review and to lack of credible reference standards. These were defined as a) culture of bacteria from bronchoalveolar lavage, lung aspirate, or lung biopsy; b) culture of bacteria from blood or pleural fluid; c) detection of bacterial antigen or DNA in blood or urine; d) rising antibody titer to a specific bacterium.

A study of 84 patients between the ages of 2 months and 15 years (Swischuk, 1986) reported 90% accuracy for radiography when evaluated using clinical criteria (duration of illness, fever, leukocytosis, and response to antibiotics). Microbiological confirmation was not used in this study. The authors were confident that they could distinguish atelectasis (common in viral disease in children but not adults) from consolidation, which they cited as the most common source of error in interpreting chest x-rays in children with lower respiratory tract infection.

A follow-up study (Bettenay, 1988) used Swischuk’s clinical and radiological criteria in 58 patients with pneumonia in whom an aetiological agent had been isolated, and compared results with the microbiologic diagnosis. The clinical criteria for bacterial pneumonia had an 18% positive predictive value and an 81% negative predictive value. The radiographic criteria for bacterial pneumonia had a 30% positive predictive value and a 92% negative predictive value. Both sets of criteria therefore overestimated the incidence of bacterial pneumonia, although they would have been of value (in combination) in excluding that diagnosis.

A review of imaging in children with community-acquired pneumonia (Donnelly, 1999) also found the high negative predictive value of chest radiography for bacterial pneumonia useful in identifying those children who did not need antibiotics.

A study in 156 children of CRP compared with WBC, ESR, or temperature (McCarthy, 1978) found that a positive CRP (if found at a serum dilution of 1:50) had the best correlation with lobar infiltrates. The authors, acknowledging that false positives and negatives could occur, recommended CRP be used in conjunction with clinical assessment and radiological data.

A series of later studies (Heiskanen-Kosma, 2000; Toikka, 2000; Jaye, 1997; Korppi, 1997; Saijo, 1996; Nohynek, 1995) however, have concluded that CRP, WBC and ESR have little or no value in differentiating viral and bacterial pneumonias. The results of blood cultures are positive in fewer than 10% of children with bacterial pneumonia (Lepage, 1997; Turner, 1987; Teele, 1975). More promisingly, a recent study in 72 children (Moulin, 2001) found that procalcitonin (PCT) concentrations above 1mcg/litre had a specificity of 86% (versus 40% for CRP) for differentiating viral and bacterial pneumonias.

Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. *Pediatr Radiol* 1988;18:453-4

Donnelly LF. Maximizing the usefulness of imaging in children with community-acquired pneumonia. *Am J Roentgenol* 1999;172:505-12

Heiskanen-Kosma T, Korppi M. Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings. *Scand J Infect Dis* 2000;32:399-402

Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. *Pediatr Infect Dis J* 1997;16:735-46

- Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Europ Resp J* 1997;10:1125-9
- Lepage P. Are radiological and biological investigations useful for antibiotic treatment of pediatric community acquired pneumonia? *Pediatr Pulmonol Suppl* 1997;16:43-4
- McCarthy PL, Frank AL, Ablow RC, et al. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. *J Pediatr* 1978;92:454-6
- Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. *Arch Dis Child* 2001;84:332-6
- Nohynek H, Valkeila E, Leinonen M, et al. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. *Pediatr Infect Dis J* 1995;14:484-90
- Saijo M, Ishii T, Kokubo M, et al. White blood cell count, C-reactive protein and erythrocyte sedimentation rate in respiratory syncytial virus infection of the lower respiratory tract. *Acta Paediatr Jpn* 1996;38:596-600
- Swingler GH. Radiologic differentiation between bacterial and viral lower respiratory infection in children: a systematic literature review. *Clin Pediatr* 2000;39:627-33
- Swischuk LE, Hayden CK. Viral vs. bacterial pulmonary infections in children (Is roentgenographic differentiation possible?) *Pediatr Radiol* 1986;16:278-84
- Teele DW, Pelton SI, Grant MJ, et al. Bacteremia in febrile children under 2 years of age: results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" clinic. *J Pediatr* 1975;87:227-30
- Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. *Pediatr Infect Dis J* 2000;19:598-602
- Turner RB, Lande AE, Chase P, et al. Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Pediatr* 1987;111:194-200

### **Evidence Level: III**

#### **What is the "best" antibiotic for community acquired pneumonia in children (in general/UK/Stoke)? What is the recommended route of administration and length of treatment?**

A study of 168 ambulatory children with CAP (Wubbel, 1999) found that the clinical response to therapy was similar for the three antibiotic regimens evaluated, including those with bacterial infection. The regimens were: either azithromycin suspension for 5 days or a 10-day course of amoxiclav for those <5 years or erythromycin estolate suspension for those > or = 5 years. As definitive information about causative organisms is usually lacking, antibiotic treatment is mostly empiric (McCracken, 2000). Most guidelines suggest initial treatment with orally administered amoxicillin or amoxiclav with intravenous cefuroxime for patients needing hospitalisation. A review from France (Olivier, 2000) confirmed that oral cefuroxime was effective up to a break-point of 4 mg/L, after which intravenous therapy was indicated; patients rapidly stabilised on intravenous therapy could be switched to oral cefuroxime axetil after 24-72 hours and may be able to return home. Early switching from intravenous to oral antibiotics was also recommended by a controlled randomized study in 62 children (Amir, 1996) that compared oral amoxiclav with oral cefixime after initial intravenous ceftriaxone. The emergence of drug-resistant *S. pneumoniae* has led the Centers for Disease Control in the US to recommend oral beta-lactams including cefuroxime axetil, amoxicillin and amoxiclav as appropriate first line therapy for ambulatory patients of all ages (McCracken, 2000).

Macrolides are increasingly recommended as first-line therapy in ambulatory patients with a macrolide plus cefuroxime in hospitalised patients (Ruuskanen, 1999;Schaad, 1999). A multicentre, parallel group, double blind trial in 420 patients (Harris, 1998) found that oral azithromycin once daily for 5 days produced similar results to amoxiclav or erythromycin three times a day for 10 days with significantly fewer side effects. A similar study (Roord, 1996) found a 3-day, 3-dose course of azithromycin comparable in effect to a 10-day, 30-dose of erythromycin.

Canadian consensus guidelines (Jadavji, 1997) have concluded that oral antibiotics provide adequate coverage for most mild to moderate forms of pneumonia in children, with parenteral therapy reserved for neonates and patients with severe pneumonia who are admitted to hospital.

Amir J, Harel L, Eidlitz-Markus T, et al. Comparative evaluation of cefixime versus amoxicillin-clavulanate following ceftriaxone therapy of pneumonia. *Clin Pediatr* 1996;35:629-33

Harris JA, Kolokathis A, Campbell M, et al. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. *Pediatr Infect Dis J* 1998;17:865-71

Jadavji T, Law B, Lebel MH, et al. A practical guide for the diagnosis and treatment of pediatric pneumonia. *CMAJ* 1997;156:S703-11

McCracken GH. Diagnosis and management of pneumonia in children. *Pediatr Infect Dis J* 2000;19:924-8

Olivier C. Clinical use of cefuroxime in paediatric community-acquired pneumonia. *Paediatr Drugs* 2000;2:331-43

Roord JJ, Wolf BH, Gossens MM, et al. Prospective open randomized study comparing efficacies and safeties of a 3-day course of azithromycin and a 10-day course of erythromycin in children with community-acquired acute lower respiratory tract infections. *Antimicrob Agents Chemother* 1996;40:2765-8

Ruuskanen O, Mertsola J. Childhood community-acquired pneumonia. *Semin Respir Infect* 1999;14:163-72

Schaad UB. Antibiotic therapy of childhood pneumonia. *Pediatr Pulmonol Suppl* 1999;18:146-9

Wubbel L, Muniz L, Ahmed A, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatr Infect Dis J* 1999;18:98-104

### **Evidence Level: III**

### **Should a macrolide antibiotic (erythromycin etc) be added empirically to treatment?**

Please see evidence for previous question.

### **What is the value of follow-up x-rays in pneumonia?**

A review of imaging in children with CAP (Donnelly, 1999) concludes that follow-up radiography in otherwise healthy children who have had pneumonia is unnecessary, and should be reserved for those who have persistent or recurrent symptoms or an underlying condition such as immunodeficiency. The radiographic findings of pneumonia can persist for 2-4 weeks, even when clinical recovery is taking place, so any follow-up radiography (if indicated) should not be performed until at least 2-3 weeks have passed (Donnelly, 1999).

Donnelly LF. Maximizing the usefulness of imaging in children with community-acquired pneumonia. *Am J Roentgenol* 1999;172:505-12

### **Evidence Level: V**

## **What are the most commonly described complications?**

Parapneumonic effusions are the most common complication of bacterial pneumonia (Donnelly, 1999). Less common complications include parenchymal complications such as cavitary necrosis (which in children generally resolves without surgical intervention) or lung abscess, and purulent pericarditis. CT identifies many more of these complications than does radiography (Donnelly, 1998). Pneumatocele has been identified in 2.4% of infants and children with pneumonia (Amitai, 1983; Victoria, 1981).

Amitai I, Mogle P, Godfrey S, et al. Pneumatocele in infants and children: report of 12 cases. *Clin Pediatr* 1983;22:420-2

Donnelly LF, Klosterman LA. The yield of CT of children who have complicated pneumonia and noncontributory chest radiography. *AJR Am J Roentgenol* 1998;170:1627-31

Donnelly LF. Maximizing the usefulness of imaging in children with community-acquired pneumonia. *Am J Roentgenol* 1999;172:505-12

Victoria MS, Steiner P, Rao M. Persistent postpneumonic pneumatoceles in children. *Chest* 1981;79:359-61

**Evidence Level: V**

**November 2001**

## **PNEUMONIA IN CHILDHOOD**

### **Supporting information**

#### **The oral route is preferable to the IV route for the administration of antibiotics?**

A Cochrane review of two RCTs in 1836 children (Rojas, 2006) concluded that “Oral antibiotics appear to be as effective as parenteral antibiotics in the treatment of severe pneumonia in children”. Patient acceptance and compliance is significantly better with oral administration, which is thus to be preferred wherever possible.

Rojas MX, Granados C. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. The Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD004979

**Evidence Level: I**

**Last amended May 2006**

# SALICYLATE POISONING IN CHILDHOOD

## Supporting information

**Children < 10 years of age have an increased risk of salicylate toxicity and may require haemodialysis at an earlier stage?**

An “evidence based flowchart” (Dargan, 2002) states that “Children (< 12 y) and the elderly (> 65 y) are more susceptible to the effects of salicylate poisoning and tend to get more severe clinical effects at lower blood concentrations”. No reference for this is given.

A letter to the Lancet (Mendelson, 1975) remarks that “Although the sensitivity of children to aspirin is often noted, no direct studies, to our knowledge, have been carried out to test the influence of age on salicylate toxicity”.

Dargan PI, Wallace CI, Jones AL. An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. Emerg Med J 2002;19:206-9

Mendelson J, Grisolia S. Age-dependent sensitivity to salicylate. Lancet 1975;II:974

**Evidence Level: V**

**Last amended May 2006**

# STRIDOR AND CROUP IN CHILDHOOD

## Supporting information

### **Glucocorticoids are of value in the treatment of croup?**

A Cochrane review (Russell, 2004) of 31 studies in 3736 children found glucocorticoid treatment to be associated with an improvement in the Westley score at 6 hours with a weighted mean difference of -1.2 (95% CI -1.6 to -0.8) and at 12 hours -1.9 (95% CI -2.4 to -1.3). The improvement was no longer significant at 24 hours. Fewer return visits and readmissions occurred in patients treated with glucocorticoids (RR 0.50; 95% CI 0.36-0.70). Length of time spent in hospital or A&E was also significantly decreased (weighted mean difference 12 hours, 95% CI 5-19 hours). The authors concluded that dexamethasone and budesonide were effective in relieving the symptoms of croup as early as 6 hours after treatment.

Russell K, Wiebe N, Saenz A, et al. Glucocorticoids for croup. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD001955

**Evidence Level: I**

### **Nebulised adrenaline (epinephrine) is of value in the treatment of severe croup?**

A Cochrane review on this subject is currently underway (Mathew, 2005). There is a lack of randomised trial data comparing adrenaline (epinephrine) with placebo. Adrenaline (epinephrine) has been shown to be less strongly effective in patients treated with dexamethasone (Kuusela, 1988).

Kuusela AL, Vesikari T. A randomized double-blind, placebo-controlled trial of dexamethasone and racemic epinephrine in the treatment of croup. *Acta Paediatr Scand* 1988;77:99-104

Mathew ME, John CM, Neto G. Nebulised adrenergic agonists for acute croup. (Protocol) *The Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD005439

**Evidence Level: III**

**Last amended May 2006**

# TACHYCARDIA IN CHILDHOOD

## Supporting information

### **Supraventricular tachycardia (SVT) carries a small risk of mortality?**

The mortality rate for SVT in childhood is estimated at 1% in congenital heart disease and 0.25% in normal anatomy (Wiest, 2006).

The author of a review (Gillette, 1985) has only encountered sudden death in SVT with two mechanisms: junctional automatic focus tachycardia and Wolff-Parkinson-White syndrome,

Gillette PC. Supraventricular arrhythmias in children. J Am Coll Cardiol 1985;5:122B-129B

Wiest DB, Uber WE. Congenital heart defects and supraventricular tachycardia in children. <http://www.accp.com/p5b9sample02.pdf> (Pharmacotherapy Self-Assessment Program Fifth Edition (PSAP V))

**Evidence Level: V**

**Last amended May 2006**

# TRICYCLIC ANTIDEPRESSANT POISONING IN CHILDHOOD

## Supporting information

### **Flumazenil is contraindicated in mixed tricyclic and benzodiazepine overdose?**

Flumazenil has been known to induce convulsions and ventricular arrhythmias in the presence of both types of drugs (Weinbroum, 1997; Haverkos, 1994; Burr, 1989).

Burr W, Sandham P, Judd A. Death after flumazenil. *BMJ* 1989;298:1713

Haverkos GP, DiSalvo RP, Imhoff TE. Fatal seizure after flumazenil administration in a patient with mixed overdose. *Ann Pharmacother* 1994;28:1347-9

Weinbroum A, Rudick V, Sorkine P, et al. A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Saf* 1997;17:181-96

**Evidence Level: V**

Last amended May 2006

# URINARY TRACT INFECTION IN CHILDHOOD

## *Supporting Information*

### **Prophylactic antibiotics prevent urinary tract infection and/or subsequent scarring?**

AAP guidelines (AAP, 1999) recommend that, “after a 7- to 14-day course of antimicrobial therapy and sterilization of the urine, infants and young children 2 months to 2 years of age with UTI should receive antimicrobials in therapeutic or prophylactic dosages until the imaging studies are completed (strength of evidence: good)”.

This advice is based on the association between recurrent bouts of febrile UTI and renal scarring, which “follows an exponential curve” (Jodal, 1987).

A Cochrane review of 10 trials in a total of 652 children (Michael, 2004) has concluded that a 2-4 day course of antibiotics is as effective as a 7-14 day course.

A systematic review of antimicrobial prophylaxis (Le Saux, 2000) found that most studies identified by a literature search were case series or cohort studies and that the six RCTs found were of low quality. Concern over bacterial resistance and antimicrobial side effects led the authors to conclude that more and better-designed trials were necessary in order to optimise the use of this therapy.

A Cochrane systematic review (Williams, 2002) came to the same conclusion. Although some antibiotics did prevent some infections, adverse effects outweighed benefits overall and more trials were needed.

A literature review on the subject (Mangiarotti, 2000), whilst acknowledging the risks and the lack of knowledge regarding the precise mechanism of action of low-dose antibiotics, concludes that “proper use may be of great value in clinical practice, by reducing the frequency and clinical expression of UTIs and, in some cases such as VUR, significantly helping to resolve the underlying pathology.”

Another review (Smith, 1999) notes that pre-school children with recurrent UTI, mild to moderate (international grades III-V) reflux, or both are “usually managed with prophylactic trimethoprim (2 mg/kg/day) or nitrofurantoin (1-2 mg/kg/day), although this approach does not completely guarantee that scarring will not occur”.

American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843-52

Jodal U. The natural history of bacteriuria in childhood. *Infect Dis Clin North Am* 1987;1:713-29

Le Saux N, Pham B, Moher D. Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review. *CMAJ* 2000;163:523-9

Mangiarotti P, Pizzini C, Fanos V. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. *J Chemother* 2000;12:115-23

Michael M, Hodson EM, Craig JC, et al. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. London: John Wiley & Sons.

Smith J, Finn A. Antimicrobial prophylaxis. *Arch Dis Child* 1999;80:388-92

Williams GJ, Lee A, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. London: John Wiley & Sons.

**Evidence Level: V (Systematic reviews having not reached a firm conclusion)**

### **The following tests should be recommended?**

- a) All children with proven UTI should have a renal ultrasound scan**
- b) Young children <1 year old should have a micturating cystourethrogram**
- c) Children <3 yrs should have a DMSA scan even if the ultrasound scan is negative**

American Academy of Pediatrics consensus guidelines (AAP, 1999) recommend imaging of the urinary tract in every febrile infant or young child with a first UTI in order to identify those with abnormalities that predispose to renal damage. Imaging should consist of urinary tract ultrasonography to detect dilatation secondary to obstruction and a study to detect VUR.

Renal ultrasound scans have been shown to be positive less frequently in patients between 2 and 10 years of age (Heldrich, 2000) and further investigation is required if scans are negative.

In one study of 124 children (Alon, 1999), and another in 255 (Zamir, 2004), the authors concluded that routine renal ultrasound had a “negligible influence” on clinical management.

Repeat ultrasound scans are also considered unnecessary (Lowe, 2004).

The AAP guidelines recommend voiding cystourethrography (VCUG) or radionuclide cystography (RNC) in all patients “to be performed at the earliest convenient time” in order to detect VUR. In a retrospective review of 468 patients (Kass, 2000), 23% of children with a normal renal scan and ultrasonogram showed VUR on VCUG. Another, Australian study in 129 children (Ditchfield, 1998) concluded that DMSA was needed in addition to VCUG.

A systematic review and meta-analysis (Gordon, 2003) has demonstrated that VCUG is a weak predictor of renal damage in paediatric patients hospitalised with UTI. A positive test result increased the risk of renal damage by 20%, but a negative result increased the chance of no renal involvement by only 8%.

Whilst acknowledging the sensitivity of renal cortical scintigraphy with <sup>99m</sup>Tc-DMSA, the AAP guidelines consider its role is “unclear and requires additional study”.

A later study retrospectively reviewing data on 260 patients (Heldrich, 2000) found a positive DMSA renal scan indicative of pyelonephritis and colony counts of >1,000 CFU/mL (single organism) as diagnostic of UTI, a lower concentration than that accepted by the AAP. The AAP guidelines are criticised for using colony count data from 1982, which was before the widespread introduction of DMSA.

The current UK guidelines (RCP, 1991) are rather older than their US counterparts, but are broadly in agreement with them. The exceptions were that consensus could not be reached on appropriate investigations for 1 to 7 year olds, with most group members feeling that voiding cystourethrography should be confined to children with one of the following:

Abnormalities shown in renal ultrasound/plain abdominal radiography

Clinical history suggestive of acute pyelonephritis

Family history of reflux or reflux nephropathy

Recurrent infections

Under the age of 1 year, voiding cystourethrography was recommended in all cases. Concern was expressed about the variable quality and interpretation of DMSA scans, although the recommendation was still that all patients should receive one. A survey of 30 Belgian experts in the field (Piepsz, 1999) reveals wide consensus for the use of DMSA for detection of renal sequelae.

A retrospective review of 164 patients aged 0-12 years (Deshpande, 2001), on the other hand, concludes that the routine use of DMSA scans in children over 1 year with a straightforward simple infection “is unhelpful and unnecessary”. The authors argue that, on the basis of £120 per DMSA scan, the cost of detecting one scar in their series of patients was £1,100. This, coupled with the lack of evidence of impact on management (Hoberman, 2003), plus the psychological

risks to the patient, supports the authors' contention that guidelines in 1991 were not prepared with the same attention to risks/benefits that now pertains.

Alon US, Ganapathy S. Should renal ultrasonography be done routinely in children with first urinary tract infection? *Clin Pediatr* 1999;38:21-5

American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: The diagnosis, treatment and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843-52

Deshpande PV, Jones KV. An audit of RCP guidelines on DMSA scanning after urinary tract infection. *Arch Dis Child* 2001;84:324-7

Ditchfield MR, Nadel HR. The DMSA scan in paediatric urinary tract infection. *Australas Radiol* 1998;42:318-20

Gordon I, Barkovics M, Pindoria S, et al. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. *J Am Soc Nephrol* 2003;14:739-44

Heldrich FJ, Barone MA, Spiegler E. UTI: diagnosis and evaluation in symptomatic pediatric patients. *Clin Pediatr* 2000;39:461-72

Hoberman A, Charron M, Hickey RW, et al. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med* 2003;348:195-202

Kass EJ, Kernen KM, Carey JM. Paediatric urinary tract infection and the necessity of complete urological imaging. *BJU Int* 2000;86:94-6

Lowe LH, Patel MN, Gatti JM, et al. Utility of follow-up renal sonography in children with vesicoureteral reflux and normal initial sonogram. *Pediatrics* 2004;113:548-50

Piepsz A, Blafox MD, Gordon I, et al. Consensus on renal cortical scintigraphy in children with urinary tract infection. Scientific Committee of Radionuclides in Nephrourology. *Semin Nucl Med* 1999;29:160-74

Royal College of Physicians. Research Unit Working Group. Guidelines for the management of acute urinary tract infection in childhood. *J R Coll Physicians Lond* 1991;25:36-42

Zamir G, Sakran W, Horowitz Y, et al. Urinary tract infection: is there a need for routine renal ultrasonography? *Arch Dis Child* 2004;89:466-8

## **Evidence Level: IV**

### **Is surgery ever required for reflux?**

In the United States, enthusiasm for surgical correction of VUR remains high (Marotte, 2001; Schiepers, 2001; Elder, 2000) and this may also be the case in Australia (Webster, 2000). Endoscopic correction is also supported (Caldamone, 2001; Ogan, 2001; Elder, 2000). In the UK and the rest of Europe, however, several well-designed studies have found no long-term difference in renal function or progression of scarring between medical and surgical treatment (Smellie, 2001; Olbing, 2000; Jodal, 1999).

Most renal damage occurs at a very early stage and thus severely damaged or dysplastic kidneys either remain stable or progress to end-stage renal failure despite all efforts to cure the reflux (Nijman, 2001).

Caldamone AA, Diamond DA. Long-term results of the endoscopic correction of vesicoureteral reflux in children using autologous chondrocytes. *J Urol* 2001;165:2224-7

Elder JS. Guidelines for consideration for surgical repair of vesicoureteral reflux. *Curr Opin Urol* 2000;10:579-85

Jodal U, Hansson S, Hjalmas K. Medical or surgical management for children with vesico-ureteric reflux? *Acta Paediatr Suppl* 1999;88:53-61

Marotte JB, Smith DP. Extravesical ureteral reimplantations for the correction of primary reflux can be done as outpatient procedures. *J Urol* 2001;165:2228-31

Nijman RJ. Vesicoureteric reflux: to operate or not? *Lancet* 2001;357:1309-10

Ogan K, Pohl HG, Carlson D, et al. Parental preferences in the management of vesicoureteral reflux. *J Urol* 2001;166:240-3

Olbing H, Hirche H, Koskimies O, et al. Renal growth in children with severe vesicoureteral reflux: 10-year prospective study of medical and surgical treatment: the International Reflux Study in Children (European Branch). *Radiology* 2000;216:731-7

Schiepers C, Mesotten L, Proesmans W, et al. Surgical correction of vesicoureteral reflux: 5-year follow-up with <sup>99</sup>Tcm-DMSA scintigraphy. *Nucl Med Comm* 2001;22:217-24

Smellie JM, Barratt TM, Chantler C, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. *Lancet* 2001;357:1309-10

Webster RI, Smith G, Farnsworth RH, et al. Low incidence of new renal scars after ureteral reimplantation for vesicoureteral reflux in children: a prospective study. *J Urol* 2000;163:1915-8

## **Evidence Level: II**

### **Is testing fresh urine for nitrites and leukocytes an effective method for detecting urinary tract infection?**

A study of 689 fresh paediatric urine samples from patients with symptoms of UTI (Lohr, 1993) found 102 (14.8%) with positive culture results. These were compared with dipstick analysis of leukocyte esterase and nitrite. The combination of dipstick analysis and microscopic examination had a sensitivity of 100% and a negative predictive value (NPV) of 100%. The nitrite test had a specificity of 100% and a positive predictive value (PPV) of 100%. All patients with a positive culture result had positive results on the dipstick test or bacteriuria test or both (i.e. no false-negatives). Negative results on both of these tests in combination predicted a sterile culture with 100% accuracy.

Similar results (PPV of 100% if both nitrites and leukocytes detected, NPV of 100% if neither found) were obtained in another study of 133 paediatric samples (Woodward, 1993).

Other studies have produced seemingly opposite results. In a study of 146 urine cultures from 56 women at risk for recurrent pyelonephritis (Lenke, 1981) the nitrite test failed to detect 14 of 18 positive cultures (a sensitivity of 22%).

In another study, 420 samples from patients of both sexes and all ages (Zaman, 1998) were tested for both nitrites and leukocytes, with a PPV of 51% and NPV of 82%. Sensitivity was 23%, leading the authors to conclude that dipstick tests were not suitable for screening for UTI.

A more recent study involving 225 samples from patients of both sexes and all ages (van Nostrand, 2000) found the following:

Leukocyte esterase test: sensitivity 75%, specificity 72%, PPV 42.9%, NPV 91.1%

Nitrite test: sensitivity 19.2%, specificity 94.9%, PPV 50.0, NPV 81.7%

The authors argue that increasing resistance among common urinary tract pathogens makes culturing necessary if patients are to receive appropriate antibiotic treatment. They also point out that one third to one half of the patients treated in their study would have received unnecessary antibiotics due to the low PPV of both tests.

### **Addendum, 19/11/01:**

A practice guideline from the American Academy of Pediatrics (AAP 1999) states that, whilst urinalysis cannot substitute for urine culture to confirm the presence of UTI, it can be valuable in

selecting individuals for prompt initiation of treatment while waiting for the results of the urine culture. A positive leukocyte esterase or nitrite test is “suggestive (although not diagnostic) of UTI”. Recommendation 5 in the guideline is “Diagnosis of UTI requires a culture of the urine (strength of evidence: strong).”

A systematic literature review and meta-analysis (Gorelick, 1999) found that urine dipstick tests had a sensitivity of 0.88 for the presence of either leukocyte esterase or nitrite and a specificity of 0.04 for the presence of both.

A recent retrospective review of 11,089 patients (Bachur, 2001) gave a sensitivity of 82% for the standard urinalysis test, which did not vary according to the clinical situation in patients with fever who were younger than 2 years of age.

American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: The diagnosis, treatment and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843-52

Bachur R, Harper MB. Reliability of the urinalysis for predicting urinary tract infections in young febrile children. *Arch Pediatr Adolesc Med* 2001;155:60-5

Gorelick MH, Shaw KN. Screening tests for urinary tract infection in children: a meta-analysis. *Pediatrics* 1999;104:e54

Lenke RR, van Dorsten JP. The efficacy of the nitrite test and microscopic urinalysis in predicting urine culture results. *Am J Obstet Gynecol* 1981;140:427-9

Lohr JA, Portilla MG, Geuder TG, et al. Making a presumptive diagnosis of urinary tract infection by using a urinalysis performed in an on-site laboratory. *J Pediatr* 1993;122:22-5

van Nostrand JD, Junkins AD, Bartholdi RK. Poor predictive ability of urinalysis and microscopic examination to detect urinary tract infection. *Am J Clin Pathol* 2000;113:709-13

Woodward MN, Griffiths DM. Use of dipsticks for routine analysis of urine from children with acute abdominal pain. *BMJ* 1993;306:1512

Zaman Z, Borremans A, Verhaegen J, et al. Disappointing dipstick screening for urinary tract infection in hospital inpatients. *J Clin Pathol* 1998;51:471-2

## **Evidence Level: IV**

### **It is beneficial to screen the urine of children attending outpatients or children admitted as emergencies to children’s wards?**

The prevalence of UTI in febrile young children in the emergency department has been estimated at 3%-5% (Shaw, 1998). This study of 3873 infants under 2 years of age concluded that the most cost-effective strategy was to send urine for culture in all suspect cases and “begin presumptive treatment only on those with a significantly positive dipstick result”. Another emergency department study involving 236 children (Craver, 1997) found detection rates for UTI to be identical for dipstick testing only and for complete urinalysis. The authors recommended routine testing by dipstick only with microscopic analysis requested for positive results.

A retrospective review of 1019 symptomatic paediatric outpatients (Weinberg, 1991) recommends the dipstick for initial patient assessment, on the basis of its high NPV of 99.6%. American Academy of Pediatrics guidelines (AAP, 1999) recommend that, between the ages of 2 months and 2 years, unexplained fever should prompt investigation for UTI.

No evidence suggests that there is benefit from screening completely asymptomatic children in either the emergency or outpatient departments.

American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: The diagnosis, treatment and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843-52

Craver RD, Abermanis JG. Dipstick only urinalysis screen for the pediatric emergency room. *Pediatr Nephrol* 1997;11:331-3

Shaw KN, McGowan KL, Gorelick MH, et al. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics* 1998;101:e1

Weinberg AG, Gan VN. Urine screen for bacteriuria in symptomatic pediatric outpatients. *Pediatr Infect Dis J* 1991;10:651-4

## **Evidence Level: V**

### **Can renal scarring be prevented by early diagnosis and management of vesico-ureteric reflux?**

A retrospective UK study of 52 children aged 1-12 years with bilateral renal scarring and severe vesico-ureteric reflux (VUR) (Smellie, 1994) found that there had been delay in diagnosis or effective treatment of urinary infection in 50 of the 52 children. The severity of scarring was significantly related to delay in diagnosis. Although the authors concluded that early diagnosis and treatment might have prevented some or all of the scarring that occurred, the retrospective design of the study could not confirm this.

Most studies on this subject comprise small numbers or are retrospective; no large-scale study has evaluated the results of surgical or medical treatment of VUR during childhood for the long-term risk of renal failure in the ones with established renal scarring (Jacobson, 1999).

Early diagnosis may be problematic; DMSA scintigraphy appears to be the best single means for identifying children at risk of renal scarring, but if performed at the time of the acute infection, results will be no better than C-reactive protein, since so many acute defects are transient (Jakobsson, 1999). However, the predictability will improve if the investigation is delayed for more than 2 months after the acute infection.

The evidence is equally unclear concerning early treatment. It is known that prophylaxis with long-term, low-dose antibacterial agents has the same long-term outcome as anti-reflux surgery (Bollgren, 1999). Again, however, the lack of suitable studies makes it difficult to evaluate the benefits of treatment. The authors consider an aggressive attitude to management of reflux reasonable in view of the high rates of renal impairment and hypertension in adults with a history of childhood reflux and scar formation.

The "Goteberg Study", a prospective epidemiologic study of 600 children, found that 41 girls who suffered therapeutic delay had four times the level of renal damage seen in 440 girls whose treatment began promptly (Winberg, 1982).

The Birmingham Reflux Study (Birmingham Reflux Study Group, 1987) first confirmed the equivalency of medical and surgical treatment, but concluded that neither was capable of completely protecting the kidneys from progression of scarring, or even, on occasion, the formation of a new scar.

New scars were detected by urography in 6% of the patients in the Birmingham study, and in the International Reflux Study in Children (the only other randomised trial) the figures were 13% in the European branch and 26% in the US branch (Olbing, 1992).

The most recent guidelines on the subject (Jodal, 1999), based on the available evidence, recommend ultrasonography within 2-4 weeks and voiding cystourethrography (VCU) within 1-2 months for children below 2 years of age who have reflux and UTI. For children 2 years of age and older, ultrasonography within 1-2 months and DMSA scintigraphy after 6-12 months (or VCU if unavailable, or if there are uptake defects or a side distribution with one kidney having below 45% of total function).

At least 1 year of antibacterial prophylaxis is recommended for patients with reflux grade III-IV at first examination.

Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. *BMJ* 1987;295:237-41

Bollgren I. Antibacterial prophylaxis in children with urinary tract infection. *Acta Paediatr Suppl* 1999;431:48-52

Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. *Acta Paediatr Suppl* 1999;431:22-30

Jakobsson B, Jacobson SH, Hjalmas K. Vesico-ureteric reflux and other risk factors for renal damage: identification of high- and low-risk children. *Acta Paediatr Suppl* 1999;431:31-9

Jodal U, Lindberg U. Guidelines for management of children with urinary tract infection and vesico-ureteric reflux: recommendations from a Swedish state-of-the-art conference. *Acta Paediatr Suppl* 1999;431:87-9

Olbing H, Claesson I, Ebel KD, et al. Renal scars and parenchymal thinning in children with vesicoureteral reflux: a 5-year report of the International Reflux Study in Children (European branch). *J Urol* 1992;148:1653-6

Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. *BMJ* 1994;308:1193-6

Winberg J, Bollgren I, Kallenius G, et al. Clinical pyelonephritis and focal renal scarring: a selected review of pathogenesis, prevention, and prognosis. *Pediatr Clin N Am* 1982;29:801-14

**Evidence Level: III**

**Last amended March 2004**