

Acid suppressing drugs in children (to include zantac, prilosec, pantoprazole, lansoprazole, omeprazole); Clinical trials and some reviews.

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130 citations with abstracts

1. Aanpreung, P., Vanprapar, N., Susiva, C., Parkpreaw, C., and Boonyachart, C. A randomized clinical trial comparing the efficacy of ranitidine and famotidine on intragastric acidity in critically ill pediatric patients. *J Med Assoc Thai* 81: 185-189, 1998.

We examined the efficacy of intravenous ranitidine and famotidine on raising intragastric pH in each of 10 critically ill pediatric patients. The severity of illness was assessed by using the modified zinner index score. The study had 3 phases and each phase took 24 hours. Intragastric pH was measured by continuous pH monitoring digitrapper for 72 hours. In phase 1 and 3, the patients did not receive any H₂ blockers. In phase 2, they were randomized to receive intravenous ranitidine or famotidine. The majority of cases had intragastric pH < 4 in day 1 (base line). Ranitidine and famotidine increased total time of intragastric pH > or = 4 from the base line during day 2, 38.2 +/- 16.9 per cent and 60.3 +/- 24.8 per cent respectively (P0.004), but there was no statistical difference between the 2 medications in both Zinner index score 1 and score greater than 1 group (P 0.08, 0.45). Three cases in the famotidine group had successful prophylaxis with total time pH > or = 4 more than 80 per cent. Famotidine appeared to have a trend toward increasing intragastric pH in critically ill pediatric patients.

2. Ameen, V.Z., Pobiner, B.F., Giguere, G.C., and Carter, E.G. Ranitidine (Zantac) syrup versus Ranitidine effervescent tablets (Zantac) EFFERdose) in children: a single-center taste preference study. *Paediatr Drugs* 8: 265-270, 2006.

BACKGROUND: The histamine H₂ receptor antagonist ranitidine is US FDA-approved for the treatment of gastroesophageal reflux disease and healing of erosive esophagitis in children >or=1 month of age. A low-dose strength of ranitidine is now available in a citrus-flavored 25 mg effervescent tablet (dissolved in 5 mL of water); this formulation was developed to facilitate use in infants and smaller children. Ranitidine syrup is available in a peppermint-flavored 15 mg/mL formulation. OBJECTIVE: To compare taste preferences for ranitidine (Zantac) syrup and ranitidine effervescent tablets dissolved in water (Zantac EFFERdose) in healthy children aged 4-8 years and their adult caregivers. STUDY DESIGN AND METHODS: A randomized, single-blind, crossover, taste test trial was conducted in 102 children and 102 parents/legal guardians. All subjects received a single 45 mg dose of each formulation. After tasting both preparations children were asked: "Now that you have tasted both medicines, which one of these medicines do you think tastes better?" Adults were asked four questions to assess whether they would administer the medication to the children. RESULTS: Seventy-one percent (72/102) of the children preferred the taste of the ranitidine effervescent tablets compared with

29% (30/102) who preferred the syrup ($p < 0.001$). The majority of adults (71%) responded that they would prefer to administer the effervescent formulation based on taste. Adverse events consistent with product labeling were mild and were reported in four children and three adults: headache ($n = 3$), drowsiness ($n = 1$), abdominal pain/cramps ($n = 2$), and bloating/gas ($n = 1$). CONCLUSION: The taste of the ranitidine effervescent formulation dissolved in water is preferred over the ranitidine syrup. Better taste acceptance may facilitate ease of administration and compliance in pediatric patients.

3. Andersson, T., Hassall, E., Lundborg, P., Shepherd, R., Radke, M., Marcon, M., Dalvag, A., Martin, S., Behrens, R., Koletzko, S., Becker, M., Drouin, E., and Gothberg, G. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. *Am J Gastroenterol* 95: 3101-3106, 2000.

OBJECTIVES: The aim of this study was to examine the pharmacokinetics of orally administered omeprazole in children. METHODS: Plasma concentrations of omeprazole were measured at steady state over a 6-h period after administration of the drug. Patients were a subset of those in a multicenter study to determine the dose, safety, efficacy, and tolerability of omeprazole in the treatment of erosive reflux esophagitis in children. Children were 1-16 yr of age, with erosive esophagitis and pathological acid reflux on 24 h-intraesophageal pH study. The "healing dose" of omeprazole was that at which subsequent intraesophageal pH study normalized. Children remained on this dose for 3 months, and during this period the pharmacokinetics were measured. RESULTS: A total of 57 children were enrolled in the overall healing phase of the study. Pharmacokinetic study was optional for subjects and was performed in 25 of the 57 enrolled. The doses of omeprazole required were substantially higher doses per kilogram of body weight than in adults. Values of the pharmacokinetic parameters of omeprazole were generally within the ranges previously reported in adults. However, the plasma levels, area under the plasma concentration versus time curve (AUC), plasma half-life ($t(1/2)$), and maximal plasma concentration (C_{max}), were lower in the younger age group, when the AUC and C_{max} were normalized to a dose of 1 mg/kg. Furthermore, within the group as a whole, these values showed a gradation from lowest in the children 1-6 yr of age to higher in the older age groups. CONCLUSIONS: The pharmacokinetics of omeprazole in children showed a trend toward higher metabolic capacity with decreasing age, being highest at 1-6 yr of age. This may explain the need for higher doses of omeprazole on a per kilogram basis, not only in children overall compared with adults but, in many cases, particularly in younger children.

4. Apte, N.M., Karnad, D.R., Medhekar, T.P., Tilve, G.H., Morye, S., and Bhawe, G.G. Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: a randomized, controlled trial. *Crit Care Med* 20: 590-593, 1992.

OBJECTIVE: To study the effects of pharmacologically increasing gastric pH on gastric colonization and the development of pneumonia in intubated critically ill patients. **DESIGN:** Randomized, controlled trial. **SETTING:** Medical ICU in a university hospital. **PATIENTS:** Thirty-four tracheotomized patients with tetanus. **INTERVENTIONS:** Sixteen patients received iv ranitidine to increase gastric pH greater than 4 (ranitidine group), while 18 patients received no prophylaxis for upper gastrointestinal bleeding (control group). **MEASUREMENTS AND MAIN RESULTS:** Mean gastric pH was higher in the ranitidine group (median 4.7, range 3.6 to 6.1) than in the control group (median 2.1, range 1.2 to 4.9; p less than .05). Gastric colonization occurred in 15 (94%) of 16 patients who received ranitidine, 2 days (median; range 1 to 5) after intubation; gastric colonization also occurred in all control patients (median 4 days, range 1 to 9; p less than .05). Pneumonia occurred in 13 (81%) of 16 patients who received ranitidine, 3 days (median, range 1 to 5) after intubation and in nine (50%) of 18 control patients (p less than .01) 5 days after tracheal intubation (median, range 3 to 14; p less than .01). Prior gastric colonization by the pathogen that caused pneumonia was demonstrable in nine (56%) of 16 patients who received ranitidine vs. eight (44%) of 18 control patients (p greater than .05). The risk for developing pneumonia in the ranitidine-treated group was highest in the first 4 days after tracheal intubation. There was no difference in the frequency of upper gastrointestinal hemorrhage in the two groups. **CONCLUSIONS:** Pharmacologically increasing gastric pH increases the risk for developing pneumonia in intubated critically ill patients. The pneumonia occurs earlier than in untreated control patients.

5. Ashorn, M., Rago, T., Kokkonen, J., Ruuska, T., Rautelin, H., and Karikoski, R. Symptomatic response to *Helicobacter pylori* eradication in children with recurrent abdominal pain: double blind randomized placebo-controlled trial. *J Clin Gastroenterol* 38: 646-650, 2004.

BACKGROUND: Controlled trials considering the effect of *Helicobacter pylori* (H. pylori) eradication on gastrointestinal symptoms in children are scant. We aimed to study the connection between recurrent abdominal pain and dyspepsia and H. pylori infection in children. **STUDY:** This was a double blind randomised controlled trial. Twenty children with recurrent abdominal pain (RAP) being H. pylori positive as measured with the C urea breath test (UBT) were randomized either to receive omeprazole, amoxicillin and clarithromycin (n = 10), or omeprazole and 2 placebos (n = 10) for 1 week after gastroscopy. Symptoms were registered prior to the treatment and at follow up visits 2, 6, 24, and 52 weeks after stopping the treatment. Control UBT was performed on all patients 6 weeks post-treatment and again at the 52 week follow-up visit, when also re-endoscopy with biopsies was done to all participants. **RESULTS:** All infected children had histologic gastritis. Bacterial eradication was achieved in 8/10 in the triple treatment group and in none in the placebo group. There was no change in symptom index in either group at 2 weeks post treatment. At 52 weeks a similar reduction in symptom index was observed in both groups irrespective of the healing of gastritis, which was more commonly achieved along the eradication.

CONCLUSIONS: Bacterial eradication and healing of gastric inflammation does not lead to symptomatic relief of chronic abdominal pain in children.

6. Ashorn, M., Ruuska, T., and Makiperna, A. Helicobacter pylori and iron deficiency anaemia in children. *Scand J Gastroenterol* 36: 701-705, 2001.

BACKGROUND: Both iron deficiency anaemia and Helicobacter pylori infection are rare in developed countries. A possible connection has been suggested between these two diseases and our aim was to define the clinical picture and to study the effect of bacterial eradication in H. pylori colonized children with severe anaemia. METHODS: Eight children with iron deficiency anaemia refractory to iron supplementation were examined with gastroscopy because of suspicion of H. pylori infection. Anaemia was treated with oral ferrous sulphate. Two patients needed blood transfusions. Eradication therapy was given either with combination of colloidal bismuth subcitrate and metronidazole or with omeprazole, clarithromycin and amoxicillin. Eradication was confirmed by urea breath test 4 weeks post-treatment. RESULTS: H. pylori infection was confirmed histologically and microbiologically in all children, who also presented with chronic, active gastritis. Bacteria were successfully eradicated in 7/8 patients. Correction of haemoglobin values was observed post-treatment, iron stores still being deficient at control in 4/8 children. CONCLUSIONS: Our results suggest that H. pylori might have a role in causing iron deficiency anaemia in school-age children. Screening for H. pylori should be extended to cover those patients with other clinical manifestations than symptoms from gastrointestinal tract.

7. Bahremand, S., Nematollahi, L.R., Fourutan, H., Tirgari, F., Nouripour, S., Mir, E., and Aghakhani, S. Evaluation of triple and quadruple Helicobacter pylori eradication therapies in Iranian children: a randomized clinical trial. *Eur J Gastroenterol Hepatol* 18: 511-514, 2006.

BACKGROUND: Clinical trials in children concerning Helicobacter pylori eradication treatments are scarce. The purpose of this study was to assess the efficacy of proton pump inhibitor (PPI)-based triple therapy using PPI, amoxicillin and clarithromycin in Iranian children. We also evaluated the efficacy of quadruple therapy with PPI, metronidazole, amoxicillin and bismuth citrate in Iranian children. METHODS: This was a randomized clinical trial performed in Emam Khomeini Hospital between 2003 and 2004. Patients with confirmed H. pylori infection by histology were divided into two groups in a randomized 1:1 scheme: the triple regimen group (omeprazole, clarithromycin and amoxicillin for 10 days) and the quadruple regimen group (omeprazole, amoxicillin, metronidazole and bismuth citrate for 10 days). The eradication was assessed by the C-urea breath test 4 weeks after the end of treatment and analyzed by per-protocol and intention-to-treat approaches. RESULTS: One hundred and twenty-two patients (mean age 12.36±3.06 years) were entered into the study. Only 100 patients completed the study (50 patients in each regimen group). The eradication rates by triple therapy were 92% and 75.5% for the "per-protocol" and

"intention-to-treat" approaches, respectively. In the quadruple regimen group, the eradication rates were 84% by the per-protocol approach and 68.8% in the intention-to-treat approach. Symptom responses to therapy were reported in all patients with successful eradication (88% of all patients). CONCLUSION: With regard to recent recommendations, we also suggest PPI, amoxicillin and clarithromycin triple therapy as a first-line eradication treatment, and quadruple therapies as a second-line option, in Iranian children.

8. Bardhan, K., Bayerdorffer, E., Veldhuyzen Van Zanten, S.J., Lind, T., Megraud, F., Delchier, J.C., Hellblom, M., Stubberod, A., Burman, C.F., Gromark, P., and Zeijlon, L. The HOMER Study: the effect of increasing the dose of metronidazole when given with omeprazole and amoxicillin to cure *Helicobacter pylori* infection. *Helicobacter* 5: 196-201, 2000.

BACKGROUND: *Helicobacter pylori* eradication with omeprazole, amoxycillin, and metronidazole is both effective and inexpensive. However, eradication rates with different dosages and dosing vary, and data on the impact of resistance are sparse. In this study, three different dosages of omeprazole, amoxycillin, and metronidazole were compared, and the influence of metronidazole resistance on eradication was assessed. METHODS: Patients (n = 394) with a positive *H. pylori* screening test result and endoscopy-proven duodenal ulcer in the past were enrolled into a multicenter study performed in four European countries and Canada. After baseline endoscopy, patients were randomly assigned to treatment for 1 week with either omeprazole, 20 mg twice daily, plus amoxycillin, 1,000 mg twice daily, plus metronidazole, 400 mg twice daily (low M); or omeprazole, 40 mg once daily, plus amoxycillin, 500 mg three times daily, plus metronidazole, 400 mg three times daily (medium M); or omeprazole, 20 mg twice daily, plus amoxycillin, 1,000 mg twice daily, plus metronidazole, 800 mg twice daily (high M). *H. pylori* status at entry was assessed by a ¹³C urea breath test and a culture. Eradication was defined as two negative ¹³C-urea breath test results 4 and 8 weeks after therapy. Susceptibility testing using the agar dilution method was performed at entry and in patients with persistent infection after therapy. RESULTS: The eradication rates, in terms of intention to treat (ITT) (population n = 379) (and 95% confidence interval [CI]) were as follows: low M 76% (68%, 84%), medium M 76% (68%, 84%), and high M 83% (75%, 89%). By per-protocol analysis (population n = 348), the corresponding eradication rates were: low M 81%, medium M 80%, and high M 85%. No *H. pylori* strains were found to be resistant to amoxycillin. Prestudy resistance of *H. pylori* strains to metronidazole was found in 72 of 348 (21%) of the cultures at entry (range, 10%-39% in the five countries). The overall eradication rate in prestudy metronidazole-susceptible strains was 232 of 266 (87%) and, for resistant strains, it was 41 of 70 (57%; p <.001). Within each group, the results were as follows (susceptible/resistant): low M, 85%/54%; medium M, 86%/50%; and high M, 90%/75%. There were no statistically significant differences among the treatment groups. 23 strains susceptible to metronidazole before treatment were recultured after therapy failed; 20 of these had now developed resistance. CONCLUSIONS:

H. pylori eradication rates were similar (approximately 80%) with all three regimens. Metronidazole resistance reduced efficacy; increasing the dose of metronidazole appeared not to overcome the problem or significantly improve the outcome. Treatment failure was generally associated with either prestudy or acquired metronidazole resistance. These findings are of importance when attempting H. pylori eradication in communities with high levels of metronidazole resistance.

9. Barron, J.J., Tan, H., Spalding, J., Bakst, A.W., and Singer, J. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr* 45: 421-427, 2007.

OBJECTIVE: Practice patterns regarding pediatric gastroesophageal reflux disease include acid suppression for infants meeting certain clinical criteria. This study aimed to examine the use of proton pump inhibitors (PPI) in infants and neonates. **PATIENTS AND METHODS:** This retrospective observational study used data from 1999 to 2004 from 4 health care plans in the United States. Infants age <12 months with at least 1 pharmacy claim for a PPI were identified. Demographic information and PPI utilization patterns were assessed. Medical charts were reviewed in a subset of patients to gather dosing information. **RESULTS:** Identified infants (N = 2469) were 58% male. PPI use rose 4-fold from 2000 to 2003; lansoprazole and omeprazole were almost exclusively used. Treatment for almost half of the patients was initiated by their fourth month of life. The most common diagnoses identified through medical claims included gastroesophageal reflux (59%), problems feeding (23%), upper respiratory infections (23%), esophagitis (21%), and pain from gas (20%). Preindex H2 blockade was evident in 58% of the patients; preindex metoclopramide was used in 38% of the patients. Longer duration of PPI therapy was associated with patients who had more comorbidities. Through chart review of 388 patients, a subset of 272 patients with dosing information revealed that a median daily dosage in patients receiving lansoprazole was 1.74 mg . kg . day compared with 1.21 mg . kg . day for omeprazole. **CONCLUSIONS:** PPI use in the study population increased steadily from 1999 to 2004. These data offer valuable information on current PPI dosing patterns that may be used to design future clinical trials for assessment of gastroesophageal reflux disease regimens and clinical outcomes in the infant population.

10. Behrens, R., Lang, T., Keller, K.M., Bindl, L., Becker, M., Rodeck, B., Kuster, P., Wundisch, G.F., and Stolte, M. Dual versus triple therapy of Helicobacter pylori infection: results of a multicentre trial. *Arch Dis Child* 81: 68-70, 1999.

OBJECTIVE: To compare dual therapy (omeprazole and amoxicillin) with triple therapy (omeprazole, amoxicillin, and clarithromycin) in the treatment of Helicobacter pylori infection. The efficacy of 1 mg/kg/day omeprazole was randomly compared with 2 mg/kg/day. **STUDY DESIGN:** 252 patients (median age, 11.0 years; range, 3-18) presenting with chronic abdominal pain underwent

endoscopy and a ¹³C-urea breath test. Gastric biopsy specimens were taken for histological examination and for the rapid urease test. Patients were treated for two weeks: group A (n = 63) received amoxicillin (50 mg/kg; maximum, 2 g/day), group B (n = 73) received amoxicillin and clarithromycin (20 mg/kg; maximum, 1 g/day). Both groups were randomly treated with either 1 or 2 mg/kg omeprazole (maximum, 80 mg/day). Diagnostic procedures were repeated four weeks after the end of treatment. RESULTS: 11 patients were excluded; 136 patients were H pylori positive (56%), 105 of whom were re-examined after treatment. Helicobacter pylori was eradicated in 52% of group A and 83% of group B. The dose of omeprazole had no influence on the eradication rate. Specificity and sensitivity of the rapid urease test were 94% and 93%, respectively. Specificity and sensitivity of the ¹³C-urea breath test were 93% and 95%, respectively. CONCLUSIONS: Dual therapy can no longer be recommended. Triple therapy is more effective than dual therapy in the eradication of H pylori infection. The lower dose of 1 mg/kg omeprazole was as effective as 2 mg/kg.

11. Bishop, J., Furman, M., and Thomson, M. Omeprazole for gastroesophageal reflux disease in the first 2 years of life: a dose-finding study with dual-channel pH monitoring. *J Pediatr Gastroenterol Nutr* 45: 50-55, 2007.

BACKGROUND AND AIM: Gastroesophageal reflux occurs in the majority of infants, with severity ranging from asymptomatic to severe esophagitis and failure to thrive. Omeprazole is recognized as a safe and effective treatment of gastroesophageal reflux in older children, at an initial dosage of 0.7 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾. To our knowledge, no dose-finding studies have been carried out in children under 2 years of age. The aim of the present study was to prospectively determine the dosage of omeprazole required to treat symptomatic gastroesophageal reflux in children younger than 2 years. PATIENTS AND METHODS: Children under 2 years with clinical suspicion of gastroesophageal reflux underwent 24-hour dual-channel intraesophageal/gastric pH monitoring. A reflux index above 10% in children under 1 year and above 6% in children older than 1 year was deemed significant. Treatment with omeprazole at an initial dosage of 0.7 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾ (in 2 divided doses) was followed by dual-channel pH study after 14 days. The dosage was increased in increments of 0.7 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾, and pH studies were repeated until the gastroesophageal reflux was controlled. RESULTS: Ten children (5 male, 5 female), mean age 7.75 months (range, 1.25-20 months), were investigated. The initial median reflux index was 18.5% (range, 6.5%-56.3%). Follow-up median reflux index was improved at 1.6% (0.1%-8.1%) (P < 0.05). The median dosage required was 1.05 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾. Four children required 1.4 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾, and 1 required 2.8 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾. Corrected reflux index improved from 34.8% (16.8%-90.8%) to 20.1% (0.4%-100%) but did not achieve statistical significance. There were no serious complications or side effects. CONCLUSIONS: Omeprazole is an effective treatment for gastroesophageal reflux in children younger than 2 years. The majority respond to a dosage of 0.7 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾, but increased dosages up to 2.8 mg x kg⁽⁻¹⁾ x day⁽⁻¹⁾ may be required.

12. Boccia, G., Manguso, F., Miele, E., Buonavolonta, R., and Staiano, A. Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? *Am J Gastroenterol* 102: 1291-1297, 2007.

OBJECTIVES: To evaluate the efficacy of acid-suppressive maintenance therapy for gastroesophageal reflux disease (GERD) in children, after the healing of reflux esophagitis. METHODS: Forty-eight children (median age 105 months, range 32-170) with erosive reflux esophagitis were initially treated with omeprazole 1.4 mg/kg/day for 3 months. Patients in endoscopic remission were assigned in a randomized, blinded manner by means of a computer-generated list to three groups of 6-month maintenance treatment: group A (omeprazole at half the starting dose, once daily before breakfast), group B (ranitidine 10 mg/kg/day, divided in two doses), and group C (no treatment). Endoscopic, histological, and symptomatic scores were evaluated at: T0, enrollment; T1, assessment for remission at 3 months after enrollment (healing phase); T2, assessment for effective maintenance at 12 months after T0 (3 months after the completion of the maintenance phase). Relapse was defined as the recurrence of macroscopic esophageal lesions. After the completion of the maintenance phase, patients without macroscopic esophagitis relapse were followed up for GERD symptoms for a further period of 30 months. RESULTS: Of 48 initially treated patients, 46 (94%) healed and entered the maintenance study. For all patients, in comparison to T0, the histological, endoscopic, and symptomatic scores were significantly reduced both at T1 and T2 ($P < 0.0001$, for each). No significant difference was found in these three scores, comparing group A, B, and C at T1 and T2. A relapse occurred in one patient only, who presented with macroscopic esophageal lesions at T2. Three months after the completion of the maintenance phase, 12 (26%) patients complained of symptoms sufficiently mild to discontinue GERD therapy, excluding the patient who showed macroscopic esophagitis relapse. Three of 44 (6.8%) patients reported very mild GERD symptoms within a period of 30 months after maintenance discontinuation. CONCLUSIONS: Our pediatric population showed a low rate of erosive esophagitis relapse and GERD symptom recurrence long term after healing with omeprazole, irrespective of the maintenance therapy.

13. Bohmer, C.J., Niezen-de Boer, M.C., Klinkenberg-Knol, E.C., Tuynman, H.A., Voskuil, J.H., Deville, W.L., and Meuwissen, S.G. Gastroesophageal reflux disease in intellectually disabled individuals: leads for diagnosis and the effect of omeprazole therapy. *Am J Gastroenterol* 92: 1475-1479, 1997.

OBJECTIVES: The therapeutic approach to gastroesophageal reflux disease (GERD) in intellectually disabled individuals has not been studied extensively. So far, only low response rates to medical and surgical therapy of GERD have been reported. However, the efficacy of proton pump inhibitors, to date the most effective medical therapy for GERD, has never been evaluated in this population. Our purpose, therefore, was to study the effect of omeprazole on healing and

symptom relief in the intellectually disabled. METHODS: The treatment scheme was as follows: omeprazole 40 mg was given once daily (o.d.) as a healing dose for 3 months, and omeprazole 20 mg o.d. was given as a maintenance dose for another 3 months, to intellectually disabled subjects with endoscopically proven esophagitis, grades I-IV, according to Savary-Miller classification. After 3 and 6 months, the result of this treatment was evaluated by symptom scoring and/or endoscopy. In case of relapse, the dose was increased. RESULTS: At the first endoscopy, 40 of 107 patients (37%) had grade I, 36 (34%) grade II, 18 (17%) grade III, and 13 (12%) grade IV esophagitis. In 92 of 104 patients (88%), the treatment scheme was effective in healing the esophagitis and keeping patients in remission, independent of the severity of esophagitis. In 11 of 104 (11%) patients, a symptomatic relapse was observed after the dose was decreased to 20 mg o.d. However, all of these patients became symptom free again after the dose was increased to 40 mg o.d., and all were healed endoscopically at the end of the study. One (1%) patient needed omeprazole 60 mg o.d. for healing, but in this patient, no relapse was seen while on a maintenance dose of omeprazole 40 mg o.d. Marked improvement of persistent vomiting, hematemesis, regurgitation, food refusal, iron deficiency anemia, and depressive symptoms was seen at the end of the study. CONCLUSIONS: This study indicates that omeprazole is highly effective for all grades of esophagitis in the intellectually disabled. The dose needed to maintain them in remission can be titrated according to the reflux symptoms.

14. Bohmer, C.J., Niezen-de Boer, R.C., Klinkenberg-Knol, E.C., and Meuwissen, S.G. Omeprazole: therapy of choice in intellectually disabled children. *Arch Pediatr Adolesc Med* 152: 1113-1118, 1998.

OBJECTIVE: To study extensively the therapeutic approach of gastroesophageal reflux disease in intellectually disabled children. DESIGN: We studied the effect of omeprazole sodium on healing and symptom relief in 52 institutionalized intellectually disabled children (male-female, 21:31; mean age, 15.4 years; range, 4-19 years). INTERVENTION: Endoscopically proven esophagitis (grades I-IV, Savary-Miller classification) was treated with omeprazole sodium, 40 mg/d (20 mg/d for children weighing <20 kg) as healing dose for 3 months, and 20 mg/d (10 mg/d for children weighing <20 kg) as maintenance dose for another 3 months. After 3 and 6 months, results of treatment were evaluated using symptom scoring and/or endoscopy. For patients with relapse, the dose was increased. RESULTS: At first endoscopy, 19 patients (36%) of 52 showed grade I esophagitis; 20 (38%), grade II; 6 (12%), grade III; and 7 (13%), grade IV. In 44 (86%) of 51 patients, treatment was effective in healing esophagitis and keeping patients in remission, independent of the severity of esophagitis. In 7 patients (14%), a symptomatic relapse was observed after decreasing the dose. However, these patients became symptom free again after increasing the dose and showed healing on endoscopy at the end of the study. One child did not finish the study for reasons not related to therapy. Marked improvement of persistent vomiting, regurgitation, food refusal, iron deficiency anemia, and signs

of depression was seen at the end. CONCLUSIONS: Omeprazole is highly effective for all grades of esophagitis in intellectually disabled children, without adverse effects. The dose needed to maintain the remission can be titrated according to the reflux symptoms. One disadvantage of medical therapy is that it is open ended, in contrast to operation, but surgery in this population has high mortality and complication rates.

15. Cadranet, S., Bontemps, P., Van Biervliet, S., Alliet, P., Lauvau, D., Vandenhoven, G., and Vandenas, Y. Improvement of the eradication rate of *Helicobacter pylori* gastritis in children is by adjunction of omeprazole to a dual antibiotherapy. *Acta Paediatr* 96: 82-86, 2007.

AIM: The possible improvement of efficacy and tolerability of a 7-day dual antibiotherapy amoxicillin-clarithromycin (AC) on the eradication of *Helicobacter pylori* (*H. pylori*) gastritis in children by the adjunction of omeprazole (OAC) was studied. METHODS: Forty-six children presenting with *H. pylori* gastritis, assessed at inclusion by endoscopy, *H. pylori* urease test, histology and/or culture were randomised to a twice-daily regimen of AC or OAC. A (13)C-urease breath test was performed 4-6 weeks after the end of the treatment period to evaluate *H. pylori* eradication. RESULTS: A larger proportion of patients was *H. pylori* negative (69%) in the OAC regimen treatment 4-6 weeks after eradication treatment compared with those who received dual AC therapy (15%). A total of seven patients (three in the OAC and four in the AC group) reported adverse events (AEs). Only vomiting was reported in more than one patient (one in each treatment regimen) and only one AE was severe (urticaria: in the OAC group, but considered not related to treatment). CONCLUSION: A larger eradication rate of *H. pylori* was obtained in the triple OAC group than in the dual AC group. Both therapy regimens can be safely administered to children for 7 days.

16. Cezard, J.P. Managing gastro-oesophageal reflux disease in children. *Digestion* 69 Suppl 1: 3-8, 2004.

Gastro-oesophageal reflux (GOR) and gastro-oesophageal reflux disease (GORD) have a higher prevalence among infants than among children or adults. This is linked to the immaturity of the oesophagus and stomach and the higher liquid intake of infants. Genetic factors could also be contributory in some families. Clinical symptoms in infants are mainly regurgitation and vomiting, which usually disappear between 1 and 3 years of age. Symptoms in children are similar to those in adults. Treatment in children depends on age and GORD severity. With GOR or mild GORD, particularly in infants, explanation and reassurance together with thickening of formula feed and lifestyle changes are usually effective. Prokinetics either have unproven efficacy (metoclopramide, domperidone) or have been withdrawn (cisapride). Chronic antacid therapy is not recommended. In moderate to severe GORD, histamine-2-receptor antagonists and particularly proton pump inhibitors (PPIs) are effective, especially when oesophagitis is present. PPIs, in particular omeprazole and lansoprazole, have

proven efficacy in infants and children. They are well tolerated, with pharmacokinetics similar to those in adults. However, dosages should be adapted in neonates and children under 10 years old. Fundoplication should be avoided before 2 to 3 years of age if possible.

17. Christensen, S., Farrow-Gillespie, A., and Lerman, J. Effects of ranitidine and metoclopramide on gastric fluid pH and volume in children. *Br J Anaesth* 65: 456-460, 1990.

To determine the effects of ranitidine and metoclopramide on gastric fluid in children, 40 healthy children (aged 2-8 yr) were allocated randomly to groups of 10 to receive one of four oral premedications 4 h before surgery: no premedication, metoclopramide 0.1 mg kg⁻¹, ranitidine 2 mg kg⁻¹ and metoclopramide 0.1 mg kg⁻¹ with ranitidine 2 mg kg⁻¹. After tracheal intubation, gastric fluid was aspirated and analysed for pH and total fluid volume. Ranitidine, with or without metoclopramide, increased gastric fluid pH significantly compared with control (P less than 0.05). Gastric fluid volume did not change significantly.

18. Claessens, A.A., Heerdink, E.R., van Eijk, J.T., Lamers, C.B., and Leufkens, H.G. Determinants of headache in lansoprazole users in The Netherlands: results from a nested case-control study. *Drug Saf* 25: 287-295, 2002.

OBJECTIVE: During proton pump inhibitor (PPI) use, in clinical trials, headache is one of the most frequently reported adverse events (frequency 1.3 to 8.8%), while results of one observational study indicate that headache is the fifth most frequently reported adverse event (incidence densities 2.5 to 4.6 per 1000 patient-months of exposure). However, there are no observational studies performed regarding the occurrence and features of headache during use of PPIs in daily practice. For this reason this study was set up with the aim to assess the incidence and characteristics of headache and to investigate possible associated co-factors in PPI users in daily practice. DESIGN: Data were used from a prospective, observational study in which 10 008 lansoprazole users were followed over time. The study was designed according to the Safety Assessment of Marketed Medicines guidelines. A nested case-control design was used to compare PPI users reporting headache or not. RESULTS: The frequency of headache was 2.5% in users of lansoprazole and the incidence density was 7.2 per 1000 patient-months of PPI lansoprazole use. Two-thirds of patients with headache had tension headache and one-third had migraine. The analysis of co-factors revealed that women, patients with previous use of analgesics and patients reporting several adverse events, were at risk to develop headache during PPI use. Patients with headache also, significantly more often, reported diarrhoea, nausea and dizziness. A discontinuation of PPI therapy resulted in a cessation or reduction of the headache in 80.0% (20 of 25). CONCLUSIONS: As can be expected, headache was reported less frequently in this study compared with clinical trials with lansoprazole. The incidence density was comparable with other observational data of lansoprazole and omeprazole users. Besides several

commonly accepted co-factors such as female gender and a history of analgesic use, we also found the reporting of other adverse events to be associated with the reporting of headache during lansoprazole use. The cessation of headache after a discontinuation of use of the PPI and the observed dose relationship suggested that headache was indeed an adverse effect of lansoprazole use.

19. Cothran, D.S., Borowitz, S.M., Sutphen, J.L., Dudley, S.M., and Donowitz, L.G. Alteration of normal gastric flora in neonates receiving ranitidine. *J Perinatol* 17: 383-388, 1997.

OBJECTIVES: To determine if the administration of ranitidine to neonates leads to an increase in gastric pH to $>$ or $=$ 4 and if this increase in gastric pH correlates with gastric colonization. STUDY DESIGN: 628 pH measurements and 276 gastric cultures were obtained from 86 neonates. Twenty-three patients received ranitidine and 63 patients served as controls. RESULTS: Treated patients had a mean gastric pH of 5.6 compared with a control mean pH of 4.4 ($p < 0.0001$). Gastric pH was significantly affected by feeding and postnatal age. 54 patients were colonized with pathogenic bacteria and/or yeast ($n = 20$ treated, $n = 34$ control). Length of hospitalization ($p < 0.0001$), increase in gastric pH ($p < 0.01$), days of antibiotics before culture ($p < 0.0001$), and ranitidine use ($p < 0.0001$) were associated with an increased rate of colonization. CONCLUSIONS: The use of ranitidine did lead to a significant increase in gastric pH and with this increase in gastric pH gastric colonization rates increased. No increased frequency of infection was found in ranitidine-treated infants.

20. Croom, K.F., and Scott, L.J. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs* 65: 2129-2135; discussion 2136-2127, 2005.

Lansoprazole is a proton pump inhibitor that inactivates the H(+)/K(+)-ATPase pump in parietal cells, thus inhibiting gastric acid secretion and increasing intragastric pH. In an open-label, uncontrolled trial in children aged 1-11 years with gastro-oesophageal reflux disease (GORD), treatment with lansoprazole 15 or 30 mg (depending on weight) once daily for 8-12 weeks improved symptoms compared with baseline in 76% of patients (47 of 62) based on patient diaries and healed erosive oesophagitis (confirmed endoscopically) in all 27 children who had it at baseline. In adolescents aged 12-17 years with GORD, 8 weeks' treatment with lansoprazole 15 mg (in 64 patients with non-erosive disease) or 30 mg (in 23 patients with erosive oesophagitis) once daily reduced the frequency and severity of symptoms by 63% and 69% compared with baseline, based on patient diaries. In this open-label, uncontrolled trial, 96% of evaluable patients with erosive disease (21 of 22) had mucosal healing by week 8, as confirmed by endoscopy; mucosal healing did not occur after an additional 4 weeks' treatment in one patient. Lansoprazole was generally well tolerated in children and adolescents, with the most common treatment-related adverse events being gastrointestinal events and headache.

21. Cucchiara, S., Minella, R., Campanozzi, A., Salvia, G., Borrelli, O., Ciccimarra, E., and Emiliano, M. Effects of omeprazole on mechanisms of gastroesophageal reflux in childhood. *Dig Dis Sci* 42: 293-299, 1997.

Prolonged recordings of esophageal motility have shown that dynamic changes of lower esophageal sphincter (LES) pressure such as transient LES relaxation and LES pressure drifts are the most common mechanisms underlying gastroesophageal reflux (GER). The coexistence of a delayed gastric emptying has also been reported in a high proportion of patients with reflux disease. However, not much information is available on the effects of antireflux therapy on the pathogenetic mechanisms of GER. The purpose of this study was to determine in a group of children with severe reflux disease the effect of omeprazole therapy on motor changes of LES underlying GER as well as on gastric emptying time. Twenty-two children (median age: 6.6 years) with GER disease, refractory to combined ranitidine and cisapride administration, entered into an eight-week omeprazole course. Ten subjects with moderate GER disease served as controls (median age: 6.0 years). Before and after omeprazole administration, the following variables were assessed: esophagitis grading, fasting and fed simultaneous prolonged recording of distal esophageal sphincter pressure (with a sleeve catheter) and intraesophageal pH, LES and esophageal peristalsis amplitude, and gastric emptying time of a mixed solid-liquid meal (measured with gastric ultrasound). As compared to controls, patients showed a higher rate of transient LES relaxation and LES pressure drift ($P < 0.01$), a reduced amplitude of basal sphincter pressure ($P < 0.01$) and peristalsis ($P < 0.05$), and a more prolonged gastric emptying time ($P < 0.05$). After ending omeprazole, there was no significant change in any of the motor abnormalities of the esophagus and in gastric emptying time despite a marked improvement of symptoms and esophagitis in all patients. Sixteen patients were symptomatic when reevaluated on a clinical basis two months after ending therapy. We conclude that in children with severe GER disease, an abnormally high rate of both transient LES relaxation and LES pressure drift and slow gastric emptying are not affected by omeprazole treatment, even though esophageal mucosal damage is markedly improved or cured. These abnormalities represent a primary motor disorder and can be implicated in the refractoriness of reflux disease.

22. Cucchiara, S., Minella, R., Iervolino, C., Franco, M.T., Campanozzi, A., Franceschi, M., D'Armiento, F., and Auricchio, S. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. *Arch Dis Child* 69: 655-659, 1993.

Thirty two consecutive patients (age range 6 months-13.4 years) with severe reflux oesophagitis were randomised to a therapeutic trial for eight weeks during which they received either standard doses of omeprazole (40 mg/day/1.73 m² surface area) or high doses of ranitidine (20 mg/kg/day). Twenty five patients completed the trial (12 on omeprazole, 13 on ranitidine). At entry and at the end

of the trial patients underwent symptomatic score assessment, endoscopic and histological evaluation of the oesophagus, and simultaneous oesophageal and gastric pH measurement; results are given as median (range). Both therapeutic regimens were effective in decreasing clinical score (omeprazole before 24.0 (15-33), after 9.0 (0-18); ranitidine before 19.5 (12-33), after 9.0 (6-12)), in improving the histological degree of oesophagitis (omeprazole before 8.0 (6-10), after 2.0 (0-60); ranitidine before 8.0 (8-10), after 2.0 (2-6), and in reducing oesophageal acid exposure, measured as minutes of reflux at 24 hour pH monitoring (omeprazole before 129.4 (84-217), after 44.6 (0.16-128); ranitidine before 207.3 (66-306), after 58.4 (32-128)) as well as intragastric acidity, measured as median intragastric pH (omeprazole before 2.1 (1.0-3.0), after 5.1 (2.2-7.4); ranitidine before 1.9 (1.6-4), after 3.4 (2.3-5.3)). Serum gastrin concentration was > 150 ng/l in four patients on omeprazole and in three patients on ranitidine. It is concluded that in children with refractory reflux oesophagitis high doses of ranitidine are comparable with omeprazole for the healing of oesophagitis and relief of symptoms; both drugs resulted in efficacious reduction of intragastric acidity and intra-oesophageal acid exposure.

23. Cucchiara, S., Raia, V., Minella, R., Frezza, T., De Vizia, B., and De Ritis, G. Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 128: 485-488, 1996.

Intestinal dysmotility is commonly reported in patients with cystic fibrosis (CF); however, gastric motor activity has rarely been investigated. We measured with real-time ultrasonography the antral distention and gastric emptying time of a solid-liquid meal in 29 patients with CF (age range, 5 to 17 years). A significantly prolonged gastric emptying time was present in 26 patients compared with 13 healthy control subjects (age range, 5 to 16 years); an exaggerated antral distention in the fed period was also detected. The patients with CF and delayed gastric emptying were randomly allocated to receive cisapride or ranitidine for 4 weeks. Twelve patients treated with ranitidine and 11 with cisapride completed the trial. There was a marked decrease in gastric emptying time, antral distention, and dyspeptic symptomatic score in patients receiving ranitidine but not in patients treated with cisapride. We conclude that gastric dysmotility is commonly detected in patients with CF and that H₂ receptor blockers are more effective than prokinetics in improving dyspeptic symptoms and gastric emptying and distention.

24. De Giacomo, C., Bawa, P., Franceschi, M., Luinetti, O., and Fiocca, R. Omeprazole for severe reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 24: 528-532, 1997.

BACKGROUND: Severe esophagitis is a rare complication of gastroesophageal reflux in children. In adults, omeprazole therapy of severe erosive esophagitis has become the gold standard short-term treatment of the disease. In children,

data on its use are limited, and problems about the dosage are unresolved. The aim of this study was to evaluate the efficacy of a simplified, body-weight-based daily dosage of omeprazole in children with severe esophagitis. METHODS: Ten children (median age 75.6 months; range 25-109 months) with severe esophagitis were prospectively investigated. All patients were evaluated by endoscopy, histology, and 24-h pH-metry study before and after 3 months of omeprazole. The starting dose of omeprazole was 20 mg as a single daily dose in children weighing less than 30 kg, and 40 mg daily for those weighing over 30 kg. RESULTS: A significant improvement in all the children was demonstrated after 3 months of treatment by clinical, endoscopic, and pH-metry assessment. However, histologic study failed to show significant improvement of both inflammatory and hyperplastic findings. Relapse occurred in six of 10 patients after discontinuation of therapy. CONCLUSIONS: Omeprazole is effective in the short-term treatment of severe oesophagitis in children. The daily dose of the drug could be easily based on the body weight. The persistence of histologic features of esophagitis in spite of clinical and endoscopic healing could be an indicator of poor outcome.

25. Di Mario, F., Dotto, P., Vianello, F., Germana, B., Grassi, S.A., Del Favero, G., Faggian, D., Plebani, M., and Naccarato, R. Effects of H2 blockers and omeprazole on peptic secretion: a prospective, randomized study in duodenal ulcer subjects. *Acta Gastroenterol Belg* 56: 223-228, 1993.

Aim of the present study has been to investigate the possible modifications of peptic secretion after a period with H2 blockers and omeprazole, evaluating in the same patient pepsinogen group A levels in gastric mucosa and pepsin in gastric juice. 54 active duodenal ulcer were studied: during an upper gastrointestinal endoscopy a sample of gastric juice and one fundus biopsy were taken before and after four weeks 300 mg/daily ranitidine (23 patients), 40 mg/daily famotidine (7 patients), 300 mg/daily nizatidine (12 patients) therapy and 40 mg/daily omeprazole (12 patients) therapy. Results: H2-blockers and omeprazole treatment determines a non statistically significant decrease of pepsin in gastric juice and in pepsinogen group A in gastric mucosa.

26. Dobrilla, G., Di Matteo, G., Doderò, M., Fratton, A., Iaquinto, G., Loriga, P., Marchi, S., Marzio, L., Muratori, R., Pacini, D., Saggioro, A., Savarino, V., Spinelli, P., Zamboni, G., Fina, P., Tosatto, R., and Olivieri, A. Ranitidine bismuth citrate with either clarithromycin 1 g/day or 1.5 g/day is equally effective in the eradication of *H. pylori* and healing of duodenal ulcer. *Aliment Pharmacol Ther* 12: 63-68, 1998.

BACKGROUND: No randomized double-blind studies have been performed to compare clarithromycin 1 g/day with higher doses of the macrolide (1.5 g/day) when combined with ranitidine bismuth citrate (RBC). AIM: To compare *H. pylori* eradication and ulcer healing rates of RBC 400 mg b.d. for 4 weeks combined for the first 2 weeks either with clarithromycin 500 mg b.d. (Group A) or

clarithromycin 500 mg t.d.s. (Group B). METHODS: Two hundred and seventy-three patients with H. pylori-positive active duodenal ulcer were included. H. pylori infection was detected by CLO-test and histology on antral and corpus biopsies before and at least 4 weeks after the end of therapy. Eradication was assumed if both CLO-test and histology results were negative for H. pylori. RESULTS: Eradication/healing rates according to intention-to-treat and per protocol analysis were 76/82% and 87/92% for Group A and 78/85% and 88/95% for Group B, respectively (P = N.S.). Adverse events were reported by 7% and 12% of patients in Groups A and B, respectively, and they were generally mild. CONCLUSIONS: RBC in co-prescription with clarithromycin 500 mg b.d. is as effective as RBC plus clarithromycin 500 t.d.s. in eradicating H. pylori and healing duodenal ulcers.

27. Eddleston, J.M., Booker, P.D., and Green, J.R. Use of ranitidine in children undergoing cardiopulmonary bypass. *Crit Care Med* 17: 26-29, 1989.

Sixty children aged 6 wk to 10 yr were studied. The children were undergoing cardiopulmonary bypass (CPB) for correction of congenital heart defects. The aim of the study was to provide prophylaxis for stress-induced gastric ulceration by elevating the gastric pH to at least 3.5. Two infusion regimes of ranitidine were compared: 0.1 and 0.2 mg/kg.h. The period of study was from induction of anesthesia until the end of the first 24 h after surgery. Both regimes were effective. The 0.2-mg/kg.h infusion produced a significantly higher plasma concentration of ranitidine throughout the study period without any additional clinical benefit. Both regimes produced, within 3 h of cessation of CPB, a significant elevation in mean gastric pH to at least 5.3. This paper concludes that 0.1-mg/kg.h infusion of ranitidine is a safe and efficacious regime for the critically ill pediatric patient.

28. Faure, C., Michaud, L., Shaghghi, E.K., Popon, M., Laurence, M., Mougnot, J.F., Hankard, R., Navarro, J., and Jacoz-Aigrain, E. Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis. *Aliment Pharmacol Ther* 15: 1397-1402, 2001.

BACKGROUND: Data on the proton pump inhibitor lansoprazole in paediatric patients are limited. AIM: To investigate the pharmacokinetics, optimal dosage and efficacy of lansoprazole in paediatric patients. METHODS: A 24-h gastric pH recording and a pharmacokinetic study were performed after 7 days of lansoprazole, 17 mg/m², in 23 patients with reflux oesophagitis (median age, 3.5 years). Response was defined as pH > 3 for > 65% of the recording. The dosage was doubled in non-responders. Patients with no response on day 14 were excluded. Responders underwent endoscopy after 4 weeks on the response-inducing dosage; abnormal findings led to a repeat endoscopy after four additional weeks. RESULTS: Nine patients responded to 17 mg/m² and six to 30.3 mg/m². On day 7, time with pH > 3 was significantly correlated with the area under the plasma concentration-time curve (P=0.003). The area under the

plasma concentration-time curve was significantly greater in the nine responders to 17 mg/m² than in the 14 other patients. Pharmacokinetic parameters were similar in responders and non-responders to the higher dose. After 4 weeks, oesophagitis was healed in 80% of responders. Adverse events occurred in three patients and required treatment discontinuation in one. CONCLUSIONS: Lansoprazole is effective and safe in children. The optimal starting dosage is 30 mg/m² or 1.4 mg/kg.

29. Faure, C., Michaud, L., Shaghghi, E.K., Popon, M., Turck, D., Navarro, J., and Jacqz-Aigrain, E. Intravenous omeprazole in children: pharmacokinetics and effect on 24-hour intragastric pH. *J Pediatr Gastroenterol Nutr* 33: 144-148, 2001.

BACKGROUND: Omeprazole is a proton pump inhibitor, acting selectively on the gastric parietal cell H⁺K⁺-adenosine triphosphatase. Data on the intravenous route are limited in children and not available in infants. OBJECTIVE: This study was designed to determine the pharmacokinetics and the optimal dosage of intravenous omeprazole in patients younger than 30 months of age. METHODS: Nine children (three girls), aged 4.5 to 27 months, with normal liver and renal functions requiring intravenous omeprazole were studied. After enrollment in the study and randomization, omeprazole was administered once daily, at 8 am, as a 1-hour infusion. Group 1, consisting of the first four patients, received 20 mg/1.73 m², and group 2, consisting of the following five patients, received 40 mg/1.73 m². At day 3, a 24-hour intragastric pH and a pharmacokinetic study of omeprazole were performed. Plasma concentrations were measured by high-performance liquid chromatography. RESULTS: Patients in group 2 had a significantly higher median pH (6.99 vs. 3.35; P = 0.01) and percent of monitored time with gastric pH >4 than children given 20 mg/1.73 m² (90.6% vs. 44.8%; P < 0.01). Four had a pH more than 4 during more than 90% of the time versus none of the patients of group 1. The plasma concentration versus time curves showed rapid elimination of the drug. The median area under the curve of omeprazole was 0.78 microg. mL⁻¹. h⁻¹ (range, 0.55-1.64 microg. mL⁻¹. h⁻¹) and 3.95 microg. mL⁻¹. h⁻¹ (range, 1.9-4.9 microg. mL⁻¹. h⁻¹), respectively, in groups 1 and 2 (P < 0.05). Systemic clearance was not different between the two groups: median values were 0.68 and 0.42 L. kg⁻¹. h⁻¹ (P = 0.22). CONCLUSIONS: In critical situations, intravenous administration of omeprazole may be required in infants. The authors demonstrate that the dose of 20 mg/1.73 m² is not effective in maintaining 24-hour gastric pH of more than 4 and that a dose of 40 mg/1.73 m² is required.

30. Fiedorek, S., Tolia, V., Gold, B.D., Huang, B., Stolle, J., Lee, C., and Gremse, D. Efficacy and safety of lansoprazole in adolescents with symptomatic erosive and non-erosive gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 40: 319-327, 2005.

OBJECTIVES: To assess the efficacy and safety of lansoprazole in the treatment

of adolescents with symptomatic, endoscopically proven, non-erosive gastroesophageal reflux disease and erosive esophagitis. METHODS: Adolescents between 12 and 17 years of age with esophagitis were enrolled in this open-label trial and treated with lansoprazole 15 mg (non-erosive) or 30 mg (erosive) once daily for 8 weeks. If unhealed at week 8, those with erosive esophagitis were treated with an additional 4 weeks of lansoprazole 30 mg once daily. RESULTS: Lansoprazole produced a significant reduction from baseline in the median percentage of days with reflux symptoms (91 to 43% in the 64 adolescents with non-erosive disease and 85 to 16% in the 23 adolescents with erosive esophagitis, $P < \text{or} = 0.001$ for each comparison). At week 8, mucosal healing had occurred in 95% (21 of 22) of those with erosive esophagitis. Treatment-related adverse events were reported by 19% of patients with non-erosive and 4% of patients with erosive esophagitis. Headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%) were the most frequently reported adverse events. One patient discontinued treatment early because of dizziness and vomiting. An elevation in mean serum gastrin from baseline (59 pg/mL at pretreatment to 80 pg/mL at final visit) was observed. CONCLUSION: Lansoprazole 15 mg or 30 mg once daily reduced symptoms of gastroesophageal reflux in adolescents with non-erosive gastroesophageal reflux disease and erosive esophagitis, respectively. Lansoprazole 30 mg once daily for 8 weeks was effective in healing erosive esophagitis. Both treatment regimens were considered safe.

31. Fontana, M., Tornaghi, R., Petrillo, M., Lora, E., Bianchi Porro, G., and Principi, N. Ranitidine treatment in newborn infants: effects on gastric acidity and serum prolactin levels. *J Pediatr Gastroenterol Nutr* 16: 406-411, 1993.

Data about the use of ranitidine in the early postnatal period are lacking. In this study, 30 term newborn infants < 2 days old with bleeding erosions in their upper gastrointestinal tracts were treated with ranitidine by continuous i.v. infusion (0.2 mg/kg/h) for 48 h and thereafter by mouth (5 mg/kg b.i.d.) for 1 month. Mean gastric pH (SD) rose from 4.27 (1.62) to 5.70 (0.95) during i.v. infusion; after oral therapy it was still 5.55 (1.25). Serum ranitidine concentrations were 642.4 (376.5) and 321.5 (368.2) ng/ml after i.v. and oral therapy, respectively, with wide interindividual variations; the correlation between serum ranitidine and gastric pH was found to be weak. No untoward effect was observed either on the cardiorespiratory rate or on creatinine and aminotransferase values. Mean serum prolactin concentration after i.v. therapy was found to be lower, although within the reference range, than in control infants; no significant correlation was observed between serum ranitidine and prolactin concentrations. From these data, a < 0.2 mg/kg/h rate seems to be advisable for continuous ranitidine infusion in neonates, whereas the 5 mg/kg b.i.d. regimen could be considered adequate for oral therapy.

32. Francavilla, R., Lionetti, E., Castellaneta, S.P., Magista, A.M., Boscarelli, G., Piscitelli, D., Amoroso, A., Di Leo, A., Miniello, V.L., Francavilla, A., Cavallo, L.,

and Ierardi, E. Improved efficacy of 10-Day sequential treatment for *Helicobacter pylori* eradication in children: a randomized trial. *Gastroenterology* 129: 1414-1419, 2005.

BACKGROUND & AIMS: The currently recommended first-line eradication treatment of *Helicobacter pylori* in children is usually successful in about 75%. Recently, in adults, a novel 10-day sequential treatment has achieved an eradication rate of 95%. The aim of the study was to assess the *H pylori* eradication rate of the sequential treatment regimen compared with conventional triple therapy in children. **METHODS:** Seventy-eight consecutive children with *H pylori* infection were randomized to receive either sequential treatment (omeprazole plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus tinidazole for another 5 days) (n = 38; 15 boys [39.5%]; median age, 11.0 years [range, 3.3-16 years]) or triple therapy (omeprazole, amoxicillin, and metronidazole) for 1 week (n = 37; 15 boys [40.5%]; median age, 9.9 years [range, 4.3-16 years]). *H pylori* infection was based on 2 out of 3 positive tests results: ¹³C-urea breath test, rapid urease test, and histologic analysis. Eradication was assessed by ¹³C-urea breath test 8 weeks after therapy. **RESULTS:** Seventy-four patients completed the study. *H pylori* eradication was achieved in 36 children receiving sequential treatment (97.3%; 95% confidence interval, 86.2-99.5) and 28 children receiving triple therapy (75.7%; 95% confidence interval, 59.8-86.7) (P < .02). Compliance with therapy was good (>95%) in all. **CONCLUSIONS:** Our study shows, for the first time in children, that 10-day sequential treatment achieves a higher eradication rate than standard triple therapy, which is consistent with the results of adult studies.

33. Francisco, M.P., Wagner, M.H., Sherman, J.M., Theriaque, D., Bowser, E., and Novak, D.A. Ranitidine and omeprazole as adjuvant therapy to pancrelipase to improve fat absorption in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 35: 79-83, 2002.

BACKGROUND: Inadequate treatment of pancreatic insufficiency in patients with cystic fibrosis (CF) causes malabsorption of nutrients with significant sequelae. The objective of this study was to measure the effect of acid suppressant therapy on fat absorption in patients with CF who received a pH-sensitive, enteric-coated microtablet enzyme product. **METHODS:** A double-blind, placebo-controlled crossover study of 12 children and 10 adults with pancreatic insufficient CF was performed. All subjects were receiving pancrelipase therapy (Pancrease MT10 and MT16; Ortho-McNeil, Springhouse, PA, U.S.A.) and for the study also received either placebo or ranitidine (Zantac; Glaxo-Wellcome, Research Triangle Park, NC U.S.A.) 5 mg/kg or 10 mg/kg daily. The adult subjects also received omeprazole therapy (Prilosec; AstraZeneca/Merck, Wilmington, DE, U.S.A.), 20 mg daily, as adjuvant therapy to pancreatic enzymes. Serial 3-day fat-balance studies were performed in the Clinical Research Center. The data were analyzed using individual paired t tests that compared each treatment with placebo and two repeated-measures, general linear model F tests. **RESULTS:**

The linear model for all subjects showed no overall adjuvant drug effect on fat absorption, $P = 0.32$. A second linear model F test analysis of adult subjects, comparing all four drug treatments (placebo, ranitidine 5 and 10 mg/kg daily and omeprazole), also showed no difference in fat absorption, $P = 0.15$. Paired t test subgroup analysis of the adults showed an improvement of 4.97% ($P = 0.003$) in mean fat absorption comparing low-dose ranitidine to placebo. All other t test analyses showed no significant change in fat absorption between placebo and acid suppressant treatment. There was marked intersubject and intrasubject variability in fat absorption. CONCLUSIONS: No overall significant improvement in fat absorption could be demonstrated with adjuvant therapy. Fat absorption measured by 3-day fat-balance studies varied greatly even when comparing the same subject for placebo and baseline treatments, despite identical dietary fat and enzyme intakes. The large variability limited our ability to test for a difference in fat absorption and has significant implication for the use of this test, considered the gold standard, for determining enzyme dosage adequacy.

34. Franco, M.T., Salvia, G., Terrin, G., Spadaro, R., De Rosa, I., Iula, V.D., and Cucchiara, S. Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood. *Dig Liver Dis* 32: 660-666, 2000.

BACKGROUND: Acid suppressive therapy is the mainstay of pharmacologic treatment of gastro-oesophageal reflux disease. Use of proton pump inhibitors in children is still limited and has only included omeprazole in a few controlled studies. AIM: To determine efficacy of lansoprazole, a relatively new proton pump inhibitor, on symptoms and oesophagitis in a group of children with gastro-oesophageal reflux disease refractory to H₂ receptor antagonists. The required dose of the drug for inhibiting gastric acidity was also determined. PATIENTS AND METHODS: A series of 35 children (median age: 7.6 years, range: 3-15) with oesophagitis refractory to H₂ receptor antagonists received a 12-week therapeutic course with lansoprazole. Prior to the study children underwent symptomatic and endoscopic assessment, oesophageal manometry and 24-hour intragastric and intra-oesophageal pH test. The latter was repeated after one week of therapy while patients were on treatment in order to monitor the degree of acid suppression and adjust the dose of the drug. Symptomatic assessment and endoscopy were repeated at the end of the trial RESULTS AND CONCLUSIONS: In 12 patients (group A), the initial dose of the drug was efficacious (1.3 to 1.5 mg/kg/day), whereas in 23 [group B) the initial dose (0.8 to 1.0 mg/kg/day) was increased by half because of insufficient inhibition of intragastric acidity (i.e., when the intra-gastric pH remained below 4.0 for more than 50% of the recording time). Nine patients in group A (75%) and 8 in group B (53.5%) healed ($\chi^2: 3.6, p < 0.05$); 1 patient in group A [8.3%) and 7 in group B (30.5%) remained unchanged ($\chi^2: 6.9, p < 0.01$); 2 patients in group A and 8 in group B improved and underwent a further month of therapy. The two groups did not differ as far as concerns baseline pH, endoscopic and clinical variables. In both groups, those patients failing to respond at the end of the trial showed a more impaired oesophageal motility than improved or healed patients. The drug

was well tolerated and no significant laboratory abnormalities occurred. In children with gastro-oesophageal reflux disease refractory to H₂ receptor antagonists, a 12-week course of lansoprazole is effective both in healing oesophagitis and improving symptoms. An initial dose of 1.5 mg/kg/day of the drug is suggested. However, if during treatment, patients remain symptomatic the dose should be increased and a prolonged intra-gastric and intra-oesophageal pH test performed to evaluate the acid suppression efficacy of the adjusted dose. A short course of lansoprazole appears to be safe and well tolerated in paediatric age.

35. Gessner, B.D., Bruce, M.G., Parkinson, A.J., Gold, B.D., Muth, P.T., Dunaway, E., and Baggett, H.C. A randomized trial of triple therapy for pediatric *Helicobacter pylori* infection and risk factors for treatment failure in a population with a high prevalence of infection. *Clin Infect Dis* 41: 1261-1268, 2005.

BACKGROUND: Few trials of treatment for *Helicobacter pylori* infection have been conducted in high-prevalence or pediatric populations, and risk factors for treatment failure are poorly understood. **METHODS:** As part of a study evaluating the effect of *H. pylori* therapy on iron deficiency, we conducted a household-randomized, open-label treatment trial involving children aged 7-11 years in 10 villages in western Alaska. We screened 690 children, of whom 219 with iron deficiency and *H. pylori* infection (determined on the basis of positive results of the ¹³C urea breath test) were enrolled in the treatment phase of the study. These 219 children received treatment with iron sulfate alone (the control group) or with iron sulfate combined with a 2-week course of lansoprazole, clarithromycin, and amoxicillin (the intervention group). Children in the intervention group who were allergic to amoxicillin or macrolides received metronidazole. Children in the intervention group who did not respond to treatment were re-treated with a 2-week course of metronidazole-based quadruple therapy. **RESULTS:** Two months after initiating therapy, 34% of 104 children in the intervention group and 0.90% of 111 children in the control group tested negative for *H. pylori*. Among children in the intervention group, risk factors for treatment failure were lack of metronidazole (adjusted odds ratio [aOR], 145), fewer treatment doses (aOR, 0.74), larger household population (aOR, 1.5), and lower body mass index (aOR, 0.69). These 4 variables predicted most of the variation in *H. pylori* infection status. Among 50 children who were re-treated, 84% tested negative for *H. pylori* at the 8-month follow-up visit, including those with poor treatment compliance. **CONCLUSIONS:** Among disadvantaged populations with a high prevalence of *H. pylori* infection, the response to standard treatment regimens may be low. Treatment compliance, household crowding, and re-treatment may influence treatment success. Metronidazole may be appropriate first-line therapy.

36. Gibbons, T.E., and Gold, B.D. The use of proton pump inhibitors in children: a comprehensive review. *Paediatr Drugs* 5: 25-40, 2003.

Proton pump inhibitors (PPIs) belong to a group of chemically related compounds whose primary function is the inhibition of acid production in the final common metabolic pathway of gastric parietal cells. PPIs are highly selective and effective in their action and have few short- or long-term adverse effects. These pharmacologic features have made the development of PPIs the most significant advancement in the management of acid peptic related disorders in the last two decades. There are numerous published adult studies that describe the pharmacology, efficacy and safety of these anti-secretory agents; however, in the pediatric population, there are very few comparable studies, particularly multicenter studies with significant patient enrollment. In preparing this article, our aim was to perform a comprehensive review of the literature on the clinical pharmacology and use of PPIs in the pediatric population, and to briefly review some recent articles. Relevant literature was identified by performing MEDLINE/Pubmed searches from January 1990 to December 2001. Combinations of the following search terms were used to analyze these databases: proton pump inhibitor, children, pediatrics, gastroesophageal reflux disease (GERD), esophagitis, intestinal metaplasia, Helicobacter pylori, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and safety. Abstracts from the 14th annual conference of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) 2001, and the Disease and Digestive Week 2001, were also included in the review. All pediatric studies reviewed were limited to either omeprazole or lansoprazole. The dosage range used for the management of GERD and related disorders with lansoprazole was 0.73-1.66 mg/kg/day (maximum 30 mg/day). The dosage range for GERD management using omeprazole was 0.3-3.5 mg/kg (maximum 80 mg/day). The dosage range for omeprazole used for H. pylori was 0.5-1.5 mg/kg/day, with a maximum dosage of 40 mg/day, and lansoprazole-containing regimens for H. pylori eradication used dosages ranging from 0.6-1.2 mg/kg/day, with a maximum dosage of 30 mg/day. Few severe adverse events were reported with the use of either drug. Eradication rates for H. pylori were 56-87% for lansoprazole-based triple therapy, and 75-94% for omeprazole-based eradication regimens. To date, there are no published controlled trials of sufficient power comparing the efficacy of the five commercially available PPIs in children, for a variety of acid peptic diseases. Studies suggest that PPIs are highly effective for the management of GERD and related disorders, and are a critically needed component of triple therapy to eradicate H. pylori. PPIs have a very good tolerability profile in adults and children, but long-term tolerability studies are needed, particularly in the pediatric population. Multicenter studies are critically needed to evaluate the second-generation PPIs, to compare PPI efficacy to each other, and to assess the importance of developmental and genetic pharmacology of these drugs in children with acid-peptic disease.

37. Gilger, M.A., Tolia, V., Vandenplas, Y., Youssef, N.N., Traxler, B., and Illueca, M. Safety and tolerability of esomeprazole in children with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 46: 524-533, 2008.

OBJECTIVES: To evaluate safety, tolerability, and symptom improvement with once-daily esomeprazole in children with endoscopically proven gastroesophageal reflux disease (GERD). **PATIENTS AND METHODS:** In this 8-week, multicenter, randomized, uncontrolled, double-blind study, children ages 1 to 11 years were stratified by weight to receive esomeprazole 5 or 10 mg (children <20 kg) or 10 or 20 mg (children ≥20 kg) once daily. Safety and tolerability was assessed by evaluating adverse events (AEs; both treatment- and non-treatment-related AEs) and changes from baseline in medical history, physical examinations, and clinical laboratory tests. Investigators scored symptom severity every 2 weeks using the Physician's Global Assessment (PGA). Patients' parents rated GERD symptoms of heartburn, acid regurgitation, and epigastric pain (none to severe, 0-3) at baseline (based on past 72 hours) and daily (from past 24 hours). **RESULTS:** Of 109 patients randomized, 108 had safety data. AEs were experienced by 68.0% and 65.2% of children <20 kg receiving esomeprazole 5 and 10 mg, respectively, and 83.9% and 82.8% of children ≥20 kg receiving esomeprazole 10 and 20 mg, respectively, regardless of causality. Overall, only 9.3% of patients reported 13 treatment-related AEs; the most common were diarrhea (2.8% [3/108]), headache (1.9% [2/108]), and somnolence (1.9% [2/108]). Vomiting, a serious AE in 2 patients, was not judged by the investigator to be related to treatment. At the final visit, PGA scores improved significantly from baseline ($P < 0.001$). Of 58 patients with moderate to severe baseline PGA symptom scores, 91.4% had lower scores by the final visit. GERD symptom scores were significantly improved from baseline to the final week of the study in all of the treatment groups ($P < 0.01$). **CONCLUSIONS:** In children ages 1 to 11 years with endoscopically proven GERD, esomeprazole (at daily doses of 5, 10, or 20 mg) was generally well tolerated. The frequency and severity of GERD-related symptoms were significantly reduced during the active treatment period.

38. Gold, B.D., Gunasekaran, T., Tolia, V., Wetzler, G., Conter, H., Traxler, B., and Illueca, M. Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 45: 520-529, 2007.

OBJECTIVES: The primary objective was to assess the safety of esomeprazole 20 or 40 mg once daily in adolescents with clinically diagnosed gastroesophageal reflux disease (GERD). A secondary aim was to assess changes in GERD symptoms after esomeprazole therapy. **PATIENTS AND METHODS:** In this multicenter, randomized, double-blind study, adolescents ages 12 to 17 years inclusive received esomeprazole 20 or 40 mg once daily for 8 weeks. Adverse events and changes in clinical parameters (eg, physical examination, laboratory measurements) were evaluated to assess safety. Patients or their parents or guardians scored symptom severity daily, and investigators scored overall GERD symptom severity every 2 weeks using a 4-point scale. **RESULTS:** In the 148 adolescents with safety data, treatment-related and non-treatment-related adverse events were reported by 75% and 78% of patients in the esomeprazole

20- and 40-mg groups, respectively. Twenty-two patients (14.9%) experienced adverse events that were considered related to treatment; the most common were headache (8%, 12/148), abdominal pain (3%, 4/148), nausea (2%, 3/148), and diarrhea (2%, 3/148). No serious adverse events or clinically important findings in other safety assessments were observed. At baseline, 68% (100/147) had heartburn, 63% (93/147) had epigastric pain, 57% (84/147) had acid regurgitation, and 15% (22/147) had vomiting symptoms. Symptom scores decreased significantly in both the esomeprazole 20-mg and 40-mg groups by the final study week ($P < 0.0001$). Investigators rated 63.1% (94/149) of the patients as having moderate or severe symptoms at baseline; at the final visit, this percentage decreased significantly to 9.3% (13/140; $P < .0001$).

CONCLUSIONS: In adolescent patients with GERD, esomeprazole 20 or 40 mg daily for 8 weeks was well tolerated, and GERD-related symptoms were significantly reduced from baseline values in both groups.

39. Gombar, S., Dureja, J., Kiran, S., Gombar, K., and Chhabra, B. The effect of pre-operative intake of oral water and ranitidine on gastric fluid volume and pH in children undergoing elective surgery. *J Indian Med Assoc* 95: 166-168, 1997.

The effect of pre-operative intake of oral water and ranitidine on gastric fluid volume and pH was studied in 75 children of American Society of Anesthetists (ASA) grade I and grade II undergoing elective surgery. Group I patients fasted from midnight and acted as control. Group II patients received 5 ml/kg plain water orally 3 hours before surgery. Group III children received 5 ml/kg of plain water and 2 mg/kg of ranitidine orally 3 hours before surgery. Mean volume of gastric aspirate was comparable in all 3 groups ($p > 0.05$). Mean pH was significantly higher in ranitidine treated patients (5.12 +/- 1.73) as compared to non-ranitidine treated patients (2.26 +/- 0.57 and 2.53 +/- 0.79 in group I and group II respectively). Number of patients at risk (pH \leq 2.5 and volume \geq 0.4 ml/kg) was not significantly different in group I and group II. Mean thirst and behaviour scores were significantly higher in fluid treated patients (groups II and III) as compared to control ($p < 0.01$). To conclude, administration of pre-operative water (5 ml/kg) along with ranitidine (2 mg/kg) favourably modifies gastric fluid volume and pH, improves patient behaviour and minimises the number of patients at risk of aspiration pneumonitis, should the child aspirate.

40. Gopal, B., Singhal, P., and Gaur, S.N. Gastroesophageal reflux disease in bronchial asthma and the response to omeprazole. *Asian Pac J Allergy Immunol* 23: 29-34, 2005.

The objective of this study was to determine the incidence of gastroesophageal reflux disease (GERD) in bronchial asthma and the role of omeprazole for asthmatics with symptoms of GERD. Seventy asthmatics were screened for GERD by questionnaire. Patients with a history suggestive of GERD were confirmed by Bernstein test and further investigated for airway responsiveness to instillation of HCl in the esophagus. Symptom score, drug score and spirometric

values were recorded initially and after four weeks of treatment with omeprazole. It was found that 74.28% of asthmatics had a history of GERD. Forty patients tested positive by Bernstein test and also showed airway responsiveness to instillation of HCl in the esophagus. There was a significant improvement in symptom scores ($p < 0.001$), drug scores ($p < 0.001$) and spirometric values ($p < 0.001$) after adding omeprazole to their treatment regimen. It was concluded that bronchial asthma and GERD are associated in the majority of patients (57.14%) and such patients are likely to improve with omeprazole.

41. Goresky, G.V., Finley, G.A., Bissonnette, B., and Shaffer, E.A. Efficacy, duration, and absorption of a paediatric oral liquid preparation of ranitidine hydrochloride. *Can J Anaesth* 39: 791-798, 1992.

The objectives of this study were to assess the clinical efficacy of a new oral ranitidine liquid preparation in reducing gastric acidity and volume, to determine the degree of absorption of the drug, and to determine the duration of drug effect. Eighty preoperative children between the ages of one and six years were enrolled in each of three centres. Each subject was allocated to one of the following groups: Group A - apple juice, 5 ml.kg⁻¹ plus placebo liquid; Group B - apple juice, 5 ml.kg⁻¹ plus ranitidine hydrochloride 2 mg.kg⁻¹; Group C - water, 5 ml and placebo liquid; or Group D - water, 5 ml and ranitidine liquid 2 mg.kg⁻¹. All study agents were administered at least two hours before surgery along with a dye marker, sulfobromophthalein 1 ml (50 mg.ml⁻¹). Following induction of anaesthesia, gastric fluid was aspirated, and analyzed for pH, volume, and sulfobromophthalein content (as an index of the ingested fluids). A serum sample was also drawn and analyzed for ranitidine content by high performance liquid chromatography. Groups B and D had fewer subjects with pH below 2.5 and gastric volume > 0.4 ml.kg⁻¹. The duration of reduced volume and acidity was shown to be greatest from two to four hours after drug administration. Thirty-three percent of subjects receiving oral ranitidine, 2 mg.kg⁻¹ hydrochloride as a single dose demonstrated no measurable effect on gastric pH and volume; 28 of those subjects had adequate ranitidine serum levels.

42. Gottrand, F., Kalach, N., Spyckerelle, C., Guimber, D., Mougnot, J.F., Tounian, P., Lenaerts, C., Roquelaure, B., Lachaux, A., Morali, A., Dupont, C., Maurage, C., Husson, M.O., and Barthelemy, P. Omeprazole combined with amoxicillin and clarithromycin in the eradication of *Helicobacter pylori* in children with gastritis: A prospective randomized double-blind trial. *J Pediatr* 139: 664-668, 2001.

OBJECTIVES: The aim of this multicenter prospective, randomized, double-blind study was to assess the efficacy of the combination of omeprazole, amoxicillin, and clarithromycin (OAC) for the treatment of *Helicobacter pylori* gastritis in children. STUDY DESIGN: Seventy-three children with dyspeptic symptoms were included in the trial (mean age 10.8 years; range, 3.3 to 15.4). Patients were randomized to receive OAC or amoxicillin and clarithromycin (AC) for 7 days. *H pylori* status was assessed before and 4 weeks after eradication treatment, by

use of the carbon 13-labeled urea breath test. RESULTS: In intent-to-treat analysis (n = 63), eradication rates were 74.2% (95% CI, 58.7 to 89.6) in the OAC group and 9.4% (95% CI, 0 to 19.5) in the AC group. In per-protocol analysis (n = 53), the eradication rate increased to 80% (95% CI, 64.3 to 95.7), remaining significantly higher than in AC group (10.7%; 95% CI, 0 to 22.2). Resistance of strains to clarithromycin was rare (3/39 = 7.7%) and was not associated with failure of treatment. Adverse events were reported in 24.6% of patients and remained mild. CONCLUSION: This study shows that 1-week OAC triple therapy results in successful eradication of H pylori in 75% of children with gastritis.

43. Goudsouzian, N.G., and Young, E.T. The efficacy of ranitidine in children. *Acta Anaesthesiol Scand* 31: 387-390, 1987.

The effect of preoperative oral ranitidine on intragastric pH and volume of aspirate was evaluated in anaesthetized children. Five groups of eight randomly assigned children were evaluated. The first group acted as control and the other groups received 2, 2.5, 3, 3.5 mg kg⁻¹ ranitidine, respectively. The drug was administered 1-4 h preoperatively. The intragastric pH was measured by a pH electrode through an orogastric tube, and the volume of aspirate was recorded every hour. At the time of first measurement oral ranitidine was significantly effective (P less than 0.001) in increasing the pH of intragastric contents to above the safe level of 2.5 in 94% of the children. At the second measurement an hour later, it was effective in all the children. Ranitidine has no significant effect on the volume of gastric aspirate and also there was no significant difference in the effect on the pH of the various doses of ranitidine studied. Oral ranitidine at doses of 2-3.5 mg kg⁻¹ is effective in decreasing gastric acidity in children.

44. Gremse, D., Winter, H., Tolia, V., Gunasekaran, T., Pan, W.J., Karol, M., Chiu, Y.L., Pilmer, B., and Book, L. Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 35 Suppl 4: S319-326, 2002.

OBJECTIVES: To evaluate the pharmacokinetics and pharmacodynamics of lansoprazole in children between 1 and 11 years of age with gastroesophageal reflux disease (GERD). METHODS: In a multicenter, open-label trial of pediatric patients with symptomatic GERD, children were assigned, based on their weight, to receive lansoprazole 15 mg (patients weighing < or = 30 kg) or lansoprazole 30 mg (patients weighing > 30 kg) once daily. The effects of lansoprazole on 24-hour median intragastric pH, the percentages of time intragastric pH was above 3 and 4, and pharmacokinetic parameters were assessed at the day-5 visit and compared to baseline. RESULTS: Sixty-six children were enrolled in the study. Mean lansoprazole C(max) values of 790.9 ng/mL and 898.5 ng/mL and T(max) values of 1.5 hours and 1.7 hours were observed in the < or = 30 kg and the > 30 kg body weight treatment groups, respectively. AUC₀₋₂₄ values of 1707 ng x h/mL and 1883 ng x h/mL and T_{1/2} values of 0.68 hours and 0.71 hours were

observed in the $< \text{ or } = 30 \text{ kg}$ and $> 30 \text{ kg}$ lansoprazole body weight treatment groups, respectively. There was no statistical significant difference in AUC₀₋₂₄ between the two groups ($P = 0.2571$). After 5 days of treatment lansoprazole produced significant increases in patients' 24-hour mean intragastric pH and the percentages of time intragastric pH was above 3 and 4 compared to baseline. CONCLUSION: The observed pharmacokinetic properties of lansoprazole in children between 1 and 11 years of age with GERD were similar to those previously observed in healthy adult subjects. Lansoprazole significantly increased the mean 24-hour intragastric pH and the percentages of time intragastric pH was above 3 and 4 when children were dosed with either 15 or 30 mg according to body weight.

45. Guay, J., Santerre, L., Gaudreault, P., Goulet, B., and Dupuis, C. Effects of oral cimetidine and ranitidine on gastric pH and residual volume in children. *Anesthesiology* 71: 547-549, 1989.

The effect of orally administered cimetidine 7.5 mg/kg (group 1), ranitidine 1.5 mg/kg (group 2), ranitidine 2.0 mg/kg (group 3), or a placebo (group 4) on gastric pH and gastric residual volume of 60 healthy children 2-6 yr of age admitted for elective surgery was evaluated. Both cimetidine and ranitidine administered 1-2 h prior to induction of anesthesia effectively increased the gastric pH: 5.47 - 1.85 ml/kg (group 1), 4.92 +/- 2.1 ml/kg (group 2), 5.30 +/- 1.82 ml/kg (group 3) compared with 1.75 +/- 0.58 ml/kg (group 4) (P less than 0.001). A single dose of ranitidine 1.5 mg/kg was as effective as ranitidine 2.0 mg/kg and cimetidine 7.5 mg/kg. Neither drug decreased the gastric residual volume: 0.32 +/- 0.33 ml/kg (group 1), 0.31 +/- 0.06 ml/kg (group 2), 0.23 +/- 0.05 ml/kg (group 3), and 0.33 +/- 0.05 ml/kg (group 4). The combination of a volume greater than 0.4 ml/kg and a pH less than 2.5 was found in 33% (five of 15) of patients in the placebo group (group 4). In contrast, there were no patients with this combination in groups 1, 2, or 3 (P less than 0.001).

46. Guimaraes, E.V., Marguet, C., and Camargos, P.A. Treatment of gastroesophageal reflux disease. *J Pediatr (Rio J)* 82: S133-145, 2006.

OBJECTIVES: To review the literature on the treatment of gastroesophageal reflux disease (GERD) with emphasis on pharmacological aspects. To identify particularities of pharmacological treatment of esophageal and extraesophageal manifestations of the disease. SOURCES: Electronic search of the PubMed/MEDLINE and Cochrane Collaboration databases. Controlled and randomized studies published since 2000 and reviews representing consensus positions and directives published within the last 10 years were identified. SUMMARY OF THE FINDINGS: The drugs currently available for the treatment of GERD do not act in the primary mechanism of the disease, i.e. transitory relaxation of the lower esophageal sphincter. Pharmacological treatment of GERD with symptoms or with esophageal injury is based on the suppression of acid secretion, particularly with proton pump inhibitors. When the hyperreactivity

of the lower airways coexists with esophageal GERD symptoms, suppression of acid secretions should be of benefit in managing the respiratory disease in the presence of a causal relationship; however, this is not usual. When esophageal symptoms are not present, esophageal 24-hour pH study should be carried out prior to starting pharmacological treatment for GERD. Improvement of respiratory symptoms may be delayed with relation to esophageal symptoms. It is common for GERD to recur and pharmacological treatment should be repeated or continued indefinitely, depending on clinical presentation of the disease.

CONCLUSIONS: The strategies that have been proposed for the pharmacological treatment of GERD in children are primarily based on studies of case series or on studies with adults. There have been very few controlled and randomized studies in children. Undertaking a greater number of these studies might reinforce existing aspects or establish new aspects of management.

47. Gunasekaran, T., Gupta, S., Gremse, D., Karol, M., Pan, W.J., Chiu, Y.L., Keith, R., and Fitzgerald, J. Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. *J Pediatr Gastroenterol Nutr* 35 Suppl 4: S327-335, 2002.

OBJECTIVES: To evaluate the pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability of lansoprazole in adolescents between 12 and 17 years of age with gastroesophageal reflux disease (GERD). **METHODS:** Adolescents with symptomatic, endoscopically and/or histologically proven GERD were enrolled in this multicenter, double-blind trial and randomized to lansoprazole 15 mg or 30 mg once daily for 5 days. **RESULTS:** Sixty-three adolescents were enrolled in the study. After lansoprazole administration, T(max) occurred at 1.6 hours in those treated with lansoprazole 15 mg and at 1.7 hours in those treated with lansoprazole 30 mg. Dose-proportional increases in lansoprazole C(max) and AUC were observed in the treatment groups. Age, weight, and gender had no significant effect on T(max), C(max), or AUC. Lansoprazole produced significant increases ($P < \text{or} = 0.05$) in mean 24-hour intragastric pH and the percentages of time intragastric pH was above 3 and 4. The majority of adolescents treated with lansoprazole 15 mg (69%, 22/32) or lansoprazole 30 mg (74%, 23/31) demonstrated improvement in their reflux symptoms after 5 days of treatment. Adolescents in both dosage groups exhibited reductions from baseline in the percentage of days and nights with heartburn (or other predominant symptom of GERD), the severity of heartburn, the percentage of days antacids were used, and the number of antacid tablets used per day. Pharyngitis and headache were the most commonly reported side effects among adolescents treated with lansoprazole 15 mg and 30 mg, respectively. Five patients experienced adverse events considered to be possibly treatment-related. One patient with a history of environmental allergies experienced a mild allergic reaction after 3 days of treatment with lansoprazole 15 mg. Among those treated with lansoprazole 30 mg, 4 patients each reported one occurrence of pain (toothache), diarrhea, dizziness, and rash. **CONCLUSION:** The pharmacokinetic parameters of lansoprazole observed in

this study of adolescents are similar to those observed in studies of healthy adults. Lansoprazole 15 mg or 30 mg once daily for 5 days produces significant increases in intragastric pH, effectively relieves symptoms of reflux disease, and is well tolerated in adolescents with GERD.

48. Gunasekaran, T., Tolia, V., Colletti, R.B., Gold, B.D., Traxler, B., Illueca, M., and Crawley, J.A. Effects of esomeprazole treatment for gastroesophageal reflux disease on quality of life in 12- to 17-year-old adolescents: an international health outcomes study. *BMC Gastroenterol* 9: 84, 2009.

BACKGROUND: Although gastroesophageal reflux disease (GERD) is common in adolescents, the burden of GERD on health-related quality of life (HRQOL) in adolescents has not been previously evaluated. Therefore, the objective of the study was to examine the effect of GERD on HRQOL in adolescents.

METHODS: This international, 31-site, 8-week safety study randomized adolescents, aged 12 to 17 years inclusive, with GERD to receive esomeprazole 20 or 40 mg once daily. The Quality of Life in Reflux and Dyspepsia questionnaire (QOLRAD), previously validated in adults, consists of 25 questions grouped into 5 domains: emotional distress, sleep disturbance, food/drink problems, physical/social functioning, and vitality. The QOLRAD was administered at the baseline and week-8 (final) visits. RESULTS: Of the 149 patients randomized, 134 completed the QOLRAD at baseline and final visits and were eligible for analysis of their HRQOL data. Baseline QOLRAD scores indicated GERD had a negative effect on the HRQOL of these adolescents, especially in the domains of vitality and emotional distress, and problems with food/drink. At the final visit, mean scores for all 5 QOLRAD domains improved significantly ($P < .0001$); change of scores (ie, delta) for all domains met or exceeded the adult QOLRAD minimal clinically significant difference standard of 0.5 units. CONCLUSION: GERD had a negative effect on QOL in adolescents. After esomeprazole treatment, statistically and clinically significant improvements occurred in all domains of the QOLRAD for these adolescents. TRIAL REGISTRATION: D9614C00098; ClinicalTrials.gov Identifier NCT00241501.

49. Gunasekaran, T.S., and Hassall, E.G. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 123: 148-154, 1993.

Omeprazole, a potent inhibitor of acid secretion, is effective in adults with severe gastroesophageal reflux, but no such data are available on children. We studied 15 children in whom treatment with histamine (type 2) blockers and prokinetic agents had failed; 4 had also had one or more funduplications. Their ages were 0.8 to 17 years (mean, 8.1 years) and weights were 7.5 to 30.7 kg (mean, 18.6 kg). Of the 15 children, 8 were neurologically handicapped. All patients had endoscopic and histologic evidence of esophagitis; most had esophagitis grade 3 to 4. Patients were initially given omeprazole at 10 to 20 mg; the dose was titrated upward until results of a subsequent 24-hour intraesophageal pH study was normal. Symptoms and signs abated and evidence of esophagitis

diminished in all patients. Omeprazole was given for periods of 5.5 to 26 months (mean, 12.2 months). The effective total dose was 20 to 40 mg (0.7 to 3.3 mg/kg) in 11 patients, 10 mg (0.7 mg/kg) in 1 patient, and 60 mg (1.9 to 2.4 mg/kg) in 3 patients. The dosage range was 0.7 to 3.3 mg/kg per day (mean, 1.9 mg/kg). Mildly elevated transaminase values in 7 patients and elevated fasting gastrin levels in 11 patients were present; in 6 of the 11, gastrin levels were 3 to 5.5 times the upper limit of normal. We found omeprazole to be highly effective in this group of patients with severe esophagitis refractory to other measures. We recommend a starting dose of 0.7 mg/kg as a single morning dose; the adequacy of reflux control is then determined by follow-up 24-hour intraesophageal pH studies. Omeprazole appears to be safe for short-term use, but further studies are needed to assess long-term safety because the significance of chronically elevated gastrin levels in children is unknown.

50. Gustafsson, P.M., Kjellman, N.I., and Tibbling, L. A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-oesophageal reflux. *Eur Respir J* 5: 201-206, 1992.

In order to study the importance of gastro-oesophageal reflux (GOR) as a trigger of asthma the effect of inhibition of gastric acid secretion on asthma was assessed in a double-blind, cross-over, placebo-controlled trial over four weeks in 37 children and adolescents (mean age 14 yrs) with bronchial asthma. Ranitidine 300 mg, (150 mg if B.W. was less than 40 kg) was given as a single evening dose during four weeks. In previous investigations 18 of the 37 patients had been shown to have pathological GOR by 24 h pH monitoring in the oesophagus. The remaining 19 patients with normal GOR served as controls for possible effects of ranitidine on asthma, not related to reduction of GOR. A modest (30%) but statistically significant reduction of nocturnal asthma symptoms was produced by ranitidine in the patients with pathological GOR when compared to those with normal GOR. There was a significant correlation between the improvement in asthma symptoms and the degree of acid reflux. Side-effects of ranitidine were negligible. Acid reflux appears to be only a weak stimulus for bronchoconstriction in children and adolescents with bronchial asthma and pathological GOR. Further confirmative trials with more potent inhibitors of gastric acid secretion are, however, warranted.

51. Haizlip, J.A., Lugo, R.A., Cash, J.J., and Vernon, D.D. Failure of nasogastric omeprazole suspension in pediatric intensive care patients. *Pediatr Crit Care Med* 6: 182-187, 2005.

OBJECTIVES: To determine the efficacy of nasogastric administration of omeprazole suspension in raising the gastric pH >4 in critically ill pediatric patients and to determine the most appropriate dosing regimen for this indication. DESIGN: Open-label pharmacodynamic study. SETTING: Twenty-six bed tertiary-care pediatric intensive care unit. PATIENTS: Mechanically ventilated children aged 1-18 yrs with an additional risk factor for stress ulcer formation.

INTERVENTIONS: Continuous gastric pH monitoring was performed during administration and dose titration of omeprazole suspension to achieve the goal of gastric pH >4 for greater than 75% of the dosing interval. **MEASUREMENTS AND MAIN RESULTS:** Data were collected from 18 patients. Subjects were categorized based on the pharmacologic response to nasogastric administration of 1 mg/kg omeprazole suspension (maximum 20 mg) as rapid (n = 9), late (n = 5), and nonresponders (n = 4). Rapid responders required 0.72 mg/kg per day omeprazole suspension to achieve adequate gastric pH elevation for stress ulcer prophylaxis. Late responders required 1.58 mg/kg per day. Nonresponders did not achieve adequate elevation of gastric pH for stress ulcer prophylaxis. **CONCLUSIONS:** Nasogastric administration of omeprazole suspension has variable efficacy in critically ill pediatric patients. Half of the studied subjects either required significant dose titrations to achieve gastric acid suppression or did not respond to nasogastric administration of omeprazole suspension.

52. Hallerback, B., Glise, H., Johansson, B., Rosseland, A.R., Hulten, S., Carling, L., and Knapstad, L.J. Gastro-oesophageal reflux symptoms--clinical findings and effect of ranitidine treatment. *Eur J Surg Suppl*: 6-13, 1998.

BACKGROUND: This study was performed to study the demography, effect of treatment with ranitidine and relapse pattern in patients with reflux symptoms. **METHODS:** Patients with reflux symptoms were examined by endoscopy and included in a double-blind, comparative trial of placebo and ranitidine 150 mg b.i.d. for two weeks. At two weeks satisfied patients continued the same treatment. Non-satisfied patients were randomised to ranitidine 150 mg b.i.d. or q.i.d for another two weeks. After four weeks medication was stopped and satisfied patients were followed for 24 weeks. No further endoscopy was performed. **RESULTS:** Four hundred and twenty-seven patients were randomised. At two weeks there was no significant difference between placebo and ranitidine, regarding the proportion of patients with complete relief from symptoms or satisfied with treatment. Ranitidine was superior to placebo in improving symptoms at two weeks. Ranitidine, 150 mg q.i.d. offered no additional advantage in weeks three to four over prolonging treatment with 150 mg b.i.d. after the first two weeks. Patients with oesophagitis at inclusion relapsed more than those with symptoms only, 67% compared with 52%, ($p = 0.013$). **CONCLUSIONS:** The effect of ranitidine was marginal compared to placebo. The relapse rate was high after treatment stopped.

53. Hassall, E. Wrap session: is the Nissen slipping? Can medical treatment replace surgery for severe gastroesophageal reflux disease in children? *Am J Gastroenterol* 90: 1212-1220, 1995.

For over 20 yr, antireflux surgery has been the treatment of choice for severe gastroesophageal (GE) reflux disease in children, and antireflux operations are said to be the commonest major surgical procedures performed by pediatric surgeons in North America. Yet, only recently have the results of surgery been

more closely examined; both the surgical morbidity and operative failure rates have been found to be particularly high in children with neurological impairment, repaired esophageal atresia, and chronic lung disease. Of interest, these groups of children are among those most at risk for developing severe GE reflux disease in the first place. Close examination of surgical reports also raises some questions about the indications for surgery in some children, specifically whether the presence of severe GE reflux disease had been established before surgery and whether a trial of appropriate medical management had been given. Failure of medical management has always been an accepted indication for surgery. However, in the past the medical management that was available for children was ineffective because drug dosages were not optimized (H2-receptor antagonists), the drugs had side effects precluding their use long term or in high doses (bethanechol, metoclopramide), or they were simply insufficiently potent to treat severe GE reflux disease (all the above drugs plus cisapride). Thus, in the past, failure of medical management did not mean failure of very much. In contrast, the proton pump inhibitor omeprazole has recently been shown to be effective and safe for the treatment of severe childhood GE reflux disease refractory to other medical treatments and where antireflux surgery has failed. The issues of why certain groups of children are at highest risk for severe GE reflux disease are discussed as are the outcomes and roles of surgical and medical treatment for all groups of children with severe GE reflux disease. The options of antireflux surgery or omeprazole should be reserved for those children with severe GE reflux disease, e.g., GE reflux accompanied by a complication.

54. Hassall, E., Israel, D., Shepherd, R., Radke, M., Dalvag, A., Skold, B., Junghard, O., and Lundborg, P. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. International Pediatric Omeprazole Study Group. *J Pediatr* 137: 800-807, 2000.

OBJECTIVES: To determine the efficacy, safety, and tolerability of omeprazole in children and to determine the doses required to heal chronic, severe esophagitis. **STUDY DESIGN:** Open multicenter study in children aged 1 to 16 years with erosive reflux esophagitis. The healing dose of omeprazole used was that with which the duration of acid reflux was <6% of a 24-hour intraesophageal pH study. Follow-up endoscopy was performed after 3 months of treatment with the healing dose. **RESULTS:** At entry, two thirds of 57 patients who completed the study had esophagitis grade 3 or 4 (scale 0-4); some 50% had neurologic impairment or repaired esophageal atresia. Of the 57 patients, 54 healed; 3 did not heal and left the study, and 3 healed with a second course. Doses required for healing were 0.7 to 3.5 mg/kg/d: 0.7 mg/kg/d in 44% of patients and 1.4 mg/kg/d in another 28%. Healing dose correlated with grade of esophagitis but not with age or underlying disease. Reflux symptoms improved dramatically in almost all of the 57 patients, including the unhealed patients. **CONCLUSIONS:** Omeprazole is well tolerated, highly effective, and safe for treatment of erosive esophagitis and symptoms of gastroesophageal reflux in children, including children in whom

antireflux surgery or other medical therapy has failed. On a per-kilogram basis, the doses of omeprazole required to heal erosive esophagitis are much greater than those required for adults.

55. Heine, R.G., Catto-Smith, A.G., and Reddihough, D.S. Effect of antireflux medication on salivary drooling in children with cerebral palsy. *Dev Med Child Neurol* 38: 1030-1036, 1996.

Salivary drooling is a common and debilitating problem in cerebral palsy (CP). We hypothesised that gastro-oesophageal reflux (GOR) may exacerbate drooling by stimulation of the oesophago-salivary reflex. The aim of our study was to assess the role of GOR in children with CP and severe drooling. Twenty-four children with CP and severe drooling underwent oesophageal pH monitoring (N = 23) or oesophagoscopy (N = 1). Nine had pathological GOR and were enrolled in a double blinded, placebo controlled cross-over trial of medical antireflux therapy (ranitidine plus cisapride) versus placebo. Drooling was measured by semi-quantitative observation (drooling quotient) and a questionnaire-based scoring system (rated by the child's caregivers). Mean drooling quotients and scores for drooling severity and frequency were not significantly different between active medication and placebo. In our study, treatment of pathological GOR did not improve salivary drooling in children with CP.

56. Hendriks, J.J., Kester, A.D., Donckerwolcke, R., Forget, P.P., and Wouters, E.F. Changes in pulmonary hyperinflation and bronchial hyperresponsiveness following treatment with lansoprazole in children with cystic fibrosis. *Pediatr Pulmonol* 31: 59-66, 2001.

SUMMARY. In this prospective open study of 14 children with cystic fibrosis (CF), we evaluated the effect of 1 year adjuvant therapy with lansoprazole, a proton pump inhibitor (PPI), on growth, fecal fat loss, body composition and lung function. Only stable patients with pancreatic insufficiency were included, and their data were compared to those of a large Dutch pediatric normal reference population. During the use of the PPI, mean weight and height did not change significantly, while body mass index improved ($P < 0.05$). An immediate significant and persistent reduction of fecal acid steatocrit ($P < 0.05$) was demonstrated. Compared to normal Dutch children, the CF patients showed significantly decreased standard deviation scores (SDS) for total body fat (TBF, -0.966) and fat-free mass (FFM, -1.826). Under lansoprazole, TBF improved significantly ($P < 0.05$), while mean FFM remained unchanged. A significant improvement in total lung capacity ($P < 0.05$), residual volume ($P = 0.055$), and maximal inspiratory mouth pressure ($P = 0.002$) was also demonstrated. Hyperinflation tended to decrease during the use of a PPI. Daily recordings of peak expiratory flow (PEF) showed a maximal diurnal variability of 28% of recent best PEF and minimal morning PEF of 72% of recent best PEF, confirming that bronchial hyperresponsiveness is increased in CF. We conclude that adjuvant therapy with lansoprazole in young CF patients with persistent fat malabsorption,

decreased fat losses and improved total body fat. Lung hyperinflation decreased, which may partly explain the improvement in inspiratory muscle performance. The simultaneous improvements in body composition and lung hyperinflation suggest a relationship between these two parameters. Further research is necessary to confirm such a relationship and to elucidate the mechanisms involved.

57. Heyman, M.B., Zhang, W., Huang, B., Chiu, Y.L., Amer, F., and Winter, H.S. Pharmacokinetics and pharmacodynamics of lansoprazole in children 13 to 24 months old with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 44: 35-40, 2007.

OBJECTIVES: To evaluate the pharmacokinetics and pharmacodynamics of lansoprazole in children between 13 and 24 months of age with gastroesophageal reflux disease (GERD). METHODS: From the population of 66 children with symptomatic GERD, erosive esophagitis (> or = grade 2) or esophageal pH < 4 for > 4.2% of the 24-h period who participated in a phase I/II, open-label, multicenter (11 sites) US study, a subanalysis of 8 toddlers between 13 and 24 months of age was performed. All children were treated, based on body weight, with lansoprazole 15 mg once daily for 8 to 12 weeks. If a child were still symptomatic after 2 weeks of treatment, then the dose of lansoprazole could be increased to twice daily at the discretion of the investigator. Pharmacokinetic parameters were assessed at day 5. Twenty-four-hour median intragastric pH and the percentage of time intragastric pH > 3 or > 4 were assessed at baseline and at day 5 of treatment. Symptom response was assessed by investigator interview and daily diary. Safety was monitored by physical examinations including vital signs, adverse event assessments and laboratory evaluations. RESULTS: Pharmacokinetic analysis of 5 children found a mean time to reach maximum concentration of 1.4 h, maximal plasma concentrations of 894 ng/mL, area under the concentration time curve of 1906 ng * h/mL and a half-life of 0.66 h. Significant (P < or = 0.027) increases from baseline to day 5 were observed in mean 24-h intragastric pH (2.76-3.52) and the percentages of time pH were > 3 (29.46%-55.36%) and pH was > 4 (16.96%-40.77%). Six of the 8 children had improvement in their overall GERD symptom severity on the basis of investigator assessment, and a reduction was seen in the percentage of days with moderate, severe or very severe GERD symptoms compared with baseline. The dosage of lansoprazole was increased in 3 of the 8 children. Median fasting serum gastrin level increased from 65.0 pg/mL at baseline to 136.5 pg/mL at the final visit. Treatment-related events were mild constipation (1 subject) and mild diarrhea (1 subject). CONCLUSIONS: Although larger studies are needed to confirm these results, lansoprazole displays pharmacokinetic and pharmacodynamic parameters in children between 13 and 24 months of age that are similar to those results observed in older children as well as adults.

58. Hussein, Z., Granneman, G.R., Mukherjee, D., Samara, E., Hogan, D.L., Koss,

M.A., and Isenberg, J.I. Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. *Br J Clin Pharmacol* 36: 391-398, 1993.

1. The pharmacokinetics and pharmacodynamics of lansoprazole, an antisecretory and antiulcer agent, were evaluated in 12 older (> 60 years) and 12 younger (< 60 years) healthy men. 2. Doses of lansoprazole (15 or 30 mg) or placebo were each given once daily for 7 consecutive days in this randomized, double-blind, three-way crossover study. Plasma concentrations and urinary excretion of lansoprazole and its metabolites, and gastric acid secretion were monitored after dosing on days 1 and 7 of each treatment period. 3. Within each age group, lansoprazole pharmacokinetics were linear. The mean clearance and elimination half-life of lansoprazole were about 40% lower and higher, respectively, in the older subjects (CL₀: 12-14 vs 20-24 l h⁻¹); t_{1/2,z}: 1.90-2.19 vs 1.26-1.44 h). 4. At each dose level, acid secretion was more inhibited in the older group. However, the AUC associated with a 50% decrease in acid secretion was similar (849 vs 892 ng ml⁻¹ h) for both age groups. Multiple dosing decreased the maximum possible inhibition more in the older group than in the younger group. 5. Since the decrease in acid output associated with equivalent AUCs on day 1 was similar for the two age groups, the greater difference between day 1 and day 7 secretion in the older group indicates that recovery of secretory activity may decline with increasing age.

59. Ikenoue, T., Ito, J., Matsuda, Y., and Hokanishi, H. Effects of ranitidine on maternal gastric juice and neonates when administered prior to caesarean section. *Aliment Pharmacol Ther* 5: 315-318, 1991.

Ranitidine hydrochloride, a histamine H₂-receptor antagonist, was intravenously administered to 61 pregnant women at a dose of 50 mg as premedication for caesarean section; its effects on gastric secretion were studied in the mother and the newborn. The volume of the maternal gastric juice collected immediately after the induction of anaesthesia averaged 14.0 ± 10.0 ml with pH 3.48 ± 1.70, and at the time of extubation, 3.6 ± 2.8 ml with pH 4.19 ± 1.79, respectively. Forty-four full-term neonates whose mothers had received ranitidine were selected to investigate the effects of ranitidine. Another 45 full-term normal newborns delivered vaginally, and 14 by caesarean section, served as controls. No effects of ranitidine infusion in the mothers were detected in the newborn children. The gastric pH of the newborn at birth and 24 hours after birth, gastrointestinal symptoms and the general growth checked at the regular one-month work-up after birth did not differ in test and control groups.

60. Ito, S., Weitzman, S., Klein, J., Greenberg, M., Lau, R., Atanakovic, G., and Koren, G. Lack of cisplatin-ranitidine kinetic interactions: in vivo study in children, and in vitro study using dog renal brush border membrane vesicles. *Life Sci* 62: PL387-392, 1998.

The interactions between cisplatin and organic ions have been extensively

investigated in animal models for the potential to reduce cisplatin cellular uptake and resultant nephrotoxicity. To further investigate the beneficial interaction clinically, we studied the effects of the organic cation, ranitidine, on the renal handling of cisplatin in children. In parallel, we examined the effects of cisplatin on the uptake kinetics of organic cations and anions by brush border membrane vesicles (BBMV) prepared from dog renal cortex. The results indicate that: 1) there is no measurable effect of ranitidine on renal clearance of cisplatin in children; and 2) BBMV uptake of anionic p-aminohippurate, but not cationic N-methylnicotinamide, is inhibited by cisplatin at concentrations of <1 mM. These findings suggest that cisplatin may not share transport systems with organic cations to a clinically significant degree. Assuming that renal tubular transport is a prerequisite for cisplatin nephrotoxicity, the lack of apparent kinetic interactions between cisplatin and organic cations may preclude clinical use of organic cations as a modality to prevent cisplatin nephrotoxicity.

61. Kato, S., Konno, M., Maisawa, S., Tajiri, H., Yoshimura, N., Shimizu, T., Toyoda, S., Nakayama, Y., and Inuma, K. Results of triple eradication therapy in Japanese children: a retrospective multicenter study. *J Gastroenterol* 39: 838-843, 2004.

BACKGROUND: Large-scale clinical trials in children are lacking concerning *Helicobacter pylori* eradication therapies. The purpose of this study was to assess the efficacy of proton pump inhibitor (PPI)-based triple therapies in Japanese children. **METHODS:** This was a retrospective analysis of the first- and second-line PPI-based triple therapies from pediatric gastrointestinal units between 1996 and 2003. Data collected included doses and duration of regimens, drug compliance, success or failure of eradication, ulcer healing, and symptom response of those with dyspepsia and no ulcers. The results of antibiotic susceptibility tests were also reported in cases where these were performed. **RESULTS:** A total of 149 pediatric patients (mean age, 12.6 years) were studied, including 123 patients who received first-line therapy: 115 received a PPI plus amoxicillin and clarithromycin (PAC) and 8 received a PPI plus amoxicillin and metronidazole (PAM). Overall eradication rates of the first-line PAC and PAM therapies were 77.4% and 87.5%, respectively ($P = 0.68$). All 14 patients with failed PAC therapy received the second-line PAM regimen, resulting in an eradication rate of 100%. Mild side effects were reported only in PAC regimens (13.8%). Primary resistance to amoxicillin, clarithromycin, and metronidazole was detected in 0%, 34.7%, and 12.5% of the strains, respectively. The PAC regimen showed a high eradication rate for clarithromycin-susceptible strains (91.7%), but was relatively ineffective for resistant strains (40.0%) ($P < 0.01$). Eradication of *H. pylori* was associated with ulcer healing and symptomatic improvement among those with gastritis only (both; $P < 0.001$). Among 17 patients with iron-deficiency anemia, post-treatment hemoglobin levels were higher than the pretreatment levels ($P < 0.001$). **CONCLUSIONS:** The PAC regimen is effective in children. Clarithromycin resistance is associated with eradication failure. Metronidazole is a good substitute for clarithromycin as the

second-line option for children.

62. Kato, S., Ritsuno, H., Ohnuma, K., Iinuma, K., Sugiyama, T., and Asaka, M. Safety and efficacy of one-week triple therapy for eradicating *Helicobacter pylori* in children. *Helicobacter* 3: 278-282, 1998.

BACKGROUND: Proton pump inhibitor-based eradication therapy of *Helicobacter pylori* has been widely studied in adults, but there have been only a few reports about this therapy in children. The purpose of this study was to investigate the safety and efficacy of 1-week triple therapy for eradication of *H. pylori* and ulcer healing in children. **PATIENTS AND METHODS:** We prospectively studied 15 patients aged 2-17 years (5 with gastric ulcers, 8 with duodenal ulcers, and 2 with nodular gastritis alone). Three patients had H2 blocker-resistant duodenal ulcers. Patients received 0.75 mg/kg of lansoprazole b.i.d., 25 mg/kg of amoxicillin b.i.d., and 10 mg/kg of clarithromycin b.i.d. for 7 days. No additional therapy (including antisecretory drugs) was administered to any patients following eradication therapy. Patients underwent endoscopy to obtain antral biopsies (culture, urease test and histology) and to evaluate the mucosal status, and underwent a ¹³C-urea breath test before and 4-8 weeks after the completion of a 1-week course of therapy. **RESULTS:** All patients received the full drug regimen. Endoscopy showed complete healing of ulcers in 12 of 13 patients with peptic ulcer disease (92%). *H. pylori* was eradicated in 13 of 15 patients (87%). Diarrhea and/or an altered taste sensation occurred in 5 patients (33%). There were no hematological or biochemical abnormalities related to therapy. **CONCLUSION:** The 1-week triple therapy was safe and effective for eradicating *H. pylori*. The present study showed that ulcer healing in juveniles is closely associated with eradication of *H. pylori*, and that no additional therapy is required when *H. pylori* is eradicated. A shorter course of eradication therapy than 2 weeks may be suitable for children with *H. pylori* infection.

63. Kato, S., Takeyama, J., Ebina, K., and Naganuma, H. Omeprazole-based dual and triple regimens for *Helicobacter pylori* eradication in children. *Pediatrics* 100: E3, 1997.

OBJECTIVE: To evaluate the efficacy and safety of omeprazole-based dual and triple regimens for the treatment of children with *Helicobacter pylori* infection. **METHODS:** Twenty-two patients (3 with gastric ulcer, 12 with duodenal ulcer, and 7 with nodular gastritis alone) were studied. Twelve ulcer patients also had nodular gastritis. The dual regimen included a 2-week course of omeprazole (0.6 mg/kg twice a day) and amoxicillin (30 mg/kg twice a day) (n = 10), and the triple regimen included the dual regimen plus clarithromycin (15 mg/kg twice a day) (n = 12). In patients with active ulcers, omeprazole once daily was administered for another 4 weeks. Endoscopic biopsies were taken before therapy and 4 weeks after completion of a 2-week course of therapy, and patients were followed for 6 months. The gastritis score (grade 0 to 3) and serum anti-*H. pylori* IgG antibody titers were also determined. **RESULTS:** The regimens were tolerated by all

patients. Eradication rates for the dual and triple regimens were 70% and 92%, respectively. Active ulcers completely healed within 6 weeks. Patients with nodular gastritis alone showed different clinical responses to therapy. Pretreatment histology showed chronic gastritis in all patients. Successful H pylori eradication significantly reduced the mean gastritis score from 2.9 to 1.3, but unsuccessful eradication did not reduce it. The disappearance of antral nodularity often coincided with the success of eradication. Successful eradication significantly decreased pretreatment serum anti-H pylori IgG antibody titers by 29% at 1 month, by 52% at 3 months, and by 67% at 6 months. Side effects were mild and were reported in 23% of patients. CONCLUSION: An omeprazole-based regimen is safe and may be a better option for eradication of H pylori in children. Antral nodularity is a macroscopic marker of H pylori infection.

64. Kaufman, S.S., Loseke, C.A., Young, R.J., and Perry, D.A. Ranitidine therapy for esophagitis in children with developmental disabilities. *Clin Pediatr (Phila)* **35**: 451-456, 1996.

Esophagitis is common in children with cerebral palsy. Because histamine₂-receptor antagonists such as ranitidine have not been uniformly effective, we treated disabled children with esophagitis with greater than usual doses. Endoscopy and pH monitoring were used to monitor dose and response to treatment. A dose of 9.3 +/- 0.9 mg/kg/day did not improve visual or microscopic esophagitis after 3 months. A dose of 14.8 +/- 3.9 mg/kg/day resulted in only slight microscopic improvement, but symptoms were improved. There was no correlation between esophageal reflux index at enrollment and either severity of esophagitis or response to treatment. Elevation of gastric pH by ranitidine was infrequent. These results affirm that pH monitoring does not reliably identify disabled children with reflux esophagitis nor does ranitidine reliably heal this disorder.

65. Kearns, G.L., Andersson, T., James, L.P., Gaedigk, A., Kraynak, R.A., Abdel-Rahman, S.M., Ramabadran, K., and van den Anker, J.N. Omeprazole disposition in children following single-dose administration. *J Clin Pharmacol* **43**: 840-848, 2003.

Omeprazole is frequently used to treat gastroesophageal reflux in infants and children despite the lack of age-specific pharmacokinetic and dosing information in the approved product labeling. To address this challenge, the authors examined the potential influence of development and cytochrome P450 2C19 (CYP2C19) genotype on omeprazole disposition by conducting two pharmacokinetic (PK) studies in children and adolescents (ages 2-16 years) after a single oral 10- or 20-mg dose of the drug. Plasma omeprazole concentrations were determined by HPLC-MS from seven plasma samples obtained over a 6-hour postdose period. Pharmacokinetic parameters were determined by noncompartmental methods. Subjects were genotyped for CYP2C19 by PCR-RFLP. Data were available from 37 patients (19 female), 10 of whom were < or =

5 years of age. No drug-associated adverse events were observed. The numbers of functional CYP2C19 alleles per subject in the cohort were 2 (n = 25), 1 (n = 11), and 0 (n = 1). Pharmacokinetic parameters (mean +/- SD, range) were as follows: t_{max} (2.1 +/- 1.2, 1-6 h), C_{max} (331.1 +/- 333.6, 20.8-885.8 ng/mL), $AUC_{0-\infty}$ (809.5 +/- 893.8, 236.9-1330.9 ng/mL.h), $t_{1/2}$ (0.98 +/- 0.22, 0.7-1.4 h), and CL/F (1.8 +/- 1.4, 0.3-5.8 L/h/kg). Comparison of mean $AUC_{0-\infty}$ values normalized for dose (i.e., per 1 mg/kg) between subjects with one versus two functional CYP2C19 alleles revealed no statistically significant difference. In addition, the CL/F and apparent elimination rate constant (λ_z) for omeprazole were not significantly different for subjects with one versus two functional CYP2C19 alleles. No association between age and CL/F, $t_{1/2}$, or λ_z was observed. The range of $t_{1/2}$ values for omeprazole was similar to those reported in adults (1-1.5 h). CONCLUSIONS: (1) in children ages 2 to 16 years receiving 10 or 20 mg of omeprazole as a single oral dose, the PK are quite comparable to values reported for adults, and (2) in pediatric patients who are CYP2C19 extensive metabolizers, there was no association between genotype and the pharmacokinetics of omeprazole.

66. Kearns, G.L., Blumer, J., Schexnayder, S., James, L.P., Adcock, K.G., Reed, M.D., Daniel, J.F., Gaedigk, A., and Paul, J. Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. *J Clin Pharmacol* 48: 1356-1365, 2008.

The primary objective was to determine the pharmacokinetics of single oral and intravenous doses of pantoprazole in children 2 to 16 years of age. The secondary objective was to assess the safety and tolerability of these doses. Male and female hospitalized and nonhospitalized patients from ages 5 to 16 years received single oral doses (20 mg or 40 mg), and those from ages 2 to 16 years received single intravenous doses (0.8 mg/kg or 1.6 mg/kg) of pantoprazole. The plasma concentration-time data for each patient were analyzed using noncompartmental methods. Routine safety and tolerability assessments were also obtained. The mean values for peak plasma concentration and total area under the plasma concentration-time curve increased with increasing dose. Pharmacokinetic values were similar in patients from ages 2 to 16 years and to those previously obtained in adults. Statistically significant differences were observed for dose-normalized pantoprazole area under the plasma concentration-time curve when compared between CYP2C19 extensive metabolizers with 1 versus 2 functional alleles. All adverse events were mild in severity and considered to be unrelated to study drug. The pharmacokinetic profile of oral and intravenous pantoprazole was similar in children ages 2 to 16 years. The doses used here were safe and well tolerated in this population.

67. Kearns, G.L., and Winter, H.S. Proton pump inhibitors in pediatrics: relevant pharmacokinetics and pharmacodynamics. *J Pediatr Gastroenterol Nutr* 37 Suppl 1: S52-59, 2003.

SUMMARY: A marked discordance between the disposition of proton pump inhibitors (PPIs) in plasma and the kinetics of effect suggests the need for new approaches to characterize the clinical pharmacology of PPIs in infants and children. An assessment of pharmacokinetics and pharmacodynamics must take into account the genetic polymorphism of CYP2C19 and the impact of ontogeny on the activity of this and other enzymes (e.g., CYP3A4) which affect the biotransformation of the PPIs and, thus, their plasma clearance. In addition, the potential effects of extemporaneous formulations of the drugs on their rate and extent of absorption must be considered. Because of the apparent safety of PPIs and a well-demonstrated dose-response-effect relationship in adults, pediatric pharmacokinetic data and an exposure correlate, such as the dose-area-under-the-plasma-concentration-versus-time-curve relationship, can be used as a bridge to determine pediatric dosing.

68. Kelly, D.A. Do H₂ receptor antagonists have a therapeutic role in childhood? *J Pediatr Gastroenterol Nutr* **19**: 270-276, 1994.

Studies of the therapeutic efficacy and indications for the use of histamine (H₂)-receptor antagonists (H₂RAs) in children are reviewed. In adequate dosages, both ranitidine and cimetidine reduce acid output and increase intragastric pH, and H₂RAs have been shown to be effective in the treatment of acid-peptic disease. Ranitidine is a more potent drug with a longer duration of action than cimetidine and thus requires less frequent administration. Dosage requirements vary according to age and clinical condition, and children require a relatively higher drug dosage (mg/kg) than adults. There is insufficient information on the long-term paediatric use of famotidine to validate its use in children, and the endocrinological side effects associated with cimetidine therapy in adults essentially preclude its long-term use in children. It is suggested that ranitidine administration is safe and effective in children with acid-peptic disease and should be considered as first-line treatment for children with severe oesophagitis or peptic ulceration and for the prophylaxis of stress ulceration and aspiration pneumonitis.

69. Kemmotsu, O., Mizushima, M., Morimoto, Y., Numazawa, R., Kaseno, S., Yamamura, T., and Yokota, S. Effect of preanesthetic intramuscular ranitidine on gastric acidity and volume in children. *J Clin Anesth* **3**: 451-455, 1991.

STUDY OBJECTIVE: To evaluate the effects of preanesthetic administration of intramuscular (IM) ranitidine on pH and volume of gastric contents in children. DESIGN: Three randomized treatment groups. SETTING: Central operating rooms at a university hospital. PATIENTS: Forty children age 1 to 10 years undergoing a variety of elective surgical procedures requiring general anesthesia with endotracheal intubation. INTERVENTIONS: IM ranitidine 1 mg/kg (n = 15) or 2 mg/kg (n = 15) was administered 2 hours prior to induction of anesthesia. Ten patients without ranitidine served as the control group. An orogastric tube was

inserted into each patient. MEASUREMENTS AND MAIN RESULTS: Gastric fluid pH and volume were measured every hour in the three groups. Plasma ranitidine concentrations were measured in ten patients of the ranitidine-treated groups. The mean volume of gastric fluid at induction of anesthesia was significantly lower in the ranitidine-treated patients (2.4 ml for ranitidine 1 mg/kg, 3.2 ml for ranitidine 2 mg/kg) than in the controls (8.6 ml; p less than 0.05). The mean pH values at induction of anesthesia were significantly higher in the ranitidine-treated patients (4.6 for 1 mg/kg, 6.7 for 2 mg/kg) than in the controls (2.1; p less than 0.05). Dose-dependent plasma ranitidine concentrations were obtained. CONCLUSIONS: Preanesthetic IM ranitidine 1 to 2 mg/kg resulted in a higher pH and lower volume of gastric fluid at the time of induction and in a higher pH during 3 hours of anesthesia. This therapy may be a useful adjunct to premedication for children who have a greater than normal risk of pulmonary aspiration during anesthesia.

70. Khoshoo, V., and Dhume, P. Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 46: 352-354, 2008.

Proton pump inhibitors such as lansoprazole are used in the treatment of gastroesophageal reflux disease (GERD), but dosing guidelines for infants have not been determined. The objective of this study was to assess the clinical efficacy of 2 dosing regimens of lansoprazole in infants with GERD using the revised infant gastroesophageal reflux questionnaire scores (I-GERQ-R). Thirty consecutive infants (3-7 months) with GERD, whose conditions were diagnosed by I-GERQ-R scores of $>$ or $=16$, were randomly assigned to receive 1 of 2 lansoprazole dosing regimens: 15 mg given once per day (group A) or approximately 7.5 mg given 2 times per day (group B). Matched infants in a control group were treated with an extensively hydrolyzed formula (group C). Daily I-GERQ-R scores were gathered, and the scores after 1 and 2 weeks of treatment were used for analysis. The mean pretreatment scores were similar in groups A, B, and C (26.6, 26.9, and 25.9, respectively). After treatment there was a similar drop in the mean scores in groups A and B (20.6 and 20.0, respectively), but not in group C (25.8). At the end of the first week of treatment, in group A, 5 of 15 infants (33%) had a significant reduction in their I-GERQ-R scores, whereas in group B, 10 of 15 infants (67%) had a significant reduction in their I-GERQ-R scores ($P < 0.05$). At the end of the second week of treatment, groups A and B had similar numbers of patients with significant improvement (60% and 67%), which was higher than in group C (3/15, 20%). Overall, there was no difference in the symptom response, as measured by I-GERQ-R scores, between 15 mg of lansoprazole given once per day and 7.5 mg given twice per day in infants with GERD, but the twice-daily regimen produced a faster symptom response. Both regimens were significantly better than treatment of infants with an extensively hydrolyzed formula.

71. Khoshoo, V., and Haydel, R., Jr. Effect of antireflux treatment on asthma

exacerbations in nonatopic children. *J Pediatr Gastroenterol Nutr* 44: 331-335, 2007.

OBJECTIVE: To evaluate the asthma outcome of treatment with ranitidine or esomeprazole plus metoclopramide in older children with moderate-persistent asthma and gastroesophageal reflux disease (GERD). **PATIENTS AND METHODS:** The study patients included 44 patients with asthma and GERD who had received 1 year of treatment with a proton pump inhibitor/prokinetic combination and had shown significant clinical improvement in asthma symptoms and no exacerbations for more than 3 months. For further treatment, 30 of the 44 patients continued treatment with esomeprazole/metoclopramide (group A), and 14 switched to ranitidine (group B). Nine patients with GERD and asthma who had previously undergone fundoplication were used as control individuals (group C). All patients were followed up closely for exacerbation of asthma symptoms and treated according to a standardized protocol. **RESULTS:** During the 6-month follow-up, group B patients experienced significantly more exacerbations per patient (2.2) than did those in group A (0.33) or group C (0.77) ($P < 0.05$). **CONCLUSIONS:** Fundoplication or continued treatment with esomeprazole and metoclopramide is associated with significantly fewer exacerbations of asthma symptoms in children with moderate-persistent asthma and concomitant GERD in comparison with treatment with ranitidine.

72. Kocsis, I., Arato, A., Bodanszky, H., Szonyi, L., Szabo, A., Tulassay, T., and Vasarhelyi, B. Short-term omeprazole treatment does not influence biochemical parameters of bone turnover in children. *Calcif Tissue Int* 71: 129-132, 2002.

Gastric proton pump inhibitors are widely used in the treatment of dyspeptic problems and for the eradication of *H. pylori* infection. Data are not available on whether omeprazole, a representative of proton pump inhibitors, influences the function of osteoclastic H⁺-pump in children. We studied the impact of short-term omeprazole administration on the biochemical parameters of bone turnover in pediatric patients. Urinary calcium excretion, serum total alkaline phosphatase activity, collagen type 1 crosslinked C-telopeptide, and osteocalcin levels were determined in 34 children [20 girls (9 prepubertal) and 14 boys (6 prepubertal)] before and after 2 weeks of omeprazole treatment at a dose of 20 mg/day. The measured parameters were within the healthy reference range in each patient. None of them altered during the study in any age or in any gender. We conclude that omeprazole, at a dose of 20 mg/day, does not significantly influence the investigated biochemical parameters of osteoclast and osteoblast function in pediatric patients.

73. Kuusela, A.L. Long-term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 78: F151-153, 1998.

AIM: To determine the optimal doses of ranitidine for both preterm and term

infants. **METHOD:** The effect of ranitidine treatment was measured from the long-term intraluminal gastric pH in 16 preterm (gestational age under 37 weeks) and term infants treated in neonatal intensive care. The infants received three different bolus doses of ranitidine: 0.5 mg, 1.0 mg, and 1.5 mg per kilogram of body weight to keep the intraluminal gastric pH above 4 on a 24 hour basis. **RESULTS:** Critically ill neonates, including very low birth weight infants, were capable of gastric acid formation, and ranitidine treatment increased the intraluminal gastric pH. The effect of a single dose lasted longer in preterm than in term infants. The time needed for reaching the maximum gastric pH was significantly longer in preterm than in term infants. The ranitidine given correlated with the duration of increased gastric pH in a dose dependent manner both in preterm and term infants. **CONCLUSION:** Preterm infants need significantly smaller doses of ranitidine than term neonates to keep their intraluminal gastric pH over 4. The required optimal dose of ranitidine for preterm infants is 0.5 mg/kg/body weight twice a day and that for term infants 1.5 mg/kg body weight three times a day.

74. Kuusela, A.L., Ruuska, T., Karikoski, R., Laippala, P., Ikonen, R.S., Janas, M., and Maki, M. A randomized, controlled study of prophylactic ranitidine in preventing stress-induced gastric mucosal lesions in neonatal intensive care unit patients. *Crit Care Med* 25: 346-351, 1997.

OBJECTIVE: To assess endoscopically the effect of prophylactic short-term ranitidine treatment in the prevention of stress-induced gastric lesions in neonatal intensive care unit (ICU) patients. **DESIGN:** Prospective, randomized study. **SETTING:** Department of Neonatal Intensive Care, University Hospital of Tampere. **PATIENTS:** Fifty-three infants were enrolled in a randomized, controlled study. Forty-eight (90%) of these patients underwent endoscopic examination and were evaluated. **INTERVENTIONS:** A histamine-2-receptor blocker, ranitidine, was given prophylactically after birth for 4 days to infants mechanically ventilated and treated in the neonatal ICU. The gastric mucosa was both visually and histologically evaluated after 3 to 6 days, and the outcome of the infants was registered. **MEASUREMENTS AND MAIN RESULTS:** In the 23 infants prophylactically treated with ranitidine, the gastric mucosa was visually classified as normal in 14 (61%) infants as compared with five (20%) of 25 controls ($p < .004$). Histologic lesions showed parallel results (57% vs. 16%, $p < .004$). Eight gastric ulcers were diagnosed endoscopically in the control group vs. none in the treatment group. The ulcers were all clinically "silent" at the time of endoscopy. According to logistic regression modeling, the decreased risk for gastric mucosal lesions in infants receiving prophylactic ranitidine was 0.03 (95% confidence interval 0.003 to 0.178). Surfactant treatment for infant respiratory distress syndrome also decreased the risk for stress-induced gastric mucosal lesions (odds ratio 0.083; 95% confidence interval 0.009 to 0.788), whereas other variables (birth weight, gestational age, Apgar scores, cord blood pH, and duration of intubation) had no significant effect. No side effects could be attributed to the ranitidine treatment. **CONCLUSION:** We conclude that short-

term prophylactic ranitidine treatment prevents gastric mucosal lesions in newborn infants under stress.

75. Lalkin, A., Loebstein, R., Addis, A., Ramezani-Namin, F., Mastroiacovo, P., Mazzone, T., Vial, T., Bonati, M., and Koren, G. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 179: 727-730, 1998.

OBJECTIVES: Our purpose was to determine whether omeprazole use during pregnancy is associated with an increased risk of malformations, spontaneous abortions, decreased birth weight, or perinatal complications. STUDY DESIGN: In a multicenter, prospective controlled study, pregnant women exposed to omeprazole during gestation were matched with controls exposed to nonteratogens and with disease-paired controls who used histamine blockers for similar indications. The primary end point was the incidence of major malformations. RESULTS: One hundred thirteen pregnant women were exposed to omeprazole during pregnancy. Rates of major malformations in the omeprazole group (4%) did not differ from controls exposed to nonteratogens (2%) ($P = .68$, relative risk = 1.94, 95% confidence interval 0.36 to 10.36) and disease-paired controls (2.8%). Birth weight, gestational age at delivery, preterm deliveries, and neonatal complications were comparable among the three groups. CONCLUSIONS: No association was found between exposure to omeprazole during the period of organogenesis and increased risk for major malformations. Exposure throughout pregnancy is not associated with increased risk of spontaneous abortions, decreased birth weight, or perinatal complications.

76. Li, J., Zhao, J., Hamer-Maansson, J.E., Andersson, T., Fulmer, R., Illueca, M., and Lundborg, P. Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: A randomized, open-label study. *Clin Ther* 28: 419-427, 2006.

OBJECTIVE: The aim of this study was to assess the pharmacokinetic (PK) properties and tolerability of esomeprazole 20 and 40 mg after single and repeated oral doses in adolescents with symptoms of gastroesophageal reflux disease (GERD). RESULTS: The study included 15 boys and 13 girls (mean age, 14.3 years). Geometric mean AUC(0-infinity) values (overall drug exposure) were 1.58 and 5.57 micromol . h/L (0.027 and 0.083 pmol x h x L(-1)/kg) after single-dose administration of esomeprazole 20 and 40 mg, respectively, on day 1. Corresponding values with repeated doses (day 8) were 3.65 and 13.86 micromol x h/L (0.064 and 0.207 micromol x h x L(-1)/kg). Geometric mean C_{max} values were 0.67 and 2.78 micromol/L (0.012 and 0.041 micromol/L x kg(-1)) with single-dose administration of esomeprazole 20 and 40 mg, respectively, and 1.45 and 5.13 micromol/L (0.026 and 0.075 micromol/L x kg(-1)), respectively, with repeated doses (day 8). These mean AUC(0-infinity) and C_{max} values were >2-fold with the 40 mg dose compared with the 20-mg dose with single- and repeated-dose administration. The most common adverse event was headache

(2 [7.1%] patients). CONCLUSIONS: The results of this study suggest that the PK parameters of esomeprazole were both dose- and time-dependent in these adolescents with GERD. Both doses of esomeprazole were well tolerated in this study population.

77. Lopez-Herce Cid, J., Albajara Velasco, L., Codoceo, R., Delgado Dominguez, M.A., Jimenez, E., and Ruza Tarrio, F. Ranitidine prophylaxis in acute gastric mucosal damage in critically ill pediatric patients. *Crit Care Med* 16: 591-593, 1988.

We determined the ranitidine dosage necessary to maintain gastric pH at or above 4 in 40 critically ill children. The patients were divided into four groups of ten patients each. They were treated with ranitidine in the following dosages: a) 2 mg/kg by NG tube every 12 h; b) 4 mg/kg by NG tube every 12 h; c) 0.75 mg/kg iv every 6 h; d) 1.5 mg/kg iv every 6 h. The fourth group had a higher median pH than the other groups, in spite of also having the highest risk of acute gastric mucosal damage (AGMD). Eight (80%) of ten patients in the fourth group had a pH greater than or equal to 4 or more than 80% of the study period. We recommend 1.5 mg/kg iv every 6 h for gastric acid inhibition in AGMD prophylaxis in children.

78. Lopez-Herce, J., Dorao, P., Elola, P., Delgado, M.A., Ruza, F., and Madero, R. Frequency and prophylaxis of upper gastrointestinal hemorrhage in critically ill children: a prospective study comparing the efficacy of almagate, ranitidine, and sucralfate. The Gastrointestinal Hemorrhage Study Group. *Crit Care Med* 20: 1082-1089, 1992.

OBJECTIVE: To determine the occurrence of upper gastrointestinal hemorrhage in critically ill children, and the efficacy of prophylaxis with almagate (antacid), ranitidine, and sucralfate. DESIGN: Prospective, randomized, controlled trial. SETTING: Pediatric ICU of a tertiary care pediatric hospital. PATIENTS: During a 2-yr study period, 165 patients with one or more upper gastrointestinal hemorrhage risk factors were randomized into one of four groups. Twenty-five patients were excluded because of protocol violations. A total of 140 patients completed the study, with 35 patients in each group. INTERVENTIONS: Patients received no treatment in the control group. The antacid group received almagate 0.25 to 0.5 mL/kg every 2 hrs by nasogastric tube. The ranitidine group received 1.5 mg/kg every 6 hrs iv. The sucralfate group received 0.5 to 1 g every 6 hrs by nasogastric tube. METHODS: Gastric pH and macroscopic bleeding were determined every 2 hrs in all patients until the end of the study. Macroscopic bleeding was classified as nonhemorrhage, slight, or important. Microscopic gastric bleeding was researched with guaiac testing in 72 patients (680 samples). The severity of illness was evaluated by using the Therapeutic Intervention Scoring System, Physiologic Stability Index, and the Multiorgan System Failure scores. The risk of upper gastrointestinal hemorrhage was evaluated by the Zinner and Tryba indices, and was modified for children. MEASUREMENTS AND

MAIN RESULTS: The occurrence rate of important upper gastrointestinal hemorrhage was higher (by 20%) in the control group than in the rest of the groups (5.7%), p less than .01. There were no differences between the other groups (almagate 5.7%, ranitidine 8.5%, and sucralfate 2.8%). There was a statistically significant correlation between the occurrence rate of important upper gastrointestinal hemorrhage, the scores of severity of illness indices (Therapeutic Intervention Scoring System, Physiologic Stability Index, and the Multiorgan System Failure scoring system), the risk of upper gastrointestinal hemorrhage indices (Zinner and Tryba), and mortality rate. The Zinner index better classified the patients in relation to the onset of important upper gastrointestinal hemorrhage (sensitivity 76.9%, specificity 85.8%). **CONCLUSIONS:** Upper gastrointestinal hemorrhage is an important complication in critically ill children. Prophylaxis with almagate, ranitidine, or sucralfate reduces the occurrence rate of clinically important gastrointestinal hemorrhage.

79. Madrazo-de la Garza, A., Dibildox, M., Vargas, A., Delgado, J., Gonzalez, J., and Yanez, P. Efficacy and safety of oral pantoprazole 20 mg given once daily for reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 36: 261-265, 2003.

OBJECTIVES: To investigate the efficacy and safety of oral pantoprazole, 20 mg (0.5 to 1.0 mg/kg/day) once daily for 28 days, in pediatric patients with reflux esophagitis. **METHODS:** Patients in this study ($n = 15$; 6 to 13 years old, 9 boys) had reflux esophagitis grade Ic or II (Vandeplass classification). The efficacy of pantoprazole to reduce esophageal acid exposure time ($\text{pH} < 4$), reduce the number and duration of reflux episodes, and to increase the percentage of time with gastric $\text{pH} > 3$ was assessed by continuous 24-hour pH monitoring. The intensity of 5 common symptoms of esophagitis was scored before and after treatment on a 4-point scale. Esophagitis was assessed at baseline and after treatment by visual inspection and by the histology of biopsies from the distal third of the esophagus. **RESULTS:** Before treatment, the median percentage of time with intra-esophageal $\text{pH} < 4$ was 9.3%. After 28 days of therapy with pantoprazole, this value decreased to 2.7% ($P = 0.0006$). The median percentage of time with intragastric $\text{pH} > 3$ increased from 21% at baseline to 39% on day 28 of therapy ($P = 0.005$). After 28 days of treatment, all patients experienced at least partial relief from reflux symptoms. Endoscopically confirmed healing of esophagitis was seen in 47% of children (Savary-Miller classification). Histologic evidence of healing was not observed. Median serum gastrin levels were slightly elevated over baseline levels (from 74 pg/ml to 93 pg/ml). In one patient there was a transient elevation of serum GOT and GPT during treatment. **CONCLUSIONS:** Oral pantoprazole 20 mg daily provided gastric acid control in 15 pediatric patients with reflux esophagitis with partial clinical improvement of symptoms after 28 days of treatment. Pantoprazole was safe and well tolerated.

80. Marchant, J., Summers, K., McIsaac, R.L., and Wood, J.R. A comparison of two ranitidine intravenous infusion regimens in critically ill patients. *Aliment*

Pharmacol Ther 2: 55-63, 1988.

The effect of two ranitidine intravenous infusion regimens on intragastric pH was studied in 134 critically ill patients admitted to 15 intensive care units. Intragastric pH was determined hourly for 30 hours. Those patients whose intragastric acidity fell below pH 4.0 for 3 or more of the first 6 hours were considered 'at risk' of developing stress-related gastric lesions and randomized to receive a 50 mg bolus of ranitidine together with a continuous intravenous infusion of either 0.125 or 0.25 mg kg⁻¹ h⁻¹ ranitidine for 24 hours. The maximal elevation in intragastric pH was achieved within 12 hours. The median intragastric pH for the last 20 hours of the infusion period was 5.9 for the higher dose group and 5.6 for the lower dose group. The increase in intragastric pH achieved by the two dosage regimens did not differ significantly throughout the 24 hour period. Patients having two or more of five major risk factors (head injury, major trauma, sepsis, respiratory failure/insufficiency and major surgery) had better overall control of intragastric pH on the higher dose of ranitidine than those receiving the lower dose. The majority of intensive care patients are likely to receive satisfactory treatment with the lower dosage regimen that was tested (0.125 mg kg⁻¹ h⁻¹). Those with multiple risk factors may, however, require treatment with higher doses of ranitidine (0.25 mg kg⁻¹ h⁻¹).

81. Marchetti, F., Gerarduzzi, T., and Ventura, A. Proton pump inhibitors in children: a review. *Dig Liver Dis* 35: 738-746, 2003.

Proton pump inhibitors are often used to treat disorders associated with gastric hypersecretion in children, despite the lack of pediatric formulations. They are highly effective in the treatment of ulcers, gastro-esophageal reflux disorders and hypersecretory diseases. They provide a high level of gastric acid inhibition with few adverse effects. The aim of this article is to review the available studies concerning the use of proton pump inhibitors in pediatric populations and to point out: indications for use in children, optimal dosage, risk of adverse effects and consequences of the mechanism of action, and drug interactions. We performed a Medline and Embase search of publications printed from January 1980 to December 2002 concerning the use of proton pump inhibitors in children. We consider the available randomised controlled trials and several other uncontrolled studies conducted in the pediatric population, including all available information concerning the pediatric use of proton pump inhibitors. In children as well as in adults, there are clinical conditions (i.e., severe esophagitis or eradication of *Helicobacter pylori*) in which proton pump inhibitors offer clear advantages over histamine-2 receptor antagonists. The relatively common use of acid inhibitors (proton pump inhibitors and histamine-2 receptor antagonists) in uncomplicated gastro-esophageal reflux disorders or in the prevention of non-steroidal anti-inflammatory drugs/steroid gastropathy is often unsubstantiated and should be limited to very specific situations. Multicentre randomised controlled studies are needed to better define the efficacy profile, the optimal dosage with respect to the different indications and the safety profile for chronic therapy of proton pump

inhibitors in children.

82. Marier, J.F., Dubuc, M.C., Drouin, E., Alvarez, F., Ducharme, M.P., and Brazier, J.L. Pharmacokinetics of omeprazole in healthy adults and in children with gastroesophageal reflux disease. *Ther Drug Monit* 26: 3-8, 2004.

Studies of the pharmacokinetics of omeprazole in children with gastroesophageal reflux disease (GERD) remain scarce despite the vast number of reports on its efficacy. The objectives of this study were to assess the pharmacokinetics of omeprazole in healthy adults and in children with GERD. Omeprazole (Losec, delayed-release capsules) was administered orally to 18 healthy adults (mean age 36.8 years) and 12 children with GERD (mean age 6.1 years). Blood samples were collected over 5 hours, and plasma concentrations were assessed using liquid chromatography. Population pharmacokinetic parameters were calculated using NONMEM. A 1-compartment model with zero-order absorption and a lag time was used. The population approach was well suited to the limited number of samples available, and residual variability was low. Oral clearance (CL/F) and apparent volume of distribution (V(ss)/F) in healthy adults (Mean +/- SD: 0.62 +/- 0.27 L/h/kg and 0.76 +/- 0.26 L/kg, respectively) were not significantly different than those in children with GERD (0.51 +/- 0.34 L/h/kg and 0.66 +/- 0.25 L/kg, respectively). Healthy adults displayed a statistically significantly longer delay in drug absorption (Lag time: 0.62 +/- 0.15 hours) as compared with that observed in children with GERD (0.12 +/- 0.03 hours, P < 0.05). On the basis of these findings, omeprazole dosings on a milligram-per-kilogram basis are recommended with no further adjustments for the treatment of GERD in children.

83. Martin, P.B., Imong, S.M., Krischer, J., Noblett, H.R., and Sandhu, B.K. The use of omeprazole for resistant oesophagitis in children. *Eur J Pediatr Surg* 6: 195-197, 1996.

Following failure of conventional therapy for reflux oesophagitis, 15 children were treated with omeprazole 20 mg daily for a period of up to three months initially. Treatment resulted in a marked symptomatic improvement as measured by incidence of pain, vomiting, dysphagia and haematemesis. Four children failed treatment and required fundoplication. No complications from the use of omeprazole were recorded and some children have continued long-term treatment.

84. McAuley, D.M., Moore, J., Dundee, J.W., and McCaughey, W. Oral ranitidine in labour. *Anaesthesia* 39: 433-438, 1984.

Ranitidine 150 mg orally was given every 6 hours to 909 women in labour, while a control group of 378 women received conventional alkali therapy. No differences in incidences of operative intervention, placental retention or post-partum haemorrhage were observed between groups. Gastric sampling during

emergency anaesthesia revealed a pH less than 2.5 in four of 51 women who received ranitidine and in two of 31 women who received magnesium trisilicate. Gastric volumes were slightly lower (mean 83 ml) in the study group than in the control group (mean 122 ml). Absorption of ranitidine was greatly slowed following narcotic administration and gastric volume was significantly higher in those patients given narcotics in labour. Apgar scores were similar in both groups of infants, and babies whose mothers were given ranitidine showed no delay in achieving high gastric acidity and no increase in bacterial colonization of the gastro-intestinal tract. Low levels only of ranitidine were found in the blood of babies at 2-3 hours and approximately 12 hours after birth.

85. Meyrick Thomas, R.H., Browne, P.D., and Kirby, J.D. The effect of ranitidine, alone and in combination with clemastine, on allergen-induced cutaneous wheal-and-flare reactions in human skin. *J Allergy Clin Immunol* 76: 864-869, 1985.

The effect of intradermal ranitidine (administered alone and in combination with clemastine) on allergen-mediated wheal-and-flare reactions has been evaluated in a double-blind study on 10 healthy atopic volunteers. Ranitidine alone, administered in doses over a 10(4)-fold concentration range, had no effect on the size either of allergen-induced wheal or flare reactions. Clemastine alone evoked a dose-related inhibition of both wheal and flare. Compared to the inhibition achieved by clemastine alone, the combination of ranitidine with clemastine produced a small but significant increase in inhibition of allergen-induced flare at ranitidine concentrations of 10(-5) mol/L (p less than 0.001) and 10(-6) mol/L (p less than 0.01), and of allergen-induced wheal at ranitidine concentration 10(-5) mol/L (p less than 0.01). Our results provide further evidence for the presence of cutaneous histamine H₂ receptors and their participation in the formation of allergen-mediated skin reactions but indicate that the contribution of cutaneous histamine H₂-receptor stimulation to the production of immediate wheal-and-flare reactions evoked by allergen is only modest.

86. Mikawa, K., Nishina, K., Maekawa, N., Asano, M., and Obara, H. Lansoprazole reduces preoperative gastric fluid acidity and volume in children. *Can J Anaesth* 42: 467-472, 1995.

The purpose of this study was to explore the efficacy of lansoprazole, a proton pump inhibitor, in reducing the acidity and volume of gastric aspirate in children immediately following the induction of anaesthesia. One hundred healthy in-patients aged 3-11 yr undergoing elective surgery were randomly allocated to four groups (n = 25 each): lansoprazole-lansoprazole, placebo-placebo, placebo-lansoprazole, and lansoprazole-placebo. For each treatment regimen, the first medication was administered at 9:00 pm on the night before surgery and the second at 5:30 am on the morning of the day of surgery (three hours preoperatively). The dose of lansoprazole was 30 mg (approximately 1.4 mg.kg⁻¹ mean). Children were offered 10 ml.kg⁻¹ apple juice three hours before induction of anaesthesia. After induction of anaesthesia and tracheal intubation, gastric

fluid was aspirated through a large-bore, multiorifice orogastric tube and analyzed for pH and total fluid volume. Lansoprazole increased gastric fluid pH and decreased gastric fluid volume regardless of whether it was administered before or after placebo. Two consecutive doses of lansoprazole was the most effective means of increasing the pH and reducing the volume of gastric aspirate; in this group, there were no subjects with gastric aspirate volume > 0.4 ml.kg⁻¹ and pH < 2.5. Oral lansoprazole, at least 30 mg, given on the night before surgery or on the morning of surgery will improve the gastric environment at the time of induction of paediatric anaesthesia. The most effective regimen was two doses (at bedtime and on the morning) of lansoprazole.

87. Moore, D.J., Tao, B.S., Lines, D.R., Hirte, C., Heddle, M.L., and Davidson, G.P. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *J Pediatr* 143: 219-223, 2003.

OBJECTIVE: To assess the efficacy of omeprazole in treating irritable infants with gastroesophageal reflux and/or esophagitis. STUDY DESIGN: Irritable infants (n=30) 3 to 12 months of age met the entry criteria of esophageal acid exposure >5% (n=22) and/or abnormal esophageal histology (n=15). They completed a 4-week, randomized, double-blind, placebo-controlled crossover trial of omeprazole. Cry/fuss diary (minutes/24 hours) and a visual analogue scale of infant irritability as judged by parental impression were obtained at baseline and the end of each 2-week treatment period. RESULTS: The reflux index fell significantly during omeprazole treatment compared with placebo (-8.9%+/-5.6%, -1.9%+/-2.0%, P<.001). Cry/fuss time decreased from baseline (267+/-119), regardless of treatment sequence (period 1, 203+/-99, P<.04; period 2, 188+/-121, P<.008). Visual analogue score decreased from baseline to period 2 (6.8+/-1.6, 4.8+/-2.9, P=.008). There was no significant difference for both outcome measures while taking either omeprazole or placebo. CONCLUSIONS: Compared with placebo, omeprazole significantly reduced esophageal acid exposure but not irritability. Irritability improved with time, regardless of treatment.

88. Moshkowitz, M., Konikoff, F.M., Peled, Y., Brill, S., Hallak, A., Tiomny, E., Santo, M., Bujanover, Y., and Gilat, T. One week triple therapy with omeprazole, clarithromycin and tinidazole for Helicobacter pylori: differing efficacy in previously treated and untreated patients. *Aliment Pharmacol Ther* 10: 1015-1019, 1996.

BACKGROUND: Triple therapy with omeprazole, clarithromycin, and tinidazole (OCT) has been found to be highly effective against Helicobacter pylori infection. However, its efficacy as a second line regimen for patients who failed metronidazole-based triple therapy has not been evaluated. AIM: The aim of this study was to evaluate the efficacy of low-dose, short-term OCT therapy in an Israeli population, and to compare results obtained in previously treated and untreated patients. METHODS: Patients with duodenal or gastric ulcers and chronic antral gastritis with H. pylori infection as assessed by rapid urease test

and/or 14C urea breath test (14C-UBT), were studied. All patients received omeprazole 20 mg b.d., clarithromycin 250 mg b.d. and tinidazole 500 mg b.d. for 7 days. Eradication was assessed by 14C-UBT 4 weeks after treatment.

RESULTS: One hundred and forty-four patients (M/F = 81/63) were enrolled (mean age 48.1 years, range 12-78). Eradication of *H. pylori* was significantly different between patients who were initially treated with this regimen (90/94, 96%) and patients who had previously failed to eradicate *H. pylori* with standard triple therapy (27/50, 54%). Moreover, the eradication rate was significantly decreased in patients with more than one previous failure (9/22, 41%) compared to that in patients with only one failure (18/29, 62%). No other differences such as age, gastric pathology, ethnic origin, smoking habits, or pre-treatment urease activity were found to influence the eradication rate. CONCLUSIONS: One-week low-dose triple therapy with OCT is highly effective as an initial therapy in eradicating *H. pylori* infection. The efficacy is significantly lower when given as a second line treatment in patients who have previously failed to eradicate *H. pylori* with bismuth-based standard triple therapy.

89. Moshkowitz, M., Reif, S., Brill, S., Ringel, Y., Arber, N., Halpern, Z., and Bujanover, Y. One-week triple therapy with omeprazole, clarithromycin, and nitroimidazole for *Helicobacter pylori* infection in children and adolescents. *Pediatrics* 102: e14, 1998.

BACKGROUND: Resolution of *Helicobacter pylori* infection is important in the management of peptic ulcer disease and reduces peptic ulcer recurrence in both adults and children. Various anti-*H. pylori* treatment regimens have been proposed, reflecting the incomplete clinical success of each. A combination of omeprazole, clarithromycin, and tinidazole, given for 1 week, has been shown to be highly tolerable and effective, achieving a success rate of >90% in the adult population. OBJECTIVE: The aim of this study was to evaluate this short-term regimen in pediatric and adolescent populations. METHODS: The study group consisted of 35 children referred for evaluation of dyspeptic symptoms. They all underwent upper gastrointestinal endoscopy, in which *H. pylori* infection was confirmed by rapid urease test and/or histologic staining. They were given omeprazole (20 mg twice daily), clarithromycin (250 mg twice daily), and tinidazole or metronidazole (500 mg twice daily) for 1 week. The patients were divided into two groups: those who received the first course of anti-*H. pylori* therapy during this study (group 1) and those who had previously received standard metronidazole and bismuth combination therapies that failed to eradicate *H. pylori* (group 2). Therapeutic efficacy was assessed by a 13C-urea breath test performed 4 weeks after completion of treatment. Results. The 35 study patients had a mean age of 15.9 years (range, 10 to 19) and included 19 males and 16 females, of whom 22 were born in Israel and 13 were immigrants from the former USSR. There were 27 patients (77. 1%) in group 1 and 8 patients (22.9%) in group 2. Endoscopic findings were nodular gastritis (14), gastritis (11), gastric ulcer (1), duodenal ulcer (5), and duodenitis (4). *H. pylori* resolution was significantly higher in group 1 patients (24/27, 88.9%) than in

group 2 patients (1/8, 12.5%). There was no difference between patients with nodular gastritis and those with nonnodular gastritis, and between Israeli-born patients and patients born in the former USSR. Compliance in both groups was equally good, and no major side effects were recorded. CONCLUSIONS: One-week omeprazole/clarithromycin/tinidazole triple therapy is highly tolerable and effective for treating H pylori in the pediatric age group, but previous treatment failure diminishes the likelihood of success with this regimen.

90. Narin, N., Akcoral, A., Aslin, M.I., and Elmastas, H. Ranitidine administration in Henoch-Schonlein vasculitis. *Acta Paediatr Jpn* 37: 37-39, 1995.

In this study, we discuss 12 patients with gastrointestinal (GI) bleeding who were diagnosed as having Henoch Schoenlein vasculitis (HSV) in Dr Behcet Uz Children's Hospital, Izmir, between January 1991 and January 1992. Seven male and five female patients were included in the study. Their ages ranged between 6-14 years. The patients were separated into two identical groups and were given ranitidine or a placebo. Both groups were followed up for abdominal pain and GI bleeding. In the group administered ranitidine the duration and severity of abdominal pain and gastrointestinal bleeding decreased significantly as compared to the group taking placebo ($P < 0.05$). No side effects of ranitidine were observed. As a result, it was concluded that ranitidine could be used to treat HSV with GI symptoms.

91. Nelson, S.P., Kothari, S., Wu, E.Q., Beaulieu, N., McHale, J.M., and Dabbous, O.H. Pediatric gastroesophageal reflux disease and acid-related conditions: trends in incidence of diagnosis and acid suppression therapy. *J Med Econ* 12: 348-355, 2009.

Abstract Objective: To describe the incidence of diagnosis of gastroesophageal reflux disease and acid-related conditions (GERD/ARC) throughout childhood and characterize patterns of diagnosis and treatment with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H(2)RAs). Methods: Cohorts of GERD/ARC children (age 0-18 years) were identified from a large US administrative claims database covering 1999-2005 using ICD-9 codes. Incidence, healthcare utilization (HCU), costs, therapy discontinuation and switching rates were compared between various age and patient groups. Results: Between 2000 and 2005 annual incidence of GERD/ARC diagnosis among infants (age ≤ 1 year) more than tripled (from 3.4 to 12.3%) and increased by 30% to 50% in other age groups. Patients diagnosed by GI specialists (9.2%) were more likely to be treated with PPIs compared to patients diagnosed by primary care physician (PCP). PPI-initiated patients doubled (from 31.5% in 1999 to 62.6% in 2005) and, when compared with H(2)RA-initiated patients, were associated with 30% less discontinuation and 90% less therapy switching in the first month, and with higher comorbidity burden and pre-treatment total HCU and costs when diagnosed by GI specialists. Limitations: The use of an exploratory definition for GERD/ARC, administrative claims data

and potential coding errors in diagnosis codes used in selection process may limit the generalizability of the results. Conclusions: GERD/ARC incidence increased for children of all ages between 2000 and 2005. PCPs made the majority of diagnoses. PPI initiations have now surpassed H(2)RA initiations.

92. Nijevitch, A.A., Farztdinov, K.M., Sataev, V.U., Khasanov, R., Katayev, V.A., Khusnutdinov, S.M., Akhunov, E.D., and Kazykhanov, N.S. Helicobacter pylori infection in childhood: results of management with ranitidine bismuth citrate plus amoxicillin and tinidazole. *J Gastroenterol Hepatol* 15: 1243-1250, 2000.

BACKGROUND AND AIMS: To verify whether a triple therapy bismuth citrate plus amoxicillin and tinidazole eradicates H. pylori infection in pediatric patients. **METHODS:** Fifty children (30 females; mean age 12.4 +/- 1.1 years, range 10-15 years) suffering from upper abdominal complaints and Helicobacter pylori (H. pylori)-associated gastroduodenal disease were treated with a 4 week course of ranitidine bismuth citrate (400 mg, twice daily) plus oral tinidazole (20 mg/kg) and amoxicillin (50 mg/kg) for the first 2 weeks. **RESULTS:** The endoscopic diagnoses were: esophagitis (seven cases), gastritis (six cases), gastroduodenitis (43 cases), duodenitis (one case), gastric ulcer (two cases) and duodenal ulcer (13 cases). Helicobacter pylori was eradicated in 40 (80%) patients and clinical improvement was noticed in 39 (78%) of symptomatic subjects. Duodenal ulcers were healed in all the children, but lymphoid nodular hyperplasia was persistent in all patients, independent of the H. pylori status. The potentially drug-related adverse events (blackening of the tongue, six patients; diarrhea, one patient; disturbance of taste, two patients) were registered in seven (14%) patients and dark stools were observed in 48 (96%) patients. No children withdrew from the study because of either side-effects or clinical laboratory changes. No patient had toxic levels of blood bismuth (values ranged between 2.1 and 5.4 microg/L, mean value 3.4 +/- 1.04 microg/L). **CONCLUSIONS:** Findings suggest that the present treatment regimen is effective enough in the resolution of H. pylori-associated peptic ulcer disease of childhood.

93. Nilforoushzadeh, M.A., Jaffary, F., Ansari, N., Siadat, A.H., Nilforoushan, Z., and Firouz, A. A comparative study between the efficacy of systemic meglumine antimoniate therapy with standard or low dose plus oral omeprazole in the treatment of cutaneous leishmaniasis. *J Vector Borne Dis* 45: 287-291, 2008.

BACKGROUND & OBJECTIVES: Pentavalent antimony compounds are the first line of drugs in the treatment of cutaneous leishmaniasis. However, because of their potential toxic effects, many investigations are performed to find an effective and safe treatment for cutaneous leishmaniasis patients. Our objective in this investigation was to compare the effect of oral omeprazole and low dose systemic meglumine antimoniate (MA) and standard dose of systemic MA in the treatment of cutaneous leishmaniasis. **METHODS:** This was a randomized double-blinded clinical trial. In 150 patients with cutaneous leishmaniasis who were randomly divided into three groups and were treated with: (i) MA 60

mg/kg/day/ IM and oral placebo for three weeks; (ii) MA 30 mg/kg/day/IM and oral omeprazole 40 mg/day for three weeks; and (iii) MA 30 mg/kg/day/IM and oral placebo for three weeks. All the patients were visited every two weeks from the beginning of the trial up to six weeks and then at 8 and 12 weeks. The effectiveness of the treatment was classified in three levels as complete response, partial response and no response. Data were analyzed by SPSS 10 using KI square, Mann-Whitney, Kaplan-Mayer and ANOVA tests. RESULTS: Rate of complete response for three months (12 weeks) after starting the treatments was 93% for the group treated with standard dose of glucantime and placebo, 89% for the group treated with omeprazole and low dose glucantime and 80% for the group treated with low dose glucantime and placebo and these differences were significant ($p < 0.05$). The highest response rate was for the group treated with standard dose of glucantime and placebo. INTERPRETATION & CONCLUSION: Although oral omeprazole and low dose of systemic MA showed less efficacy in comparison to standard dose of systemic MA in the treatment of cutaneous leishmaniasis, it still can be considered as a replacement therapy in high risk patients (such as patients with heart, kidney and/or liver disease) under close supervision of physician.

94. Nishina, K., Mikawa, K., Maekawa, N., Tamada, M., and Obara, H. Omeprazole reduces preoperative gastric fluid acidity and volume in children. *Can J Anaesth* 41: 925-929, 1994.

To explore the effects of oral omeprazole on preoperative gastric fluid pH and volume in children, 104 healthy in-patients aged 4-9 yr were randomly allocated to four groups (n = 26). Subjects in the Omeprazole-Omeprazole Group received two doses of omeprazole (20 mg per dose), those in the Placebo-Placebo Group, two doses of placebo, those in the Placebo-Omeprazole and Omeprazole-Placebo Groups, one dose each of the two preparations by mouth. For each treatment regimen, the first medication was administered at 9:00 p.m. on the night before surgery and the second at 5:30 a.m. on the morning of the day of surgery (three hours preoperatively). Children undergoing elective surgery were offered 10 ml.kg⁻¹ of apple juice three hours before induction of anaesthesia. After induction of anaesthesia and tracheal intubation, gastric fluid was aspirated through a large-bore, multiorifice orogastric tube and analyzed for pH and total fluid volume. The administration of omeprazole at bedtime before surgery increased gastric pH (3.3 +/- 1.3 vs 2.0 +/- 0.6, $P < 0.05$) in comparison with placebo, as did two doses of omeprazole (pH = 4.8 +/- 1.6, $P < 0.05$). A single dose of omeprazole administration on the morning of the day of surgery failed to increase gastric pH. There was a reduction in the number of children with a pH < 2.5 and a volume > 0.4 ml.kg⁻¹ in the Omeprazole-Omeprazole and Omeprazole-Placebo Groups, compared with the Placebo-Placebo or Placebo-Omeprazole Groups.(ABSTRACT TRUNCATED AT 250 WORDS)

95. Oderda, G., Marinello, D., Lerro, P., Kuvidi, M., de'Angelis, G.L., Ferzetti, A., Cucchiara, S., Franco, M.T., Romano, C., Strisciuglio, P., and Pensabene, L.

Dual vs. triple therapy for childhood *Helicobacter pylori* gastritis: a double-blind randomized multicentre trial. *Helicobacter* 9: 293-301, 2004.

BACKGROUND: Data on the efficacy of eradication treatment for *Helicobacter pylori* gastritis in children are scarce. **AIM:** To evaluate the efficacy of triple therapy with lansoprazole plus amoxicillin and tinidazole vs. dual therapy with amoxicillin and tinidazole in a double-blind randomized multicentre trial, and the usefulness of eradication in terms of long-term symptom resolution. **SUBJECTS:** We enrolled 43 consecutive children undergoing endoscopy for upper gastrointestinal dyspepsia with *H. pylori* gastritis. They underwent a ¹³C-urea breath test, completed a 2-week symptom diary card, and were randomized. Treatment was given in a Redidose box (Redidose Company Ltd., Brighton, UK) containing either lansoprazole-amoxicillin-tinidazole (triple therapy) or placebo plus amoxicillin-tinidazole (dual therapy) for 1 week. The completion of a 2-week symptom diary card and the performance of a breath test were repeated 6 weeks and 6 months after the end of therapy. One to two years later, a structured telephone interview was conducted with 36 of the children. **RESULTS:** According to the breath test, 6 weeks after the end of therapy *H. pylori* was eradicated in 15 of 22 children on triple therapy [68.2%; 95% confidence interval (CI) = 45-88] and in 15 of 21 children on dual therapy (71%; 95% CI = 48-89; not significant), and 6 months after the end of therapy it was eradicated in 16 of 22 children on triple therapy (72.7%) and in 15 of 21 children on dual therapy. Six months after therapy, symptoms were analysed in 11 *H. pylori*-positive and 31 *H. pylori*-negative children, and it was found that dyspeptic symptoms had disappeared or improved in both groups, with no difference between them. One to two years later, 36 children were interviewed. Epigastric pain had recurred in three of 26 *H. pylori*-negative and in seven of 10 *H. pylori*-positive children ($p = .001$); in three of the latter, pain was severe and required additional treatment. **CONCLUSION:** One-week triple or dual therapy with two antibiotics achieved similar eradication rates. Soon after treatment, symptoms disappeared or improved in most children irrespective of eradication, but epigastric pain recurred in the majority of the still-infected children within 2 years.

96. Omari, T., Davidson, G., Bondarov, P., Naucler, E., Nilsson, C., and Lundborg, P. Pharmacokinetics and acid-suppressive effects of esomeprazole in infants 1-24 months old with symptoms of gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 45: 530-537, 2007.

OBJECTIVES: To evaluate the pharmacokinetics and acid-suppressive effects of esomeprazole in infants with gastroesophageal reflux disease (GERD).

PATIENTS AND METHODS: In this single-blind, randomized, parallel-group study, 50 infants 1 to 24 months old with symptoms of GERD, and $\geq 5\%$ of time with intraesophageal pH < 4 during 24-hour dual pH monitoring, received oral esomeprazole 0.25 mg/kg ($n = 26$) or 1 mg/kg ($n = 24$) once daily for 1 week. Intraesophageal and intragastric pH were recorded at 1 week, and blood samples were taken for pharmacokinetic analysis. **RESULTS:** At baseline, mean

percentages of time with intragastric pH >4 and intraesophageal pH <4 were 30.5% and 11.6%, respectively, in the esomeprazole 0.25 mg/kg group and 28.6% and 12.5% in the esomeprazole 1 mg/kg group. After 1 week of treatment, times with intragastric pH >4 were 47.9% and 69.3% in the esomeprazole 0.25 mg/kg and 1 mg/kg groups, respectively (P < 0.001 vs baseline), and times with intraesophageal pH <4 were 8.4% (P < 0.05 vs baseline) and 5.5% (P < 0.001 vs. baseline), respectively. The mean number of acid reflux episodes of >5 minutes duration decreased from 6 at baseline to 3 and 2 with esomeprazole 0.25 mg/kg and 1 mg/kg, respectively. The geometric mean AUC_{0-t} of esomeprazole were 0.24 and 1.79 micromol x h/L for the 0.25 mg/kg and 1 mg/kg dosages of esomeprazole, respectively. Both esomeprazole dosages were well tolerated. CONCLUSIONS: Oral treatment with esomeprazole 0.25 mg/kg and 1 mg/kg was well tolerated and provided dose-related acid suppression, dose-related exposure to esomeprazole, and decreased esophageal acid exposure in infants 1-24 months old with GERD.

97. Omari, T., Lundborg, P., Sandstrom, M., Bondarov, P., Fjellman, M., Haslam, R., and Davidson, G. Pharmacodynamics and systemic exposure of esomeprazole in preterm infants and term neonates with gastroesophageal reflux disease. *J Pediatr* 155: 222-228, 2009.

OBJECTIVE: To characterize the pharmacodynamics and systemic exposure of esomeprazole in 26 preterm infants and term neonates with symptoms of gastroesophageal reflux and pathologic acid exposure. STUDY DESIGN: Enrolled patients received oral esomeprazole 0.5 mg/kg once daily for 7 days. Twenty-four-hour esophagogastric pH-impedance monitoring was performed at baseline and on day 7. Pharmacokinetic analysis was performed on day 7. Symptoms occurring during the baseline and day 7 studies were recorded on a symptom chart. RESULTS: There were no significant differences from baseline to day 7 of therapy in the frequency of bolus reflux, consistency of bolus reflux (liquid, mixed, or gas), extent of bolus reflux, or bolus clearance time. Acid bolus reflux episodes were reduced on therapy (median 30 vs 8, P < .001), as was the reflux index (mean % time esophageal pH < 4, 15.7% vs 7.1%, P < .001). The estimated geometric mean of area under the plasma concentration time curve during the dosing interval and observed maximum plasma concentration was 2.5 micromol x h/L and 0.74 micromol/L, respectively. The number of gastroesophageal reflux symptoms recorded over 24 hours was lower on therapy (median 22 vs 12, P < .05). CONCLUSIONS: In preterm infants and term neonates esomeprazole produces no change in bolus reflux characteristics despite significant acid suppression.

98. Omari, T.I., Haslam, R.R., Lundborg, P., and Davidson, G.P. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. *J Pediatr Gastroenterol Nutr* 44: 41-44, 2007.

INTRODUCTION: Proton pump inhibitor (PPI) therapy is increasingly being used

to treat premature infants with gastroesophageal reflux disease (GERD); however, the efficacy of PPI on acid production in this population has yet to be assessed in this patient group. The aim of this study was to determine the effect of 0.7 mg/kg/d omeprazole on gastric acidity and acid gastroesophageal reflux in preterm infants with reflux symptoms and pathological acid reflux on 24-h pH probe. METHODS: A randomized, double blind, placebo-controlled, crossover design trial of omeprazole therapy was performed in 10 preterm infants (34-40 weeks postmenstrual age). Infants were given omeprazole for 7 d and then placebo for 7 d in randomized order. Twenty-four-hour esophageal and gastric pH monitoring was performed on days 7 and 14 of the trial. RESULTS: Compared to placebo, omeprazole therapy significantly reduced gastric acidity (%time pH <4, 54% vs 14%, $P < 0.0005$), esophageal acid exposure (%time pH <4, 19% vs 5%, $P < 0.01$) and number of acid GER episodes (119 vs 60 episodes, $P < 0.05$). CONCLUSIONS: Omeprazole is effective in reducing esophageal acid exposure in premature infants with pathological acid reflux on 24-h pH probe; however, the far more complex issues of safety and efficacy have yet to be addressed.

99. Orenstein, S.R., Blumer, J.L., Faessel, H.M., McGuire, J.A., Fung, K., Li, B.U., Lavine, J.E., Grunow, J.E., Treem, W.R., and Ciociola, A.A. Ranitidine, 75 mg, over-the-counter dose: pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther* 16: 899-907, 2002.

BACKGROUND: The use of over-the-counter antacids has increased in children under the age of 12 years, and has been followed by an apparent increase in the use of over-the-counter histamine-2 receptor antagonists. However, the pharmacokinetic and pharmacodynamic effects of over-the-counter histamine-2 receptor antagonists in the paediatric population are largely unknown. AIM: To evaluate the pharmacokinetics and pharmacodynamics of a single dose of the over-the-counter histamine-2 receptor antagonist, ranitidine, 75 mg, in children with symptoms of gastro-oesophageal reflux disease. METHODS: Children aged between 4 and 11 years with symptoms of heartburn suspected to be due to gastro-oesophageal reflux disease were recruited at six clinical centres. Following a single dose of either oral ranitidine, 75 mg ($n=19$), or placebo ($n=10$), recording of intragastric pH and serial blood sampling were carried out for 6 h. RESULTS: The estimated pharmacokinetic parameters of ranitidine, 75 mg, were as follows: the median C_{max} value of 477 ng/mL occurred within a median of 2.5 h after dosing, and the median half-life was 2.0 h. The intragastric pH began to rise approximately 30 min after dosing with ranitidine to a peak of pH; 4. The pH in the ranitidine group remained higher than that in the placebo group throughout the 6-h evaluation period. Adverse events were generally mild. CONCLUSIONS: Ranitidine, 75 mg, significantly increased the intragastric pH in children aged 4-11 years. The pharmacokinetic and pharmacodynamic profiles were similar to those in adults. Ranitidine, 75 mg, appears to be effective for the control of intragastric acidity for 5-6 h in children aged 4-11 years.

100. Orenstein, S.R., Hassall, E., Furmaga-Jablonska, W., Atkinson, S., and Raanan, M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr* 154: 514-520 e514, 2009.

OBJECTIVE: To assess the efficacy and safety of lansoprazole in treating infants with symptoms attributed to gastroesophageal reflux disease (GERD) that have persisted despite a \geq 1-week course of nonpharmacologic management. STUDY DESIGN: This multicenter, double-blind, parallel-group study randomized infants with persisting symptoms attributed to GERD to treatment with lansoprazole or placebo for 4 weeks. Symptoms were tracked through daily diaries and weekly visits. Efficacy was defined primarily by a \geq 50% reduction in measures of feeding-related crying and secondarily by changes in other symptoms and global assessments. Safety was assessed based on the occurrence of adverse events (AEs) and clinical/laboratory data. RESULTS: Of the 216 infants screened, 162 met the inclusion/exclusion criteria and were randomized. Of those, 44/81 infants (54%) in each group were responders--identical for lansoprazole and placebo. No significant lansoprazole-placebo differences were detected in any secondary measures or analyses of efficacy. During double-blind treatment, 62% of lansoprazole-treated subjects experienced 1 or more treatment-emergent AEs, versus 46% of placebo recipients ($P = .058$). Serious AEs (SAEs), particularly lower respiratory tract infections, occurred in 12 infants, significantly more frequently in the lansoprazole group compared with the placebo group (10 vs 2; $P = .032$). CONCLUSIONS: This study detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. SAEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo.

101. Osman, H. Ranitidine versus cimetidine prior to emergency obstetric anesthesia. *Middle East J Anesthesiol* 13: 205-211, 1995.

Twenty parturients in labour received emergency obstetric anesthesia were randomly divided into two equal groups. Group "R" received 150 mg oral ranitidine tablet on admission, followed by 50 mg infusion in 250 ml dextrose 5% over 30 minutes prior to anesthetic induction. Group "Ce" received 400 mg cimetidine oral tablet and 100 mg infusion in 250 ml dextrose 5% over 30 minutes. Ten parturients were considered as control. Ranitidine significantly reduced the maternal gastric volume with marked alkalinization of gastric pH. No significant changes were detected in the height, frequency or amplitude of uterine contraction or neonatal assessment.

102. Osteyee, J.L., and Banner, W., Jr. Effects of two dosing regimens of intravenous ranitidine on gastric pH in critically ill children. *Am J Crit Care* 3: 267-272, 1994.

BACKGROUND: Gastric bleeding in children is associated with critical illness, shock, and physical trauma. Histamine-2 receptor antagonist therapy is used prophylactically to treat gastric bleeding, but it is not known whether bolus dosing or continuous infusion dosing is more effective. **OBJECTIVES:** To compare the effects of continuous infusion intravenous ranitidine and intravenous bolus dosing of ranitidine on gastric pH in critically ill children and to look for correlation between illness severity scores and gastric pH. **METHODS:** Sixteen critically ill children were randomized into two groups. Children in group 1 received bolus dosing on day 1 and continuous infusion of ranitidine on day 2. Group 2 received the continuous infusion on day 1 and bolus dosing on day 2. Equivalent doses of ranitidine were based on weight. Continuous infusion regimen: ranitidine bolus of 0.15 mg/kg followed by continuous infusion at 0.15 mg/kg per hour for 12 hours. Bolus regimen: 1 mg/kg, two doses 6 hours apart. Pediatric risk of mortality scores were recorded upon admission to the study. **RESULTS:** There was no statistically significant difference between regimens. Both raised gastric pH values above 4.0 during the treatment phase. There was no correlation between illness severity scores and gastric pH values. **CONCLUSIONS:** Both bolus dosing and continuous infusion dosing of 4 mg/kg per day of intravenous ranitidine were effective at raising and maintaining gastric pH in critically ill children.

103. Pfefferkorn, M.D., Croffie, J.M., Gupta, S.K., Molleston, J.P., Eckert, G.J., Corkins, M.R., and Fitzgerald, J.F. Nocturnal acid breakthrough in children with reflux esophagitis taking proton pump inhibitors. *J Pediatr Gastroenterol Nutr* **42**: 160-165, 2006.

OBJECTIVES: We aimed to determine if nocturnal acid breakthrough occurs in children receiving proton pump inhibitors for reflux esophagitis, and to compare the healing of esophagitis in children with nocturnal acid breakthrough receiving proton pump inhibitors +/- ranitidine. **METHODS:** This is a prospective, double-blind study. Endoscopic and histologic esophagitis were scored 0-4 and 0-3, respectively. Patients were treated with a proton pump inhibitor twice daily and esophagogastric pH monitoring was performed at week 3. Patients with nocturnal acid breakthrough were randomized. One group received ranitidine and the other received placebo at bedtime in addition to proton pump inhibitor therapy. Endoscopy was performed on all patients (with pH monitoring on patients with nocturnal acid breakthrough) during the 17th week of therapy. **RESULTS:** We enrolled 18 patients, ages 1 to 13 years (mean = 10.3 years). Mean baseline endoscopic and histologic scores were 3.1 +/- 1.4 and 1.8 +/- 0.7, respectively. Mean dose of proton pump inhibitor was 1.3 mg/kg +/- 0.6. Nocturnal acid breakthrough was documented in 16/18 (89%) patients. Seven patients received ranitidine and 9 received placebo. The reflux index improved: mean of 14.3 at baseline, 2.0 at week 3 (P = 0.0001), and 5.1 at week 17 (P = 0.09). Nocturnal acid breakthrough persisted in 9/12 (75%) patients, 3 of whom received ranitidine at bedtime. Esophagitis improved in all patients following therapy: mean endoscopy and histology scores were 1.6 +/- 1.8 (P = 0.0020) and 0.8 +/- 0.9 (P

= 0.0013), respectively. Symptoms significantly improved from a mean score of 2.0 at baseline to 0.4 at week 17 ($P = 0.0001$). CONCLUSIONS: Nocturnal acid breakthrough is common in pediatric patients treated with proton pump inhibitors. Reflux index remains normal in spite of nocturnal acid breakthrough. Symptoms and esophagitis continued to improve during therapy in spite of nocturnal acid breakthrough. There appears to be no additional benefit to supplementation with ranitidine at bedtime.

104. Proesmans, M., and De Boeck, K. Omeprazole, a proton pump inhibitor, improves residual steatorrhoea in cystic fibrosis patients treated with high dose pancreatic enzymes. *Eur J Pediatr* 162: 760-763, 2003.

Despite treatment with supra-physiological doses of pancreatic enzyme supplements, residual steatorrhoea is a common problem in patients with cystic fibrosis (CF) and pancreatic insufficiency. Strategies to enhance the activity of pancreatic enzymes include decreasing duodenal acidity. The aim of this study was to evaluate the effect of omeprazole (Losec), a proton-pump inhibitor, on fat absorption in CF patients with residual steatorrhoea despite high dose pancreatic enzyme supplements ($> \text{ or } = 10,000 \text{ U lipase/kg per day}$). A random cross-over design was chosen. Fat digestion was evaluated with and without omeprazole by means of chemical fat measurements in 3-day stool collections together with 3-day weighed food records for calculation of fat absorption. The results of 15 patients (3 girls and 12 boys) with confirmed steatorrhoea during the control evaluation were analysed. Median age was 8.7 years (range 3.5-15.9 years). Median daily lipase intake was 13,500 U/kg per day (range 10,000-22,000 U/kg per day). During treatment with omeprazole, median faecal fat loss (g fat/day) decreased from 13 g (quartiles 11.5-16.5 g/day) to 5.5 g (quartiles 4.9-8.1 g/day) ($P < 0.01$). The same improvement was noted when fat absorption was calculated: 87% (quartiles 81-89%) without versus 94% (quartiles 90-96%) with omeprazole ($P < 0.001$). CONCLUSION: Omeprazole improves fat digestion and absorption in cystic fibrosis patients with residual faecal fat loss despite maximal pancreatic enzyme substitution.

105. Sakurane, M., Shiotani, A., and Furukawa, F. Therapeutic effects of antibacterial treatment for intractable skin diseases in Helicobacter pylori-positive Japanese patients. *J Dermatol* 29: 23-27, 2002.

In order to understand the pathogenic relationship between Helicobacter pylori (H. pylori) and skin diseases, we examined the serum levels of IgG antibody against H. pylori and then performed gastroscopic examinations in Japanese patients with chronic skin diseases. These H. pylori-positive patients were treated with antibacterial eradication therapy, and therapeutic efficacy was evaluated. A total of 198 patients who were resistant to conventional therapies were randomly selected. They included 50 cases with chronic urticaria, 32 with pruritus cutaneous, 74 with atopic dermatitis, 15 with nummular dermatitis, 17 with prurigo chronica multiformis, 6 with psoriasis vulgaris, and 4 with

erythroderma. Positive anti-*H. pylori* antibody was detected in 102 out of these 198 patients; more than half of the ones with chronic urticaria, pruritus cutaneous, nummular dermatitis, and prurigo chronica multiformis had positive antibodies. Gastroscopy was then performed in 48 cases with positive antibodies. Eradication therapy was effective in 60% of the patients with chronic urticaria, in 58% with pruritus cutaneous, in 54% with nummular dermatitis, and in 50% with prurigo chronica multiformis. In chronic skin diseases, persistent infection with *H. pylori* may be an eruption trigger and may cause deterioration of the disease into an intractable and chronic form.

106. Sandhar, B.K., Goresky, G.V., Maltby, J.R., and Shaffer, E.A. Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. *Anesthesiology* 71: 327-330, 1989.

Eighty-eight children (mean age 5.6 yr, range 1-14 yr) about to undergo elective outpatient surgery were randomly assigned to four groups. All children were given phenolsulfonphthalein (PSP) orally 2-3 h before the scheduled time of surgery as a marker dye to assess gastric emptying. Immediately after receiving PSP they were given: group A--liquids, up to 5 ml/kg + placebo (glucose water 0.2 ml/kg); group B--liquids, up to 5 ml/kg + ranitidine 2 mg/kg in glucose water 0.2 ml/kg; group C--placebo only; group D--ranitidine only. Gastric contents were aspirated after induction of anesthesia. Mean volume (range) in ml/kg of aspirated gastric fluid in each group was: group A--0.34 (0-1.0); group B--0.17 (0.07); group C--0.25 (0-1.1); group D--0.16 (0-0.6). The pH mean (range) value was: group A--1.83 (0.9-3.6); group B--4.76 (2.0-7.7); group C--2.10 (1.2-4.1); group D--3.97 (1.3-7.3). PSP could not be detected in the gastric samples from children in whom the ingestion-sampling interval was more than 2.25 h. In comparison with prolonged starvation, administration of oral liquids without ranitidine 2-3 h preoperatively did not produce a significant increase in mean volume of gastric aspirate, and there was no increase in the number of patients with gastric aspirate greater than 0.4 ml/kg. Administration of ranitidine with or without fluids resulted in a decrease in both volume and acidity of gastric contents.

107. Scott, L.J. Lansoprazole: in the management of gastroesophageal reflux disease in children. *Paediatr Drugs* 5: 57-61; discussion 62, 2003.

Lansoprazole, a proton pump inhibitor, inactivates the H(+)/K(+)-ATPase pump in parietal cells, thereby suppressing basal and stimulated gastric acid secretion and increasing intragastric pH. After 8-12 weeks' treatment with lansoprazole, all children (n = 27) with esophagitis at baseline were healed (confirmed by endoscopy) and 76% of 62 evaluable children experienced improvements in overall gastroesophageal reflux disease (GERD) symptoms. In this noncomparative trial, 66 children (aged 1-11 years) with GERD with or without esophagitis received oral lansoprazole 15 or 30 mg once daily dependent on their weight. The drug is generally well tolerated in children with GERD. In the

largest study, the most common treatment-related adverse events occurring during therapy were constipation and headache.

108. Sevvell, S., Ananthakrishnan, N., and Kate, V. Role of histamine-2 receptor antagonists after simple closure of perforated duodenal ulcer--a double blind randomised, controlled study. *Trop Gastroenterol* 17: 227-229, 1996.

INTRODUCTION: Definitive surgery at the time of primary laparotomy for perforated duodenal ulcer is often deferred because of its increased morbidity. However simple closure alone is associated with a high rate of recurrence. In view of this H2 blockers have been administered along with simple closure to promote ulcer healing. Only 4 series have been published so far, all lacking either a control group or endoscopic follow up. The results are contradictory. AIMS: This study was done to assess the effect of administration of H2 blockers after simple closure on ulcer healing in a randomised, controlled, double blind fashion. METHODS: One hundred patients were entered in the study. Fifty patients randomly selected either received ranitidine or a placebo after simple closure. Follow up endoscopy was done at 1, 2 and 6 months. If persistence of ulcer was seen at 4 weeks, patients on placebo were converted to ranitidine and those on ranitidine were continued on the drug. RESULTS: Endoscopically assessed rate of persistent or recurrent ulcer at 4 weeks was 39% in the ranitidine group and 29% in the placebo group. At 6 months the corresponding figures were 33% and 30% respectively. The differences between the two groups were not significant. CONCLUSIONS: Ranitidine, therefore, does not appear to promote healing of a perforated duodenal ulcer after simple closure.

109. Shashidhar, H., Peters, J., Lin, C.H., Rabah, R., Thomas, R., and Tolia, V. A prospective trial of lansoprazole triple therapy for pediatric Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr* 30: 276-282, 2000.

BACKGROUND: Triple therapy with a proton-pump inhibitor and two antibiotics is widely used in the treatment of Helicobacter pylori infection in adults. Experience with such therapy in the pediatric population is limited. This was a prospective, nonrandomized, open-label trial to evaluate safety and efficacy of a combination of lansoprazole, clarithromycin, and amoxicillin in symptomatic children with H. pylori infection. METHODS: Children with H. pylori gastritis diagnosed by endoscopy performed for persistent nausea, vomiting, recurrent abdominal pain, and diarrhea with consistent histology were treated with the regimen of 0.45 mg/kg per day lansoprazole divided into two doses (maximum dose, 15 mg twice daily), amoxicillin 40 mg/kg per day in two doses (maximum dose, 1.0 g twice daily), and 250 mg clarithromycin twice daily (<10 years old) or 500 mg twice daily (>10 years old) for 2 weeks. Pre- and posttreatment endoscopic biopsy specimens were graded for the severity of gastritis and H. pylori density by a blinded pathologist. A questionnaire for assessing the severity of symptoms at the time of initial and second endoscopy were completed by patient and/or parent. RESULTS: Thirty-two children (age range, 1-25 years; mean age, 11

years; 19 females, 13 males) were treated with this regimen during an 18-month period. *H. pylori* organisms with varying grades of gastritis were present in tissue specimens of all patients. Only 28 children had follow-up endoscopy, which showed eradication of *H. pylori* in 15 (54%) children. Histologic symptoms of gastritis improved after therapy in the whole group. Overall, symptoms of vomiting, abdominal pain, diarrhea, anorexia, and halitosis significantly improved ($P < 0.05$). Minor adverse effects of therapy occurred in 25% of patients. CONCLUSIONS: Symptoms, histologic, and endoscopic findings improved after triple therapy in children with *H. pylori* gastritis; however, eradication of bacteria was achieved in only 56% of children.

110. Solana, M.J., and Lopez-Herce, J. Pharmacokinetics of intravenous omeprazole in critically ill paediatric patients. *Eur J Clin Pharmacol* 66: 323-330, 2010.

The proton pump inhibitors are first-line drugs for the treatment of a number of gastrointestinal diseases. These drugs have a good safety profile, making it possible to use them in paediatric patients. Although their pharmacokinetics in children has not been extensively studied, research performed suggests that the dose used should be varied as a function of age, as this factor affects the drug's metabolism. Proton pump inhibitors can be used in critically ill children for the prophylaxis and treatment of gastrointestinal haemorrhage, although there is still little experience with this. The most widely used proton pump inhibitor at the present time is omeprazole. As there are specific characteristics of these patients that could alter the pharmacokinetics of the drugs, studies need to be performed to determine the most suitable dose and dosage interval.

111. Sopo, S.M., Radzik, D., and Calvani, M. Does treatment with proton pump inhibitors for gastroesophageal reflux disease (GERD) improve asthma symptoms in children with asthma and GERD? A systematic review. *J Investig Allergol Clin Immunol* 19: 1-5, 2009.

OBJECTIVE: To evaluate pediatric studies of the effect on asthma symptoms of treatment with proton pump inhibitors (PPI) used to treat gastroesophageal reflux disease (GERD). METHODS: We entered the MeSH terms "gastroesophageal reflux AND asthma AND children" in the PubMed tool Clinical Queries, selecting "therapy" and "broad, sensitive search." The search ended on April 14, 2008. We included only clinical trials performed in pediatric patients. RESULTS: Four studies were considered to be relevant, although only 1 was a randomized, double-blind, placebo-controlled trial. The 3 nonrandomized trials showed that PPIs benefited patients with asthma. The randomized, double-blind, placebo-controlled trial found that omeprazole did not improve asthma symptoms. An improved (although not statistically significant) score was observed in the quality of life questionnaire in children with a reflux index greater than 10% and in those with more severe asthma treated with omeprazole compared with the placebo group. CONCLUSIONS: Scant data in these studies mean that we cannot make solid recommendations. However, in specific cases, we think that treatment of

asthma symptoms with a PPI is valid as long as at least 2 conditions are satisfied: asthma must not respond to standard treatment, and 1 instrumental parameter of GERD severity must be satisfied, that is, a reflux index greater than or equal to 10 must be present.

112. Springer, M., Atkinson, S., North, J., and Raanan, M. Safety and pharmacodynamics of lansoprazole in patients with gastroesophageal reflux disease aged <1 year. *Paediatr Drugs* 10: 255-263, 2008.

BACKGROUND: The use of proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD) in pediatric patients <1 year of age is increasing. However, few studies with PPIs have been reported in such patients. **OBJECTIVES:** To assess the effect of once-daily lansoprazole on safety and to characterize the pharmacodynamic profile of lansoprazole in a subset of subjects <1 year of age. The effect of lansoprazole on predefined GERD-associated symptoms was also assessed. **METHODS:** Two phase I, single- and repeated-dose, randomized, parallel-group, open-label, multicenter studies were performed. Both studies involved either a 7- or 14-day pre-treatment period, with a dose administration period of 5 days, and a follow-up period of 30 days for adverse events collection. A total of six investigative sites were involved: four university hospital/medical centers (three in Poland, one in the US), one large regional medical center (Poland), and one private practice (US). The studies involved 24 neonates (<or=28 days of age) and 24 infants (>28 days but <1 year of age) with GERD-associated symptoms diagnosed by medical history and the clinical judgment of the treating physician. Eligible subjects were randomized to receive either lansoprazole 0.5 or 1.0 mg/kg/day (neonates), or 1.0 or 2.0 mg/kg/day (infants), for 5 days. Safety and pharmacodynamic parameters were the primary outcome measures. Safety and GERD symptoms were assessed in all participants. Intra-gastric/intraesophageal pH monitoring was performed in a subset of six neonates and six infants at baseline and on dose administration days 1 and 5. **RESULTS:** Over 5 days of daily dose administration, lansoprazole was well tolerated in neonates and infants. Four neonates and one infant experienced mild to moderate treatment-related adverse events during the dose administration period. One neonate experienced a serious adverse event that was unrelated to treatment. Lansoprazole increased the percentage of time that intra-gastric pH was above 3, 4, 5, and 6 over the 24-hour post-dose period on days 1 and 5 when compared with baseline. Mean 24-hour integrated gastric acidity decreased from baseline to day 5 in both populations. The daily number of episodes of regurgitation/vomiting was lower than at baseline among neonates after 5 days of lansoprazole treatment; among infants, both the prevalence and the average daily number of episodes of several individual GERD-associated symptoms were lower than at baseline. **CONCLUSIONS:** After 5 days of open-label administration, lansoprazole was well tolerated and increased intra-gastric pH in pediatric subjects <1 year of age. A decrease in the frequency of GERD symptoms was also observed.

113. Stavroulaki, P. Diagnostic and management problems of laryngopharyngeal reflux disease in children. *Int J Pediatr Otorhinolaryngol* 70: 579-590, 2006.

OBJECTIVE: Reflux is a common pediatric disorder and an association between reflux and otolaryngological conditions has been described. However, to prove a causal relationship a pathophysiological pathway must be identified, diagnostic test with high specificity and sensitivity must be developed and conservative or surgical treatment of reflux should be shown to predictably improve the otolaryngological problems. This review study aims at examining the available evidence for the above controversial issues. METHODS: Articles on pediatric laryngopharyngeal reflux published in English during the last decade were searched using Ovid and PubMed. RESULTS: A lack of consensus was found in four separate but interdependent areas: clinical manifestations, diagnostic testing, interpretation of findings and treatment. Although clinical experience and uncontrolled case series suggest that laryngopharyngeal reflux may possibly contribute to apnea, recurrent upper respiratory infections, laryngeal symptoms (mainly laryngomalacia and subglottic stenosis), sinusitis and otitis convincing data are lacking. For pediatric studies, the diagnostic role of pH monitoring, barium esophagram, scintigraphy, impedance monitoring, laryngoscopic examination, laryngeal biopsy and symptom assessment questionnaires remain to be defined. Interpretation of pharyngeal reflux events is controversial and the lack of established normative values as well as the existing variability in the diagnostic criteria (reflux definition, duration and number of pathological reflux events) limits the ability to directly compare results. Proposed laryngopharyngeal reflux treatment (lifestyle modification, medical or surgical therapy) is mostly empiric, with no significant placebo-controlled trials of treatment and outcomes. CONCLUSIONS: Limited evidence exists to support a causative relationship between reflux and any otorhinolaryngological condition or the effectiveness of treatment. Epidemiological and large-scale prospective controlled studies are required to clarify these issues.

114. Stordal, K., Johannesdottir, G.B., Bentsen, B.S., Knudsen, P.K., Carlsen, K.C., Closs, O., Handeland, M., Holm, H.K., and Sandvik, L. Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. *Arch Dis Child* 90: 956-960, 2005.

BACKGROUND: Epidemiological studies have shown an association between gastro-oesophageal reflux disease (GORD) and asthma, and oesophageal acid perfusion may cause bronchial constriction. However, no causative relation has been proven. AIM: To assess whether acid suppression would lead to reduced asthma symptoms in children with concomitant asthma and GORD. METHODS: Thirty eight children (mean age 10.8 years, range 7.2-16.8; 29 males) with asthma and a reflux index $>$ or $=5.0$ assessed by 24 hour oesophageal pH monitoring were randomised to 12 weeks of treatment with omeprazole 20 mg daily or placebo. The groups were similar in age, gender, mean reflux index, and asthma severity. Primary endpoints were asthma symptoms (daytime wheeze,

symptoms at night, in the morning, and during exercise) and quality of life (PAQLQ). Secondary endpoints were changes in lung function and the use of short acting bronchodilators. At the end of the study a repeated pH study was performed to confirm the efficacy of acid suppression. RESULTS: The change in total symptom score did not differ significantly between the omeprazole and the placebo group, and decreased by 1.28 (95% CI -0.1 to 2.65) and 1.28 (95% CI -0.72 to 3.27) respectively. The PAQLQ score increased by 0.62 (95% CI 0.29 to 0.95) in the omeprazole group compared to 0.50 (95% CI 0.29 to 0.70) in the placebo group. Change in lung function and use of short acting bronchodilators were similar in the groups. The acid suppression was adequate (reflux index <5.0) under omeprazole treatment. CONCLUSION: Omeprazole treatment did not improve asthma symptoms or lung function in children with asthma and GORD.

115. Strauss, R.S., Calenda, K.A., Dayal, Y., and Mobassaleh, M. Histological esophagitis: clinical and histological response to omeprazole in children. *Dig Dis Sci* 44: 134-139, 1999.

Many children with esophagitis demonstrate histological changes without gross evidence of esophagitis by esophagoscopy. The effect of omeprazole on the histological healing of esophagitis in children is unknown. Therefore, the aim of this study was to determine the effect of omeprazole on refractory histological esophagitis in pediatric patients. Eighteen patients with histological evidence of esophagitis and recurrent symptoms despite therapy with H₂-receptor antagonists and prokinetic agents were prospectively treated with omeprazole. Dosing was adjusted by monitoring intragastric pH, and esophagoscopy was repeated after 8-12 weeks of omeprazole treatment. Two patients did not complete the study due to either worsening symptoms or hypergastrinemia. Of the remaining patients, 76% were asymptomatic with omeprazole treatment and 24% reported improvement in their symptoms. Approximately 40% demonstrated complete histological healing of their esophagitis. Three patients (17%) had persistent elevations in serum gastrin levels while on omeprazole treatment, which was associated with both younger patient age and higher omeprazole dosing; however, all elevated gastrin levels returned to normal after discontinuation of the medication. All patients had recurrence of their symptoms after completing a course of omeprazole, even patients with complete histological healing. Omeprazole is efficacious in treating children with esophagitis refractory to H₂-receptor antagonist and prokinetic agents. However, none of the patients were able to discontinue acid suppressive therapy even after documented healing of their esophagitis.

116. Szajewska, H., Albrecht, P., and Topczewska-Cabanek, A. Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on *Helicobacter pylori* eradication rates and side effects during treatment in children. *J Pediatr Gastroenterol Nutr* 48: 431-436, 2009.

OBJECTIVE: To determine the effectiveness of *Lactobacillus GG* (LGG) in children with *Helicobacter pylori* infection undergoing eradication therapy. **MATERIALS AND METHODS:** We conducted a double-blind, placebo-controlled, randomized trial comparing a 7-day, triple eradication regimen consisting of 2 antibiotics (amoxicillin tablets, 25 mg/kg twice per day, and clarithromycin tablets, 10 mg/kg twice per day) plus a proton pump inhibitor (omeprazole capsules, 0.5 mg/kg twice per day) supplemented with LGG (109 colony-forming units) or placebo in 83 children with *H. pylori* infection confirmed by 2 of 3 tests (13C-urea breath test, histopathology, rapid urease test). The primary outcome measure was the *H. pylori* eradication rate. The secondary outcome measure was the proportion of patients who experienced therapy-related adverse effects during anti-*H. pylori* treatment. **RESULTS:** The groups did not differ with respect to *H. pylori* eradication rates. Of the 34 children in the LGG group, 23 (69%) experienced eradication, compared with 22 of 32 children (68%) in the placebo group (RR 0.98, 95% CI 0.7-1.4). The groups did not differ with respect to adverse effects. **CONCLUSIONS:** In children with *H. pylori* infection, supplementation of standard triple therapy with LGG did not significantly alter the eradication rate or side effects.

117. Tam, Y.H., Yeung, C.K., and Lee, K.H. Seven-day is more effective than 4-day ranitidine bismuth citrate-based triple therapy in eradication of *Helicobacter pylori* in children: a prospective randomized study. *Aliment Pharmacol Ther* 24: 81-86, 2006.

BACKGROUND: *Helicobacter pylori* infection is common in paediatric population. To date, there is still no universally accepted recommendation on the treatment of this infection in children. Ranitidine bismuth citrate-based triple therapy has been shown to be effective in *H. pylori* eradication in adults but its use has rarely been validated in children. **AIM:** To investigate the efficacy of ranitidine bismuth citrate-based triple therapy in eradication of *H. pylori* in children and to determine the shortest duration of treatment required. **PATIENTS AND METHODS:** We conducted a prospective randomized study comparing ranitidine bismuth citrate plus amoxicillin plus clarithromycin given for 4 days vs. 7 days in *H. pylori*-infected children diagnosed by (13)C-urea breath test. Eradication was evaluated by repeat (13)C-urea breath test at 6 weeks after treatment. **RESULTS:** A total of 206 children were recruited (median age 12 years, 97 boys and 109 girls). Ninety-eight (47.6%) and 108 (52.4%) children were randomized to receive 7-day and 4-day regimen respectively. The eradication rate of 4-day treatment arm was 77.8% (both intention-to-treat and per protocol) compared with 88.8% (intention-to-treat, $P = 0.036$) and 89.7% (per protocol, $P = 0.022$) of 7-day regimen. There was no statistical difference in terms of side effects between the two groups. **CONCLUSIONS:** Seven-day ranitidine bismuth citrate-based triple therapy is an effective and well-tolerated treatment for eradication of *H. pylori* in children.

118. Tighe, M.P., Afzal, N.A., Bevan, A., and Beattie, R.M. Current pharmacological management of gastro-esophageal reflux in children: an evidence-based

systematic review. *Paediatr Drugs* 11: 185-202, 2009.

Gastro-esophageal reflux (GER) is a common phenomenon, characterized by the regurgitation of the gastric contents into the esophagus. Gastro-esophageal reflux disease (GERD) is the term applied when GER is associated with sequelae or faltering growth. The main aims of treatment are to alleviate symptoms, promote normal growth, and prevent complications. Medical treatments for children include (i) altering the viscosity of the feeds with alginates; (ii) altering the gastric pH with antacids, histamine H(2) receptor antagonists, and proton pump inhibitors; and (iii) altering the motility of the gut with prokinetics, such as metoclopramide and domperidone. Our aim was to systematically review the evidence base for the medical treatment of gastro-oesophageal reflux in children. We searched PubMed, AdisOnline, MEDLINE, and EMBASE, and then manually searched reviews from the past 5 years using the key words 'gastro-esophageal' (or 'gastroesophageal'), 'reflux', 'esophagitis', and 'child\$' (or 'infant') and 'drug\$' or 'therapy'. Articles included were in English and had an abstract. We used the levels of evidence adopted by the Centre for Evidence-Based Medicine in Oxford to assess the studies for all reported outcomes that were meaningful to clinicians making decisions about treatment. This included the impact of clinical symptoms, pH study profile, and esophageal appearance at endoscopy. Five hundred and eight articles were reviewed, of which 56 papers were original, relevant clinical trials. These were assessed further. Many of the studies considered had significant methodological flaws, although based on available evidence the following statements can be made. For infant GERD, ranitidine and omeprazole and probably lansoprazole are safe and effective medications, which promote symptomatic relief, and endoscopic and histological healing of esophagitis. Gaviscon(R) Infant sachets are safe and can improve symptoms of reflux. There is less evidence to support the use of domperidone or metoclopramide. More evidence is needed before other anti-reflux medications can be recommended. For older children, acid suppression is the mainstay of treatment. The largest evidence base supports the early use of H(2) receptor antagonists or proton pump inhibitors.

119. Tindberg, Y., Casswall, T.H., Blennow, M., Bengtsson, C., Granstrom, M., and Sorberg, M. Helicobacter pylori eradication in children and adolescents by a once daily 6-day treatment with or without a proton pump inhibitor in a double-blind randomized trial. *Aliment Pharmacol Ther* 20: 295-302, 2004.

AIM: To evaluate two simplified Helicobacter pylori eradication treatment alternatives for children and adolescents. METHODS: Study subjects were identified by enzyme-linked immunosorbent assay and immunoblot in a family screening project. Helicobacter pylori infected 10-21 year olds were offered treatment, individuals with abdominal pain underwent upper endoscopy and those with peptic ulcers were excluded. Participants were randomized to either azithromycin 500 mg daily and tinidazole 500 mg two tablets daily in combination with lansoprasole 30 mg daily for 6 days (ATL-group) or with placebo (ATP-

group). Urea Breath Test was performed at inclusion and after a minimum of 6 weeks after end of therapy. RESULTS: In total, 131 individuals were randomized, of whom 31 (24%) had undergone upper endoscopy. Full compliance was achieved in 93% (122 of 131). The intention-to-treat eradication rate was 67% (44 of 66) and 58% (38 of 65) for the ATL- and the ATP-group, respectively. CONCLUSION: The double-blind randomized clinical trial did not identify a simplified, successful once daily H. pylori treatment for children and adolescents. Thus, twice daily proton pump inhibitor (PPI)-based triple therapies for 7 days remain as the choice of treatment in children. Further, powerful and controlled studies are needed to elucidate the best treatment strategies for H. pylori eradication in this age group.

120. Tipnis, N.A., and Rudolph, C.D. Treatment Options in Pediatric GERD. *Curr Treat Options Gastroenterol* 10: 391-400, 2007.

Gastroesophageal reflux (GER) is a common physiologic phenomenon in infants and children. GER that results in symptoms or complications--hence the evolution to GER disease (GERD)--warrants targeted evaluation and appropriate treatment. Judicious use of acid-suppression therapy remains the mainstay of pharmacologic treatment of GERD. However, recognition of treatment goals and potentials risks of acid suppression must be considered prior to initiation of therapy. The role of surgical intervention for GERD remains limited.

121. Tiren, U., Sandstedt, B., and Finkel, Y. Helicobacter pylori gastritis in children: efficacy of 2 weeks of treatment with clarithromycin, amoxicillin and omeprazole. *Acta Paediatr* 88: 166-168, 1999.

Thirty-eight children with Helicobacter pylori gastritis diagnosed by histopathology, and/or bacteriological culture were treated with omeprazole, amoxicillin and clarithromycin. Follow-up endoscopy was performed in 34 children. Outcome was measured by negative histology and culture for H. pylori. Six patients were excluded. Of the 32 remaining children eradication was achieved in 75% (95% confidence interval 60-90%).

122. Tofil, N.M., Benner, K.W., Fuller, M.P., and Winkler, M.K. Histamine 2 receptor antagonists vs intravenous proton pump inhibitors in a pediatric intensive care unit: a comparison of gastric pH. *J Crit Care* 23: 416-421, 2008.

PURPOSE: The aim of this study was to assess gastric pH in critically ill pediatric patients receiving intravenous stress ulcer medication. MATERIALS AND METHODS: A prospective study was done in 48 patients with a gastric tube in place who were receiving either ranitidine or a proton pump inhibitor and no enteral nutrition. Daily peak and trough gastric pHs were measured. RESULTS: The median age was 7 years 5 months (range, 1 month to 19 years), the median weight was 31 kg (range, 3-130 kg), and the median pediatric risk of mortality 2 (PRISM2) score was 12.5 (range, 0-31). All patients were intubated and 8

received dialysis. The average trough pH was 4.4 +/- 1.6 in the ranitidine group, 4.9 +/- 1.8 in the once daily proton pump inhibitor group, and 5.0 +/- 1.2 in the twice daily proton pump inhibitor group (P = .16). The average peak pH was 5.3 +/- 1.8 in the ranitidine group, 5.9 +/- 1.6 in the once daily proton pump inhibitor group, and 6.0 +/- 1.0 in the twice daily proton pump inhibitor group (P = .06). Three (10%) of 28 trough pH measurements in the twice daily proton pump inhibitor group were more acidic than 4 vs 24 (40%) of 60 in the ranitidine group, and 22 (40%) of 56 in the once daily proton pump inhibitor group (P = .02). One (4%) of 27 peak pH measurements in the twice daily proton pump inhibitor group were more acidic than 4 vs 13 (20%) of 61 in the ranitidine group, and 9 (16%) of 56 in the once daily proton pump inhibitor group (P = .12). Three patients (6%; 95% confidence interval, 0.51%-16%) developed upper gastrointestinal bleeding, and 4 patients (8%; 95% confidence interval, 0%-13%) developed ventilator-acquired pneumonia. CONCLUSIONS: Many critically ill pediatric patients receiving stress ulcer prophylaxis have a trough or peak gastric pH more acidic than 4.

123. Tolia, V., Bishop, P.R., Tsou, V.M., Gremse, D., Soffer, E.F., and Comer, G.M. Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5-11 years) with symptomatic gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 42: 384-391, 2006.

OBJECTIVE: To evaluate symptom improvement in 53 children (aged 5-11 years) with endoscopically proven gastroesophageal reflux disease (GERD) treated with pantoprazole (10, 20 and 40 mg) using the GERD Assessment of Symptoms in Pediatrics Questionnaire. METHODS: The GERD Assessment of Symptoms in Pediatrics Questionnaire was used to measure the frequency and severity over the previous 7 days of abdominal/belly pain, chest pain/heartburn, difficulty swallowing, nausea, vomiting/regurgitation, burping/belching, choking when eating and pain after eating. Individual symptom scores were based on the product of the frequency and usual severity of each symptom. The sum of the individual symptom score values made up the composite symptom score (CSS). The primary end point was the change in the mean CSS from baseline to week 8. RESULTS: Mean frequency and severity of each symptom significantly decreased (from P < 0.006 to P < 0.001) over time. Similar significant decreases in CSS at week 8 versus baseline (P < 0.001) were seen in all groups. Significant decreases from baseline in CSS were noted from weeks 1 to 8 in the 20-mg (P < 0.003) and 40-mg (P < 0.001) groups. The 20- and 40-mg doses were significantly (P < 0.05) more effective than the 10-mg dose in improving GERD symptoms at week 1. Adverse events were similar among the treatment groups. CONCLUSIONS: Pantoprazole (20 and 40 mg) is effective in reducing endoscopically proven GERD symptoms in children. Both 20 and 40 mg pantoprazole significantly reduced symptoms as early as 1 week.

124. Tolia, V., Ferry, G., Gunasekaran, T., Huang, B., Keith, R., and Book, L. Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children. *J*

OBJECTIVES: To assess the efficacy of lansoprazole for the relief of symptoms due to gastroesophageal reflux disease (GERD) in children 1 to 11 years of age. In addition, the efficacy in healing of erosive esophagitis (EE) was determined in those children with EE who were enrolled in the study. **METHODS:** In this phase I/II, open-label, multicenter (11 sites) U.S. study, children with symptomatic GERD, EE by endoscopy, and/or intraesophageal pH < 4 for greater than 4.2% of the time based on 24-hour pH testing were assigned, on the basis of body weight, to lansoprazole 15 mg (< or = 30 kg) or 30 mg (> 30 kg) once daily for 8 to 12 weeks. At the discretion of the investigator, the dosage of lansoprazole was increased up to 60 mg daily in children who continued to be symptomatic after 2 weeks of treatment. Symptom response was assessed by investigator interview and daily diary. Esophagitis healing was evaluated by repeat endoscopy after 8 and, if applicable, 12 weeks of treatment. **RESULTS:** Sixty-six children were enrolled. At week 8, 78% (21/27) of the children with EE at baseline had healed; the remaining six children were healed by week 12 (100%, 6/6). By investigator interview, 70% of children experienced resolution or improvement in their overall symptoms of GERD by their final visit. Statistically significant reductions from baseline in the severity of each symptom were reported with the exceptions of wheezing, hematemesis, and melena. Based on daily diary data, improvement in overall GERD symptoms was reported in 76% (47/62) of all children. With few exceptions, significant (P < 0.05) reductions from baseline occurred during each of the 2-week treatment intervals of the study period in the percentage of days and the average daily severity of GERD symptoms, the percentage of days antacid was used, and the average number of antacid tablets used per day. **CONCLUSION:** In children 1 to 11 years of age, lansoprazole is efficacious in healing EE and in relieving GERD-related symptoms.

125. Tolia, V., Fitzgerald, J., Hassall, E., Huang, B., Pilmer, B., and Kane, R., 3rd. Safety of lansoprazole in the treatment of gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr* 35 Suppl 4: S300-307, 2002.

OBJECTIVES: To evaluate the safety of lansoprazole in children between 1 and 11 years of age. **METHODS:** In a phase I/II, open-label, multicenter (11 sites) study, children with symptomatic gastroesophageal reflux disease (GERD), erosive esophagitis (> or = grade 2), and/or esophageal pH < 4 for > 4.2% of the 24-hour period were assigned, on the basis of body weight, to lansoprazole 15 mg (< or = 30 kg) or 30 mg (> 30 kg) once daily for 8 to 12 weeks. At the discretion of the investigator, the dosage of lansoprazole was increased up to 60 mg daily in children who continued to be symptomatic after 2 weeks of treatment. Safety for all study participants was monitored by adverse event reports and laboratory evaluations. **RESULTS:** Sixty-six children were enrolled in the study and were included in the safety analysis. Throughout the treatment period, no child discontinued therapy because of an adverse event and no clinically significant changes in laboratory values were observed. Three of the 32 children

(9%) who received lansoprazole 15 mg once daily (mean exposure 50.3 days) and 6 of the 34 children (18%) who received the 30 mg once-daily dose (mean exposure 49.4 days) experienced one or more treatment-related adverse events before any dose increase. The three children in the lansoprazole 15 mg treatment group were treated with doses of 0.6 mg to 1.2 mg/kg/day; those in the lansoprazole 30 mg treatment group were treated with doses of 0.7 mg to 0.9 mg/kg/day. Only one child experienced a new treatment-related adverse event after an increase in lansoprazole dose to 1.3 mg/kg/day. Treatment-related events experienced by two or more children were: constipation (lansoprazole 15 mg QD, two children; lansoprazole 30 mg QD, one child), and headache (lansoprazole 30 mg QD, two children). Mean fasting serum gastrin levels were significantly increased from 58.0 pg/mL at baseline to 112.4 pg/mL at week 2 and 121.9 pg/mL at the final visit ($P \leq 0.001$ for each comparison). However, the median fasting serum gastrin levels at the week 2 and the final visit were within the normal range (25-111 pg/mL). CONCLUSION: Lansoprazole, when administered on the basis of body weight in children between 1 and 11 years of age, is safe and well-tolerated.

126. Tolia, V., Youssef, N.N., Gilger, M.A., Traxler, B., and Illueca, M. Esomeprazole for the treatment of erosive esophagitis in children: an international, multicenter, randomized, parallel-group, double-blind (for dose) study. *BMC Pediatr* 10: 41, 2010.

BACKGROUND: Acid suppression with a proton pump inhibitor is standard treatment for gastroesophageal reflux disease and erosive esophagitis in adults and increasingly is becoming first-line therapy for children aged 1-17 years. We evaluated endoscopic healing of erosive esophagitis with esomeprazole in young children with gastroesophageal reflux disease and described esophageal histology. METHODS: Children aged 1-11 years with endoscopically or histologically confirmed gastroesophageal reflux disease were randomized to esomeprazole 5 or 10 mg daily (< 20 kg) or 10 or 20 mg daily (> or = 20 kg) for 8 weeks. Patients with erosive esophagitis underwent an endoscopy after 8 weeks to assess healing of erosions. RESULTS: Of 109 patients, 49% had erosive esophagitis and 51% had histologic evidence of reflux esophagitis without erosive esophagitis. Of the 45 patients who had erosive esophagitis and underwent follow-up endoscopy, 89% experienced erosion resolution. Dilatation of intercellular space was reported in 24% of patients with histologic examination. CONCLUSIONS: Esomeprazole (0.2-1.0 mg/kg) effectively heals macroscopic and microscopic erosive esophagitis in this pediatric population with gastroesophageal reflux disease. Dilatation of intercellular space may be an important histologic marker of erosive esophagitis in children. TRIAL REGISTRATION: D9614C00097; ClinicalTrials.gov identifier NCT00228527.

127. Tsou, V.M., Baker, R., Book, L., Hammo, A.H., Soffer, E.F., Wang, W., and Comer, G.M. Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with

gastroesophageal reflux disease (GERD). *Clin Pediatr (Phila)* 45: 741-749, 2006.

An age-appropriate questionnaire (GASP-Q) was used to assess the frequency and severity of the gastroesophageal reflux disease (GERD) symptoms: abdominal/belly pain, chest pain/heartburn, pain after eating, nausea, burping/belching, vomiting/regurgitation, choking when eating, and difficulty swallowing, in adolescents age 12 to 16 years. The primary objective was to compare the mean composite symptom score (CSS) at week 8 with baseline after treatment with 20 or 40 mg of pantoprazole. Statistically significant ($p < 0.001$) improvement in CSS occurred in both groups. Safety was comparable between the 2 groups. Pantoprazole was safe, well tolerated, and effective in reducing symptoms of GERD in adolescents.

128. Wells, T.G., Heulitt, M.J., Taylor, B.J., Fasules, J.W., and Kearns, G.L. Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 38: 402-407, 1998.

The pharmacokinetics and pharmacodynamics of ranitidine were studied in 13 term neonates with stable renal and hepatic function who were treated with extracorporeal membrane oxygenation (ECMO). Ranitidine was initially administered as a single 2 mg/kg dose over 10 minutes and intragastric pH was monitored to determine response. Within 90 minutes after administration of ranitidine, intragastric pH for all of the patients whose initial reading was ≤ 4 had increased to > 5 . Intragastric pH remained > 4 for a minimum of 15 hours. Mean \pm 1 standard deviation elimination half-life was 6.61 \pm 2.75 hours, and 41.5 \pm 22.2% of the single dose was eliminated in urine within 24 hours. Total plasma clearance of ranitidine correlated well with estimated glomerular filtration rate. Twenty-four hours after the initial dose, a continuous infusion of ranitidine (2 mg/kg/24 hr) was started and continued for 72 hours or until ECMO was discontinued. Eleven patients completed 48 hours of continuous infusion and seven completed all 72 hours. Plasma clearance and elimination half-life were determined from steady-state plasma ranitidine concentrations 24, 48, and 72 hours after the start of the infusion. There were no significant differences in clearance between these intervals. These data suggest that for term neonates with stable renal and hepatic function, ranitidine does not need to be administered more frequently than every 12 hours. A continuous infusion of 2 mg/kg/24 hours maintained intragastric pH above 4 in more than 90% of our patients, and in our opinion is the preferred method for delivering ranitidine to term neonates undergoing ECMO who require H₂ antagonists. Response to therapy should be monitored by repeated measurement of gastric pH and the dose should be adjusted accordingly.

129. Wheatley, E., and Kennedy, K.A. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr* 155: 516-521, 2009.

OBJECTIVE: To determine whether anti-reflux medications reduce bradycardia episodes attributed to clinically suspected gastroesophageal reflux (GER). **STUDY DESIGN:** We conducted a masked trial comparing metoclopramide, 0.2 mg/kg/dose q 6 hours, and ranitidine, 2 mg/kg/dose q 8 hours, with saline placebo. Each infant served as his own control. Preterm infants having >3 bradycardia episodes per 2 days were eligible if the clinician intended to begin anti-reflux medications for bradycardia attributed to GER. **RESULTS:** The mean (SD) birth weight was 1238 (394) g and gestational age was 29 (3) weeks. Eighteen infants were enrolled at 35 (22) days of age. There were 4.6 (3.1) and 3.6 (2.7) bradycardia episodes per day in the drug and placebo periods, respectively. The mean difference (drug minus placebo) was 0.94 (95% CI, 0.04 to 1.95) ($P = .04$ by t test). There was a decrease in bradycardia episodes over time ($P < .001$ by nonparametric repeated-measures analysis of variance). **CONCLUSIONS:** Anti-reflux medications did not reduce, and may have increased, bradycardia episodes in preterm infants with GER. Because there was an improvement of bradycardia episodes over time, unrelated to treatment, unmasked therapeutic trials of medications are likely to lead to misleading conclusions.

130. Zhang, W., Kukulka, M., Witt, G., Sutkowski-Markmann, D., North, J., and Atkinson, S. Age-dependent pharmacokinetics of lansoprazole in neonates and infants. *Paediatr Drugs* 10: 265-274, 2008.

BACKGROUND: Evidence suggests that age may affect the pharmacokinetics of lansoprazole in pediatric patients, but little information is available in neonates and infants. **OBJECTIVE:** To determine the pharmacokinetics of lansoprazole in neonates and infants <1 year of age with gastroesophageal reflux disease (GERD)-associated symptoms. **METHODS:** Two single- and repeated-dose, randomized, open-label, multicenter studies were conducted. Studies involved a pretreatment period of 7 or 14 days, a dose administration period of 5 days, and a follow-up period of 30 days for adverse events collection. The studies were conducted in both hospital and private clinic settings. The studies were performed in 24 neonates (aged ≤ 28 days) and 24 infants (aged >28 days, but <1 year) with GERD-associated symptoms diagnosed by medical history and the clinical judgment of the treating physician. Participants received lansoprazole 0.5 or 1.0 mg/kg/day (neonates) or 1.0 or 2.0 mg/kg/day (infants) for 5 days. Plasma pharmacokinetic parameters on dose administration day 1 were calculated, and plasma concentrations on day 5 were obtained. **RESULTS:** The pharmacokinetics of lansoprazole were approximately dose proportional. After a single dose in neonates, the mean maximum plasma concentrations (C_{max}) were 831 and 1672 ng/mL, and the mean area under the plasma concentration-time curve (AUC) values were 5086 and 9372 ng · h/mL for lansoprazole doses of 0.5 and 1.0 mg/kg, respectively. The time to C_{max} (t_{max}) [3.1 hours] and harmonic mean terminal elimination half-life ($t_{1/2}$) [2.8 hours] were slightly longer in neonates receiving 0.5 mg/kg than the t_{max} (2.6 hours) and $t_{1/2}$ (2.0 hours) values observed in neonates receiving 1.0 mg/kg. Mean oral

clearance (CL/F) was identical for the two doses (0.16 L/h/kg). After a single 1.0 or 2.0 mg/kg dose in infants, the lansoprazole C(max) values were 959 and 2087 ng/mL and the mean AUC values were approximately 2203 and 5794 ng . h/mL, respectively. The mean t(max) and mean t((1/2)) were 1.8 hours and 0.8 hours, respectively, for both doses (1.0 or 2.0 mg/kg), while mean CL/F was 0.71 and 0.61 L/h/kg, respectively. In both patient groups, mean plasma concentrations on day 5 were similar to day 1 concentrations. No clinically meaningful accumulation was observed following 5 days' dose administration. Plots of lansoprazole pharmacokinetics against chronologic age showed that dose-normalized C(max), t((1/2)), and AUC were two, three, and five times higher, respectively, in study participants aged ≤ 10 weeks than in study participants aged >10 weeks-1 year. Lansoprazole was well tolerated in all patients. CONCLUSIONS: The pharmacokinetics of lansoprazole in pediatric patients are age dependent, with those aged ≤ 10 weeks showing higher plasma exposure and lower plasma clearance than those aged >10 weeks-1 year. Thus, pediatric patients aged ≤ 10 weeks require a lower dose of lansoprazole than pediatric patients aged >10 weeks to achieve similar plasma exposure.

131. Zhao, J., Li, J., Hamer-Maansson, J.E., Andersson, T., Fulmer, R., Illueca, M., and Lundborg, P. Pharmacokinetic properties of esomeprazole in children aged 1 to 11 years with symptoms of gastroesophageal reflux disease: a randomized, open-label study. *Clin Ther* 28: 1868-1876, 2006.

OBJECTIVE: The aim of this study was to assess the overall exposure, other pharmacokinetic (PK) properties, and tolerability of esomeprazole magnesium after repeated oral doses of 5, 10, and 20 mg in pediatric patients who had symptoms of gastroesophageal reflux disease (GERD). METHODS: This randomized, open-label study was conducted at West Coast Clinical Trials, Long Beach, California. Boys and girls aged 1 to 11 years who had a clinical diagnosis of GERD were included and stratified by age (1-5 years [younger group] and 6-11 years [older group]). For this 5-day study, children in the younger group were randomly assigned to receive 1 esomeprazole 5- or 10-mg capsule p.o. QD, and those in the older group were randomly assigned to receive 1 esomeprazole 10- or 20-mg capsule p.o. QD. On days 1 to 4, study medications were administered with the supervision of the study personnel 1 hour before breakfast. Blood samples were collected within 0.5 hour before and 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after study drug administration on day 5. Plasma concentrations of esomeprazole were measured using reverse-phase liquid chromatography and mass-spectrometric detection. Tolerability assessments were performed by reviewing the number and severity of adverse events (collected via spontaneous reporting and direct questioning) and findings from the physical examination, which included vital-sign measurements and laboratory analysis (hematology, biochemistry, and urinalysis). Site personnel supervised the administration of the study drug to ensure compliance with treatment. RESULTS: The study included 31 children (17 boys, 14 girls; mean age, 5 years; 18 children in the younger group, 13 in the older group). A total of 27 children were included in the PK

analysis. In the younger group, the geometric mean AUC(0-infinity) and Cmax values in the esomeprazole 10-mg group were >2-fold that in the 5-mg group (AUC(0-infinity), 4.83 and 0.74 pmol x h/L [0.32 and 0.04 micromol x h x L(-1)/kg], respectively; Cmax, 2.98 and 0.62 micromol/L [0.19 and 0.03 micromol/L x kg(-1)], respectively). In the older group, the geometric mean AUC(0-infinity) and Cmax values for the 20-mg dose group were approximately 2-fold those for the 10-mg dose group (AUC(0-infinity), 6.28 and 3.70 micromol x h/L [0.21 and 0.12 pmol x h x L(-1)/kg], respectively; Cmax, 3.73 and 1.77 micromol/L [0.13 and 0.06 micromol/L x kg¹], respectively). For the 10-mg esomeprazole dose, the geometric mean body-weight-normalized apparent oral clearance was approximately 50% higher in the younger group compared with the older group (0.40 and 0.25 L/h x kg(-1), respectively). Thirty patients were included in the tolerability analysis. The adverse events that occurred were skin excoriation, discolored feces, and skin laceration (1 [3.3%] patient each); none were considered related to treatment. CONCLUSIONS: The results of this small study suggest that, in children aged 1 to 11 years who had GERD, the PK properties of esomeprazole may be both dose and age dependent and that younger children might have a more rapid metabolism of esomeprazole per kilogram of body weight compared with older children. Esomeprazole was well tolerated at doses of 5, 10, and 20 mg in the pediatric patients studied.

132. Zimmermann, A.E., Walters, J.K., Katona, B.G., Souney, P.E., and Levine, D. A review of omeprazole use in the treatment of acid-related disorders in children. *Clin Ther* 23: 660-679; discussion 645, 2001.

BACKGROUND: Acid peptic disease is a common problem, with a similar prevalence of gastroesophageal reflux disease (GERD) in adults and children. The presentation of GERD in infants and children varies from crying, irritability, or sleep disturbance to feeding difficulties, vomiting, or rumination. Helicobacter pylori (HP)-related diseases and gastric and duodenal ulcers are much more common in adults than in children, who are more likely to have gastritis or duodenitis. However, because HP infection is most likely acquired in childhood, treatment of children with endoscopically documented active HP disease may minimize the potential risk for peptic ulcer or gastric cancer in adulthood, although this is yet to be proved. OBJECTIVE: Omeprazole has been shown to be effective in the treatment of acid-related diseases. This paper reviews the literature on the use and administration of omeprazole for the treatment of GERD, peptic ulcer disease, HP infection, and other acid-related conditions in children. METHODS: Studies were identified through searches of MEDLINE and Science Citation Index for the period 1986 to November 2000, and from the reference lists of identified articles. The search terms used included omeprazole, proton pump inhibitor (PPI), children, pediatrics, routes of administration, GERD, HP infection, esophagitis, and administration. In addition, the manufacturer of omeprazole was asked for relevant unpublished information. RESULTS: Marketed and extemporaneous formulations of omeprazole have been administered to children aged 2 months to 18 years for the treatment of erosive

esophagitis, gastric ulcer, duodenal ulcer, HP infection, and related conditions at dosages of 5 to 80 mg/d (0.2-3.5 mg/kg/d) for periods ranging from 14 days to 36 months with a low incidence of adverse effects. The initial dose most consistently reported to heal esophagitis and provide relief of symptoms of GERD appears to be 1 mg/kg per day. CONCLUSIONS: In uncontrolled clinical trials and case reports to date, omeprazole has been effective and well tolerated for the acute and chronic treatment of esophageal and peptic ulcer disease in children, particularly those who had failed to respond to previous treatment with histamine₂-receptor antagonists. Should future long-term, controlled clinical trials in children demonstrate safety and efficacy, this PPI is likely to find a place in the armamentarium of pediatric pharmacotherapy.

**Eunice Kennedy Shriver National Institute of Child Health
and Human Development (NICHD)
Obstetric and Pediatric Pharmacology Branch (OPPB)
Best Pharmaceuticals for Children Act (BPCA)**

Selected Citations–Cyproheptadine

1. **Akhondzadeh, S., S. Erfani, M.R. Mohammadi, M. Tehrani-Doost, H. Amini, S.S. Gudarzi, and M.T. Yasamy. "Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial." *Journal of Clinical Pharmacy and Therapeutics* 29.2 (2004): 145-150.**

Abstract

OBJECTIVE: Autism is a childhood-onset disorder of unknown, possibly of multiple aetiologies. The core symptoms of autism are abnormalities in social interaction, communication and behaviour. The involvement of neurotransmitters such as 5-HT has been suggested in neuropsychiatric disorders and particularly in autistic disorder. Increased platelet 5-HT levels were found in 40% of the autistic population, suggesting that hyperserotonemia may be a pathologic factor in infantile autism. Therefore, it is of interest to assess the efficacy of cyproheptadine, a 5-HT₂ antagonist in the treatment of autistic disorder. In this 8-week double-blind, placebo-controlled trial, we assessed the effects of cyproheptadine plus haloperidol in the treatment of autistic disorder.

METHODS: Children between the ages 3 and 11 years (inclusive) with a DSM IV clinical diagnosis of autism and who were outpatients from a specialty clinic for children at Roozbeh Psychiatric Teaching Hospital were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to cyproheptadine + haloperidol (Group A) or haloperidol + placebo (Group B) for an 8-week, double-blind, placebo-controlled study. The dose of haloperidol and cyproheptadine was titrated up to 0.05 and 0.2 mg/kg/day respectively. Patients were assessed by a third-year resident of psychiatry at baseline and after 2, 4, 6 and 8 weeks of starting medication. The primary measure of the outcome was the Aberrant Behaviour Checklist-Community (ABC-C) and the secondary measure of the outcome was the Childhood Autism Rating Scale (relating to people and verbal communication). Side effects and extrapyramidal symptoms were systematically recorded throughout the study and were assessed using a checklist and the Extrapyramidal Symptoms Rating Scale, administered by a resident of psychiatry during weeks 1, 2, 4, 6 and 8.

RESULTS: The ABC-C and the Childhood Autism Rating Scale scores improved with cyproheptadine. The behaviour of the two treatments was not homogeneous across time (groups-by-time interaction, Greenhouse-Geisser correction; $F = 7.30$, d.f. = 1.68, $P = 0.002$; $F = 8.21$, d.f. = 1.19, $P = 0.004$ respectively). The difference between the two treatments was significant as indicated by the effect of group, and the between-subjects factor ($F = 4.17$, d.f. = 1, $P = 0.048$; $F = 4.29$, d.f. = 1, $P = 0.045$ respectively). No significant difference was observed between the two groups in terms of extrapyramidal symptoms ($P = 0.23$). The difference between the two groups in the frequency of side effects was not significant.

CONCLUSION: The results suggest that the combination of cyproheptadine with a conventional antipsychotic may be superior to conventional antipsychotic alone for children with autistic disorder. However the results need confirmation by a larger randomized controlled trial.

2. **Andersen, J.M., K.S. Sugerman, J.R. Lockhart, and W.A. Weinberg. "Effective prophylactic therapy for cyclic vomiting syndrome in children using amitriptyline or cyproheptadine." *Pediatrics* 100.6 (1997): 977-981.**

Abstract

OBJECTIVE: To evaluate our experience using the antimigraine prophylactic drugs, amitriptyline and cyproheptadine, for the prophylactic management of cyclic vomiting syndrome (CVS) in children.

METHODS AND PATIENTS: Twenty-seven patients (16 males) ranging in age from 2 to 16 years at diagnosis, fulfilling the diagnostic criteria for CVS and treated prophylactically with either amitriptyline (22) or/and cyproheptadine (6) were identified through retrospective chart review. Individual patient

data were corroborated by the attending physician and/or interviews with patients and families. Minimum follow-up time before entry into the study group was 5 months. Patients were stratified according to three treatment outcomes: 1) complete response-no attacks, 2) partial response-50% or greater reduction in frequency of attacks, and 3) no response-less than 50% decrease in frequency of attacks.

RESULTS: Of the 22 patients treated with amitriptyline, 16 (73%) had a complete response while 4 (18%) had a partial response. Of the 6 patients treated with cyproheptadine, 4 (66%) had a complete response and 1 (17%) had a partial response. Thus, 91% of the amitriptyline group and 83% of the cyproheptadine group had at least a partial response to therapy. No patients experienced significant side effects to either medication.

CONCLUSION: The antimigraine prophylactic drugs, amitriptyline and cyproheptadine, represent effective prophylactic agents for the management of CVS in the vast majority of patients fulfilling the diagnostic criteria for this syndrome.

3. **Arisaka, O., N. Shimura, Y. Nakayama, and K. Yabuta. "Cyproheptadine and growth." *American Journal of Diseases of Children* 142.9 (1988): 914-915.**
(No Abstract Available)
4. **Balottin, U., and C. Termine. "Recommendations for the management of migraine in paediatric patients." *Expert Opinion on Pharmacotherapy* 8.6 (2007): 731-744.**

Abstract

Migraine is a common and disabling condition in children and adolescents. The complexity of migraine on a pathogenetic and clinical level results from the interaction between biological, psychological and environmental factors. Appropriate management requires an individually tailored strategy giving due consideration to both pharmacological and non-pharmacological measures. Ibuprofen (7.5-10.0 mg/kg) and acetaminophen (15 mg/kg) are safe and effective, and should be considered for symptomatic treatment. Sumatriptan nasal spray (5 and 20 mg) is also likely to be effective, but at the moment, should be considered for the treatment of adolescents only. With reference to prophylactic drug treatment, the available data suggest that flunarizine (5 mg/day) is likely to be effective and pizotifen and clonidine are likely to be ineffective. The efficacy data regarding propranolol, nimodipine and trazodone are conflicting. Insufficient evidence is available on cyproheptadine, amitriptyline, divalproex sodium, topiramate, levetiracetam, gabapentin or zonisamide. The management of migraine in children needs an individualised therapeutic approach, directed to the whole person of the child, taking into account the developmental perspective and the high rate of psychiatric comorbidities. It is the authors' opinion that for the prophylaxis of migraine, interventions such as identification and avoidance of trigger factors, regulation of lifestyle, relaxation, biofeedback, cognitive behavioural treatment and psychological or psychotherapeutic interventions (e.g., psychodynamics) could be much more effective than pharmacotherapy.

5. **Calka, O., A. Metin, H. Dülger, and R. Erkoç. "Effect of cyproheptadine on serum leptin levels." *Advances in Therapy* 22.5 (2005): 424-428.**

Abstract

Leptin is a 167 amino acid protein encoded by the obesity gene that is synthesized in adipose tissue and interacts with receptors in the hypothalamus linked to the regulation of appetite and metabolism. It is known to suppress appetite and increase energy expenditure. Cyproheptadine is a piperidine antihistamine that increases appetite through its antiserotonergic effect on 5-HT₂ receptors in the brain. Although both leptin and cyproheptadine are effective in controlling appetite, their interaction has not been addressed in clinical studies. This study evaluated serum leptin concentrations in patients who received cyproheptadine to treat a variety of disorders. Sixteen patients aged 7 to 71 years (mean, 26.25 years) were given cyproheptadine 2 to 6 mg/day for a minimum of 7 days. Body weight was measured and blood samples were obtained at baseline and after 1 week of treatment. Serum leptin levels were determined by leptin radioimmunoassay. The mean body weight at baseline (52.59 kg) did not differ significantly from that at 1 week after treatment (52.84 kg; $P > .05$), but the mean leptin level after 1 week of treatment with cyproheptadine (3.14 ng/mL) was 14.2% higher than

that at baseline (2.75 ng/mL; $P < .05$). This increase may suggest that both leptin and cyproheptadine may affect appetite via similar receptors and that cyproheptadine does not impair leptin activity through these receptors. Further study will be necessary to clarify this relationship.

- 6. Couluris, M., J.L. Mayer, D.R. Freyer, E. Sandler, P. Xu, and J.P. Krischer. "The effect of cyproheptadine hydrochloride (peractin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia." *Journal of Pediatric Hematology/Oncology* 30.11 (2008): 791-797.**

Abstract

BACKGROUND: Children with cancer frequently have associated cachexia and malnutrition. Failure to thrive affects nearly 40% of oncology patients with advanced or progressive disease. Malnutrition can erode quality of life and adversely impact disease prognosis. Appetite stimulation and increased food intake is 1 approach to combat cancer-related cachexia.

MATERIALS AND METHODS: Cyproheptadine hydrochloride (CH), an appetite stimulant, was administered to children with cancer-associated cachexia to prevent further weight loss. All participants started CH and were evaluated for response after 4 weeks. Efficacy of megestrol acetate (MA) was evaluated in patients who did not respond to CH. Medical evaluation, weight measurements, prealbumin, and serum leptin levels were performed at follow-up visits.

RESULTS: Seventy patients were enrolled. Of the 66 evaluable patients, 50 demonstrated a response to CH (average weight gain 2.6 kg and mean weight-for-age z-score change of 0.35, $P=0.001$). Seven of the 16 nonresponders received MA. Six patients completed 4 weeks of MA, 5 responded (average weight gain of 2.5 kg). The most commonly reported side effect of CH was drowsiness. One patient on MA developed low cortisol levels and hyperlipidemia.

CONCLUSIONS: This study demonstrates that CH is a safe and effective way to promote weight gain in children with cancer/treatment-related cachexia.

- 7. Daviss, W.B., and J. Scott. "A chart review of cyproheptadine for stimulant-induced weight loss." *Journal of Child and Adolescent Psychopharmacology* 14.1 (2004): 65-73.**

Abstract

Youths with attention deficit hyperactivity disorder often experience weight loss on stimulants, which may limit optimal dosing and compliance. Cyproheptadine has been shown in medical samples to stimulate weight gain. We conducted a retrospective chart review of 28 consecutive pediatric psychiatry outpatients prescribed cyproheptadine for weight loss or insomnia while on stimulants. Of these, 4 patients never took cyproheptadine consistently, and 3 discontinued it within the first 7 days due to intolerable side effects. Data were analyzed for 21 other patients (age range 4-15 years) who continued with 4-8 mg of cyproheptadine nightly (mean final dose = 4.9 mg/day) for at least 14 days (mean duration = 104.7 days). Most had lost weight on stimulant alone (mean weight loss was 2.1 kg, mean weight velocity was -19.3 g/day). All 21 gained weight taking concomitant cyproheptadine, with a mean gain of 2.2 kg (paired $t = 6.87$, $p < 0.0001$) and a mean weight velocity of 32.3 g/day. Eleven of 17 patients who had reported initial insomnia on stimulant alone noted significant improvements in sleep with cyproheptadine added. We conclude that concomitant cyproheptadine may be useful in youths with attention deficit hyperactivity disorder for stimulant-induced weight loss, pending future randomized controlled trials.

- 8. Eiland, L.S., L.S. Jenkins, and S.H. Durham. "Pediatric migraine: pharmacologic agents for prophylaxis." *The Annals of Pharmacotherapy* 41.7 (2007): 1181-1190.**

Abstract

OBJECTIVE: To identify and evaluate the data regarding medication use for migraine prophylaxis in the pediatric population.

DATA SOURCES: Literature was obtained through searches in PubMed (Mid 1950s-March 2007), Iowa Drug Information Service/Web (1966-February 2007), International Pharmaceutical Abstracts (1970-February 2007), and the Cochrane Library. The terms migraine, prophylaxis, child, and children

were used and cross referenced with all drug names. Reference citations from publications identified were also reviewed and included.

STUDY SELECTION AND DATA EXTRACTION: Only trials that evaluated migraine headaches in the pediatric population were included. Trials including adolescent and adult populations are briefly listed, but not reviewed. Trials involving non-prescription medication were also included in the evaluation. Due to the limited information, all clinical trials, retrospective reviews, and abstracts evaluated were included in this review.

DATA SYNTHESIS: Few controlled clinical trials regarding prophylaxis therapy are available. Currently, no medications are approved by the Food and Drug Administration for prophylaxis of migraines in children. Seventeen drugs were identified and included in the review. Of the drugs with available data, topiramate, valproic acid, flunarizine, amitriptyline, and cyproheptadine have shown efficacy in decreasing migraine frequency and duration in children. However, larger clinical trials are necessary to validate the utility of these agents. Conflicting data exist for propranolol and pizotifen, and additional data are needed for gabapentin, levetiracetam, zonisamide, naproxen, and trazodone. In clinical trials, nimodipine, clonidine, and natural supplements have shown a lack of efficacy versus placebo for prophylaxis of migraines in children.

CONCLUSIONS: Topiramate, valproic acid, and amitriptyline have the most data on their use for prophylaxis of migraines in children. Numerous agents have limited data in this population and several agents lack efficacy. Prospective, well designed, controlled clinical trials that include quality-of-life and functional outcomes are needed for guiding therapy of migraine prophylaxis for children.

9. **Goldberg, S.C., E.D. Eckert, K.A. Halmi, R.C. Casper, J.M. Davis, and M. Roper. "Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa." *Archives of General Psychiatry* 37.9 (1980): 1083.**
(No Abstract Available)
10. **Hikita, T., H. Kodama, N. Nakamoto, F. Kaga, K. Amakata, K. Ogita, S. Kaneko, Y. Fujii, and Y. Yanagawa. "Effective prophylactic therapy for cyclic vomiting syndrome in children using valproate." *Brain & Development* 31.6 (2009): 411-413.**

Abstract

This trial sought to evaluate our experience using the antimigraine prophylactic drug, use of valproate for the prophylactic management of cyclic vomiting syndrome (CVS) in children. Thirteen children diagnosed with severe CVS were enrolled. Prophylactic therapy consisted of valproate administered at a dose of 10-40 mg/kg/day. Upon enrollment in the study, all patients underwent diagnostic tests to rule out organic causes of their symptoms. Vomiting was severe enough in all patients to cause dehydration requiring hospitalization for intravenous rehydration. Nine of 13 patients did not respond to numerous previous medical therapies like propranolol, amitriptyline, cyproheptadine, phenobarbital, phenytoin, and carbamazepine. Three of 13 patients required combination therapy with valproate and phenobarbital. Of the 13 patients, two showed complete resolution of their symptoms, nine had marked improvement in their symptoms, as evidenced by infrequent attacks of reduced severity, and two failed to respond to valproate therapy. Four patients experienced relapse with a decreased dosage of valproate. Side effects associated with long-term valproate administration were not observed. Valproate appears to be effective for the prophylactic management of severe CVS, with 85% of all patients achieving at least a reduction in the frequency of attacks.

11. **Hirfanoglu, T., A. Serdaroglu, O. Gulbahar, and A. Cansu. "Prophylactic drugs, cytokine, and leptin levels in children with migraine." *Pediatric Neurology* 41.4 (2009): 281-287.**

Abstract

The study objective was to evaluate levels of the cytokines tumor necrosis factor alpha, interleukin-1beta, and interleukin-6 and of leptin, and then to determine the relationship between these levels and clinical responses in children with migraine after prophylactic therapy with one of four drugs. In all, 77 children who needed prophylactic drugs were treated with cyproheptadine, amitriptyline, propranolol, or flunarizine. Serum levels of the cytokines and leptin were measured before and 4 months after the treatment. Results were compared by drug for headache frequency, severity, and

duration, the PedMIDAS score, and levels of each cytokine and of leptin. Each of the four drugs not only decreased the frequency and duration but also the severity of headache, and the PedMIDAS score. None of the drugs was found to be superior to others in terms of reduction in cytokine levels ($P > 0.05$). Both cyproheptadine and flunarizine (but not amitriptyline and propranolol) caused an increase in leptin levels ($P < 0.05$). These data suggest that cytokine levels are related to clinical responses, and might help in objective evaluation of clinical response in migraine. To our knowledge, the present study is the first trial to compare the effects of prophylactic drugs, cytokine levels, and leptin levels in children with migraine.

- 12. Homnick, D.N., J.H. Marks, K.L. Hare, and S.K. Bonnema. "Long-term trial of cyproheptadine as an appetite stimulant in cystic fibrosis." *Pediatric Pulmonology* 40.3 (2005): 251-256.**

Abstract

Appetite stimulants have been used to help overcome decreased appetite and malnutrition in children and adults with various chronic illnesses, including cystic fibrosis (CF). Stimulants have included megestrol acetate (MA), cyproheptadine hydrochloride (CH), cannabinoids, hydrazine sulfate, anabolic hormones, and growth hormone. Many of these, including MA, have substantial side effects and may not be suitable for prolonged use. We previously studied the effects of CH on weight gain in a short-term (12 week) trial in CF with good results compared to placebo. Side effects were few, and weight gain was significant. In this study, we sought to determine the effects of CH over a longer term in order to assess its suitability for prolonged use. Sixteen CF children and adults enrolled in the original short-term study subsequently entered this study, and 12 completed the 9-month trial. All patients receiving placebo in the original short-term study received CH 4 mg up to four times a day in the long-term study continuation, and those receiving CH in the short-term study continued on the drug. No pill counts were done, and patients were queried at quarterly visits as to their CH use. Anthropometrics and spirometry were also done quarterly, and antibiotic use was quantified. Subjects who had changed from placebo (CH2 group) gained weight significantly over 3-6 months, and those continuing on CH (CH1 group) generally maintained previously gained weight over the duration of the study. Select spirometric measures improved in both groups but not significantly, and side effects were mild. CH appears to be an effective appetite stimulant in CF, and generally maintains its effect over time with an acceptable side-effect profile.

- 13. Lehrer, J.F.. "Cyproheptadine's antiserotonin effects are responsible for its antimigraine activity." *Headache* 44.9 (2004): 935.**

(No Abstract Available)

- 14. Lewis, D., S. Ashwal, A. Hershey, D. Hirtz, M. Yonker, S. Silberstein, American Academy of Neurology Quality Standards Subcommittee, and Practice Committee of the Child Neurology Society. "Practice parameter: pharmacological treatment of migraine headache in children, and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee, and the Practice Committee of the Child Neurology Society." *Neurology* 63.12 (2004): 2215-2224. Print.**

Abstract

OBJECTIVE: To review evidence on the pharmacologic treatment of the child with migraine headache.

METHODS: The authors reviewed, abstracted, and classified relevant literature. Recommendations were based on a four-tiered scheme of evidence classification. Treatment options were separated into medications for acute headache and preventive medications.

RESULTS: The authors identified and reviewed 166 articles. For acute treatment, five agents were reviewed. Sumatriptan nasal spray and ibuprofen are effective and are well tolerated vs placebo. Acetaminophen is probably effective and is well tolerated vs placebo. Rizatriptan and zolmitriptan were safe and well tolerated but were not superior to placebo. For preventive therapy, 12 agents were evaluated. Flunarizine is probably effective. The data concerning cyproheptadine, amitriptyline, divalproex sodium, topiramate, and levetiracetam were insufficient. Conflicting data were found concerning propranolol and trazodone. Pizotifen, nimodipine, and clonidine did not show efficacy.

CONCLUSIONS: For children (>age 6 years), ibuprofen is effective and acetaminophen is probably effective and either can be considered for the acute treatment of migraine. For adolescents (>12 years of age), sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine. For preventive therapy, flunarizine is probably effective and can be considered, but is not available in the United States. There are conflicting or insufficient data to make any other recommendations for the preventive therapy of migraine in children and adolescents. For a clinical problem so prevalent in children and adolescents, there is a disappointing lack of evidence from controlled, randomized, and masked trials.

15. Lewis, D.W., M. Yonker, P. Winner, and M. Sowell. "The treatment of pediatric migraine." *Pediatric Annals* 34.6 (2005): 448-460.

Abstract

The management of pediatric migraine requires a balance of biobehavioral measures coupled with agents for acute treatment and, if needed, daily preventive medicines. A recent American Academy of Neurology practice parameter has critically reviewed the limited data regarding the efficacy and safety of medicines for the acute and preventive therapy of pediatric migraine. The first step is to establish the headache frequency and degree to which the migraines impact upon lifestyle and performance. The next step is to institute nonpharmacologic measures such as regulation of sleep (improved sleep hygiene), moderation of caffeine, regular exercise, and identification of provocative influences (eg, stress, foods, social pressures). A wide variety of therapeutic options exist for patients whose migraine headaches occur with sufficient frequency and severity to produce functional impairment. The most rigorously studied agents for the acute treatment of migraine are ibuprofen, acetaminophen, and sumatriptan nasal spray, all of which have shown safety and efficacy in controlled trials. Daily preventive drug therapies are warranted in about 20% to 30% of young migraine sufferers. The particular drug selected for the individual patient requires an appreciation of comorbidities such as affective or anxiety disorders, co-existent medical conditions such as asthma or diabetes, and acceptability of potential toxicities such as weight gain, sedation, or tremor.

16. Lewis, D.W., and P. Winner. "The pharmacological treatment options for pediatric migraine: an evidence-based appraisal." *Journal of the American Society for Experimental Neurotherapeutics* 3.2 (2006): 181-191.

Abstract

The treatment of children and adolescents who suffer from migraine headaches must be individually tailored, flexible, and balanced with a blend of bio-behavioral measures, agents for acute treatment and, if needed, daily preventive medicines. While controlled data is limited, there is now enough evidence available to provide a rational framework to build treatment plans appropriate for the pediatric population. Essentially, the pharmacological management of pediatric migraine divides into agents for the acute attacks and agents used daily to prevent or reduce the frequency of attacks. For the acute treatment, the most rigorously studied agents are ibuprofen, acetaminophen, and the nasal spray forms of sumatriptan and zolmitriptan, all of which have shown both safety and efficacy in controlled trials. For preventive treatment the calcium channel blocker flunarizine has the best efficacy profile in controlled trials, but is not available in the U.S. A growing body of data, mostly uncontrolled, is emerging regarding the use of several anti-epileptic agents (e.g. topiramate, disodium valproate, levateracetam), as well as the antihistamine cyproheptadine and the anti-depressant amitriptyline.

17. Li, B.U., F. Lefevre, G.G. Chelimsky, R.G. Boles, S.P. Nelson, D.W. Lewis, S.L. Linder, R.M. Issenman, C.D. Rudolph, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis, and management of cyclic vomiting syndrome." *Journal of Pediatric Gastroenterology, and Nutrition* 47.3 (2008): 379-393.

Abstract

Cyclic vomiting syndrome (CVS) is a disorder noted for its unique intensity of vomiting, repeated emergency department visits and hospitalizations, and reduced quality of life. It is often misdiagnosed due to the unappreciated pattern of recurrence and lack of confirmatory testing. Because no accepted approach to management has been established, the task force was charged to develop a report on diagnosis and treatment of CVS based upon a review of the medical literature and expert opinion. The key issues addressed were the diagnostic criteria, the appropriate evaluation, the prophylactic therapy, and the therapy of acute attacks. The recommended diagnostic approach is to avoid "shotgun" testing and instead to use a strategy of targeted testing that varies with the presence of 4 red flags: abdominal signs (eg, bilious vomiting, tenderness), triggering events (eg, fasting, high protein meal), abnormal neurological examination (eg, altered mental status, papilledema), and progressive worsening or a changing pattern of vomiting episodes. Therapeutic recommendations include lifestyle changes, prophylactic therapy (eg, cyproheptadine in children 5 years or younger and amitriptyline for those older than 5), and acute therapy (eg, 5-hydroxytryptamine receptor agonists, termed triptans herein, as abortive therapy, and 10% dextrose and ondansetron for those requiring intravenous hydration). This document represents the official recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition for the diagnosis and treatment of CVS in children and adolescents.

18. Mahachoklertwattana, P., S. Wanawong, P. Poomthavorn, L. Choubtum, and A. Sriphrapradang. "Short-term cyproheptadine therapy in underweight children: effects on growth and serum insulin-like growth factor-I." *Journal of Pediatric Endocrinology & Metabolism* 22.5 (2009): 425-432.

Abstract

BACKGROUND: Cyproheptadine, an appetite stimulant, has been used in poor-appetite underweight children. Its beneficial effects on enhancing growth rate have been demonstrated. In contrast, an adverse effect on blunting growth hormone (GH) secretion has also been reported. To date, however, its effect on insulinlike growth factor-I (IGF-I), a GH-mediated growth factor, has not been documented.

AIM: To examine the effect of cyproheptadine therapy on growth and serum IGF-I in underweight children.

METHODS: Twenty-one underweight, otherwise healthy children were recruited. They were randomly assigned into cyproheptadine administration (n = 10) and placebo (n = 11) groups. The former received cyproheptadine for 4 months. Serum IGF-I levels were measured in both groups.

RESULTS: Weight and height velocities and IGF-I z-scores during cyproheptadine therapy were significantly greater in the intervention group than those of the placebo group.

CONCLUSION: Cyproheptadine therapy in underweight children increased caloric intake and serum IGF-I concentration and consequently enhanced growth velocity.

19. Paton, D.M., and D.R. Webster. "Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines)." *Clinical Pharmacokinetics* 10.6 (1985): 477-497.

Abstract

This article reviews clinical pharmacokinetic data on the H1-receptor antagonists, commonly referred to as the antihistamines. Despite their widespread use over an extended period, relatively little pharmacokinetic data are available for many of these drugs. A number of H1-receptor antagonists have been assayed mainly using radioimmunoassay methods. These have also generally measured metabolites to greater or lesser extents. Thus, the interpretation of such data is complex. After oral administration of H1-receptor antagonists as syrup or tablet formulations, peak plasma concentrations are usually observed after 2 to 3 hours. Bioavailability has not been extensively studied, but is about 0.34 for chlorpheniramine, 0.40 to 0.60 for diphenhydramine, and about 0.25 for promethazine. Most of these drugs are metabolised in the liver, this being very extensive in some instances (e.g. cyproheptadine and terfenadine). Total body clearance in adults is generally in the range of 5 to 12 ml/min/kg (for astemizole, brompheniramine, chlorpheniramine, diphenhydramine, hydroxyzine, promethazine and triprolidine), while their elimination half-lives range from about 3 hours to about 18 days [cinnarizine about 3 hours; diphenhydramine about 4 hours; promethazine 10 to 14 hours;

chlorpheniramine 14 to 25 hours; hydroxyzine about 20 hours; brompheniramine about 25 hours; astemizole and its active metabolites about 7 to 20 days (after long term administration); flunarizine about 18 to 20 days]. They also have relatively large apparent volumes of distribution in excess of 4 L/kg. In children, the elimination half-lives of chlorpheniramine and hydroxyzine are shorter than in adults. In patients with alcohol-related liver disease, the elimination half-life of diphenhydramine was increased from 9 to 15 hours, while in patients with chronic renal disease that of chlorpheniramine was very greatly prolonged. Little, if any, published information is available on the pharmacokinetics of these drugs in neonates, pregnancy or during lactation. The relatively long half-lives of a number of the older H1-receptor antagonists such as brompheniramine, chlorpheniramine and hydroxyzine suggest that they can be administered to adults once daily.

- 20. Phan, H., M.L. Moeller, and M.C. Nahata. "Treatment of allergic rhinitis in infants and children: efficacy and safety of second-generation antihistamines and the leukotriene receptor antagonist montelukast." *Drugs* 69.18 (2009): 2541-2576.**

Abstract

Allergic rhinitis (AR) affects a large percentage of paediatric patients. With the wide array of available agents, it has become a challenge to choose the most appropriate treatment for patients. Second-generation antihistamines have become increasingly popular because of their comparable efficacy and lower incidence of adverse effects relative to their first-generation counterparts, and the safety and efficacy of this drug class are established in the adult population. Data on the use of the second-generation antihistamines oral cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine, and the leukotriene receptor antagonist montelukast as well as azelastine nasal spray in infants and children are evaluated in this review. These agents have been found to be relatively safe and effective in reducing symptoms associated with AR in children. Alternative dosage forms such as liquids or oral disintegrating tablets are available for most agents, allowing ease of administration to most young children and infants; however, limited data are available regarding use in infants for most agents, except desloratadine, cetirizine and montelukast. Unlike their predecessors, such as astemizole and terfenadine, the newer second-generation antihistamines and montelukast appear to be well tolerated, with absence of cardiotoxicities. Comparative studies are limited to cetirizine versus ketotifen, oxatomide and/or montelukast. Although second-generation antihistamines and montelukast are deemed relatively safe for use in paediatric patients, there are some noteworthy drug interactions to consider when selecting an agent. Given the wide variety of available agents for treatment of AR in paediatric patients, the safety and efficacy data available for specific age groups, type of AR, dosage form availability and cost should be considered when selecting treatment for AR in infants and children.

- 21. Rossignol, D.A.. "Novel and emerging treatments for autism spectrum disorders: a systematic review." *Annals of Clinical Psychiatry* 21.4 (2009): 213-236.**

Abstract

BACKGROUND: Currently, only one medication (risperidone) is FDA-approved for the treatment of autism spectrum disorders (ASD). Perhaps for this reason, the use of novel, unconventional, and off-label treatments for ASD is common, with up to 74% of children with ASD using these treatments; however, treating physicians are often unaware of this usage.

METHODS: A systematic literature search of electronic scientific databases was performed to identify studies of novel and emerging treatments for ASD, including nutritional supplements, diets, medications, and nonbiological treatments. A grade of recommendation ("Grade") was then assigned to each treatment using a validated evidence-based guideline as outlined in this review: A: Supported by at least 2 prospective randomized controlled trials (RCTs) or 1 systematic review. B: Supported by at least 1 prospective RCT or 2 nonrandomized controlled trials. C: Supported by at least 1 nonrandomized controlled trial or 2 case series. D: Troublingly inconsistent or inconclusive studies or studies reporting no improvements. Potential adverse effects for each treatment were also reviewed.

RESULTS: Grade A treatments for ASD include melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory

treatments, oxytocin, and vision therapy. Grade C treatments for ASD include carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

CONCLUSIONS: The reviewed treatments for ASD are commonly used, and some are supported by prospective RCTs. Promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the reviewed treatments are currently considered off-label for ASD (ie, not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed. Physicians treating children with an ASD should make it standard practice to inquire about each child's possible use of these types of treatments.

**Eunice Kennedy Shriver National Institute of Child Health
and Human Development (NICHD)
Obstetric and Pediatric Pharmacology Branch (OPPB)
Best Pharmaceuticals for Children Act (BPCA)**

Selected Citations-Ursodeoxycholic Acid

1. **Barshop, N.J., C.B. Sirlin, J.B. Schwimmer, and J.E. Lavine. "Review article: epidemiology, pathogenesis and potential treatments of paediatric non-alcoholic fatty liver disease." *Alimentary Pharmacology & Therapeutics* 28.1 (2008): 13-24.**

Abstract

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of paediatric liver disease. Similar to NAFLD in adults, NAFLD in children is associated with obesity and insulin resistance and requires liver histology for diagnosis and staging. However, significant histological differences exist between adult and paediatric NAFLD to warrant caution in extrapolation of adult data.

AIM: To review the available data on the epidemiology, pathogenesis, diagnosis and treatment of paediatric NAFLD.

METHODS: Relevant articles were identified by Medline searches using the keywords: nonalcoholic fatty liver disease, steatohepatitis, obesity and children.

RESULTS: The rise in childhood obesity has been accompanied by an increase in paediatric NAFLD. Age, gender and race/ethnicity are significant determinants of risk, and sex hormones, insulin sensitivity and adipocytokines are implicated in the pathogenesis of paediatric NAFLD. There is no consensus for treatment of NAFLD; however, data suggest that diet, exercise and some pharmacological therapies may be of benefit.

CONCLUSIONS: To evaluate and effectively treat paediatric NAFLD, the pathophysiology and natural history of the disease should be clarified and non-invasive methods for screening, diagnosis, and longitudinal assessment developed. Randomized, controlled, double-blind trials of pharmacological therapies in children with biopsy-proven disease are necessary.

2. **Btaiche, J.F., and N. Khalidi. "Parenteral nutrition-associated liver complications in children." *Pharmacotherapy* 22.2 (2002): 188-211.**

Abstract

Parenteral nutrition is a life-saving therapy for patients with intestinal failure. It may be associated with transient elevations of liver enzyme concentrations, which return to normal after parenteral nutrition is discontinued. Prolonged parenteral nutrition is associated with complications affecting the hepatobiliary system, such as cholelithiasis, cholestasis, and steatosis. The most common of these is parenteral nutrition-associated cholestasis (PNAC), which may occur in children and may progress to liver failure. The pathophysiology of PNAC is poorly understood, and the etiology is multifactorial. Risk factors include prematurity, long duration of parenteral nutrition, sepsis, lack of bowel motility, and short bowel syndrome. Possible etiologies include excessive caloric administration, parenteral nutrition components, and nutritional deficiencies. Several measures can be undertaken to prevent PNAC, such as avoiding overfeeding, providing a balanced source of energy, weaning parenteral nutrition, starting enteral feeding, and avoiding sepsis.

3. **Cowles, R.A., K.A. Ventura, M. Martinez, S.J. Lobritto, P.A. Harren, S. Brodlie, J. Carroll, and D.M. Jan. "Reversal of intestinal failure-associated liver disease in infants and children on parenteral nutrition: experience with 93 patients at a referral center for intestinal rehabilitation." *Journal of Pediatric Surgery* 45.1 (2010): 84-87.**

Abstract

PURPOSE: Intestinal failure (IF)-associated liver disease (IFALD) complicates the treatment of children with IF receiving parenteral nutrition (PN). We hypothesized that prevention or resolution of IFALD was possible in most children and that this would result in improved outcomes.

METHODS: We reviewed prospectively gathered data on all children referred to the intestinal rehabilitation and transplantation center at our institution. Total bilirubin level (TB) was used as the marker for IFALD. Patients were grouped based on TB at referral and at subsequent inpatient stays and outpatient visits. Standard treatment consisted of cycling of PN, limiting lipid infusion, enteral stimulation, use of ursodeoxycholic acid, and surgical intervention when necessary. Outcomes such as mortality, dependence on PN, and need for transplantation were assessed. Statistical analyses were performed using Fisher's exact, Mann-Whitney U, and Wilcoxon signed rank tests.

RESULTS: Ninety-three patients with intestinal failure and on PN were treated at our center from 2003 to 2009. Median age at referral was 5 months (0.5-264 months). Prematurity was a complicating factor in 63 patients and necrotizing enterocolitis was the most common diagnosis. Eighty-two children had short bowel syndrome, whereas the remaining 11 had extensive motility disorders. 97% of children required significant alteration of their PN administration. At referral, 76 of 93 children had TB 2.0 mg/dL or higher, and 17 had TB below 2.0 mg/dL. TB normalized in 57 of 76 children with elevated TB at referral, and TB remained elevated in 19. Normalization of TB was associated with a mortality of 5.2%, and transplantation was needed in 5.2%. Conversely, when TB remained elevated, mortality was 58% ($P = .0002$ vs TB normalized), and transplantation occurred in 58% owing to failure of surgical and medical rehabilitation.

CONCLUSIONS: Most children referred for treatment of IF have IFALD. A dedicated IF rehabilitation program can reverse IFALD in many children, and this is associated with improved outcome.

4. **De Marco, G., D. Sordino, E. Bruzzese, S. Di Caro, D. Mambretti, A. Tramontano, C. Colombo, P. Simoni, and A. Guarino. "Early treatment with ursodeoxycholic acid for cholestasis in children on parenteral nutrition because of primary intestinal failure." *Alimentary Pharmacology & Therapeutics* 24.2 (2006): 387-394.**

Abstract

BACKGROUND: There is conflicting evidence as to whether ursodeoxycholic acid (UDCA) reduces the incidence of parenteral nutrition-associated cholestasis.

AIM: To investigate the efficacy of UDCA on parenteral nutrition-associated cholestasis in children with intestinal failure due to short bowel syndrome or to other causes.

METHODS: Children with cholestasis received 30 mg/kg/day UDCA. Improvement or normalization of parenteral nutrition-associated cholestasis was evaluated at 6 months of therapy and at the last follow-up. In a subgroup of children, serum UDCA levels were measured while receiving UDCA and after 4 weeks withdrawal.

RESULTS: Twelve children were treated with UDCA. Full remission or partial improvement of parenteral nutrition-associated cholestasis occurred in 11 of 12 children. In three of four children, withdrawal of UDCA was associated with a rebound rise of cholestasis. Only one of 12 treated children showed no improvement and in this patient, in contrast to four other patients, plasma levels of UDCA did not increase during treatment.

CONCLUSIONS: Ursodeoxycholic acid was effective in controlling parenteral nutrition-associated cholestasis. The efficacy of UDCA also in children with short bowel is related to intestinal absorption.

5. **Desmond, C.P., J. Wilson, M. Bailey, D. Clark, and S.K. Roberts. "The benign course of liver disease in adults with cystic fibrosis and the effect of ursodeoxycholic acid." *Liver International* 27.10 (2007): 1402-1408.**

Abstract

BACKGROUND AND AIMS: The life expectancy of patients with cystic fibrosis (CF) has been increasing and the associated liver disease has emerged as a significant medical issue. Our aim was to describe the clinical features, course and effect of ursodeoxycholic acid (UDCA) on liver disease in an adult CF population.

STUDY: From 1983 to 2005, 278 patients with CF were followed up at the Alfred Hospital, an adult tertiary referral centre. Twenty-seven patients (9.7%) satisfied the criteria for liver disease and their

clinico-pathological features were assessed. The effect of UDCA on hepatobiliary symptoms and biochemical parameters was determined.

RESULTS: The mean age at liver disease diagnosis was 23 years (range 8-47 years). Portal hypertension was present in 18 (67%) patients. During a median follow-up of 7 years (range 1.5-15), variceal haemorrhage occurred in two patients and ascites in three (one spontaneously). Nine (33%) patients died and five (19%) underwent lung transplantation. There was no encephalopathy, liver transplantation or liver-related deaths. UDCA was taken by 22 patients and was associated with a significant improvement in hepatobiliary symptoms [11/22 (50%) in the pre-UDCA period vs 1/22 (4%) in the post-UDCA period; $P=0.0003$] and a significant reduction in aspartate aminotransferase ($P=0.005$); alanine aminotransferase ($P<0.001$); gamma-glutamyltranspeptidase ($P=0.021$); and alkaline phosphatase ($P<0.001$).

CONCLUSIONS: Liver disease in adults with CF is commonly complicated by portal hypertension, but morbidity and mortality associated with this in our small patient population were low. UDCA is associated with improvement in hepatobiliary symptoms and liver function tests.

6. **Festi, D., M. Montagnani, F. Azzaroli, F. Lodato, G. Mazzella, A. Roda, A.R. Di Biase, E. Roda, P. Simoni, and A. Colecchia. "Clinical efficacy and effectiveness of ursodeoxycholic acid in cholestatic liver diseases." *Current Clinical Pharmacology* 2.2 (2007): 155-177.**

Abstract

Ursodeoxycholic acid (UDCA), previously used for cholesterol gallstone dissolution, is currently considered the first choice therapy for many forms of cholestatic syndromes. Many mechanisms and sites of action have been proposed for UDCA, but definitive data are still missing regarding the key points of its efficacy and optimal dosage in order to achieve a sustained clinical effect. Among the suggested mechanisms of action of UDCA, changes in bile acid pool composition, hepatocyte membrane protection, immunomodulatory effects and bicarbonate-rich hypercholeresis have been extensively studied. However, recent evidence indicate that UDCA is a potent intracellular signalling agent that counterbalances impaired biliary secretion, inhibits hepatocyte apoptosis and protects injured cholangiocytes against toxic effects of bile acids. It is clear that the relative contribution of these mechanisms to the anticholestatic action of UDCA depends on the type and stage of the liver injury. Available clinical evidence suggest that UDCA treatment has to be initiated as early as possible and that higher doses could be more efficacious in inducing and maintaining clinical remission of cholestatic diseases. The future availability of UDCA derivatives will possibly enhance the chances to effectively treat chronic cholestatic diseases.

7. **Fujisawa, T., A. Kimura, K. Ushijima, E. Nakashima, T. Inoue, Y. Yamashita, and H. Kato. "Intestinal absorption of ursodeoxycholic acid in children and adolescents with inflammatory bowel disease." *Journal of Pediatric Gastroenterology and Nutrition* 26.3 (1998): 279-285.**

Abstract

BACKGROUND: Ursodeoxycholic acid absorption in the proximal intestine may be impaired in patients with inflammatory bowel disease.

METHODS: We examined the intestinal absorption of ursodeoxycholic acid by the oral ursodeoxycholic acid tolerance test in 19 children and adolescents with inflammatory bowel disease at various stages, including 8 patients with unoperated Crohn's disease, 3 patients with ileal-resected Crohn's disease, 8 with ulcerative colitis, and 8 healthy control subjects.

RESULTS: Ursodeoxycholic acid malabsorption was present in all patients with unoperated Crohn's disease in the first diagnosed active stage, in 3 of 5 patients in a relapsing active stage, and in 2 of 8 patients in remission. Ursodeoxycholic acid absorption was significantly lower in patients in the first diagnosed active stage than in the healthy controls ($p < 0.01$) or in patients in remission ($p < 0.01$). There was no significant difference between healthy controls and the patients in a relapsing active stage or in remission. Ursodeoxycholic acid absorption was abnormal during the first postoperative month in patients with ileal-resected Crohn's disease, but normalized over time. Malabsorption of ursodeoxycholic acid was not observed in any patients with ulcerative colitis.

CONCLUSIONS: These findings suggest that absorption of ursodeoxycholic acid in the proximal intestine is impaired in patients with Crohn's disease and that the oral ursodeoxycholic acid tolerance

test is a convenient and useful means of evaluating the absorption of bile acid in the proximal intestine in pediatric patients with ileal or ileocolic Crohn's disease.

8. **Ganschow, R.. "Cholelithiasis in pediatric organ transplantation: detection and management." *Pediatric Transplantation* 6.2 (2002): 91-96.**

Abstract

The real incidence and the underlying causes of cholelithiasis in pediatric solid organ recipients is probably not exactly known. In addition to well-established risk factors for cholelithiasis, children after heart, kidney, or liver transplantation may develop gallstones due to drug therapy, sepsis, parenteral nutrition, or surgical complications. For pediatric patients, data are very limited and heterogeneous. However, the incidence in pediatric heart recipients seems to be substantially higher compared with kidney or liver graft recipients. In this review article the present data are discussed focusing on incidence, detection, and management of cholelithiasis in pediatric organ transplantation. In general, surgery is the therapy of choice in symptomatic patients; however, the pharmacological profile of ursodeoxycholic acid and the first results on its clinical impact are promising. The value of prophylactic therapy with ursodeoxycholic acid must be determined in further studies.

9. **George, R., A. Stevens, J.W. Berkenbosch, J. Turpin, and J. Tobias. "Ursodeoxycholic acid in the treatment of cholestasis and hyperbilirubinemia in pediatric intensive care unit patients." *Southern Medical Journal* 95.11 (2002): 1276-1279.**

Abstract

BACKGROUND: The purpose of this study was to evaluate the efficacy of ursodeoxycholic acid (UDCA) in the treatment of cholestasis and hyperbilirubinemia in a pediatric intensive care unit population.

METHODS: Medical records were retrospectively reviewed to identify children and adolescents in the pediatric intensive care unit (PICU) who received UDCA for the treatment of hyperbilirubinemia and cholestasis.

RESULTS: Ursodeoxycholic acid was administered at a dose of 20 mg/kg per day to 5 PICU patients with cholestasis and hyperbilirubinemia of various etiologies. In 4 of 5 patients, there was a decrease in serum bilirubin levels following the start of UDCA therapy. There was no response to therapy in 1 patient, who developed disseminated fungal disease and died. No adverse effects related to therapy were noted.

CONCLUSIONS: These preliminary data suggest that UDCA is effective in the treatment of cholestasis and hyperbilirubinemia of various etiologies in the PICU patient. Prospective, randomized trials are warranted to further assess the efficacy of this therapy in this patient population.

10. **Gilger, M.A., M.E. Gann, A.R. Opekun, and W.A. Gleason, Jr.. "Efficacy of ursodeoxycholic acid in the treatment of primary sclerosing cholangitis in children." *Journal of Pediatric Gastroenterology and Nutrition* 31.2 (2000): 136-141**

Abstract

BACKGROUND: Ursodeoxycholic acid (UDCA) has been shown to be beneficial in reducing disease activity in adult patients with primary sclerosing cholangitis (PSC). However, there has been little published regarding PSC in children and no studies investigating the efficacy of UDCA as a treatment for PSC.

METHODS: This retrospective study included 10 children who were found to have the diagnosis of PSC during the past 15 years at the Texas Children's Hospital and Herman Hospital, both in Houston, Texas. The male:female ratio was 8:2, the median age of onset was 12 years (range, 1-17 years), and eight patients had coexistent inflammatory bowel disease (IBD; six ulcerative colitis, one Crohn's disease, one unspecified). At the time of diagnosis, five patients were asymptomatic, all of whom had IBD with elevated liver enzymes and three of whom had hepatomegaly. Nine patients were treated with UDCA. The one patient who did not receive UDCA was lost to follow-up soon after diagnosis. The mean dose of UDCA was 17 mg/kg with the doses ranging from 9 to 37 mg/kg.

RESULTS: There were no side effects from the medication recorded for any of the patients. These patients showed a significant reduction in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase at 1, 3, 6, 15, and 20 months after treatment.
CONCLUSIONS: This study demonstrates that children with PSC treated with UDCA have significant improvements in liver biochemical indices. However, the long-term effect of UDCA on clinical outcome is unknown.

11. Kelly, D.A., and M. Davenport. "Current management of biliary atresia." *Archives of Disease in Childhood* 92.12 (2007): 1132-1135.

Abstract

Extra-hepatic biliary atresia occurs in approximately 1:15,000 live births leading to about 50 new cases/year in the UK. Presentation is with prolonged jaundice, usually in a term baby who develops signs of obstructive jaundice. Management has been improved by public and professional education to encourage early referral and diagnosis to facilitate initial surgery before 8 weeks of age. Surgical management is complementary and includes an attempt to restore biliary flow (the Kasai portoenterostomy) and liver transplantation if necessary. Medical management consists of antibiotics, ursodeoxycholic acid to encourage bile flow, fat soluble vitamin supplementation and nutritional support. Centralising surgery to specialised centres has improved survival of this potentially fatal disease to over 90% in the UK. Over half of infants undergoing portoenterostomy will clear the jaundice and have a greater than 80% chance of a good quality of life, reaching adolescence without transplantation. For those children developing intractable complications of cirrhosis and portal hypertension, liver transplantation provides a 90% chance of achieving normal life.

12. Kelly, D.A.. "Intestinal failure-associated liver disease: what do we know today?." *Gastroenterology* 130.2 Suppl 1 (2006): S70-77.

Abstract

Intestinal failure-associated liver disease develops in 40% to 60% of infants who require long-term total parenteral nutrition (TPN) for intestinal failure and 15% to 40% of adults on home parenteral nutrition. The clinical spectrum includes hepatic steatosis, cholestasis, cholelithiasis, and hepatic fibrosis. Progression to biliary cirrhosis and the development of portal hypertension and liver failure occurs in a minority but is more common in infants and neonates than in adults. The pathogenesis is multifactorial. In infants it is related to prematurity, low birth weight, duration of PN, short bowel syndrome requiring multiple laparotomies, and recurrent sepsis. Other important mechanisms include lack of enteral feeding, which leads to reduced gut hormone secretion; reduction of bile flow and biliary stasis, which leads to the development of cholestasis; and biliary sludge and gallstones, which exacerbate hepatic dysfunction. In adults, IFALD is less common and related to age, length of time on PN, total caloric intake, and lipid or glucose overload. In preterm infants, a deficiency of taurine or cysteine may play a role, whereas in both adults and children, choline deficiency may exacerbate IFALD. Lipid emulsions, choline deficiency, and manganese toxicity are associated with both hepatic steatosis and cholestasis in adults and children. Management strategies for the prevention of intestinal failure-induced liver disease include early enteral feeding, a multidisciplinary approach to the management of parenteral nutrition, and aseptic catheter techniques to reduce sepsis. The addition of choline, taurine, and cysteine to PN solutions may also play a role. Oral administration of ursodeoxycholic acid may improve bile flow and reduce gallbladder stasis. Survival after either isolated small bowel or combined liver and small bowel transplantation is approximately 50% at 5 years, making this an acceptable therapeutic option in adults and children with irreversible liver and intestinal failure.

13. Kelly, D.A.. "Liver complications of pediatric parenteral nutrition--epidemiology." *Nutrition* 14.1 (1998): 153-157.

Abstract

Total parenteral nutrition (TPN)-induced liver disease develops in 40-60% of infants who require long-term TPN for intestinal failure. The clinical spectrum includes cholestasis, cholelithiasis, hepatic

fibrosis with progression to biliary cirrhosis, and the development of portal hypertension and liver failure in a significant number of children who are totally parenterally fed. The pathogenesis is multifactorial and is related to prematurity, low birth weight, and duration of TPN. The degree and severity of the liver disease is related to recurrent sepsis including catheter sepsis, bacterial translocation, and cholangitis. Lack of enteral feeding leading to reduced gut hormone secretion, reduction of bile flow, and biliary stasis may be important mechanisms in the development of cholestasis, biliary sludge, and cholelithiasis. Although it is unlikely that modern TPN solutions have a major role in the etiology of TPN liver disease, manganese toxicity recently has been recognized in children with hepatic dysfunction on TPN. Although there is a definite relationship with the degree of manganese toxicity and hepatic decompensation, it is not yet clear whether this is a primary mechanism or whether the high levels are related to reduced biliary excretion of manganese. The management strategies for the prevention of TPN-induced liver disease include early enteral feeding, a multidisciplinary approach to the management of parenteral nutrition, and aseptic catheter techniques to reduce sepsis. The administration of ursodeoxycholic acid may improve bile flow and reduce gall bladder and intestinal stasis. As survival from isolated intestinal transplantation improves, this therapeutic option should be considered before TPN liver disease becomes irreversible and combined liver and small bowel transplantation is required.

14. **Kotb, M.A.. "Review of historical cohort: ursodeoxycholic acid in extrahepatic biliary atresia." *Journal of Pediatric Surgery* 43.7 (2008): 1321-1327.**

Abstract

BACKGROUND: Ursodeoxycholic acid is a bile acid that was found to increase bile flow, protect hepatocytes, and dissolve gallstones.

PURPOSE: The objective of this study is to review ursodeoxycholic acid in infants and children with extrahepatic biliary atresia.

METHODS: We used a statistical analysis of data of records of infants and children having extrahepatic biliary atresia who underwent Kasai portoenterostomy and attended Hepatology Clinic, New Children's Hospital, Cairo University, Egypt, from May 1985 until June 2005.

RESULTS: Of 141 infants with extrahepatic biliary atresia, 108 received ursodeoxycholic acid for mean duration +/- SD of 252.6 +/- 544.9 days in a dosage of 20 mg/kg per day. The outcome of infants who did not receive ursodeoxycholic acid and those who did was the following: 8 (24.2%) and 11 (10.18%) had a successful outcome ($P = .043$), 0 (0%) and 7 (6.4%) improved ($P = .148$), 25 (75.7%) and 84 (77.7%) had a failed outcome ($P = .489$), and none vs 5 died (4.6%) ($P = .135$), respectively. The predictors of successful outcomes were age less than 65 days at portoenterostomy ($P = .008$) and absence of ursodeoxycholic acid intake ($P = .04$) with a likelihood of a successful outcome that was 2.8, that associated with ursodeoxycholic acid intake.

CONCLUSION: In this cohort of infants with extrahepatic biliary atresia, ursodeoxycholic acid was not shown to be effective, and its use was associated with a plethora of hepatic and extrahepatic complications.

15. **Kotb, M.A.. "Ursodeoxycholic acid in neonatal hepatitis and infantile paucity of intrahepatic bile ducts: review of a historical cohort." *Digestive Diseases and Sciences* 54.10 (2009): 2231-2241.**

Abstract

We retrospectively reviewed the role of ursodeoxycholic acid in infants having nonsurgical cholestasis attending the Hepatology Clinic, New Children Hospital, Cairo University, Egypt, from 1985 until 2005. Files of 496 infants with neonatal hepatitis and 97 with intrahepatic bile duct paucity were included; of them 241 (48.6%) and 52 (46.4%) received 20-40 mg/kg/day ursodeoxycholic acid for 319.2 +/- 506.9 days and 480.3 +/- 583.3 days, respectively. The outcome of infants with neonatal hepatitis with intake of ursodeoxycholic acid and those without was: 108 (44.8%) and 179 (70.2%) successful ($P = 0.000$), 11 (4.6%) and 13 (5.1%) improved ($P = 0.474$), 112 (46.5%) and 61 (23.9%) suffered failed outcome ($P = 0.000$), and 10 (4.1%) and 2 (0.78%) died ($P = 0.014$), respectively. Likelihood of successful outcome with ursodeoxycholic acid intake was 0.345 ($P = 0.000$), and that of deterioration was 2.76 ($P = 0.000$). For those having intrahepatic bile duct paucity likelihood of successful outcome

with ursodeoxycholic acid intake was 0.418 ($P = 0.040$) and that of deterioration was 2.64 ($P = 0.028$). Ursodeoxycholic acid failed in management of this cohort of infants with nonsurgical cholestasis.

16. **Lebensztejn, D.M.. "Application of ursodeoxycholic acid (UDCA) in the therapy of liver and biliary duct diseases in children." *Medical science monitor: international medical journal of experimental and clinical research* 6.3 (2000): 632-636.**

Abstract

The paper discusses the experience accumulated so far in the field of application of ursodeoxycholic acid (UDCA) in selected disorders of the liver and biliary ducts in the developmental age population. In the aforementioned diseases, chronic administration of UDCA is safe, reduces the clinical symptoms, improves the biochemical parameters, and even the histopathologic picture of the affected organ. Such a therapy should be instituted in order to improve the quality of life, reduce the incidence of complications and postpone the transplantation of the liver till the time the child is older.

17. **Levine, A., A. Maavan, R. Shamir, G. Dinari, J. Sulkes, and L. Sirota. "Parenteral nutrition-associated cholestasis in preterm neonates: evaluation of ursodeoxycholic acid treatment." *Journal of Pediatric Endocrinology & Metabolism* 12.4 (1999): 549-553.**

Abstract

BACKGROUND/OBJECTIVE: Parenteral nutrition is an integral part of the care of premature infants. Cholestatic liver disease is a frequent complication of prolonged parenteral nutrition, especially in premature infants. It has been suggested that ursodeoxycholic acid may alter the course of parenteral nutrition-associated cholestasis in children and adults. We attempted to determine the efficacy of ursodeoxycholic acid in premature infants with parenteral nutrition-associated cholestasis.

METHODS: Retrospective chart review of all infants receiving ursodeoxycholic acid for parenteral nutrition-associated cholestasis in a 40 bed neonatal intensive care unit. Efficacy of ursodeoxycholic acid was evaluated by response of bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase over a treatment period of at least 1 month.

RESULTS: Six infants with parenteral nutrition-associated cholestasis who had received ursodeoxycholic acid for one month were identified. Doses of ursodeoxycholic acid ranged from 15-30 mg/kg/day. Cholestasis appeared at a mean age of 47 +/- 17 (mean +/- SD) days after a mean of 42 +/- 15 days of parenteral nutrition. Transaminase levels decreased in three, and either increased or did not change in the other three infants. Bilirubin levels decreased in all infants. Alkaline phosphatase showed a non significant trend to decreased levels. Consistent improvement in all infants was noted only after 10 days of full enteral nutrition. No toxicity was found during ursodeoxycholic acid treatment.

CONCLUSIONS: Ursodeoxycholic acid treatment in premature infants appears to be safe, and leads to an early sustained decrease in bilirubin levels by two weeks of therapy. The response of transaminase levels was not sustained in our small cohort.

18. **Lloyd, D.A., and S.M. Gabe. "Managing liver dysfunction in parenteral nutrition." *Proceedings of the Nutrition Society* 66.4 (2007): 530-538.**

Abstract

Parenteral nutrition is life saving in patients with intestinal failure but liver dysfunction is commonly encountered, especially in neonates. Although abnormal liver function tests associated with short-term parenteral nutrition are usually benign and transient, liver dysfunction in both children and adults receiving long-term parenteral nutrition can progress to end-stage liver disease and liver failure. The aetiology of parenteral nutrition-associated liver disease is complex and multifactorial, with a range of patient, disease and nutrition-related factors implicated. Sepsis is of particular importance, as is the lack of enteral nutrition and overfeeding with intravenous glucose and/or lipid. Deficiencies of a number of amino acids including choline and taurine have also been implicated. Management of hepatic dysfunction in parenteral nutrition should initially focus on preventing its occurrence. Sepsis should be managed appropriately, enteral nutrition should be encouraged and maximised where

possible and parenteral overfeeding should be avoided. Provision of parenteral lipid should be optimised to prevent the adverse effects of both deficiency and excess, and cyclical rather than continuous parenteral feeding should be administered. There is some evidence of benefit in neonates from oral antibiotics to prevent intestinal bacterial overgrowth and from oral ursodeoxycholic acid, but less to support their use in adults. Similarly, data to support widespread use of parenteral choline or taurine supplementation are lacking at present. Ultimately, severe parenteral nutrition-associated liver disease may necessitate referral for small intestine and/or liver transplantation.

CONCLUSIONS: Ursodiol may improve the biochemical signs and clinical symptoms of PNAC. However, optimal dosing, timing, duration of therapy, and long-term effects on PNAC outcome and prognosis require further studies.

19. **Mitchell, S.A., D.S. Bansi, N. Hunt, K. Von Bergmann, K.A. Fleming, and R.W. Chapman. "A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis." *Gastroenterology* 121.4 (2001): 900-907.**

Abstract

BACKGROUND & AIMS: Ursodeoxycholic acid (UDCA) is used for the treatment of cholestatic liver diseases including primary biliary cirrhosis (PBC) for which it has a positive effect on laboratory values, may delay the development of liver failure and prolong the transplant-free disease period. Standard doses of UDCA (8-15 mg/kg daily) have been shown to be ineffective in the treatment of primary sclerosing cholangitis (PSC). We report on the findings (clinical, biochemical, histological, and cholangiographic) and side effects of a 2-year double-blind placebo-controlled preliminary study of high-dose UDCA in PSC patients.

METHODS: Twenty-six patients with PSC were randomized to high-dose (20 mg/kg daily) UDCA or placebo. Cholangiography and liver biopsy were performed at entry and after 2 years. Symptoms, clinical signs, and liver biochemical tests were recorded at 3 monthly intervals.

RESULTS: High-dose UDCA did not influence symptoms, but there was a significant improvement in liver biochemistry (serum alkaline phosphatase, $P = 0.03$; gamma-glutamyl transferase, $P = 0.01$) and a significant reduction in progression in cholangiographic appearances ($P = 0.015$) and liver fibrosis as assessed by disease staging ($P = 0.05$). In the treatment group, a significant increase in total bile acids and saturation with UDCA $>70\%$ confirmed patient compliance. No significant side effects were reported.

CONCLUSIONS: High-dose UDCA may be of clinical benefit in PSC, but trials with a larger number of participants and of longer duration are required to establish whether the effect of high-dose UDCA on liver biochemistry, histology, and cholangiography in patients with PSC is translated into improved long-term survival.

20. **Nanda, K.. "Non-alcoholic steatohepatitis in children." *Pediatric Transplantation* 8.6 (2004): 613-618.**

Abstract

Obesity has emerged as a significant new health problem in the pediatric population. Non-alcoholic steatohepatitis (NASH) is an entity in the spectrum of non-alcoholic fatty liver disease (NAFLD) ranges from fat in the liver -- simple steatosis, NASH/ steatohepatitis -- fat with inflammation and/or fibrosis to advanced fibrosis and cirrhosis when fat may no longer be present. NASH is associated with obesity, diabetes, insulin resistance (IR), and hypertriglyceridemia. While majority of individuals with risk factors like obesity and IR have steatosis only a minority develop steatohepatitis, possible mechanisms have been discussed. Clinical experience with pediatric NASH is limited. Children generally present in the prepubertal age group, have a male predominance with a higher incidence in children of Hispanic origin. Body mass index (BMI) of 25-29.9 is considered to be overweight and that $>$ or $=30$ obese. Acanthosis nigricans as a marker of IR should be looked for. As NASH is a diagnosis of exclusion, other causes of chronic liver disease must be excluded. Increased echogenicity in the liver is noted on ultrasound. Liver biopsy is considered the gold standard in establishing the diagnosis. Histopathological lesions thought to be necessary for diagnosis of NASH include steatosis (macrovesicular $>$ microvesicular), mixed mild lobular inflammation and hepatocyte ballooning. A

system of grading depending on degree of steatosis and/or inflammation and staging depending on the extent of fibrosis has also been proposed. Although there is no consensus for the treatment for NASH, effort needs to be made to prevent development of fibrosis, which results in cirrhosis and portal hypertension. Slow, consistent weight loss has been shown to be effective in childhood NAFLD, based on improvement of serum aminotransferases or liver sonogram. A low glycemic index diet has been shown to be more effective than a low fat diet in lowering BMI. Family based behavioral intervention may also enhance success with diet. Several pharmacological agents have been used including ursodeoxycholic acid, vitamin E, betaine, n-acetyl cysteine, and insulin sensitizing agents like metformin, rosiglitazone, and pioglitazone. Transplantation for overt NASH is rare, accounting for < 1% of liver transplantations in the USA. The disease can recur after liver transplantation. A strong association exists between the presence of steatosis in a donor liver and poor graft function. As a result, cadaveric donor livers with macrovesicular steatosis >40% are not used routinely. Prognosis in NASH is dependent not only on severity and number of risk factors but also on the degree of histological damage. Clinical trials are needed to identify an effective treatment that halts the progression of NAFLD to NASH in both pretransplantation and post-transplantation patients.

21. **Narkewicz, M.R., D. Smith, C. Gregory, J.L. Lear, I. Osberg, and R.J. Sokol. "Effect of ursodeoxycholic acid therapy on hepatic function in children with intrahepatic cholestatic liver disease." *Journal of Pediatric Gastroenterology and Nutrition* 26.1 (1998): 49-55.**

Abstract

Background: Ursodeoxycholic acid (UDCA) has been shown to improve pruritus, alanine aminotransferase (ALT), and cholesterol levels in children with intrahepatic cholestatic liver disease. However, the effect of UDCA on quantitative tests of hepatic function in children is uncertain.

Methods: A 2.5-year, open label, crossover study, was designed to determine the effect of UDCA (15-20 mg/kg per day for 12 months, off for 6 months, and on again for 12 months) on clinical symptoms, biochemical test results, galactose and caffeine elimination half-lives ($t_{1/2}$), and quantitative hepatic scintigraphy in 13 subjects aged 13.1 +/- 2.1 years (10 of whom completed the entire study), with intrahepatic cholestasis.

Results: Pruritus improved with UDCA in the 6 patients with pruritus on entry into the study. At 12 months, there was a significant decline in ALT, gamma-glutamyl transpeptidase, and plasma levels of copper and manganese, with no further decline in these levels at 24 months. There were no changes in bilirubin or cholyglycine levels. After therapy was discontinued at 12 months, UDCA was restarted within 1 month in 9 of 12 patients in response to a doubling of ALT ($n = 6$) or worsening pruritus ($n = 3$). Galactose $t_{1/2}$ increased after 12 months, with no further increases after 24 months of UDCA therapy, whereas caffeine $t_{1/2}$ did not change. There were no significant changes in hepatic scintigraphy throughout the study.

Conclusions: These data suggest that although UDCA therapy improves pruritus and results in a reduction in ALT and gamma-glutamyl transpeptidase, UDCA therapy did not improve quantitative measures of hepatic function in children with intrahepatic cholestasis.

22. **Ng, V.L., and W.F. Balistreri. "Treatment options for chronic cholestasis in infancy and childhood." *Current Treatment Options in Gastroenterology* 8.5 (2005): 419-430.**

Abstract

Altered bile flow physiology leads to many complications commonly seen in patients with cholestatic liver disease, regardless of the etiology. For each individual patient, a coordinated and effective treatment strategy must address the presence and the severity spectrum of malabsorption, malnutrition, vitamin and micronutrient deficiencies, pruritus, xanthomata, ascites, and liver failure, which are attributed directly or indirectly to diminished bile flow. An aggressive approach to maximizing the nutritional status of the child is vital to ensure optimal growth and development. Protein-calorie and/or fat supplementation is best discussed early. Decreasing the percentage of dietary long-chain triglycerides, providing medium-chain triglycerides, and ensuring adequate essential fatty acid and adequate protein intake may be helpful. Fat-soluble vitamin (A, D, E, and K) levels and micronutrient levels must be carefully and serially monitored and supplemented as necessary. Because the mechanisms that mediate pruritus of cholestasis remain to be determined,

the use of empirical therapies continues to be standard practice. Ursodeoxycholic acid may ameliorate pruritus. Antihistamines and rifampicin may also provide temporary relief for some children. Based on the evidence that increased central opioidergic tone is present in chronic cholestasis, the use of opiate antagonists is promising but has not been evaluated in children. Selected patients with refractory pruritus that have failed maximal medical therapy have benefited from partial external biliary diversion. Ongoing dialogue with the family regarding the indications for liver transplantation is reasonable. Optimization and adherence with the pretransplant medical management enhance the chances for a successful outcome from liver transplantation. Specific to the pediatric patient, optimizing growth, development and nutrition, minimizing discomfort and disability, and aiding the child and family in coping with the stress, social, and emotional effects of chronic liver disease remain paramount.

23. **Nousia-Arvanitakis, S., M. Fotoulaki, H. Economou, M. Xefteri, and A. Galli-Tsinopoulou. "Long-term prospective study of the effect of ursodeoxycholic acid on cystic fibrosis-related liver disease." *Journal of Clinical Gastroenterology* 32.4 (2001): 324-328.**

Abstract

GOALS: To evaluate the efficacy of UDCA in arresting the progression of the early multifocal hepatic lesion to overt CF-related NBC.

BACKGROUND: Focal biliary cirrhosis is an early hepatic pathologic change related to the ion transport defect in cystic fibrosis. The factors involved in the progression of focal to nodular biliary cirrhosis are not clear. Ursodeoxycholic--a hydrophilic, nontoxic, choleric, and hepatoprotective exogenous bile acid--has been reported to be effective in the management of cholestatic liver disease.

STUDY: For 10 years at 6-month intervals, 70 individuals with cystic fibrosis (38 men and 32 women; age range, 2--29 years) were examined using hepatosplenomegaly, liver function tests, and ultrasound liver scan. Patients demonstrating evidence of liver involvement at the onset or during the study received ursodeoxycholic acid 20 mg/kg body weight.

RESULTS: After the administration of ursodeoxycholic acid, the progression of nodular biliary cirrhosis ultrasound changes was arrested, hepatic function was preserved, and no variceal bleeding was observed. No case of focal biliary cirrhosis progressed to nodular biliary cirrhosis. Furthermore, the multifocal, multilobular changes suggestive of focal biliary cirrhosis on ultrasound scan were reversed to normal.

CONCLUSION: Ursodeoxycholic acid is effective in improving cholestasis and hepatic dysfunction in nodular biliary cirrhosis and, also, in reversing the early sonography findings suggestive of focal biliary cirrhosis. It is speculated that ursodeoxycholic acid may prove to affect the natural history of cystic fibrosis-related liver disease.

24. **Reinshagen, K., R. Adams, M. Trunk, and L.M. Wessel. "The chronic liver disease in patients with short bowel syndrome: etiology and treatment." *Minerva Pediatrica* 61.3 (2009): 273-281.**

Abstract

Short bowel syndrome is a life threatening disease with a high mortality and morbidity. Since home parenteral nutrition (PN) has been established, there is an increasing number of patients surviving the acute loss of bowel function. But on the long-time these patients suffer from different complications of PN, with loss of central venous access, recurrent sepsis and finally the syndrome of progressive cholestatic liver disease. Both loss of central venous access and especially the progressive cholestatic liver disease are the limiting factor for the long-term survival of patients suffering from intestinal failure. Interestingly, the pathophysiologic mechanisms of PN induced intrahepatic cholestasis have not been dissolved yet and seem to be of multifactorial genesis. Cholestasis has shown to be associated with prematurity, recurrent sepsis, enteral and PN, especially with lipid emulsions. Enteral feeding and a well-controlled regime of PN lower the incidence of end-stage liver disease and, therefore, has to be optimized in the therapy of these patients.

25. **Rosenbaum, J., G. Alex, and T. Clarnette. "Ursodeoxycholic acid's role in avoiding diversionary surgery in idiopathic fibrosing pancreatitis." *Journal of Paediatrics and Child Health* 45.11 (2009): 681-683.**

Abstract

Obstructive jaundice in childhood is rare but a cause of great concern and warrants aggressive investigation into its aetiology. Idiopathic fibrosing pancreatitis (IFP) is a rare cause of this phenomenon and is presently a diagnosis of exclusion with lymphoma a main differential diagnosis. IFP appears to be a self limiting occurrence and as a result the previous gold standard of therapy of surgical diversion may ultimately be unnecessary. We describe ursodeoxycholic acid as a useful adjunct to treatment allowing more time for clinicians to evaluate the nature of the underlying disease process without hastily moving towards invasive surgery until clearly indicated.

26. **San Luis, V.A., and I.F. Btaiche. "Ursodiol in patients with parenteral nutrition-associated cholestasis." *The Annals of Pharmacotherapy* 41.11 (2007): 1867-1872.**

Abstract

OBJECTIVE: To review the role of ursodeoxycholic acid (ursodiol) in treating parenteral nutrition-associated cholestasis (PNAC).

DATA SOURCES: A MEDLINE (1950-May 2007) search was performed using the key terms parenteral nutrition, cholestasis, ursodeoxycholic acid, and ursodiol.

STUDY SELECTION AND DATA EXTRACTION: All English-language articles that evaluated the safety and efficacy of ursodiol for PNAC were included in this review.

DATA SYNTHESIS: The benefits of exogenous ursodiol administration in the treatment of cholestasis can be explained by its alteration of effects on bile composition and flow and provision of cytoprotective, membrane stabilizing, and immunomodulatory effects. Two animal studies, 2 case reports, and 6 human studies (2 prospective and 3 retrospective pediatric studies, 1 adult prospective study) evaluated the efficacy of ursodiol in patients with PNAC. Ursodiol 10-30 mg/kg/day in children and 10-15 mg/kg/day in adults administered in 2-3 doses improved the biochemical and clinical signs and symptoms of PNAC. However, short-term improvement in biochemical parameters may not necessarily predict the outcome of PNAC patients. At recommended doses, ursodiol may not be effective in patients with short bowel syndrome or in those with resected terminal ileum because of reduced ursodiol absorption. Studies supporting the efficacy of ursodiol in treatment of PNAC are limited by small sample size, absence of randomization and controls, short duration, and lack of accountancy to confounding variables. Large, prospective, randomized, placebo-controlled, long-term follow-up studies evaluating the efficacy and optimal dosing and duration of ursodiol therapy for PNAC are not yet available.

27. **Setchell, K.D., L. Galzigna, N. O'Connell, G. Brunetti, and H.D. Tauschel. "Bioequivalence of a new liquid formulation of ursodeoxycholic acid (Ursofalk suspension) and Ursofalk capsules measured by plasma pharmacokinetics and biliary enrichment." *Alimentary Pharmacology & Therapeutics* 21.6 (2005): 709-721.**

Abstract

BACKGROUND: Ursodeoxycholic acid is an approved therapy for hepatobiliary disorders but in infants and children compliance is compromised because it is formulated exclusively as capsules, or tablets.

AIM: To determine the pharmacokinetics and bioequivalence of a new liquid formulation of ursodeoxycholic acid (Ursofalk suspension) with a standard capsule (Ursofalk) in a randomized, unblinded, crossover designed study of 24 healthy adults.

METHODS: Equivalence was based on single bolus oral plasma pharmacokinetics and biliary ursodeoxycholic acid enrichments after repeat doses. Biliary bile acid composition and hydrophobicity index were also compared. Ursodeoxycholic acid was measured in duodenal bile by high-performance liquid chromatography and in plasma by mass spectrometry.

RESULTS: The mean percentage biliary ursodeoxycholic acid enrichment after administration of the suspension was not significantly different from that obtained with capsules (44.2 +/- 11.7% vs. 46.9

+/- 10.2%, respectively). The equivalence ratio was 0.94 (95% CI: 0.8-1.1), establishing bioequivalence between suspension and capsules. Both formulations reduced the biliary hydrophobicity index and no differences in bile acid composition were observed between formulations. The plasma pharmacokinetics of both formulations was similar and the tolerability of the suspension was excellent.

CONCLUSIONS: A new liquid formulation of ursodeoxycholic acid suitable for paediatric patients is pharmacologically bioequivalent to capsules when given as single, or repeated oral doses.

28. **Smaropoulos, E.C., and B. Kaselas. "Ursodeoxycholic acid as a supplementary treatment in corrected biliary atresia." *European Journal of Pediatric Surgery* 16.2 (2006): 138-139. (No Abstract Available)**
29. **Socha, P., A. Horvath, P. Vajro, P. Dziechciarz, A. Dhawan, and H. Szajewska. "Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review." *Journal of Pediatric Gastroenterology and Nutrition* 48.5 (2009): 587-596.**

Abstract

BACKGROUND: Uncertainty exists regarding the treatment of patients with nonalcoholic fatty liver disease (NAFLD) who are unable to lose weight and/or change lifestyle. The present study assesses the effectiveness and safety of pharmacological and dietary supplement interventions for NAFLD.

METHODS: MEDLINE, EMBASE, and the Cochrane Library were searched for randomized controlled trials (RCTs) both in adults and in children.

RESULTS: Fifteen (2 pediatric patients and 13 adults) RCTs met the inclusion criteria. A significant effect on normalization of alanine transaminase was found in patients treated with metformin compared with vitamin E, and in those treated with high-dose (3 g) carnitine vs diet. In contrast, there was no difference in patients treated with pioglitazone combined with vitamin E versus vitamin E alone, ursodeoxycholic acid (UDCA) combined with vitamin E or alone versus placebo, or UDCA versus combination of vitamin E and vitamin C, and in patients treated with vitamin E, probucol, N-acetylcysteine, low doses of carnitine, or Yo Jyo Shi Ko compared with placebo. Aspartate aminotransferase normalization was significantly higher in those treated with UDCA combined with vitamin E versus UDCA alone or placebo, and in those treated with metformin. Small number of subjects, high drop-out rates, and numerous interventions in 1 study limit the value of many studies. Only 7 RCTs analyzed biopsy specimens, but most of them have significant methodological limitations. Pioglitazone had reduced liver necrosis and inflammation in 1 large study.

CONCLUSIONS: Limited data do not allow one to draw firm conclusions on the efficacy of various treatments for NAFLD.

30. **Speth, T.F., R.J. Miltner, S.D. Richardson, and J.E. Simmons. "Integrated disinfection by-products mixtures research: concentration by reverse osmosis membrane techniques of disinfection by-products from water disinfected by chlorination and ozonation/postchlorination." *Journal of Toxicology and Environmental Health* 71.17 (2008): 1149-1164.**

Abstract

To conduct the health-effect studies described in subsequent articles in this series, concentrated aqueous mixtures of disinfection by-products were required for the two water treatment trains described in the preceding article (Miltner et al., 2008). To accomplish this, the finished drinking waters from each treatment train were sent through cation-exchange resin columns to remove hardness and free chlorine. Reverse osmosis membranes were then used to concentrate approximately 2400 L of each finished water down to approximately 18 L. The resulting volumetric concentration factors for the chlorinated and ozonated/postchlorinated waters were 136- and 124-fold, respectively. The concentrates were spiked with select disinfection by-products (DBPs) that were lost during the concentration effort. The results, along with the rationale for choosing the method of concentration, are presented. After reintroduction of a select list of lost DBPs, the concentration methodology used herein was able to produce concentrates that retained large percentages of the

DBPs that were in the initial finished drinking waters. Further, the distributions of the DBPs in the concentrates matched those found in the finished drinking waters.

31. **van de Meeberg, P.C., R.H. Houwen, M. Sinaasappel, H.G. Heijerman, C.M. Bijleveld, and G.P. Vanberge-Henegouwen. "Low-dose versus high-dose ursodeoxycholic acid in cystic fibrosis-related cholestatic liver disease. Results of a randomized study with 1-year follow-up." *Scandinavian Journal of Gastroenterology* 32.4 (1997): 369-373.**

Abstract

Background: Ursodeoxycholic acid (UDCA) is beneficial in cholestasis related to cystic fibrosis (CF). High-dose treatment has been recommended to compensate for bile salt malabsorption. We compared the results of low-dose (10 mg/kg/day) and high-dose (20 mg/kg/day) UDCA treatment on liver biochemistry after 3 and 12 months' treatment.

Methods: Thirty CF patients (age > 5 years) with biochemical cholestasis and compensated liver disease were randomized for low-dose (n = 17) or high-dose (n = 13) UDCA. Baseline clinical variables were comparable.

Results: After 1 year one patient had died of liver failure (low dose), and three had dropped out because of pruritus (one in each group) or personal choice (low dose). In the high-dose group improvement in gamma-glutamyl transferase values was more pronounced after 3 months and 1 year (P < 0.004), and improvement of alanine aminotransferase was better after 1 year (P < 0.02).

Improvement of alkaline phosphatase and aspartate aminotransferase was comparable. Complete normalization of liver enzymes and bilirubin occurred more often in the high-dose group.

Conclusion: High-dose UDCA induces a better response of liver biochemistry values than low-dose UDCA in CF patients with cholestatic liver disease.

32. **Zapata, R., L. Sandoval, J. Palma, I. Hernández, J. Ribalta, H. Reyes, and M. Sedano. "Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience." *Liver International* 25.3 (2005): 548-554.**

Abstract

OBJECTIVE: To assess the efficacy of ursodeoxycholic acid (UDCA) in patients with intrahepatic cholestasis of pregnancy (ICP) and in the outcome of pregnancy.

METHODS: Retrospective analysis of our 12-year experience treating ICP patients with UDCA. Thirty-two patients with pruritus starting before week 34 of pregnancy and with increased serum bile salts (BS) and alanine aminotransferase (ALT) received UDCA (15 mg/kg/day) for at least 3 weeks before delivery. They were compared with 16 historical controls who did not receive UDCA. All patients were followed up until delivery and in puerperium. Newborns were followed up during 3 months.

RESULTS: UDCA treatment attenuated pruritus (P < 0.05), serum bilirubin and ALT decreased (P < 0.05) and BS declined. Delivery at term (> or = 37 weeks) occurred in 65.7% of UDCA-treated patients compared with only 12.5% in controls (P < 0.01). Infants born to mothers treated with UDCA weighed a mean of 500 g more than the controls (2882+/-582 vs 2385+/-582; P < 0.01). At 3 months, all infants developed normally. Twenty-six children whose mothers received UDCA were re-examined after 1-12 years and they and their mothers were healthy.

CONCLUSIONS: UDCA improved pruritus and biochemical cholestasis, and facilitated deliveries at term in ICP patients, with a higher birthweight compared with historical controls. The drug was well tolerated and no adverse effects were detected in their infants.

CONCLUSIONS: Ursodiol may improve the biochemical signs and clinical symptoms of PNAC. However, optimal dosing, timing, duration of therapy, and long-term effects on PNAC outcome and prognosis require further studies.

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81 citations

1. Aanpreung, P., and Vajaradol, C. Clinical use of erythromycin in children with gastrointestinal dysmotility. *J Med Assoc Thai* 84: 1021-1026, 2001.

Intolerant feeding is a common symptom in gastrointestinal disorders which is commonly found in systemic diseases. Prokinetic drugs play a role in management. A low dose of erythromycin has an effect on improvement of antroduodenal motility and gastric emptying in children and adults. The objective of this study was to evaluate the efficacy of intravenous erythromycin in the treatment of GI dysmotility in children. Retrospective studies were performed in the Department of Pediatrics, Siriraj Hospital, Mahidol University between 1996 and 2000 in 22 patients with intolerance of feeding due to GI dysmotility. Their ages ranged from 11 days to 12 years (42.1 +/- 48.1 months). The patients were divided into 2 groups: 12 critically ill and 10 non-critically ill patients. Dosages of intravenous erythromycin were 1-3 mg/kg/dose every 6 hours. The result of treatment was evaluated as: good (tolerant feeding), fair (tolerant feeding but needing erythromycin for longer than 1 month) and failed (intolerant feeding). All non-critically ill patients had improved symptoms with 9 +/- 4.3 days duration of treatment. In the other group, 8 patients had good results with 10.9 +/- 6 days of treatment. Two patients needed the drug for longer than 1 month and the other 2 patients did not respond and died due to severe infection. Low dose intravenous erythromycin had good efficacy in the treatment of intolerant feeding related to GI dysmotility in children.

2. Aly, H., Abdel-Hady, H., Khashaba, M., and El-Badry, N. Erythromycin and feeding intolerance in premature infants: a randomized trial. *J Perinatol* 27: 39-43, 2007.

OBJECTIVES: To evaluate the effectiveness of low-dose oral erythromycin to treat feeding intolerance in preterm infants. **DESIGN:** This study was a prospective, double-blind, randomized, placebo-controlled trial on 60 premature infants suffering from feeding intolerance. Thirty infants were given oral erythromycin 1 mg/kg every 8 h and 30 infants were given placebo (normal saline). Randomization was stratified on enrollment according to gestational age whether >32 weeks or <or=32 weeks. The primary end point was the length of time taken to establish full enteral feeding since enrollment. Potential adverse effects associated with erythromycin were also monitored. Groups of each corresponding stratum were compared using two-tail t-test and Mann-Whitney for continuous variables, and chi (2) and Fisher's exact for categorical variables. **RESULTS:** For infants with gestational age >32 weeks, the erythromycin group achieved full enteral feeding earlier than placebo group (10.5+/-4.1 vs 16.3+/-5.7 days, respectively; P=0.01) had fewer episodes of gastric residuals (P<0.05) and

shorter duration of parenteral nutrition (PN) ($P < 0.05$). On the other hand, in infants with gestational age ≤ 32 weeks, there were no significant differences between erythromycin and placebo groups regarding any of these variables. CONCLUSION: Low-dose enteral erythromycin is associated with better tolerance of feeding and shorter duration of PN in infants > 32 weeks gestation. A similar effect on younger preterm infants was not demonstrable.

3. Ariagno, R.L., Kikkert, M.A., Mirmiran, M., Conrad, C., and Baldwin, R.B. Cisapride decreases gastroesophageal reflux in preterm infants. *Pediatrics* 107: E58, 2001.

OBJECTIVE: Gastrointestinal prokinetic agents, such as cisapride, are commonly used in pediatric practice to improve gastric emptying, to decrease emesis, to improve lower esophageal sphincter tone, and to improve irritability and feeding aversion associated with gastroesophageal reflux (GER). Although cisapride seems to be effective in infants from 2 months to 14 years old, data for younger and preterm infants are not available. Whether reflux is a significant cause of reflex apnea or feeding intolerance in the preterm infant is controversial. The objective of this 1-year prospective study, started in 1998, was to determine the efficacy of cisapride for treatment of reflux and reflux-associated apnea (RAAP) in preterm infants. Before this study, the diagnosis of reflux was often made clinically and the effect of therapy on reflux or the decision to increase the dose of cisapride was made empirically. The clinical bias was that persistent apnea, not responding to caffeine, was caused by GER. We reasoned that a systematic approach to the diagnosis and treatment of reflux would improve the care of preterm infants and reduce the risk of toxicity, especially if an increased dose of cisapride showed no improvement in reflux or apnea. STUDY DESIGN: Twenty-four preterm infants (24-36 weeks' gestational age) had clinical apnea/pH studies when they were referred by the attending neonatologist for suspected GER. These infants were born at 28.8 ± 3.1 weeks with birth weight of 1169 ± 387 g (range: 631-2263 g). Each infant was studied before and 8 days after starting cisapride treatment. Cisapride dose was 0.09 to 0.25 mg/kg every 6 hours enterally. Treatment decisions regarding dose of cisapride were the responsibility of the attending neonatologist. The pH was recorded continuously for 24 hours at 0.25 Hz and was analyzed using EsopHogram software. A single sensor pH catheter was inserted to ~ 2 cm above the esophageal gastric junction. GER was defined as a drop in esophageal pH below 4.0 for a least 5 seconds, or pathologic GER was defined as a reflux index (RI) > 2 standard deviation (SD) from the mean based on published norms for term infants. The following parameters were calculated from the pH recording: number of reflux events per 24 hours, duration of the longest episode, number of episodes > 5 minutes per 24 hours, and RI, ie, percentage of time with pH < 4.0 . Each study had a combined time-lapse video recording and multichannel digital recording. Recorded parameters were: continuous pulse oximetry, electrocardiogram, respiratory effort (piezo sensor), and airflow (temperature sensor at nostrils and mouth). The recording was scored for central apneas of 10 to 14 seconds and ≥ 15 seconds

(prolonged) and ≥ 10 seconds for obstructive and mixed apneas. RAAP was scored when an apnea (irrespective of the type) occurred within 1 minute of a GER event. Baseline, after cisapride, and follow-up electrocardiograms were performed because of concern about prolonged QTc and cardiac arrhythmias. The infants were 35.6 \pm 4.5 weeks postconceptional age when first studied. Twelve infants (mean birth weight: 1821 \pm 749 g; gestational age: 32 \pm 2 weeks; postconceptional age: 35.6 \pm 2.6 weeks) were identified retrospectively as controls because their baseline GER parameters were within the normal range using Vandeplass' criteria. RESULTS: Overall, cisapride treatment significantly improved the RI from 16.6 \pm 15.2 to 9.1 \pm 8.4 SD. The number of reflux episodes ≥ 5 minutes was reduced from 7.1 \pm 5.8 to 4.3 \pm 4.4 SD. No significant effect was seen on the total number of refluxes (/24 hours). Eight infants (33%) had no decrease in the RI after a week of treatment. Three of these infants improved after cisapride dose was increased from 0.09 to 0.25 mg/kg/dose every 6 hours. Although 0.09 mg/kg/day is the minimum effective dose, 67% of our infants did respond to this low dose. Cisapride was discontinued in 3 infants because of prolonged QTc ≥ 0.450 seconds (0.473 in 1 and 0.470 in 2). More data about the effect of cisapride on QTc interval are reported in Pediatrics in a separate article. Only 1 infant showed no improvement with increased dose. Caffeine treatment had no effect on the baseline or follow-up GER values. Although apnea indexes for central and obstructive apnea were similar before and after cisapride, mixed apnea was less during treatment. There was a significant decrease (0.32 \pm 0.40 to 0.12 \pm 0.17/hour) in RAAP when the one infant who had increased reflux on increased dose of cisapride was excluded as an outlier. The statistical difference, before and after cisapride, for the group is significant with the outlier omitted. The clinical significance is unclear because $\sim 50\%$ of the infants had minimal changes in their apnea indexes. Furthermore, $\sim 40\%$ of infants did not have RAAP. (ABSTRACT TRUNCATED)

4. Barnett, C.P., Omari, T., Davidson, G.P., Goodchild, L., Lontis, R., Dent, J., and Haslam, R.R. Effect of cisapride on gastric emptying in premature infants with feed intolerance. *J Paediatr Child Health* 37: 559-563, 2001.

OBJECTIVE: To assess the effect of cisapride on gastric emptying and gastro-oesophageal reflux (GOR) symptoms in preterm infants with feed intolerance. METHODS: Sixteen preterm infants (gestational age 24-35 weeks) with feed intolerance were enrolled in the study. Infants were randomized to receive 7 days of cisapride 0.2 mg/kg four times a day, immediately followed by 7 days of placebo or vice versa. Gastric emptying was measured using the [^{13}C]-octanoic acid breath test prior to study entry and repeated on day 5, 6 or 7 after randomization and 5, 6 or 7 days after crossover. The symptoms of GOR were monitored during the study period using a standardized reflux chart. Weight was recorded daily. RESULTS: There was no change in gastric emptying in infants prescribed cisapride (gastric half-emptying time ($t_{1/2}$) 31.9 \pm 4.7 vs 34.2 \pm 3.9 min for placebo vs cisapride, respectively; $P = 0.65$). Infants on cisapride had slower growth and there was no change in reflux symptoms. CONCLUSIONS:

The use of cisapride in preterm infants with feed intolerance cannot be recommended.

5. Bellomo-Brandao, M.A., Collares, E.F., and da-Costa-Pinto, E.A. Use of erythromycin for the treatment of severe chronic constipation in children. *Braz J Med Biol Res* 36: 1391-1396, 2003.

The efficacy of erythromycin was assessed in the treatment of 14 children aged 4 to 13 years with refractory chronic constipation, and presenting megarectum and fecal impaction. A double-blind, placebo-controlled, crossover study was conducted at the Pediatric Gastroenterology Outpatient Clinic of the University Hospital. The patients were randomized to receive placebo for 4 weeks followed by erythromycin estolate, 20 mg kg⁻¹ day⁻¹, divided into four oral doses for another 4 weeks, or vice versa. Patient outcome was assessed according to a clinical score from 12 (most severe clinical condition) to 0 (complete recovery). At enrollment in the study and on the occasion of follow-up medical visits at two-week intervals, patient score and laxative requirements were recorded. During the first 30 days, the mean SD clinical score for the erythromycin group (N = 6) decreased from 8.2±2.3 to 2.2±1.0 while the score for the placebo group (N = 8) decreased from 7.8±2.1 to 2.9±2.8. During the second crossover phase, the score for patients on erythromycin ranged from 2.9±2.8 to 2.4±2.1 and the score for the patients on placebo worsened from 2.2±1.0 to 4.3±2.3. There was a significant improvement in score when patients were on erythromycin (P < 0.01). Mean laxative requirement was lower when patients ingested erythromycin (P < 0.05). No erythromycin-related side effects occurred. Erythromycin was useful in this group of severely constipated children. A larger trial is needed to fully ascertain the prokinetic efficacy of this drug as an adjunct in the treatment of severe constipation in children.

6. Bennett, J.R. How safe and acceptable is cisapride? *Scand J Gastroenterol Suppl* 165: 59-61, 1989.

Cisapride has not been found to have a significant frequency of adverse reactions, except for diarrhoea which occurs in about 4% of individuals taking the drug. Cisapride is devoid of antidopaminergic effects (i.e. no neuro-endocrine effects such as prolactin increase; no extrapyramidal reactions). Clinical laboratory data show no effect of cisapride on haematology, blood chemistry, liver and kidney function. It is concluded that cisapride has a favourable safety profile.

7. Bindl, L., Buderus, S., Ramirez, M., Kirchhoff, P., and Lentze, M.J. Cisapride reduces postoperative gastrocaecal transit time after cardiac surgery in children. *Intensive Care Med* 22: 977-980, 1996.

OBJECTIVE: To investigate the influence of the prokinetic drug cisapride on gastrocaecal transit time (GCTT) in children after open heart surgery. DESIGN:

Prospective, randomized and controlled study. SETTING: Interdisciplinary paediatric intensive care unit in a tertiary-care children's hospital. PATIENT: Twenty-one children with a median age of 6.2 years on day 1 after uncomplicated open heart surgery for isolated septal defects, acquired mitral or aortic valve disease or tetralogy of Fallot. Control group consisting of 10 healthy children with a median age of 8.1 years. INTERVENTIONS: Ten children were randomized to receive cisapride 0.2 mg/kg body weight, 30 min prior to measurement of GCTT. MEASUREMENTS AND RESULTS: GCTT was measured using hydrogen breath testing with a test solution containing lactulose and mannitol (0.4 g/kg and 0.1 g/kg body weight respectively). GCTT was markedly delayed in all patients compared to the control group. Within 8 h 8/10 patients in the treatment group versus 4/11 patients in the non-cisapride group achieved gastrocaecal transit. No adverse side-effects were observed. CONCLUSIONS: Cisapride accelerates gastrocaecal transit after open heart surgery in children. In intensive care patients on inotropic support or opioid medication, it may facilitate the earlier reintroduction of enteral feeding.

8. Cohen, R.C., O'Loughlin, E.V., Davidson, G.P., Moore, D.J., and Lawrence, D.M. Cisapride in the control of symptoms in infants with gastroesophageal reflux: A randomized, double-blind, placebo-controlled trial. *J Pediatr* 134: 287-292, 1999.

OBJECTIVE: To evaluate the efficacy of cisapride in the treatment of uncomplicated gastroesophageal reflux in children younger than 36 months of age. STUDY DESIGN: A total of 95 patients satisfied the entry criteria and were randomly assigned to double-blind treatment with either cisapride (n = 50), 0.2 mg/kg 4 times daily, or placebo (n = 45) for 2 weeks. At the end of the 2-week treatment period, symptom diary and parental evaluation with repeat 24-hour pH study were performed. RESULTS: Sixty-eight patients completed the trial (38 in the cisapride group and 30 in the placebo group). There were no significant differences in the symptoms of crying, vomiting, or gagging; the overall symptom intensity score; or parental global evaluations. There was a significant difference (P <.03) in the percent time pH <4, the number of reflux episodes lasting more than 5 minutes, and the duration of the longest episode. No significant difference was demonstrated for the number of episodes with pH <4 or the reflux score. CONCLUSIONS: Cisapride was no better than placebo for relief of symptoms in children with uncomplicated gastroesophageal reflux. A beneficial effect was demonstrated in the cisapride group in relation to the measured parameters for esophageal acid exposure time.

9. Costalos, C., Gavrili, V., Skouteri, V., and Gounaris, A. The effect of low-dose erythromycin on whole gastrointestinal transit time of preterm infants. *Early Hum Dev* 65: 91-96, 2001.

The aim of the study was to determine the effect of a low oral dose of erythromycin on whole gastrointestinal transit time [WGTT]. Erythromycin [EM] [1.5 mg/kg, 6 hourly] or placebo was given first over 7 days in a double blind

randomized crossover study of 21 preterm infants with feed intolerance. Median [range] birth weight was 1420 [690, 2200] g and postconceptual age 32. 5 [20, 36.4] weeks. WGTT was assessed on day 3 of each treatment, by timing the transit of carmine red through the gut. Treatments were compared using Student's paired t test. RESULTS: WGTT was significantly shorter following EM treatment as compared to placebo: mean [SD] 10.16 [4.6] h vs. 15. 9 [7.2] h, $p < 0.01$. CONCLUSION: Oral low-dose EM significantly shortens WGTT of feed-intolerant preterm infants.

10. Costalos, C., Gounaris, A., Varhalama, E., Kokori, F., Alexiou, N., and Katsarakis, I. Effect of low-dose cisapride on gastric emptying and QTc interval in preterm infants. *Acta Paediatr* 89: 1446-1448, 2000.

The aim of the study was a prospective survey of the effects of low-dose cisapride on gastric emptying and QTc interval in very low birthweight infants. Twenty low birthweight infants were studied: mean (SD) gestation 30.5 (2.2) wk; birthweight 1320 (150)g. Gastric emptying was assessed ultrasonically in 15 of these infants, in a randomized blind crossover study, following 24-h low-dose oral cisapride administration (0.1 mg/kg given 8 hourly), or placebo. The QTc interval was also determined in all 20 infants following a 7-d course of cisapride or placebo. CONCLUSIONS: Cisapride significantly shortened both gastric emptying time and QTc interval ($p < 0.05$) compared to placebo. All infants completed the study without any apparent adverse effects. In conclusion, low-dose cisapride administration significantly improves gastric emptying without increasing the QTc interval.

11. Costalos, C., Gounaris, A., Varhalama, E., Kokori, F., Alexiou, N., and Kolovou, E. Erythromycin as a prokinetic agent in preterm infants. *J Pediatr Gastroenterol Nutr* 34: 23-25, 2002.

BACKGROUND: The macrolide antibiotic erythromycin is a prokinetic agent that stimulates gastrointestinal motility. The aim of the study was to determine the effect of erythromycin on the gastrointestinal motility of preterm infants. METHODS: Erythromycin 10 mg/kg, 8 hourly or a placebo, was given orally for 7 days in a double-blind randomized, crossover study of 20 preterm infants with a median gestational age of 32 weeks (range, 26-34 weeks). Antral contractility was determined by using ultrasonography to measure the decrease in the gastric antral cross-sectional area after a feed. The whole gut transit time was assessed by timing the transit of carmine red through the gut. RESULTS: Antral contractility lasted for a shorter period of time during erythromycin treatment than during placebo treatment (mean [standard deviation], 31 minutes [9.9 minutes] vs. 70 minutes [13 minutes]; $P < 0.01$). Whole gut transit time was also shorter during erythromycin treatment (mean, 23.1 hours [12.9 hours] vs. 49.3 hours [29 hours]; $P < 0.01$). All infants tolerated the drug well. CONCLUSIONS: Oral erythromycin in food-intolerant preterm infants enhances both antral contractility and whole gut transit time.

12. Cucchiara, S., Raia, V., Minella, R., Frezza, T., De Vizia, B., and De Ritis, G. Ultrasound measurement of gastric emptying time in patients with cystic fibrosis and effect of ranitidine on delayed gastric emptying. *J Pediatr* 128: 485-488, 1996.

Intestinal dysmotility is commonly reported in patients with cystic fibrosis (CF); however, gastric motor activity has rarely been investigated. We measured with real-time ultrasonography the antral distention and gastric emptying time of a solid-liquid meal in 29 patients with CF (age range, 5 to 17 years). A significantly prolonged gastric emptying time was present in 26 patients compared with 13 healthy control subjects (age range, 5 to 16 years); an exaggerated antral distention in the fed period was also detected. The patients with CF and delayed gastric emptying were randomly allocated to receive cisapride or ranitidine for 4 weeks. Twelve patients treated with ranitidine and 11 with cisapride completed the trial. There was a marked decrease in gastric emptying time, antral distention, and dyspeptic symptomatic score in patients receiving ranitidine but not in patients treated with cisapride. We conclude that gastric dysmotility is commonly detected in patients with CF and that H₂ receptor blockers are more effective than prokinetics in improving dyspeptic symptoms and gastric emptying and distention.

13. Cucchiara, S., Staiano, A., Boccieri, A., De Stefano, M., Capozzi, C., Manzi, G., Camerlingo, F., and Paone, F.M. Effects of cisapride on parameters of oesophageal motility and on the prolonged intraoesophageal pH test in infants with gastro-oesophageal reflux disease. *Gut* 31: 21-25, 1990.

The effect of cisapride, a new gastrointestinal prokinetic drug, on oesophageal motility and acid reflux was studied in 14 children with gastro-oesophageal reflux disease, receiving either placebo or cisapride 0.15 mg/kg intravenously. Cisapride significantly (p less than 0.01) increased the lower oesophageal sphincter pressure (+124%), the amplitude (+84%) and duration (+24%) of oesophageal peristaltic waves, whereas the placebo treatment did not produce any changes. Subsequently, all 14 children underwent 24 hour oesophageal pH-monitoring before and after four weeks of treatment with oral cisapride 0.2 mg/kg tid given in addition to postural therapy and thickened feedings. The 24 hour intraoesophageal pH recordings and symptomatic scores were compared with those of 10 control patients treated only by postural therapy and thickened feedings. When compared with baseline pH data, cisapride significantly reduced the oesophageal acid exposure time, the mean duration of each reflux episode, the duration of the longest reflux episode and the number of long lasting reflux episodes; the number of reflux episodes was not influenced. The effect of cisapride was marked and consistent during fasting and sleep periods. Oesophageal acid exposure was reduced more significantly in patients given cisapride (-61%) than in controls (-24%; p less than 0.001). Symptom improvement was greater after four weeks of cisapride treatment (score

reduction: 61%) than after postural and dietary therapy alone (score reduction: 42%; p less than 0.01). No adverse effects occurred. These findings suggest that cisapride is a valuable drug in the management of gastro-oesophageal reflux disease in children.

14. Curry, J.I., Lander, A.D., and Stringer, M.D. A multicenter, randomized, double-blind, placebo-controlled trial of the prokinetic agent erythromycin in the postoperative recovery of infants with gastroschisis. *J Pediatr Surg* 39: 565-569, 2004.

BACKGROUND/PURPOSE: The recovery of gut function after repair of gastroschisis is frequently prolonged, and these infants are prone to complications associated with parenteral nutrition. This trial was designed to investigate the effect of the prokinetic agent, erythromycin, on the attainment of full enteral feeding in infants after primary repair of uncomplicated gastroschisis. **METHODS:** A multicenter, randomized, double-blind, placebo-controlled trial was used to investigate the effect of enteral erythromycin (3 mg/kg/dose 4 times daily) compared with placebo on the attainment of full enteral feeding tolerance after primary repair of uncomplicated gastroschisis. Eleven neonatal surgical units in the United Kingdom participated in the study. The primary end-point was the time taken to achieve continuous enteral feeding at 150 mL/kg/24 hours sustained for 48 hours. **RESULTS:** Of 70 eligible infants, 62 were recruited and randomly divided. There were 30 patients in group I (placebo) and 32 in group II (erythromycin). The groups were comparable in terms of mean gestational age, mean birth weight, extent of evisceration, and degree of intestinal peel. There was no statistically significant difference between the 2 groups in the time taken to achieve full enteral feeding (27.2 v 28.7 days; P = .75). Similarly, no significant differences were found in the incidence of catheter-related sepsis, duration of parenteral nutrition, or time to discharge between the 2 groups. **CONCLUSIONS:** Enterally administered erythromycin at a dose of 3 mg/kg 4 times daily conferred no advantage in the time taken to achieve full enteral feeding after primary repair of uncomplicated gastroschisis.

15. Curry, J.I., Lander, T.D., and Stringer, M.D. Review article: erythromycin as a prokinetic agent in infants and children. *Aliment Pharmacol Ther* 15: 595-603, 2001.

Erythromycin has been used as an antibiotic for more than four decades, but only in the last 10 years have other therapeutic benefits of this agent been exploited. Animal and human studies have demonstrated a prokinetic effect on the gastrointestinal tract at sub-antimicrobial doses (typically a quarter or less of the antibiotic dose). A limited number of studies have been performed in children to investigate this action. A review of this literature is particularly pertinent given the frequency of clinical problems related to gastrointestinal dysmotility in children and the limited availability of prokinetic agents in paediatric practice, compounded by the recent withdrawal of cisapride. The prokinetic effects of

erythromycin have been investigated in infants with dysmotility associated with prematurity, in low birth-weight infants recovering from abdominal surgery, and in older children with a variety of other gastrointestinal disorders. Only one randomized placebo-controlled trial has been conducted. All except one of these studies have shown a beneficial effect of erythromycin in either promoting tolerance of enteral feeds or enhancing a measured index of gastrointestinal motility. Erythromycin appears to be equally effective when given orally (as ethylsuccinate or estolate) or intravenously (as lactobionate). Significantly, no serious adverse effects have been reported in studies in which erythromycin has been used for its prokinetic effects, although fatal reactions have followed the intravenous administration of erythromycin to neonates in antibiotic doses.

16. Di Lorenzo, C., Flores, A.F., Tomomasa, T., and Hyman, P.E. Effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. *Dig Dis Sci* 39: 1399-1404, 1994.

To evaluate the effects of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms, we studied 35 consecutive subjects referred for diagnostic motility studies. We recorded fasting motility for > 4 hr, then infused in random order either 1 or 3 mg/kg erythromycin intravenously over 1 hr and continued the study for another hour. Erythromycin induced phase III in 18 of 20 children who had phase III during fasting compared to only one of 15 who did not ($P < 0.001$). The antral motility index increased after erythromycin (1596 +/- 323 vs 436 +/- 242 mm Hg/30 min before erythromycin, $P < 0.005$) but the duodenal motility index did not change. The antral motility index was greater in children receiving 3 mg/kg than in those receiving 1 mg/kg (1968 +/- 391 vs 1226 +/- 285 mm Hg/30 min, $P < 0.01$), but duodenal motility indices did not differ. Only one child receiving the lower dose erythromycin complained of abdominal pain, nausea, or vomiting vs 9 of 19 the children receiving the higher dose ($P < 0.02$). In summary, in children with chronic functional gastrointestinal disorders, erythromycin rarely induced phase III in patients who did not have it during fasting. When different doses erythromycin are compared, 1 and 3 mg/kg are equally efficacious in inducing phase III episodes; the lower dose is associated with fewer side effects and the higher dose produces a higher antral motility index.

17. Di Lorenzo, C., Lucanto, C., Flores, A.F., Idries, S., and Hyman, P.E. Effect of octreotide on gastrointestinal motility in children with functional gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 27: 508-512, 1998.

BACKGROUND: The somatostatin analogue octreotide has been proposed as a possible therapeutic agent in patients with abnormal gastrointestinal motility. This study was conducted to study the effects of 0.5 microg/kg and 1.0 microg/kg subcutaneous octreotide on antroduodenal motility in children with chronic gastrointestinal disorders. **METHODS:** Twenty-three children were studied, eight with intestinal pseudo-obstruction, six with nonulcer dyspepsia, six with

gastroesophageal reflux disease, and three with intractable constipation. After recording fasting motility for more than 4 hours, the children were randomized to receive 0.5 microg/kg or 1 microg/kg of subcutaneous octreotide. Motility was recorded for another hour after feeding in 12 children. RESULTS: Phase III of the motor migrating complex was present in 13 of 23 children before and in 21 after octreotide ($p < 0.02$). All phase III episodes after administration of octreotide except one originated in the small intestine. Phase IIIs after octreotide were longer and were propagated faster than the spontaneous phase IIIs. There were no antral contractions during fasting after octreotide. There was a significant decrease in phase II intestinal motor activity in the hour after administration of octreotide ($p < 0.001$). There was no difference in effect between the two doses. After feeding, antral contractions were present in all children, and intestinal phase IIIs were not abolished. CONCLUSIONS: In children with chronic bowel disorders, subcutaneous octreotide induced phase IIIs that differed from spontaneous phase IIIs and were not inhibited by meals. Octreotide decreased antral motility during fasting and inhibited intestinal phase II. Feeding abolished the inhibitory effect of octreotide on antral motility.

18. Di Lorenzo, C., Reddy, S.N., Villanueva-Meyer, J., Mena, I., Martin, S., and Hyman, P.E. Cisapride in children with chronic intestinal pseudoobstruction. An acute, double-blind, crossover, placebo-controlled trial. *Gastroenterology* 101: 1564-1570, 1991.

To assess the effect of cisapride on gastrointestinal motility and gastric emptying in children with chronic intestinal pseudoobstruction, 20 children (mean age, 4.9 years; 14 female and 6 male) who required special means of alimentation or who had severe symptoms confirmed by diary during 2 weeks before the study were studied. A motility catheter with recording sites in the antrum and duodenum was placed on the first day of the study and remained in place until the end of the 5-day study. Cisapride (0.3 mg/kg PO t.i.d.) or placebo was given in double-blind randomized crossover fashion, with a 2-day "washout" interval. Antroduodenal motility was recorded on days 2 and 5. Recording consisted of 4 hours of fasting and 2 hours after a complex liquid meal labeled with ^{99m}Tc . Gastric emptying was assessed for 1 hour after the meal. Based on manometry, 16 patients had neuropathic and 4 patients had myopathic disorders. Cisapride had no effect on the discrete, qualitative abnormalities found in individual records. Cisapride increased the postprandial duodenal motility index from 1180 \pm 256 mm Hg/30 min after placebo to 2385 \pm 430 mm Hg/30 min (P less than 0.05) but had no significant effect on the antral motility index. Cisapride did not alter the profound delay in gastric emptying; time to reach 50% of initial activity ($T_{1/2}$) was 105 \pm 20 vs. 93 \pm 19 minutes and percentage of retention after 60 minutes (R_{60}) 56% \pm 4% vs. 58% \pm 4% in control vs. cisapride, respectively. In summary, in children with chronic intestinal pseudoobstruction, cisapride increased postprandial duodenal motility but did not improve gastric emptying.

19. Dranove, J., Horn, D., Reddy, S.N., and Croffie, J. Effect of intravenous

erythromycin on the colonic motility of children and young adults during colonic manometry. *J Pediatr Surg* 45: 777-783, 2010.

PURPOSE: Erythromycin is successfully used as a gastroduodenal prokinetic agent. Given the limited available treatments for colonic dysmotility, further investigation into erythromycin's effect on colonic motility is warranted. We aimed to study the effect of erythromycin on colonic motility in pediatric patients with recalcitrant chronic constipation/encopresis and other suspected colonic motility disorders. **METHODS:** Patients referred for colonic manometry were eligible for enrollment. Fasting motility was recorded for 1 to 2 hours, then erythromycin lactobionate (EL), 3 mg/kg, was administered intravenously, and colonic motility was monitored for 1 to 2 hours after erythromycin. Manometry was then continued per routine. The motility index (MI) of pressure tracings at each pressure transducer was calculated for each patient for a period of 15 and 60 minutes before and after EL infusion. Change in MI was compared by Wilcoxon signed rank test. **RESULTS:** Twenty patients were enrolled. The most common indication was constipation with encopresis. Seventy percent of patients had normal colonic manometry, and 30% of patients demonstrated a neuropathy. Average MI for the 60-minute period before and after EL infusion were 254 +/- 74 mm Hg/h and 253 +/- 94 mm Hg/h, respectively (P = .55). Average MI for the 15-minute period before and after EL infusion were 64 +/- 23 mm Hg/15 min and 69 +/- 32 mm Hg/15 min, respectively (P = .45). **CONCLUSIONS:** Administration of intravenous EL resulted in no changes in colonic MI in pediatric patients referred for colonic manometry. Further studies on potential colokinetic agents are warranted in this population of patients.

20. Dutta, U., Padhy, A.K., Ahuja, V., and Sharma, M.P. Double blind controlled trial of effect of cisapride on gastric emptying in diabetics. *Trop Gastroenterol* 20: 116-119, 1999.

AIMS: Diabetic gastroparesis is a common complication seen in 20-50% of patients due to autonomic neuropathy involving vagal supply. Cisapride, a specific gastrointestinal cholinomimetic agent may thus be effective. **METHODS:** Fifty-one diabetic patients (age 12-65 years) of disease duration > 5 years were assessed for symptomatic gastroparesis, other diabetic complications and glycemic control. Gastric emptying time (GET) was estimated using a solid meal method (^{99m}Tc labeled rice based idli) and patients randomized to receive either cisapride or placebo for a period of 2 weeks. Cisapride was administered in a dose of 10 mg TID. GET and symptom scores were reassessed on the therapy after 2 weeks. **RESULTS:** Twenty nine of 51 (56.8%) patients had gastroparesis. Mean GET in the gastroparesis group was 141 +/- 66 minutes compared to 24.53 +/- 10 minutes in the non gastroparesis group (p < 0.01). GET decreased by 72% amongst the patients who received cisapride compared to 23% in the placebo group (p < 0.001). Symptom scores also improved in the cisapride group; no adverse effects were noted. **CONCLUSIONS:** Cisapride improves the symptom score and the solid gastric emptying time in patients suffering from diabetic

gastroparesis.

21. ElHennawy, A.A., Sparks, J.W., Armentrout, D., Huseby, V., and Berseth, C.L. Erythromycin fails to improve feeding outcome in feeding-intolerant preterm infants. *J Pediatr Gastroenterol Nutr* 37: 281-286, 2003.

OBJECTIVE: Approximately half of extremely low birth weight infants have feeding intolerance, which delays their achievement of full enteral feedings. Erythromycin, a motilin receptor agonist, triggers migrating motor complexes and accelerates gastric emptying in adults with feeding intolerance. Few studies have assessed the efficacy of this drug in preterm infants with established feeding intolerance. This study was designed to assess the efficacy of erythromycin in feeding-intolerant infants, as measured by gastric emptying, maturation of gastrointestinal motor patterns, and time to achieve full enteral feedings. **METHODS:** Subjects were 27 preterm infants who were admitted to the neonatal intensive care unit and who did not achieve full enteral feeding volumes (150 mL/kg/day) within 8 days of the initiation of feedings. In a controlled, randomized, double-blinded clinical trial, infants received intragastric erythromycin or placebo for 8 days without crossover. At study entry, the authors recorded motor activity in the antrum and the duodenum during fasting, in response to intragastric erythromycin (1.5 mg/kg) or placebo, and in response to feeding. Gastric emptying at 20 minutes and transit time from duodenum to anus were determined. Each infant then received erythromycin or placebo for 8 days, and feeding characteristics were prospectively tracked. **RESULTS:** Gastric emptying and characteristics of antroduodenal motor contractions were similar in the two groups, as were the transit times from duodenum to anus. Feeding outcomes were comparable in the two groups. **CONCLUSION:** Intragastric erythromycin does not improve feeding tolerance in preterm infants with established feeding intolerance because it fails to improve gastrointestinal function in the short or long term.

22. Enriquez, A., Bolisetty, S., Patole, S., Garvey, P.A., and Campbell, P.J. Randomised controlled trial of cisapride in feed intolerance in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 79: F110-113, 1998.

AIM: To assess the efficacy of cisapride in reducing the time required to establish enteral feeds in preterm infants. **METHODS:** A randomised, double blind, placebo controlled trial was conducted of 34 infants of < or = 32 weeks of gestation, assigned to receive either cisapride 0.2 mg/kg/dose four times daily (n = 18) or placebo (n = 16). **RESULTS:** The time taken by the babies to tolerate full enteral feeds was not significantly different between the groups (median 9.5 days vs 10 days). There was a significantly lower incidence of large gastric residuals and regurgitation in the treated group compared with the placebo group. The number of episodes of large gastric residuals per infant was also significantly less. No adverse effects were noted. **CONCLUSION:** The routine use of cisapride in preterm infants cannot be recommended to decrease the time to

establish enteral feeds. Its use may be justified for clinically significant gastric stasis or regurgitation.

23. Franzese, A., Borrelli, O., Corrado, G., Rea, P., Di Nardo, G., Grandinetti, A.L., Dito, L., and Cucchiara, S. Domperidone is more effective than cisapride in children with diabetic gastroparesis. *Aliment Pharmacol Ther* 16: 951-957, 2002.

BACKGROUND: Disorders of gastrointestinal motility are commonly detected in patients with insulin-dependent diabetes mellitus and are associated with significant morbidity. They contribute to poor metabolic control of diabetes. **AIM:** To assess the effect of an 8-week course of domperidone or cisapride on gastric electrical activity, gastric emptying time and dyspeptic symptoms in children with insulin-dependent diabetes mellitus and gastroparesis. **METHODS:** Dyspeptic symptoms were assessed by a score system, gastric emptying time was measured by ultrasonography and gastric electrical activity was obtained by electrogastrography. Fourteen children received domperidone and 14 received cisapride. The median (range) ages were 11.6 years (5-15 years) and 12 years (6-16.9 years), respectively. Symptom assessment, ultrasonography and electrogastrography were repeated at the end of the trial. Fasting and fed (180 min after feeding) glycaemia and haemoglobin A, C (HbA1c) levels were also measured. **RESULTS:** At the end of the trial both groups showed a significant decrease in symptomatic score; however, the score was markedly lower in the domperidone group than in the cisapride group ($P < 0.01$). Domperidone was significantly more effective than cisapride in reducing the gastric emptying time ($P < 0.05$), normalizing gastric electrical activity ($P < 0.05$) and decreasing the prevalence of episodes of gastric dysrhythmia ($P < 0.01$). Domperidone was also more effective than cisapride in improving diabetic metabolic control. No potentially drug-related adverse effects occurred. **CONCLUSIONS:** In children with insulin-dependent diabetes mellitus complicated by dyspeptic symptoms and gastroparesis, domperidone is superior to cisapride in reversing gastric emptying delay and gastric electrical abnormalities, as well as in improving dyspeptic symptoms and diabetic metabolic control.

24. Fraser, R.J., and Bryant, L. Current and future therapeutic prokinetic therapy to improve enteral feed intolerance in the ICU patient. *Nutr Clin Pract* 25: 26-31, 2010.

Malnutrition is associated with poor outcomes in critically ill patients, and providing enteral feeding to those who cannot eat is considered best practice. Enteral feeding is often unsuccessful when there is delayed gastric emptying. Recent research has given additional insight into the mechanisms underlying delayed gastric emptying. Pharmacological strategies to improve the success of feeding include prokinetic drugs such as metoclopramide and erythromycin alone or in combination. When drug treatment fails, either parenteral nutrition or direct small intestinal feeding is indicated. Simpler methods to access the duodenum and distal small bowel for feed delivery are under investigation. This review

summarizes current understanding of the mechanisms underlying enteral feeding intolerance in critical illness, together with the evidence for current treatment practices. Areas requiring further research are also described.

25. Gharpure, V., Meert, K.L., and Sarnaik, A.P. Efficacy of erythromycin for postpyloric placement of feeding tubes in critically ill children: a randomized, double-blind, placebo controlled study. *JPEN J Parenter Enteral Nutr* 25: 160-165, 2001.

BACKGROUND: Erythromycin enhances gastric emptying and has been suggested to facilitate nasoenteric feeding tube placement in adults. Our primary objective was to evaluate the effect of erythromycin on the transpyloric passage of feeding tubes in critically ill children, and second, to evaluate the effect of erythromycin on the distal migration of duodenal feeding tubes. **METHODS:** Seventy-four children were randomly assigned to receive erythromycin lactobionate (10 mg/kg) IV or equal volume of saline placebo 60 minutes before passage of a flexible weighted tip feeding tube. Abdominal radiographs were obtained 4 hours later to assess tube placement. If the tube was proximal to the third part of the duodenum, two additional doses of erythromycin/placebo were administered 6 hours apart. Those receiving additional doses had repeat radiographs 14 to 18 hours after tube placement. **RESULTS:** The number of postpyloric feeding tubes was similar in the erythromycin and placebo treated groups 4 hours after tube insertion (23/37 vs 27/37, $p = .5$). Of those with prepyloric tubes at 4 hours, none in the erythromycin group and 3 in the placebo group had the tube migrate to the postpyloric position by 14 to 18 hours ($p < .05$). Of those with postpyloric tubes proximal to the third part of the duodenum at 4 hours, additional doses of erythromycin did not cause more tubes to advance further into the intestine than did placebo ($p = .6$). **CONCLUSIONS:** Erythromycin does not facilitate transpyloric passage of feeding tubes in critically ill children. The distal migration of duodenal tubes further into the small bowel is also not enhanced by erythromycin.

26. Halabi, I.M. Cisapride in management of chronic pediatric constipation. *J Pediatr Gastroenterol Nutr* 28: 199-202, 1999.

BACKGROUND: This study was conducted to explore the use of cisapride in the treatment of chronic idiopathic constipation in children. **METHODS:** Seventy-nine children were screened. Seventy-three of them met the selection criteria that included clinical, laboratory, radiologic, and histopathologic investigations. These patients entered a week-long phase I of disimpaction using lactulose. Four of them were noncompliant and thus were excluded from the next phase. In phase II sixty-nine patients were assigned to two treatment groups: 0.3 mg/kg cisapride four times a day versus matching placebo for 8 weeks in a double-blind study. The two groups that completed phase II were similar in age and duration of symptoms, confirmed by statistical analysis. Stool frequency was assessed weekly, beginning at the end of the disimpaction phase and continuing for 9

weeks. Total gastrointestinal transit time was measured twice, on completion of phase I and 9 weeks later. Transit time is the time required for a carmine marker taken orally after overnight fast to appear in the stool. RESULTS: There was a significant difference between stool frequency per week before and after cisapride treatment, stool frequency per week at the end of phase II with cisapride versus placebo, and total gastrointestinal transit time before and after treatment with cisapride ($p < 0.05$ for all values). No such difference was demonstrated when comparing stool frequency per week or total gastrointestinal transit time before and after placebo ($p > 0.05$ for both). CONCLUSIONS: Cisapride may have a role in the management of chronic idiopathic constipation in children.

27. Hauben, M., and Amsden, G.W. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Saf* 25: 929-942, 2002.

The safety profile of erythromycin is notable for the frequent occurrence of intolerable gastrointestinal effects. One of the more serious of these is infantile hypertrophic pyloric stenosis (IHPS). A recent cluster of IHPS cases prompted an epidemiological investigation which identified oral erythromycin chemoprophylaxis of pertussis as the major risk factor. Evidence suggests an association between early postnatal erythromycin exposure and IHPS. There is no substantive evidence of a risk associated with prenatal exposure, with the single published case-control study to date producing negative findings. The epidemiological investigations of the association with early postnatal exposure have reported significantly elevated odds ratios but have a variety of methodological limitations that prevent definitive conclusions being made. Nevertheless, the concordance of findings across studies increases the strength of evidence favouring an association. The prominent gastrokinetic properties of erythromycin have been postulated as the mechanism behind this phenomenon. A comprehensive assessment of this potential adverse effect should consider its biological plausibility in light of known gastrointestinal physiology, its modulation by erythromycin, and the known pathophysiology of IHPS. Gastrointestinal motor activity in the fasted mammal consists of three phases, phase III being large amplitude contractions called migrating motor complexes (MMC) that can be initiated by motilin and erythromycin. The gastrokinetic effects of erythromycin are variable and complex and include effects on the timing, duration, amplitude and distribution of MMCs. It has been speculated that the motilinomimetic effects of erythromycin on antral smooth muscle function, such as the MMC, may mediate the effect via work hypertrophy. Although intuitively plausible and consistent with hypertrophic obstructive changes similar to IHPS observed in hyperplastic rat ileum after artificially induced mechanical obstruction, there is no direct evidence of this phenomenon. Further complicating the association is the limitations of our knowledge about the pathophysiology of IHPS, including numerous genetic abnormalities, increased parietal cell mass, and gastric hyperacidity. The implications of the reported findings with erythromycin on the

benefit-risk profiles of newer macrolides and azalides must be considered. The available data on the comparative gastrokinetic properties of macrolides are significant for the potent gastrokinetic properties and its acid degradation products, the marked variation in gastrokinetic properties associated with macrolide ring size, and the requirement for specific glycosidic linkages at the C-3 and C-5 carbons of the macrolide ring. The variation in gastrokinetic properties associated with variations in molecular structure suggests that if the association between erythromycin and IHPS is causal it may not be a class effect.

28. Hill, S.L., Evangelista, J.K., Pizzi, A.M., Mobassaleh, M., Fulton, D.R., and Berul, C.I. Proarrhythmia associated with cisapride in children. *Pediatrics* 101: 1053-1056, 1998.

BACKGROUND: Cisapride is a prokinetic agent that facilitates gastrointestinal motility and is widely used for the treatment of gastroesophageal reflux disease (GERD) in adults and children. However, reports of ventricular proarrhythmia have been noted in patients taking cisapride, particularly in conjunction with other drugs that may inhibit hepatic metabolism of cisapride via the cytochrome P450 3A4 system. **OBJECTIVE:** We designed a prospective, blinded study to evaluate the effect of cisapride on ventricular repolarization in children with GERD. **METHODS:** We analyzed the electrocardiograms (ECGs) from 35 children (age 0.4 to 18 years, mean 5.2 years) including measurement of the resting QT interval (QTc), JT interval (JTc), as well as QT and JT interlead dispersion markers. Data from these patients were compared with ECGs from a control group of 1000 normal children. **RESULTS:** Eleven (31%) of 35 patients receiving cisapride had a prolonged QTc ($>$ or $=$ 450 ms). The JTc was prolonged $>$ or $=$ 360 ms in 16 of 35 patients (46%). The mean QTc in the cisapride group was 428 ± 35 ms and mean JTc was 336 ± 35 ms. An increased QT or JT dispersion ($>$ 70 ms) was seen in only 3 of 35 children. Of the 11 children with QTc prolongation, 2 had documented torsades de pointes ventricular tachycardia. Both patients were taking cisapride concomitantly with a macrolide antibiotic. All other patients were treated with either cisapride alone or in conjunction with other GERD agents, such as ranitidine or omeprazole. **CONCLUSIONS:** Cisapride may cause prolongation of ventricular repolarization in children. There does not appear to be increased heterogeneity of repolarization or delayed depolarization in this small sample. The proarrhythmia may be exacerbated by medications that inhibit cytochrome P450 3A4 hepatic metabolism, overdose, or mechanisms that result in decreased serum clearance. ECG intervals should be monitored in children maintained on cisapride, particularly when used in combination with other known QT-prolonging medications.

29. Horn, J.R. Use of prokinetic agents in special populations. *Am J Health Syst Pharm* 53: S27-29, 1996.

The use of prokinetic agents by pediatric patients, geriatric patients, and patients

taking other drugs that may affect or be affected by the prokinetic agent is reviewed. The use of such agents to treat motility disorders has expanded over the past few years. These agents may be administered to patients who have special physiologic considerations, have other diseases, or require concomitant drug therapy. The appropriate use of prokinetic agents in these groups requires an understanding of the unique dosage considerations that may be necessary to ensure safe, effective therapy.

30. Inoue, M., Sekiguchi, T., Harasawa, S., Miwa, T., and Miyoshi, A. Dyspepsia and dyspepsia subgroups in Japan: symptom profiles and experience with cisapride. *Scand J Gastroenterol Suppl* 195: 36-38; discussion 38-39, 1993.

In 240 patients with symptoms of dyspepsia, recruited consecutively and investigated in 12 hospitals in Japan, 24.2% were diagnosed having organic dyspepsia; 75.8% had functional dyspepsia, of whom 63.2% were diagnosed by the investigator having dysmotility-like, 13.7% ulcer-like, 11.5% reflux-like, and 11.5% non-specific dyspepsia. There was, however, considerable overlap of symptom profiles. Cisapride therapy initiated in functional dyspeptic patients resulted in moderate or marked improvement in 79.1% of the patients with the highest response rates for dysmotility-like (85.2%), reflux-like (81.0%), and non-specific dyspepsia (76.1%) (versus 52.0% for ulcer-like dyspepsia).

31. Kawai, M., Kawahara, H., Hirayama, S., Yoshimura, N., and Ida, S. Effect of baclofen on emesis and 24-hour esophageal pH in neurologically impaired children with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 38: 317-323, 2004.

OBJECTIVES: Gastroesophageal reflux disease (GERD) is difficult to control with medical therapy in neurologically impaired children. The gamma-aminobutyric acid type B receptor agonist baclofen was recently reported to reduce reflux in adult patients with GERD by reducing the incidence of transient lower esophageal sphincter relaxations. The current study was undertaken to investigate the effects of baclofen on GERD in neurologically impaired children. **METHODS:** Eight neurologically impaired children with GERD between 2 months and 16 years were studied. Baclofen (0.7 mg/kg/day) was administered orally or via nasogastric tube in three divided doses 30 minutes before meals for 7 days. The frequency of emesis on and off baclofen were recorded as a measure of clinical impact. Twenty-four-hour esophageal pH monitoring was conducted before and on the seventh day of the administration of baclofen. **RESULTS:** The frequency of emesis was significantly decreased ($P = 0.03$). The total number of acid refluxes was significantly decreased both during the entire 24-hour period ($P = 0.01$) and during the postprandial period ($P = 0.049$). The number of acid refluxes longer than 5 minutes was significantly decreased during the 24-hour period ($P = 0.02$). The percentage total time of esophageal pH <4.0 and esophageal acid clearance time were not significantly different during the 24-hour period or during the postprandial period. No adverse effects were observed,

except for a slight reduction in muscle tone in one subject. CONCLUSIONS: In this 1-week trial, repetitive administration of baclofen reduced the frequency of emesis and the total number of acid refluxes in neurologically impaired children with GERD.

32. Kohl, M., Wuerdemann, I., Clemen, J., Iven, H., Katalinic, A., and Moeller, J.C. Cisapride may improve feeding tolerance of preterm infants: a randomized placebo-controlled trial. *Biol Neonate* 88: 270-275, 2005.

To evaluate the efficacy of cisapride in improving tolerance of enteral feeding, 59 premature infants were randomized into a blinded placebo-controlled study. Treatment was initiated with the introduction of enteral feeding and continued until 150 ml/kg/day of milk were tolerated. Only in extremely low birth weight (ELBW) infants, was the time to tolerate full enteral feeding shorter in the treatment group, whereas ECG recordings showed a significantly prolonged QTc interval during treatment. Two children developed cardiac rhythm disturbances. In conclusion premature infants may not benefit from routine use of the drug to improve enteral feeding, and seem to be more vulnerable to its side effects.

33. Kubota, M., Nakamura, T., Motokura, T., Mori, S., and Nishida, A. Erythromycin improves gastrointestinal motility in extremely low birthweight infants. *Acta Paediatr Jpn* 36: 198-201, 1994.

Erythromycin (EM) was administered to five extremely low birthweight infants (ELBWI) with delayed enteral feeding to evaluate the clinical effect on severely impaired gastrointestinal motility. Five patients studied responded well to EM administration without any adverse effects during the course. Four patients were given 15-30 mg/kg per day EM intravenously as a loading and thereafter 3-5 mg/kg per day as a maintenance dose. One patient responded well without loading. The infants could be fed enterally 4, 5, 6, 4 and 2 days after the initiation of EM administration, respectively. Erythromycin administration is a safe and useful way to facilitate gastrointestinal motility in ELBWI who require prolonged ventilator support with an increased risk for nutrient deprivation.

34. Kulik, W., van Weissenbruch, M.M., Menelik, N., Cranendonk, A., Kneepkens, C.M., and Lafeber, H.N. Improved use of the [¹³C]octanoic acid breath test as intra-individual parameter to study the effect of a prokinetic drug on gastric emptying in preterm infants with oral feeding intolerance. *J Chromatogr B Biomed Sci Appl* 750: 147-153, 2001.

The [¹³C]octanoic acid breath test was used for the measurement of differences in gastric emptying in preterm infants for the evaluation of pharmacological therapy. In order to perform a good intra-individual comparison of the gastric emptying in preterm infants under non-standardisable test conditions, we adjusted t_{1/2} for variations in non-recovered label (=label retention) and introduced an "effective half ¹³CO₂ breath excretion time" t_{1/2}eff = t_{1/2}/m

expressed as min per percentage of the cumulative dose recovered. In a pilot study, we investigated the action of the gastrointestinal prokinetic drug cisapride on gastric emptying in seven premature infants, of whom four suffered from gastric stasis and three had constipation. The postnatal age and weight at the start of treatment ranged from 15 to 64 days and from 815 to 1635 g, respectively. All infants received the standard formula for premature infants (Nenatal, Nutricia). Cisapride was administered orally 0.2 mg/kg, four times daily. The changes in gastrointestinal motility were studied using the total bowel transit time of carmine red. After 7 days of treatment in all children, the gastric emptying coefficient and the half $^{13}\text{CO}_2$ breath excretion time adjusted for label retention were improved (n=7, the gastric emptying coefficient range before treatment was 1.69-3.34 (mean 2.59 +/- 0.80) and after treatment it was 2.79-3.76 (mean 3.28 +/- 0.30); the half $^{13}\text{CO}_2$ breath excretion time adjusted for label retention range before treatment was 3.0-14.7 min/% dose (mean 7.0 +/- 5.0) and after treatment 2.6-4.0 min/% dose (mean 3.1 +/- 0.6). The total bowel transit time was only slightly improved in two patients (n=7, mean total bowel transit time before: 23.7 h compared to mean total bowel transit time after 7 days of treatment: 35.5 h). Side effects during cisapride treatment were not seen. We conclude that in premature infants cisapride is effective in shortening gastric emptying time and reducing gastric stasis; the therapeutic role in constipation has to be further investigated.

35. Lander, A., Redkar, R., Nicholls, G., Lawson, A., Choudhury, S.R., Corkery, J.J., Gornall, P., Buick, R.G., and Booth, I.W. Cisapride reduces neonatal postoperative ileus: randomised placebo controlled trial. *Arch Dis Child Fetal Neonatal Ed* 77: F119-122, 1997.

AIM: To assess the efficacy of cisapride in reducing ileus persisting to the tenth postoperative day after neonatal abdominal surgery. METHODS: A prospective, randomised, double blind trial comparing rectal cisapride (1.4-2.3 mg/kg/day) with placebo over seven days was undertaken in 33 neonates. RESULTS: Seven of 12 (58%) patients receiving placebo and eight of 11 (73%) receiving cisapride achieved a first sustained feed during treatment. Of those receiving cisapride, the first sustained feed occurred at 2.3 days (SEM 0.6) compared with 4.7 days (SEM 0.8) with placebo. By the seventh day the mean daily net enteral balance was 69 (SEM 18) ml/kg in the cisapride subgroup and 17 (SEM 8) ml/kg for those receiving placebo. Stool was passed on 6.3 (SEM 0.4) treatment days in the cisapride subgroup compared with 4.1 (SEM 1.0) treatment days in the placebo subgroup. CONCLUSION: Cisapride is effective in neonates with a prolonged ileus after abdominal surgery.

36. Levy, J., Hayes, C., Kern, J., Harris, J., Flores, A., Hyams, J., Murray, R., and Tolia, V. Does cisapride influence cardiac rhythm? Results of a United States multicenter, double-blind, placebo-controlled pediatric study. *J Pediatr Gastroenterol Nutr* 32: 458-463, 2001.

BACKGROUND: Major concerns about serious cardiac side effects underlie the recent decision by the FDA and Janssen Pharmaceutica (Titusville, NJ) to make cisapride available only through a limited access program. Concerns have grown despite the fact that most instances of prolonged QTc and other ventricular arrhythmias occurred while the drug was used concomitantly with contraindicated drugs. This study sought to analyze electrocardiograms (ECGs) from a multicenter pediatric study and to identify abnormalities in QTc interval associated with cisapride use. **METHODS:** Children between 6 months and 4 years of age were enrolled if they manifested symptoms of gastroesophageal reflux not responding to medical therapy for at least 6 weeks. In 49 subjects, ECGs obtained before and after randomization to receive 0.2 mg/kg dose three times daily or placebo were reviewed independently and blindly by two pediatric cardiologists. Placebo and active drug groups were compared for QTc and for change in QTc from baseline values after 3 to 8 weeks of treatment. **RESULTS:** Mean QTc among patients taking the drug was 408±18 ms. None was higher than 450 ms. Change between baseline and subsequent QTc at 3 to 8 weeks of treatment was 2±20 ms. **CONCLUSIONS:** In our study group of children without underlying cardiac disease or electrolyte imbalance, cisapride was found to have no significant effect on cardiac electrical function compared with placebo. These results are consistent with the drug's record of exceedingly infrequent cardiac events. Because the availability of this prokinetic is threatened, its safety and the safety and efficacy of alternative treatment options (including surgery) should be studied further.

37. Liehr, H., and Schmidt, R. A German drug-monitoring study in general practice patients receiving cisapride for functional dyspepsia. *Scand J Gastroenterol Suppl* 195: 54-58; discussion 58-59, 1993.

An open prospective drug monitoring study was undertaken to assess the efficacy and tolerability of 5 mg cisapride three times daily in 37,925 general practice patients with functional dyspepsia. Short-term (mean, 4 weeks) cisapride treatment was associated with a significant reduction in overall dyspeptic symptom scores and improvements in scores of all eight individual dyspeptic symptoms (epigastric discomfort, fullness, nausea, bloating, heartburn, acid regurgitation, loss of appetite, and vomiting). Physician's and patient's subjective global evaluations of antidyspeptic efficacy were good or very good in 80% to 90% of cases. The tolerability of cisapride was judged to be satisfactory, good or very good in approximately 95% of patients, with adverse drug reactions being documented in 4.8% of patients. Of these, diarrhea/loose stools (2.5% of all patients) and headache (0.7%) were most frequent. Premature treatment withdrawal due to poor tolerability was necessary in only 0.35% of patients.

38. Mascarenhas, S., and Lal, M. Erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 150: e30-31; author reply e31, 2007.

39. McClure, R.J., Kristensen, J.H., and Graaug, A. Randomised controlled trial of cisapride in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 80: F174-177, 1999.

AIM: To determine the effect of cisapride on gastrointestinal motility in preterm infants. METHODS: Cisapride (0.2 mg/kg, 8 hourly) or placebo was given first for seven days in a double blind randomised crossover study of 10 preterm infants. Gastrointestinal motility was assessed on day 3 of each treatment. The half gastric emptying time (GET_{1/2}) was determined by using ultrasonography to measure the decrease in the gastric antral cross sectional area after a feed. The whole gastrointestinal transit time (WGTT) was assessed by timing the transit of carmine red through the gut. Treatments were compared using the Wilcoxon matched pairs signed ranks test. RESULTS: Median (range) birthweight was 1200 (620, 1450) g and postconceptional age 33 (29, 34) weeks at recruitment. GET_{1/2} was significantly longer during cisapride treatment than during placebo; the median of the differences (95% confidence interval) was 19.2 (11, 30 minutes, p=0.008). WGTT was also longer during cisapride treatment, but the difference was not significant; the median of the differences was 11(-18, 52 hours, p=0.1). CONCLUSIONS: Cisapride delays gastric emptying and may delay WGTT in preterm infants. Its use to promote gastrointestinal motility in this group cannot be recommended.

40. Melis, K., and Janssens, G. Long-term use of cisapride (Prepulsid) in premature neonates. *Acta Gastroenterol Belg* 53: 372-375, 1990.

In order to study the effect of cisapride on gastric stasis and to evaluate the possible risk of cholestasis, 20 premature neonates born in the hospital during one year were orally treated with cisapride 0.15 mg/kg q.i.d., over a mean period of 38 days. The gestational age ranged from 26 to 34 weeks and the mean age at the start of the cisapride treatment was 18 days. All patients were ventilated, 13 had a respiratory distress syndrome (hyaline membrane disease), and 9 had gastro-oesophageal reflux (GOR). All patients were given a semielementary formula by means of a continuous nasogastric infusion. The gastric residue was studied during three days: 24 hour baseline and 48 hours under cisapride treatment. The mean residue decreased (p less than 0.0001) from 50.6% during the last 6 baseline hours to 12.1% during the last 6-hours of the cisapride period. The mean feeding volume increased from 24.2 ml to 34.2 ml (p less than 0.001). A group of four patients had reversible cholestasis against the background of an outbreak of Candida, three before and one during cisapride treatment. Therefore, it could not be demonstrated that cisapride plays a role in the development of cholestasis. Because of the risks of GOR and the drawbacks of delayed enteral feeding, it is concluded that the use of cisapride is justified in premature neonates with gastric stasis.

41. Murray, R.D., Li, B.U., McClung, H.J., Heitlinger, L., and Rehm, D. Cisapride for

intractable constipation in children: observations from an open trial. *J Pediatr Gastroenterol Nutr* 11: 503-508, 1990.

Twelve patients with chronic constipation refractory to the vigorous use of emollients, enemas, and/or laxatives were chosen for study of the investigational prokinetic agent, Cisapride. The patients included 8 boys and 4 girls with diagnoses of functional constipation. Ages ranged from 2 to 13 years; duration of symptoms before Cisapride use ranged from 1.5 to 9.75 years; duration of previous treatment ranged from 0.75 to 6 years. The mean number of doses of anticonstipation agents employed per week was 14. Of the 12 patients, 10 had persistent encopresis, while 11 required hospitalization for disimpaction an average of 1.6 times in the year prior to Cisapride use. Three had chronic urinary tract complaints. Anal manometry suggested a sensory deficit in 8 of 10 patients tested. Ganglion cells were identified by rectal biopsy in all 12 patients. Cisapride treatment (0.14-0.3 mg/kg/dose) spanned 26-72 weeks (61 +/- 12). Stool frequency per week was not significantly changed, but five of seven patients who had reported hard stools had softer stools on the drug (p less than 0.05). Encopresis ceased in 8 of 10 cases, while the number of episodes decreased substantially in the other 2 cases (p less than 0.05). All alternate forms of anticonstipation therapy were withdrawn in 8 of 12 cases (p less than 0.001). Urinary problems improved in two of the three patients reporting symptoms. One patient showed no improvement in any parameter while on the agent, despite 26 weeks of administration. Side effects were infrequent, generally occurred early, and were limited to cramping, nausea, mild vomiting, anorexia, and headaches. One patient ceased use of the drug for persistent headaches.(ABSTRACT TRUNCATED AT 250 WORDS)

42. Ng, E., and Shah, V. Erythromycin for feeding intolerance in preterm infants. *Cochrane Database Syst Rev*: CD001815, 2000.

BACKGROUND: Functional immaturity of gastrointestinal motility predisposes preterm infants to feeding intolerance. Motilin, a gastrointestinal peptide, stimulates propagative contractile activity during phase III of the migratory motor complex in the interdigestive state. Erythromycin (EM) is a motilin agonist with prokinetic effect at low doses (1-3mg/kg). **OBJECTIVES:** To evaluate the effectiveness of EM in promoting gastrointestinal motility in preterm infants with feeding intolerance and assess clinically significant adverse effects associated with its use. **SEARCH STRATEGY:** Systematic literature search in accordance with the Cochrane Neonatal Collaborative Review Group search strategy. Randomized and quasi-randomized controlled trials of EM use, at any dose, in preterm infants to promote gastrointestinal motility were identified by searching MEDLINE, EMBASE, CINAHL, the Cochrane Library, reference lists of published studies, personal files, and abstracts published in Pediatric Research. **SELECTION CRITERIA:** Randomized controlled trials of oral or intravenous EM use at dose range of 3 to 12 mg/kg/day in preterm infants less than or equal to 36 weeks gestational age with feeding tolerance were included in this review.

DATA COLLECTION AND ANALYSIS: Data regarding the primary clinical outcome of days to achieve full enteral feeding were compared among studies. Data on secondary outcomes including adverse effects associated with the use of EM (diarrhea, nosocomial infections, cardiac arrhythmias, or theophylline toxicity), duration of parenteral nutrition, weight gain, incidence of necrotizing enterocolitis (NEC), hypertrophic pyloric stenosis, and length of hospital stay were assessed. **MAIN RESULTS:** Two randomized controlled studies of EM use in preterm infants for improving gastrointestinal motility were identified. Since both studies involved preterm infants treated with EM at dose >12mg/kg/day at commencement of feeding, they did not meet inclusion criteria defined a priori for this review. There was no statistically significant difference in the incidence of NEC (RR 0.59, 95%CI 0.11, 3.01; RD -0.021, 95%CI -0.087, 0.045). No statistically significant difference was noted in days to achieve full enteral feeds, length of hospital stay, and adverse events between groups. **REVIEWER'S CONCLUSIONS:** EM at antimicrobial doses may not be effective in preterm infants with feeding intolerance. Further studies are needed to determine whether EM in lower doses is effective as a prokinetic agent in such infants.

43. Ng, E., and Shah, V. Erythromycin for feeding intolerance in preterm infants. *Cochrane Database Syst Rev*: CD001815, 2001.

BACKGROUND: Functional immaturity of gastrointestinal motility predisposes preterm infants to feeding intolerance. Motilin, a gastrointestinal peptide, stimulates propagative contractile activity during phase III of the migratory motor complex in the interdigestive state. Erythromycin (EM) is a motilin agonist with prokinetic effect at low doses (1-3mg/kg). **OBJECTIVES:** To evaluate the effectiveness of EM in promoting gastrointestinal motility in preterm infants with feeding intolerance and assess clinically significant adverse effects associated with its use. **SEARCH STRATEGY:** Systematic literature search in accordance with the Cochrane Neonatal Collaborative Review Group search strategy. Randomized and quasi-randomized controlled trials of EM use, at any dose, in preterm infants to promote gastrointestinal motility were identified by searching MEDLINE, EMBASE, CINAHL, the Cochrane Library, reference lists of published studies, personal files, and abstracts published in Pediatric Research. **SELECTION CRITERIA:** Randomized controlled trials of oral or intravenous EM use at dose range of 3 to 12 mg/kg/day in preterm infants less than or equal to 36 weeks gestational age with feeding tolerance were included in this review. **DATA COLLECTION AND ANALYSIS:** Data regarding the primary clinical outcome of days to achieve full enteral feeding were compared among studies. Data on secondary outcomes including adverse effects associated with the use of EM (diarrhea, nosocomial infections, cardiac arrhythmias, or theophylline toxicity), duration of parenteral nutrition, weight gain, incidence of necrotizing enterocolitis (NEC), hypertrophic pyloric stenosis, and length of hospital stay were assessed. **MAIN RESULTS:** Two randomized controlled studies of EM use in preterm infants for improving gastrointestinal motility were identified. Since both studies involved preterm infants treated with EM at dose >12mg/kg/day at

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44. Ng, E., and Shah, V.S. Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. *Cochrane Database Syst Rev*. CD001815, 2008.

BACKGROUND: Functional immaturity of gastrointestinal motility predisposes preterm infants to feeding intolerance. Erythromycin is a motilin agonist that exerts its prokinetic effect by stimulating propagative contractile activity in the interdigestive phase. **OBJECTIVES:** To evaluate the efficacy of erythromycin in the prevention and treatment of feeding intolerance in preterm infants. **SEARCH STRATEGY:** Systematic literature search was performed according to the Cochrane Neonatal Collaborative Review Group search strategy. Randomized controlled trials of erythromycin in preterm infants to promote gastrointestinal motility were identified from the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2007), MEDLINE (1966 - December 2007), EMBASE (1980 - December 2007), CINAHL (1982 - December 2007), cross-references, abstracts, and journal hand searching. **SELECTION CRITERIA:** The initial selection criteria limited the review to studies using erythromycin at 3 - 12 mg/kg/day in preterm infants less than 36 weeks gestational age with feeding tolerance. However, a significant number of studies using erythromycin at a higher dose (> 12 mg/kg/day) or as prophylaxis for those at risk of feeding intolerance were identified. A post hoc decision was made to include these studies in the review. **DATA COLLECTION AND ANALYSIS:** Studies were categorized into prevention and treatment studies, and data from each category were analyzed separately. Within each category, subgroup analyses were performed based on low (3 to 12mg/kg/day) and high doses (> 12mg/kg/day) of erythromycin. Primary outcome was days to full enteral feeding. Secondary outcomes included adverse effects associated with erythromycin, duration of total parenteral nutrition (TPN), weight gain, necrotizing enterocolitis (NEC), and length of hospital stay. **MAIN RESULTS:** Ten randomized controlled studies (three prevention and seven treatment studies) were included. Studies varied greatly in the definition of feeding intolerance and how outcomes were measured, analyzed and reported, so meta-analysis of most outcomes was impossible. It was observed, however, that the studies using erythromycin at higher treatment doses (40 to 50 mg/kg/day) or in infants > 32 weeks' GA reported more positive effects in improving feeding intolerance. Meta-analysis of high dose prevention studies showed no significant difference in NEC (typical RR 0.59, 95% CI 0.11, 3.01; typical RD -0.021, 95% CI -0.087, 0.045). Meta-analysis of high dose treatment studies showed no significant difference in septicemia

(typical RR 0.83, 95% CI 0.47, 1.45; typical RD -0.04, 95% CI -0.17, 0.08).
AUTHORS' CONCLUSIONS: There is insufficient evidence to recommend the use of erythromycin in low or high doses for preterm infants with or at risk of feeding intolerance. Future research is needed to determine if there is a more precise dose range where erythromycin might be effective as a prokinetic agent in preterm infants > 32 weeks' GA.

45. Ng, P.C. Use of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Neonatology* 95: 97-104, 2009.

Milk intolerance due to functional gastrointestinal (GI) dysmotility is a common problem in preterm infants. In the past decade, erythromycin has been used for its motilinomimetic effect to facilitate enteral feeding in preterm infants. Although earlier studies suggested that erythromycin is an effective prokinetic agent, recent randomized control trials (RCTs) reveal conflicting findings. This review assesses the evidence from all RCTs performed to date on erythromycin for preterm infants. The results suggest that oral erythromycin administered in intermediate or high doses as a rescue treatment is associated with a shorter time to attain full enteral feeding and decrease in the duration of requirement for parenteral nutrition. More importantly, the outcome study further indicates that oral erythromycin can reduce the incidence of parenteral nutrition-associated cholestasis by almost 50% and decreases the incidence of recurrent septicemia. None of the RCTs reported any sinister adverse effects, in particular, hypertrophic infantile pyloric stenosis or fatal cardiac arrhythmia. Nonetheless, as long-term outcomes have not been fully evaluated, neonatologists should use this treatment cautiously and selectively in preterm infants with moderately severe GI dysmotility.

46. Ng, P.C., Fok, T.F., Lee, C.H., Wong, W., and Cheung, K.L. Erythromycin treatment for gastrointestinal dysmotility in preterm infants. *J Paediatr Child Health* 33: 148-150, 1997.

OBJECTIVE: To report our clinical experience on the use of oral erythromycin for the treatment of severe gastrointestinal dysmotility in preterm infants.

METHODOLOGY: A case series study of seven preterm infants (six were very low birthweight) with severe intestinal dysmotility in a tertiary neonatal centre.

RESULTS: All responded favourably without adverse effects and tolerated full enteral feeding within 1-2 weeks of the commencement of the drug.

CONCLUSIONS: As prolonged total parenteral nutrition carries significant risk of complications, this therapy could be considered in selected preterm infants who fail to establish enteral feeding after an extended period, and in whom an anatomically obstructive lesion of the gastrointestinal tract has been excluded. Meanwhile, we would caution against the widespread implementation of this therapeutic approach until formal evaluation by randomized controlled trials have established the exact role of erythromycin, or its analogues, in the treatment of intestinal dysmotility in preterm infants.

47. Ng, P.C., Lee, C.H., Wong, S.P., Lam, H.S., Liu, F.Y., So, K.W., Lee, C.Y., and Fok, T.F. High-dose oral erythromycin decreased the incidence of parenteral nutrition-associated cholestasis in preterm infants. *Gastroenterology* 132: 1726-1739, 2007.

BACKGROUND & AIMS: Feeding intolerance because of functional gastrointestinal dysmotility and parenteral nutrition-associated cholestasis (PNAC) are common problems in preterm, very-low-birth-weight (VLBW) infants. This double-blind, randomized, placebo-controlled study aimed to assess the effectiveness of "high-dose" oral erythromycin as a prokinetic agent in decreasing the incidence of PNAC. Two secondary end points, including the time to achieve full enteral feeding and the duration of parenteral nutrition, were also evaluated. **METHODS:** Infants consecutively admitted to the neonatal unit were randomized to receive erythromycin (12.5 mg/kg/dose every 6 hours for 14 days) or an equivalent volume of normal saline (placebo) if they attained less than half the total daily fluid intake (<75 mL/kg/day) as milk feeds on day 14 of life. **RESULTS:** Of 182 VLBW infants enrolled, 91 received erythromycin. The incidence of PNAC was significantly lower in erythromycin-treated infants (18/91) compared with placebo infants (37/91; $P = .003$). Treated infants achieved full enteral nutrition significantly earlier (mean, 10.1; SE, 1.7 days; $P < .001$), and the duration of parenteral nutrition was also significantly decreased by 10 days ($P < .001$). Importantly, fewer infants receiving erythromycin had 2 or more episodes of septicemia ($n = 4$) compared with placebo patients ($n = 13$, $P = .03$). No serious adverse effect was associated with erythromycin treatment. **CONCLUSIONS:** High-dose oral erythromycin can be considered as a rescue measure for VLBW infants who fail to establish adequate enteral nutrition and in whom anatomically obstructive pathologies of the gastrointestinal tract have been excluded.

48. Ng, P.C., So, K.W., Fung, K.S., Lee, C.H., Fok, T.F., Wong, E., Wong, W., Cheung, K.L., and Cheng, A.F. Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 84: F177-182, 2001.

AIM: To evaluate the effectiveness of oral erythromycin as a prokinetic agent for the treatment of moderately severe gastrointestinal dysmotility in preterm very low birthweight infants. **METHODS:** A prospective, double blind, randomised, placebo controlled study in a tertiary referral centre of a university teaching hospital was conducted on 56 preterm infants (< 1500 g) consecutively admitted to the neonatal unit. The infants were randomly allocated by minimisation to receive oral erythromycin (12.5 mg/kg, every six hours for 14 days) or an equivalent volume of placebo solution (normal saline) if they received less than half the total daily fluid intake or less than 75 ml/kg/day of milk feeds by the enteral route on day 14 of life. The times taken to establish half, three quarters, and full enteral feeding after the drug treatment were compared between the two

groups. Potential adverse effects of oral erythromycin and complications associated with parenteral nutrition were assessed as secondary outcomes. RESULTS: Twenty seven and 29 infants received oral erythromycin and placebo solution respectively. The times taken to establish half, three quarters, and full enteral feeding after the drug treatment were significantly shorter in the group receiving oral erythromycin than in those receiving the placebo ($p < 0.05$, $p < 0.05$ and $p < 0.0001$ respectively). There was also a trend suggesting that more infants with prolonged feed intolerance developed cholestatic jaundice in the placebo than in the oral erythromycin group (10 v 5 infants). None of the infants receiving oral erythromycin developed cardiac dysrhythmia, pyloric stenosis, or septicaemia caused by multiresistant organisms. CONCLUSIONS: Oral erythromycin is effective in facilitating enteral feeding in preterm very low birthweight infants with moderately severe gastrointestinal dysmotility. Treated infants can achieve full enteral feeding 10 days earlier, and this may result in a substantial saving on hyperalimentation. However, until the safety of erythromycin has been confirmed in preterm infants, this treatment modality should remain experimental. Prophylactic or routine use of this medication for treatment of mild cases of gastrointestinal dysmotility is probably not warranted at this stage.

49. Ng, S.C., Gomez, J.M., Rajadurai, V.S., Saw, S.M., and Quak, S.H. Establishing enteral feeding in preterm infants with feeding intolerance: a randomized controlled study of low-dose erythromycin. *J Pediatr Gastroenterol Nutr* 37: 554-558, 2003.

OBJECTIVE: A prospective, double-blind, randomized, controlled trial was conducted to evaluate the effect of low-dose erythromycin on the time taken to attain full enteral feedings in preterm infants with very low birth weight and feeding intolerance. METHODS: Two groups of preterm infants (birth weight \leq 1500 g) with feeding intolerance were randomized to either low-dose erythromycin (5 mg/kg every 8 hours) or 5% dextrose placebo, both of which were discontinued 1 week after full enteral feedings were tolerated. The primary outcome variable was the time taken to attain full enteral feedings of at least 130 mL/kg/d. RESULTS: The gestational age at birth was similar in the two groups (erythromycin, 27.1 \pm 1.9 weeks; placebo, 27.5 \pm 2.9 weeks). The mean birth weight of the erythromycin group was lower (806.3 \pm 215.6 g) than the placebo group (981.4 \pm 285.4 g; $P = 0.18$), and included more infants who were small for gestational age (4/13 = 31% versus 1/11 = 9%; $P = 0.224$). There was no difference between the two groups with regard to the volume of feedings they were receiving at the time of enrollment. Reduction in symptoms of gastroesophageal reflux was similar in the two groups. 3 of 13 in the erythromycin group and 4 of 11 in the placebo group improved during the study ($P = 0.565$). The mean time to attain full enteral feedings after enrollment was 24.9 \pm 2.9 days in the erythromycin group and 30.8 \pm 4.1 days in the placebo group, a difference that did not reach statistical significance ($P = 0.17$). CONCLUSIONS: Low-dose erythromycin did not reduce the time taken to attain

full enteral feedings in preterm infants with very low birth weight and feeding intolerance. Gastroesophageal reflux decreased as a consequence of maturation of the gastrointestinal tract and not because of erythromycin. These preliminary results justify verification in larger multicenter trials.

50. Ni, Y.H., Lin, C.C., Chang, S.H., and Yeung, C.Y. Use of cisapride with magnesium oxide in chronic pediatric constipation. *Acta Paediatr Taiwan* 42: 345-349, 2001.

Functional constipation in children is a common problem in daily practice, however there is currently no accepted optimal treatment of choice. This study investigated the effect of cisapride in the treatment of pediatric constipation when combined with magnesium oxide (MgO). This prospective study enrolled children with chronic constipation. They were randomly assigned to either MgO (125 mg three times a day for patients weighing less than 20 kg or 250 mg three times a day for those weighing more than 20 kg), or cisapride 0.2 mg/kg (max 5mg/dose) plus MgO for 4 weeks. Twenty-one doctors in 19 major medical centers or hospitals in Taiwan with well-established pediatric departments participated in this study from October 1999 to March 2000. 84 children (51 males, 33 females, 1-7 years of age) with fewer than 2 spontaneous bowel movements per week for at least one month completed the study. After 1 week of therapy, a good response, defined as 3 or more bowel movements per week, was achieved in 30 (68.2%) of children treated with cisapride and MgO compared with 23 (57.5%) children treated with MgO alone ($p=n.s.$). At the end of the 4-week treatment period, 90.9% of the children in cisapride group compared with 67.5% of the children in MgO group achieved a good response ($p=0.013$). There was no statistical difference between the two groups in terms of the side effects and stool characteristics. In conclusion, it appears that cisapride in combination with MgO may have a synergistic effect and improves the frequency of stool passage in pediatric functional constipation.

51. Nogami, K., Nishikubo, T., Minowa, H., Uchida, Y., Kamitsuji, H., and Takahashi, Y. Intravenous low-dose erythromycin administration for infants with feeding intolerance. *Pediatr Int* 43: 605-610, 2001.

BACKGROUND: This study was undertaken to determine the efficacy of low-dose intravenous erythromycin (EM) administration in infants with feeding intolerance. **METHODS:** The subjects were 26 infants who would not accept enteral feeding within 5 days after birth. Fourteen infants (gestational age: 30.6 \pm 5.4 weeks and birthweight: 1466 \pm 825 g) were given EM intravenously at a dose of 1 mg/kg, three times daily (EM group). Doses were increased to 2 mg/kg in five infants who showed a poor response. Twelve infants (gestational age: 30.5 \pm 5.0 weeks and birthweight: 1317 \pm 672 g) were observed without EM administration (non-EM group). Blood concentrations of EM at 2 h after administration were measured on 8 (\pm 2) days after the start of EM administration in the EM group. **RESULTS:** Digestive perturbations and intestinal

gasless and/or atonic shadows on X-ray findings markedly improved in the EM group soon after the treatment. Comparing the EM group and non-EM group, the postnatal ages at the start of successful enteral feeding were 9.1+/-3.2 days and 14.0+/-4.1 days, respectively (P<0.01). The postnatal ages at feeding of 100 mL/kg per day were 15.2+/-4.0 days and 23.4+/-6.2 days, respectively (P<0.01). The blood EM concentrations of 1 mg/kg and 2 mg/kg were 0.29+/-0.28 microg/mL and 0.57+/-0.20 microg/mL, respectively (P<0.05). No adverse effect on cardiac status or in blood examinations was observed in any infant in the EM group. CONCLUSION: These results suggest that intravenous low-dose EM administration is a useful and safe treatment of feeding intolerance in infants including extremely low-birthweight infants.

52. Nuntnarumit, P., Kiatchoosakun, P., Tantiprapa, W., and Boonkasidecha, S. Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 148: 600-605, 2006.

OBJECTIVE: To determine the efficacy and safety of oral erythromycin (EM) for feeding intolerance in preterm infants < 35 weeks gestation. STUDY DESIGN: In this randomized, double-blinded, placebo-controlled trial, preterm infants with feeding intolerance were randomly allocated to a treatment group given EM ethyl succinate 10 mg/kg every 6 hours for 2 days, followed by 4 mg/kg every 6 hours for another 5 days, or to a control group given placebo. The primary outcome was time to full feeding (150 mL/kg/day) after the start of treatment. RESULTS: Each group comprised 23 preterm infants, almost all of whom were < 32 weeks gestation. Baseline characteristics were similar between the 2 groups. Times to full feeding were significantly shorter and the number of withheld feeds were significantly less in the EM group than the control group; the respective medians (interquartile ranges) were 7 days (6 to 9 days) versus 13 days (9 to 15 days) (P < .001) and 1 episode (0 to 2 episodes) versus 9 episodes (2 to 13 episodes) (P < .001). No significant differences in episodes of sepsis, necrotizing enterocolitis, and cholestasis were observed. CONCLUSIONS: Oral EM was effective and safe for treatment of feeding intolerance in preterm infants.

53. Nurko, S., Garcia-Aranda, J.A., Guerrero, V.Y., and Worona, L.B. Treatment of intractable constipation in children: experience with cisapride. *J Pediatr Gastroenterol Nutr* 22: 38-44, 1996.

To establish whether cisapride is beneficial in children with intractable constipation, an open trial was performed. Chronically constipated children who had failed at least 12 weeks of medical therapy received cisapride at a dose of 0.2 mg/kg/dose TID for 12 weeks. Children with pelvic floor dyssynergia were excluded. Patients were followed prospectively for at least 12 months. Thirty children were initially enrolled, and 27 (14 boys, 13 girls) completed the study. At the end of 12 weeks of cisapride treatment, there was a significant increase in the number of bowel movements per week (1.43 +/- 0.52 to 6.48 +/- 4.16; p < 0.05) and significant decreases in the number of accidents per day (2.86 +/- 2.71

to 0.52 +/- 1.23; $p < 0.05$) and doses of laxatives used per week (14.33 +/- 5.84 to 3.37 +/- 7.10; $p < 0.05$). Encopresis disappeared in 65.2% of cases ($p < 0.0001$) and improved in 26%. Sixty-nine percent of the patients stopped using laxatives ($p < 0.001$). After 12 weeks 18 patients (66.6%) were asymptomatic, seven (25.9%) showed some improvement in bowel movement frequency and number of accidents, and two (7.4%) showed no improvement. The cisapride was well tolerated. After long-term follow-up (20 +/- 9.8 months), 37% of patients had recovered (asymptomatic and off laxatives and cisapride) and 29.6% were still asymptomatic but were using laxatives or cisapride. There were no differences in baseline characteristics between recovered and nonrecovered patients. We conclude that cisapride is effective in the treatment of some children with intractable constipation without pelvic floor dyssynergia.

54. Nurko, S., Garcia-Aranda, J.A., Worona, L.B., and Zlochisty, O. Cisapride for the treatment of constipation in children: A double-blind study. *J Pediatr* 136: 35-40, 2000.

OBJECTIVE: To determine whether cisapride is effective in the treatment of children with constipation. STUDY DESIGN: Double-blind, placebo-controlled study in which children with chronic constipation were randomly assigned to treatment with cisapride or placebo for 12 weeks. RESULTS: Forty children were enrolled, and 36 completed the therapy. Treatment successes occurred in 13 of 17 (76%) subjects in the cisapride group and 8 of 19 (37%) subjects in the placebo group ($P < .03$). The odds ratio for response after cisapride administration was 8.2 times higher (95% CI 1.3 to 49.4). During cisapride therapy, there was a significant improvement in number of spontaneous bowel movements per week (from 0.9 +/- 0.1 to 4.1 +/- 1.1), and there was a significant decrease in number of fecal soiling episodes per day (1.8 +/- 0.5 to 0.08 +/- 0.4), percent with encopresis (82% vs 23%), number of laxative doses per week (from 10.3 +/- 2.6 to 0.8 +/- 0.6), percent using laxatives (77% to 24%), and total gastrointestinal transit time (from 115.0 +/- 3.7 hours to 77.0 +/- 11.1 hours). With placebo, there were no significant changes in the number of spontaneous bowel movements (from 1.0 +/- 0.8 to 2.2 +/- 0.6), percent with encopresis (74% vs 47%), or total gastrointestinal transit time (from 112.5 +/- 4.9 hours to 95.4 +/- 9.8 hours); but there was a significant decrease in number of fecal soiling episodes per day (from 1.3 +/- 0.4 to 0.4 +/- 0.2) and number of laxative doses used per week (from 11.5 +/- 2.9 to 2.05 +/- 0.7). The final number of spontaneous bowel movements, fecal soiling episodes, laxatives used, or percent patients with encopresis was not different when patients receiving cisapride were compared with those receiving placebo. CONCLUSION: Cisapride was effective in the treatment of children with constipation.

55. Nurko, S., Youssef, N.N., Sabri, M., Langseder, A., McGowan, J., Cleveland, M., and Di Lorenzo, C. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. *J Pediatr* 153: 254-261, 261 e251, 2008.

OBJECTIVE: To establish the efficacy and best starting dose of polyethylene glycol (PEG)3350 in the short-term treatment of children with functional constipation. **STUDY DESIGN:** Prospective, randomized, multicenter, double-blinded, placebo-controlled, dose-ranging study of PEG3350 in children with functional constipation. Patients were randomly assigned to either placebo or 0.2 g/kg per day, 0.4 g/kg per day, or 0.8 g/kg per day of PEG3350 after a 1 week run-in period, followed by 2 weeks of treatment. All received behavior modification. The primary outcome was the proportion of patients with a successful treatment response: ≥ 3 bowel movements (BM) in the second week. **RESULTS:** 103 children (mean, 8.5 \pm 3.1 years) were enrolled. 77%, 74%, and 73% of the 0.2, 0.4, and 0.8 g/kg groups were successfully treated, as compared with 42% receiving placebo ($P < .04$). There was a significant increase in BM ($P < .001$) and straining improvement ($P < .05$) with the different PEG3350 doses. Stool consistency improved significantly for doses 0.4 g/kg or higher ($P < .001$). There was more abdominal pain and fecal incontinence in patients receiving 0.8 g/kg. PEG3350 was well tolerated. **CONCLUSIONS:** This placebo-controlled study confirms the efficacy and safety of PEG3350 for the short-term treatment of children with functional constipation. We recommend a starting dose of 0.4 g/kg per day.

56. Odeka, E.B., Sagher, F., Miller, V., and Doig, C. Use of cisapride in treatment of constipation in children. *J Pediatr Gastroenterol Nutr* 25: 199-203, 1997.

BACKGROUND: Chronic constipation is a common problem in children. We observed the effects of cisapride in the management of idiopathic constipation in children. **METHODS:** Thirty-seven children with a history of constipation (i.e., pain and difficulty or delay in defecation for > 3 months) were recruited and randomly assigned to 8 weeks of treatment with either cisapride, 0.2 mg/kg three times daily, or matching placebo after a 2-week run-in period in a double-blind, parallel-group study design. In phase 1 (2 weeks), patients had plain abdominal radiographs to assess degree of faecal load, and those with impaction were given laxatives. After satisfactory clearance of faeces, total gastrointestinal transit time and oro-caecal transit time were measured. In phase 2, after 8 weeks of treatment with either cisapride or placebo (0.2 mg/kg t.d.s.), the transit studies were repeated. **RESULTS:** Compared with placebo, cisapride did not improve either stool frequency or transit time in this study population. **CONCLUSION:** This study did not demonstrate a clinical role for the use of cisapride in the treatment of idiopathic constipation in children.

57. Oei, J., and Lui, K. A placebo-controlled trial of low-dose erythromycin to promote feed tolerance in preterm infants. *Acta Paediatr* 90: 904-908, 2001.

The aim of this study was to assess the efficacy of erythromycin, a motilin agonist, in promoting enteral feed tolerance in preterm infants of $< \text{or} = 32$ wk gestation. Eligible infants were randomized to receive either low-dose (2.5 mg

kg(-1) per dose 6 hourly) oral erythromycin ethylsuccinate or placebo for 10 d from the time of the first oral feed. The data from 22 erythromycin and 21 placebo infants were analysed. Birthweights (erythromycin 1,216 +/- 380 g, placebo 1,355 +/- 228 g, $p = 0.25$), gestation (erythromycin 28.6 +/- 2.2 wk, placebo 29.3 +/- 1.7 wk, $p = 0.24$) and other clinical variables were not different between the groups. Almost all infants were fed expressed breast milk. Erythromycin infants had significantly fewer episodes of large residual gastric aspirates (>30% of the previous 6 h worth of feeds) over 10 d (erythromycin 1.1 +/- 1.9, placebo 3.6 +/- 2.2 episodes, $p = 0.0007$). Infants in the erythromycin group achieved full oral feeds more quickly (6.0 +/- 2.3 vs 7.9 +/- 3.5 d, $p = 0.04$). There were no significant differences between the groups with regard to the number of days on total parenteral nutrition or to the time needed to regain birthweight. One enrolled infant from each group died of necrotizing enterocolitis. CONCLUSION: Low-dose erythromycin promoted gastric emptying and feed tolerance in premature infants at a lower gestational age than previously reported. Increased exposure to broad-spectrum antibiotics may not be free of risk. Further studies are recommended to assess its efficacy in premature infants with established feed intolerance.

58. Omari, T.I., Benninga, M.A., Sansom, L., Butler, R.N., Dent, J., and Davidson, G.P. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. *J Pediatr* 149: 468-474, 2006.

OBJECTIVE: To evaluate the effect of baclofen, a gamma-amino-butyric-acid B receptor agonist that inhibits transient lower esophageal sphincter relaxation (TLESR), on the rates of TLESR, gastroesophageal reflux (GER), and gastric emptying (GE) in children with GER disease. STUDY DESIGN: The efficacy of 0.5 mg/kg baclofen was evaluated in a randomized, double-blinded, placebo-controlled trial in 30 children. Patients were intubated with a manometric/pH assembly and given 250 mL of cow's milk. Esophageal motility and pH were then measured for 2 hours (control period). Baclofen or placebo was then administered, and 1 hour later 250 mL of milk was given again and measurements performed for another 2 hours (test period). The GE rate was measured by the (¹³C) octanoate breath test. RESULTS: Baclofen significantly reduced the incidence of TLESR (mean, 7.3 +/- 1.5 vs 3.6 +/- 1.2 TLESR/2 hours; $P < .05$) and acid GER (mean 4.2 +/- 0.7 vs 1.7 +/- 1.0 TLESR + GER/2 hours; $P < .05$) during the test period compared with the control period. Baclofen significantly accelerated the GE rate (median [interquartile range], GE(t_{1/2}), 61 minutes [39, 81 minutes] vs 114 minutes [67, 170 minutes]; $P < .05$). Baclofen had no effect on the swallowing rate, pattern of esophageal peristalsis, or lower esophageal sphincter pressure. CONCLUSIONS: Baclofen reduces GER in children by inhibiting the triggering of TLESR. Baclofen also accelerates GE.

59. Pashankar, D.S., and Bishop, W.P. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children.

J Pediatr 139: 428-432, 2001.

OBJECTIVE: To determine efficacy, safety, and optimal dose of a laxative, polyethylene glycol (PEG) 3350, in children with chronic constipation. **STUDY DESIGN:** Children with chronic constipation (n = 24) were treated with PEG for 8 weeks at an initial dose of 1 g/kg/d. The dose was adjusted every 3 days as required to achieve 2 soft stools per day. A diary was kept to monitor dose, stool frequency and consistency, soiling, and other symptoms. Stool consistency was rated from 1 (hard) to 5 (watery). Subjects were examined for fecal retention. The Student t test and the Fisher exact test were used for data analysis. **RESULTS:** All 20 children who completed the study found PEG to be palatable and were satisfied with the treatment. There were no significant adverse effects. Weekly stool frequency increased from 2.3 +/- 0.4 to 16.9 +/- 1.6 (P <.0001) during treatment and stool consistency from 1.2 +/- 0.1 to 3.3 +/- 0.1 (P <.0001). In 9 children with soiling, weekly soiling events declined from 10.0 +/- 2.4 to 1.3 +/- 0.7 (P =.003). The mean effective dose was 0.84 g/kg/d (range, 0.27-1.42 g/kg/d). **CONCLUSION:** Daily administration of PEG at a mean dose of 0.8 g/kg is an effective, safe, and palatable treatment for constipation.

60. Patole, S., Rao, S., and Doherty, D. Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 90: F301-306, 2005.

BACKGROUND: It often takes several days or even weeks to establish full enteral feeds (FEFs) in preterm, especially extremely low birthweight neonates because of feed intolerance related to gastrointestinal hypomotility. Clinical trials of erythromycin as a prokinetic agent in preterm neonates have reported conflicting results. **AIM:** To systematically review the efficacy and safety of erythromycin as a prokinetic agent in preterm neonates. **METHODS:** Only randomised controlled trials in preterm neonates (gestation < or = 37 weeks) were considered eligible for inclusion. The primary outcome was the time to reach FEFs of 150 ml/kg/day. The secondary outcomes included the incidence of erythromycin related adverse effects such as diarrhoea, cardiac arrhythmias, and hypertrophic pyloric stenosis. No restrictions were applied on the dose (low: 3-12 mg/kg/day; antimicrobial: > or = 12 mg/kg/6-8 hours) and route (oral or intravenous) and mode (prophylactic or rescue) of administration. The standard methodology for systematic reviews was followed. A subgroup analysis was pre-planned based on the dose and mode of drug administration. **RESULTS:** Seven trials (three prophylaxis, four rescue) with various doses, routes and modes of administration, and durations of erythromycin treatment and different results were found to be eligible for inclusion in the analysis. Meta-analysis could not be performed, as specific data were either inadequate or not available. **CONCLUSION:** The conflicting trial results may be explained by differences in dose and route and mode of administration of erythromycin and in gastrointestinal motor responses in the presence of different feeding conditions- for example, fasting v fed state, intermittent v continuous feeds. Gestational and

postnatal ages during erythromycin treatment are also important.

61. Patole, S.K., Almonte, R., Kadalraja, R., Tuladhar, R., Muller, R., and Whitehall, J.S. Can prophylactic oral erythromycin reduce time to full enteral feeds in preterm neonates? *Int J Clin Pract* 54: 504-508, 2000.

Efficacy of oral, prophylactic erythromycin in reducing the time to establish full enteral feeds (150 ml/kg/day) was assessed in neonates < 32 weeks, ready for enteral feeds. Seventy-three consecutive neonates were randomised to receive oral erythromycin ethyl succinate (n = 36) or placebo (n = 37) in a double-blind trial until full enteral feeds or 14 days of therapy were reached. A prospectively designed feeding regimen, including plan of action for signs of feed intolerance, was common for all enrolled neonates. The median gestational age, birth weight and postnatal age at start of feeds were 29 versus 30 weeks (p = 0.40), 1232 versus 1280 g (p = 0.96) and 5 versus 5 days (p = 0.84) for erythromycin and placebo group, respectively. Time to achieve full feeds was not significantly different in the two groups. (median times: erythromycin 93.5 versus placebo 104 hours, p = 0.60). Erythromycin-related side-effects did not occur.

62. Pezzati, M., Dani, C., Biadaoli, R., Gambi, B., Lachina, L., and Rubaltelli, F.F. Randomised controlled trial of the effect of cisapride on the pyloric muscle in preterm infants. *Eur J Pediatr* 160: 572-575, 2001.

In this study we determined the effects of cisapride on the pyloric muscle in preterm infants. To perform a randomised, double blind, placebo controlled study, two groups each of 16 preterm newborns were given either cisapride (0.2 mg/kg every 8 h) or a placebo for at least 7 days. Infants were studied first on the day when treatment with cisapride or placebo was to be initiated (time 0), and then after 3 (time 1) and 7 days (time 2). In each group, the following parameters were studied by ultrasonography: cross-sectional diameter of the entire pylorus, muscle thickness, and length of the pyloric canal. Also, the mean daily total gastric aspirate volume was studied for the entire week of the study. At time 0, we observed no significant differences between the two groups with respect to diameter, muscle thickness and length of the pyloric muscle. At time 1 and time 2, both diameter and muscle thickness were significantly greater in the cisapride group than in the placebo group. Furthermore, the length of the pyloric canal was significantly greater in the cisapride group than in placebo group at time 2, though not so at time 1. For the entire week of the study, we found a significantly larger mean daily total gastric aspirate volume in the group of infants treated with cisapride compared to the placebo treated group. CONCLUSION: Cisapride significantly affects all of the main measurements of the pyloric muscle and causes a significantly larger amount of daily total gastric aspirate volume. Its use to promote feeding intolerance in preterm newborns cannot be recommended.

63. Premji, S.S., Wilson, J., Paes, B., and Gray, S. Cisapride: a review of the evidence supporting its use in premature infants with feeding intolerance.

Neonatal Netw 16: 17-21, 1997.

A systematic computerized search of all databases was performed to review the scientific evidence in support of the efficacy of cisapride in reducing feeding intolerance in premature infants. Reference lists from these articles were used to identify relevant scientific literature to address important aspects of the use of cisapride. Three open prospective, uncontrolled studies were found. All studies reported improved clinical outcomes as evidenced by decreased gastric residuals, decreased incidence of vomiting, increased feeding volume, decrease in all reflux parameters measured, and increased weight gain. These observational studies reflect the current state of knowledge and have important research and clinical implications because of the profound effects of feeding intolerance on infant growth and development and on length of stay within NICUs.

64. Ramirez, B., and Richter, J.E. Review article: promotility drugs in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 7: 5-20, 1993.

Prokinetic agents are drugs that increase contractile force and accelerate intraluminal transit. They are often used in treating disorders of gastrointestinal motility including gastro-oesophageal reflux disease (GERD). The most widely studied agents include bethanechol, metoclopramide, domperidone and cisapride. These drugs act either by enhancing the effect of acetylcholine or by blocking the effect of an inhibitory neurotransmitter such as dopamine. With the exception of cisapride, the clinical efficacy of the various prokinetic agents in treating GERD has not been confirmed consistently. These agents have variable effects on oesophageal and gastric motor function and are fraught with side-effects. They are effective in relieving mild reflux symptoms but do not predictably heal oesophagitis. On the other hand, cisapride is thus far the most effective prokinetic agent studied for the treatment of GERD. It relieves reflux symptoms and promotes healing of grade I-II oesophagitis, with few side-effects or tachyphylaxis. Its most important role may be in the maintenance treatment of GERD either as a single agent or in combination therapy with an H₂-antagonist after oesophagitis healing.

65. Razzaq, A., Safdar, C.A., and Ali, S. Erythromycin establishes early oral feeding in neonates operated for congenital intestinal atresias. *Pediatr Surg Int* 25: 361-364, 2009.

PURPOSE: The recovery of gastrointestinal function following surgery for congenital intestinal atresias can be prolonged and may increase morbidity and hospital stay. This study was conducted to investigate the prokinetic effect of erythromycin in neonates undergoing surgery for small bowel atresias.

METHODS: A randomized-controlled trial was conducted at the Departments of Paediatrics and Paediatric Surgery, Military Hospital, Rawalpindi, Pakistan, from January to December 2007 to study the prokinetic effect of erythromycin (3

mg/kg per dose 4 times daily). Thirty consecutive neonates undergoing primary anastomosis for congenital small bowel atresias were randomly divided into two groups: group I (erythromycin) and group II (control). The groups were similar in terms of gestational age, sex, mode of delivery, birth weight and types of atresias. Postoperative recovery of intestinal functions was measured as time taken to achieve full enteral feed (150 ml/kg per 24 h), duration of total parenteral nutrition (TPN) and hospital stay. RESULTS: Neonates receiving oral erythromycin achieved full enteral feeding early (13.07 vs. 16.13 days) required TPN for shorter duration (10.53 vs. 13.73 days) and their hospital stay was less (16.2 vs. 18.0 days) as compared to the neonates in the control group who did not receive any erythromycin. The differences were statistically significant. CONCLUSION: The administration of oral erythromycin following primary anastomosis for small intestinal atresias results in early recovery of intestinal function, fewer days on TPN and a trend for shorter hospital stay.

66. Reddy, P.S., Deorari, A.K., Bal, C.S., Paul, V.K., and Singh, M. A double-blind placebo-controlled study on prophylactic use of cisapride on feed intolerance and gastric emptying in preterm neonates. *Indian Pediatr* 37: 837-844, 2000.

OBJECTIVE: To evaluate whether prophylactic use of cisapride will reduce the incidence of feed intolerance and gastro-esophageal reflux, and improve gastric emptying in early neonatal period in preterm babies. DESIGN: Double blind randomized controlled trial. SETTING: Hospital based. SUBJECTS: Forty nine preterm babies between 29-34 weeks of gestation were administered either cisapride or placebo. METHODS: Babies were enrolled in the study once they reached 30 ml/kg/day of enteral feeding or when 25% of total fluid intake was received through the enteral route. Those with sepsis, congenital malformations and on aminophylline were excluded. The subjects were randomized to receive either cisapride or placebo in a dose of 0.2 mg/kg/dose every 8 hourly for 14 days or till discharge. During the study period babies were observed for clinical signs of feed intolerance as judged by increase in abdominal girth, increased prefeed gastric residuals or vomiting. Gastro-esophageal reflux and gastric emptying time was assessed by Technetium phytate scan on day 7 +/- 1. RESULTS: Feed intolerance was noticed in 59% of study and 41% of control population. No significant difference was noticed in the two groups in the total number of episodes of feed intolerance (1.54 +/- 2.4 vs 1.18 +/- 1.6). Nearly 50% of babies in each group had gastro-esophageal reflux. Gastric emptying time (mean (SD) and median) was found to be comparable (p = 0.70) in those on drug and placebo (58.1 (32.2 min) 48.8 min) vs (53.8 (34.6 min) 43.4 min). CONCLUSION: Cisapride does not reduce the incidence of feed intolerance, gastro-esophageal reflux and does not improve gastric emptying in normal preterm neonates.

67. Rouge, C., Piloquet, H., Butel, M.J., Berger, B., Rochat, F., Ferraris, L., Des Robert, C., Legrand, A., de la Cochetiere, M.F., N'Guyen, J.M., Vodovar, M., Voyer, M., Darmaun, D., and Roze, J.C. Oral supplementation with probiotics in

very-low-birth-weight preterm infants: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 89: 1828-1835, 2009.

BACKGROUND: Although recent reports suggest that supplementation with probiotics may enhance intestinal function in premature infants, the mechanisms are unclear, and questions remain regarding the safety and efficacy of probiotics in extremely low-birth-weight infants. **OBJECTIVE:** The objective was to evaluate the efficacy of probiotics on the digestive tolerance to enteral feeding in preterm infants born with a very low or extremely low birth weight. **DESIGN:** In a bicentric, double-blind, randomized controlled clinical trial that was stratified for center and birth weight, 45 infants received enteral probiotics (*Bifidobacterium longum* BB536 and *Lactobacillus rhamnosus* GG; BB536-LGG) and 49 received placebo. The primary endpoint was the percentage of infants receiving >50% of their nutritional needs via enteral feeding on the 14th day of life. A triangular test was used to perform sequential analysis. **RESULTS:** The trial was discontinued after the fourth sequential analysis concluded a lack of effect. The primary endpoint was not significantly different between the probiotic (57.8%) and placebo (57.1%) groups ($P = 0.95$). However, in infants who weighed >1000 g, probiotic supplementation was associated with a shortening in the time to reach full enteral feeding ($P = 0.04$). Other than colonization by the probiotic strains, no alteration in the composition of intestinal microbiota or changes in the fecal excretion of calprotectin was observed. No colonization by probiotic strains was detected in infants who weighed < or =1000 g, presumably because of more frequent suspensions of enteral feeding, more courses of antibiotic treatment, or both. **CONCLUSIONS:** Supplementation with BB536-LGG may not improve the gastrointestinal tolerance to enteral feeding in very-low-birth-weight infants but may improve gastrointestinal tolerance in infants weighing >1000 g. This trial was registered at clinicaltrials.gov as NCT 00290576.

68. Scott, R.B., Ferreira, C., Smith, L., Jones, A.B., Machida, H., Lohoues, M.J., and Roy, C.C. Cisapride in pediatric gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 25: 499-506, 1997.

BACKGROUND: Gastroesophageal reflux is a common condition that in infants may lead to serious complication. This study assessed the efficacy and safety of oral cisapride suspension in the treatment of children 6 weeks to 2 years old with daily regurgitant reflux. **METHODS:** A randomized, prospective, double-blind, placebo-controlled clinical trial was conducted at three study sites. After a 1 week baseline assessment, 45 infants 6 weeks to 2 years old were randomized to a double-blind trial in which they received a 6 week course of cisapride (0.2 mg/kg q6h) or a placebo suspension. Efficacy was assessed with 24 hour esophageal pH monitoring, esophageal manometry, and esophageal biopsy before and after the treatment period. A diary of regurgitation frequency and severity was kept by the parents. Safety was assessed by adverse event monitoring and standard laboratory measurements. **RESULTS:** Compared with placebo, cisapride significantly ($p < 0.05$) reduced the mean duration of upright and supine reflux

episodes. Compared to baseline, cisapride significantly reduced the mean duration of the longest reflux episode, and placebo increased the mean number of reflux episodes longer than 5 minutes. Cisapride was not significantly different from placebo for the following mean measurements: percent of total time pH < 4, number of reflux episodes, lower esophageal sphincter pressure, swallow pressure, regurgitation frequency or global evaluation scores. CONCLUSIONS: Cisapride is a safe, well tolerated prokinetic agent that improves the esophageal clearance of refluxed gastric acid in children under the age of 2 years.

69. Sekteera, W., Nuntnarumit, P., and Supapannachart, S. Oral erythromycin for treatment of feeding intolerance in preterm infants: a preliminary report. *J Med Assoc Thai* 85 Suppl 4: S1177-1182, 2002.

Feeding intolerance is a common problem in preterm infants resulting in a prolonged hyperalimentation which is associated with an increased risk of serious and sometimes even life threatening complications, including cholestasis jaundice, liver impairment, nutritional deficiency, biochemical rickets and catheter-related septicaemia. Erythromycin, a commonly used macrolide antibiotic, has been reported as having potent prokinetic properties and enhancing gastrointestinal motor activity. The authors, therefore, conducted a preliminary study of oral erythromycin for the treatment of feeding intolerance in preterm infants to evaluate the safety and efficacy of this drug. AIM: To evaluate the safety and efficacy of oral erythromycin as a prokinetic agent in promoting enteral feeding in preterm infants with feeding intolerance. METHOD: Preterm infants, gestational age (GA) < or = 36 wk, who met the feeding intolerance criteria, were enrolled in the study. Inclusion criteria included infants who received enteral feeding less than half of full feeding or less than 75 ml/kg/day by day 14 post-natal age or gastric residual > or = 50 per cent of a given amount of feeding, more than 2 consecutive feeds by day 7 post-natal age. All patients received oral erythromycin ethylsuccinate 12 mg/kg every six hours for 2 days, then 3 mg/kg every six hours for 5 days. The times taken to establish full enteral feeding after the drug treatment and time to stop hyperalimentation were recorded. Potential adverse effects of erythromycin were assessed. Response to treatment was defined as decreased gastric residual < 30 per cent of a similar amount of the previous feed and was able to continue to full feeding. RESULTS: Ten preterm infants were enrolled in this study with a mean GA of 30.8 weeks (26-35), mean birth weight of 1,489 g (range 900-2,560 g) and mean age at entry of 9.2 days (range 7-12 days). Nine of 10 infants responded to treatment within 24 hours. The average time to establish full enteral feeding after the drug treatment was 6.6 days (range 4-10 days). None of the infants developed adverse effects such as vomiting, diarrhea, or pyloric stenosis. CONCLUSION: The preliminary data indicates that oral erythromycin is effective and safe in facilitating enteral feeding in preterm infants with feeding intolerance. Infants can achieve full feeding within a week after treatment, and this may shorten the course of hyperalimentation. Further randomized controlled trials are warranted.

70. Shaoul, R., Shahory, R., Tamir, A., and Jaffe, M. Comparison between pediatricians and family practitioners in the use of the prokinetic cisapride for gastroesophageal reflux disease in children. *Pediatrics* 109: 1118-1123, 2002.

OBJECTIVE: The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition have recently issued treatment guidelines for the use of cisapride in children. Our hypothesis was that cisapride is misused in the community and is not prescribed according to suggested recommendations. Therefore, the aim of this study was to evaluate the knowledge of pediatricians and family practitioners regarding the prescribing practice and adverse effects of cisapride. METHODS: A standardized questionnaire was sent to a randomly selected group of pediatricians and family practitioners in Northern Israel. The questionnaire was designed to evaluate the knowledge of the physician regarding the treatment of gastroesophageal reflux disease and the use of cisapride in children (indications, dosages, duration of treatment, limitations in certain age groups, the need for pretreatment laboratory tests, interactions with other drugs, and contraindications). Replies were scored from 0 to 100 according to the treatment guidelines of both the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. In addition, 2 questions dealt with the subjective efficacy of the drug and its adverse events. RESULTS: The knowledge scores were 62% and 51% in the pediatricians and family practitioners, respectively. Other major findings were as follows: 1) 40% of pediatricians and 65% of family practitioners do not prescribe the recommended dose of cisapride, 2) 6% of pediatricians and 42% of family practitioners prescribe cisapride for infantile colic, 3) only 50% of pediatricians and 22% of family practitioners were aware of possible interactions with macrolides, and 4) only 31% of pediatricians and 54% of family practitioners were aware that cisapride might cause prolongation of the QT interval. Only minor adverse events were reported. CONCLUSIONS: The knowledge of both pediatricians and family practitioners in the use of cisapride in children is suboptimal. It is essential to improve the education of community physicians to reduce the potential for adverse events arising from the misuse of this prokinetic agent.

71. Simkiss, D.E., Adams, I.P., Myrdal, U., and Booth, I.W. Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 71: F128-129, 1994.

The motilin agonist erythromycin was used successfully in four infants receiving prolonged parenteral nutrition for severe intestinal dysmotility after gastrointestinal surgery. In a further child with a neuropathic intestinal pseudo-obstruction erythromycin induced a striking small intestinal manometric response, but was without effect in a child with an intestinal myopathy.

72. Staiano, A., Cucchiara, S., Andreotti, M.R., Minella, R., and Manzi, G. Effect of

cisapride on chronic idiopathic constipation in children. *Dig Dis Sci* 36: 733-736, 1991.

The efficacy of cisapride, a new prokinetic drug, as a treatment for chronic functional constipation of childhood was studied in 20 constipated children. Each subject had a stool frequency less than 4/week and/or total gastrointestinal transit time greater than 33 hr and was randomly assigned to double-blind treatment with either cisapride (N = 10) or placebo (N = 10) for 12 weeks. Stool habits, total gastrointestinal transit time, and anorectal motility were evaluated in all children before and at the end of the treatment period. Cisapride significantly increased stool frequency from 1.2 +/- 0.6 to 5.1 +/- 1.9 stools/week (mean +/- SD; P less than 0.05), whereas the lesser effect of placebo was not significant (1.2 +/- 0.8 to 2.8 +/- 0.8 stools/week; P = 0.4). Both treatments significantly (P less than 0.05) decreased laxative or suppository use. Total gastrointestinal transit time was decreased by cisapride (90.8 +/- 9.2 hr to 57.2 +/- 20.2 hr; P less than 0.05) but was not affected by placebo. Anorectal manometry showed that cisapride, but not placebo, significantly decreased the rectoanal inhibitory reflex threshold and the conscious rectal sensitivity threshold. It is concluded that cisapride improves gastrointestinal motility and bowel habits in children with chronic idiopathic constipation and may be useful in the management of some children with this disorder.

73. Staiano, A., Del Giudice, E., Simeone, D., Miele, E., and Marino, A. Cisapride in neurologically impaired children with chronic constipation. *Dig Dis Sci* 41: 870-874, 1996.

The efficacy of cisapride as a treatment for chronic constipation in children with severe brain damage was studied in 20 children. Each subject was randomly assigned to double-blind treatment with either cisapride (N = 10) or placebo (N = 10) for 12 weeks. Stool habits, total gastrointestinal transit time, colonic segmental transit times, and anorectal motility were evaluated in all children before and at the end of the treatment period. Although cisapride significantly (P < 0.05) increased stool frequency from baseline to week 12 and no significant change was documented in the placebo group, the mean change in stool frequency per week from baseline to 12 week was not significantly different between the two treatment groups. The use of laxatives or suppositories was significantly (P < 0.05) decreased by cisapride, but remained unchanged in the placebo group. Furthermore, cisapride significantly (P < 0.05) reduced rectal compliance but had no effect on total gastrointestinal transit time and colonic segmental transit times. In summary, in neurologically impaired children with chronic constipation, cisapride increased bowel frequency but did not alter the delay in total and segmental gastrointestinal transit times.

74. Stenson, B.J., Middlemist, L., and Lyon, A.J. Influence of erythromycin on establishment of feeding in preterm infants: observations from a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 79: F212-214, 1998.

AIM: To determine the effect of erythromycin on the establishment of enteral feeding in ventilated infants < 31 weeks gestation. METHODS: Erythromycin was randomly allocated as an antimicrobial treatment for the first 7 days of life in 76 infants: 35 received erythromycin and 41 acted as controls. Feed toleration, time taken to establish full enteral feeding, vomiting, prescription of glycerine suppositories and occurrence of necrotising enterocolitis were recorded. RESULTS: There were no significant differences between the groups for any of the outcomes. The infants treated with erythromycin reached full feeding at a median (quartile) age of 8 (5-12) days compared with 9 (6-14) days for controls. CONCLUSIONS: Intravenous erythromycin in antimicrobial doses is unlikely to benefit the introduction of feeding in preterm infants.

75. Su, B.H., and Lin, H.C. Erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 150: e30; author reply e31, 2007.
76. Su, B.H., Lin, H.C., Peng, C.T., and Tsai, C.H. Effect of erythromycin on feeding intolerance in very low birth weight infants: a preliminary observation. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 39: 324-326, 1998.

To investigate the effect of erythromycin on feeding intolerance in very low birth weight infants, from February 1997 to December 1997 twenty infants weighing less than 1500 g, with prolonged intolerance of enteral feeding, were enrolled in this study. The protocol for erythromycin treatment was: a loading dose of 30 mg/kg/day, divided into three portions given every eight hours intravenously for 1 hour over a three day period; then a maintenance dose of 3-5 mg/kg intravenously for one hour once a day was given until full feeding was well established. The assessment of erythromycin effect was the daily net orogastric balance (volume of orogastric tube feeding minus volume of orogastric aspirates). The mean gestational age was 27.1 +/- 2.0 weeks (mean +/- SD) and the mean birth weight was 1025 +/- 196 g. The mean age when erythromycin started was 19.5 +/- 14 days; the mean days after the initiation of erythromycin when orogastric tube feeding could be started and full feeding established were 2.4 +/- 1.1 days and 15.1 +/- 2.2 days, respectively. At the beginning of erythromycin treatment, the net balance of tube aspirates was -4.8 +/- 4.1 ml. The net balance rose significantly to 30.6 +/- 15.3 ml, 92.6 +/- 25.4 ml and 125.3 +/- 18.1 ml at 7, 14 and 21 days after erythromycin treatment, respectively. In conclusion, erythromycin treatment is a safe method to improve intolerance of enteral feeding in very low birth weight infants. It is suggested that the effect of erythromycin on gastrointestinal motility in these infants should be further investigated in the context of a randomized, controlled trial before widespread clinical implementation of this treatment.

77. Vandenplas, Y., Belli, D.C., Benatar, A., Cadranel, S., Cucchiara, S., Dupont, C.,

Gottrand, F., Hassall, E., Heymans, H.S., Kearns, G., Kneepkens, C.M., Koletzko, S., Milla, P., Polanco, I., and Staiano, A.M. The role of cisapride in the treatment of pediatric gastroesophageal reflux. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 28: 518-528, 1999.

BACKGROUND: Cisapride is a gastrointestinal prokinetic agent that is used worldwide in the treatment of gastrointestinal motility-related disorders in premature infants, full-term infants, and children. Efficacy data suggest that it is the most effective commercially available prokinetic drug. **METHODS:** Because of recent concerns about safety, a critical and in-depth analysis of all reported adverse events was performed and resulted in the conclusions and recommendations that follow. **RESULTS:** Cisapride should only be administered to patients in whom the use of prokinetics is justified according to current medical knowledge. If cisapride is given to pediatric patients who can be considered healthy except for their gastrointestinal motility disorder, and the maximum dose does not exceed 0.8 mg/kg per day in 3 to 4 administrations of 0.2 mg/kg (not exceeding 40 mg/d), no special safety procedures regarding potential cardiac adverse events are recommended. However, if cisapride is prescribed for patients who are known to be or are suspected of being at increased risk for drug-associated increases in QTc interval, certain precautions are advisable. Such patients include those: (1) with a previous history of cardiac dysrhythmias, (2) receiving drugs known to inhibit the metabolism of cisapride and/or adversely affect ventricular repolarisation, (3) with immaturity and/or disease causing reduced cytochrome P450 3A4 activity, or (4) with electrolyte disturbances. In such patients, ECG monitoring to quantitate the QTc interval should be used before initiation of therapy and after 3 days of treatment to ascertain whether a cisapride-induced cardiac adverse effect is present. **CONCLUSIONS:** With rare exceptions, the total daily dose of cisapride should not exceed 0.8 mg/kg divided into 3 or 4 approximately equally spaced doses. If higher doses than this are given, the precautions above are advisable. In any patient in whom a prolonged QTc interval is found, the dose of cisapride should be reduced or the drug discontinued until the ECG normalizes. If the QTc interval returns to normal after withdrawal of cisapride, and the administration of cisapride is considered to be justified because of its efficacy and absence of alternative treatment options, cisapride can be restarted at half dose with control of the QTc interval. Unfortunately, at present, normal ranges of QTc interval in children are unknown. However, a critical analysis of the literature suggests that a duration of less than 450 milliseconds can be considered to be within the normal range and greater than 470 milliseconds as outside it.

78. Veereman-Wauters, G., Ghoois, Y., van der Schoor, S., Maes, B., Hebbalkar, N., Devlieger, H., and Eggermont, E. The ¹³C-octanoic acid breath test: a noninvasive technique to assess gastric emptying in preterm infants. *J Pediatr Gastroenterol Nutr* 23: 111-117, 1996.

Gastric emptying (GE) is difficult to evaluate properly in preterm infants because of the lack of safe and reliable noninvasive methods. The ¹³C-octanoic acid breath test, a noninvasive method to assess GE, was validated in adults. The aim of this study was to adapt the methodology of the ¹³C-octanoic acid breath test regarding test meal and sampling methods and to define normal values for healthy preterm infants. We tested 11 clinically stable preterm infants who demonstrated normal fetal growth. The infants mean gestational age at birth was 33 weeks, mean birth weight was 1754 g, mean postnatal age at the day of study was 26 days, and mean weight was 2296 g. After a fasting period of 3 h, the subject was fed a test meal with low and stable ¹³C background activity mixed with 50 microliters of ¹³C-labeled octanoic acid and 1 g polyethylene glycol 3350. Breath samples were collected using a nasal prong in basal conditions and after the test meal. CO₂ production according to weight and age was used in the calculations for ¹³CO₂ enrichment of exhaled air. Results were expressed as percentage of ¹³C dose excretion per hour and percentage of cumulative ¹³C after 4h. gastric emptying coefficient (GEC), and gastric half-emptying time (t_{1/2b}). The values for percent of cumulative ¹³C after 4 h ranged from 30.7 to 52.6% (mean, 40.2%), GEC ranged from 2.7 to 3.4 (mean, 3.0), and the values for t_{1/2b} ranged from 17 to 100 min (mean, 57 min). We conclude that the ¹³C-octanoic acid breath test can be adapted to preterm infants to allow the study of GE in various conditions.

79. Venkatasubramani, N., Rudolph, C.D., and Sood, M.R. Erythromycin lacks colon prokinetic effect in children with functional gastrointestinal disorders: a retrospective study. *BMC Gastroenterol* 8: 38, 2008.

BACKGROUND: Motilin, a peptide hormone has a direct excitatory effect on circular smooth muscle strips derived from the human colon. Reduced plasma motilin concentration has been reported in adults with chronic constipation. Erythromycin, a non-peptide motilin receptor agonist, induces phase 3 of the migrating motor complex (MMC) in the antro-duodenum and also reduces oro-cecal transit time. A pediatric study has reported an improvement in clinical symptoms of constipation following erythromycin administration, but the effect on colon motility in children has not been formally evaluated. We used colon manometry to study the effect of intravenous erythromycin lactobionate at 1 mg/kg on colon motility in ten children. **METHODS:** We selected patients with normal antroduodenal and colon manometry studies that were performed simultaneously. All studies were performed for clinically indicated reasons. We quantified the effect of erythromycin on colon contraction by calculating the area under the curve (AUC). **RESULTS:** The mean (SE of mean) AUC in the colon during the fasting, post-erythromycin and postprandial phases of the study was 2.1 mmHg/sec (0.35), 0.99 mmHg/sec (0.17) and 3.05 mmHg/sec (0.70) respectively. The AUC following erythromycin was significantly less compared to the fasting phase of the study ($p < 0.01$). **CONCLUSION:** Erythromycin lacks colon prokinetic effect in children with chronic constipation evaluated by colon manometry.

80. Wiersma, H.E., van Boxtel, C.J., Butter, J.J., van Aalderen, W.M., Omari, T., and Benninga, M.A. Pharmacokinetics of a single oral dose of baclofen in pediatric patients with gastroesophageal reflux disease. *Ther Drug Monit* 25: 93-98, 2003.

Transient relaxation of the lower esophageal sphincter (TLESR) is the predominant mechanism of gastroesophageal reflux (GER) in adults and children. Baclofen [4-amino-3-(p-chlorophenyl)-butanoic acid], a gamma-aminobutyric acid (GABA)-B receptor agonist used for the management of spasticity, has been recently shown to significantly inhibit GER in healthy adults without any relevant side effects. The objective of this study was to evaluate the pharmacokinetics of baclofen in a pediatric population with GER disease. In an open-label single-dose pharmacokinetic study, eight children with the diagnosis of GER made on clinical grounds received an oral dose of baclofen, 2.5 mg. Blood samples were drawn from an indwelling venous catheter, and urine was collected during a postdose period of 8 hours. The concentration of baclofen in these body fluids was determined using a validated high-performance liquid chromatography (HPLC) method with electrochemical detection after OPA-sulfite derivatization. Pharmacokinetic data were analyzed using the nonlinear regression program Scientist. Serum concentration-time curves could be best described using a two-compartment open model with a lag time. Mean plasma clearance (Cl) was 315.9 mL/h/kg; volume of distribution (Vd) was 2.58 L/kg; and half-life (T(1/2)beta) was 5.10 hours. No side effects were noted. As half-lives were comparable with those found in adult studies, the risk for accumulation seems not greater in children than in adults. Body composition can have a strong influence on the Vd of baclofen and, therefore, on the dose needed to obtain therapeutic plasma levels. Dosing according to clearly defined age groups with the help of therapeutic drug monitoring seems preferable. In view of the negative correlation between body weight and Vd, dosing according to body weight using adult pharmacokinetic data does not seem an effective way for using baclofen in children.

81. Zatman, T.F., Hall, J.E., and Harmer, M. Gastric residual volume in children: a study comparing efficiency of erythromycin and metoclopramide as prokinetic agents. *Br J Anaesth* 86: 869-871, 2001.

Metoclopramide may be used to stimulate gastric emptying when anaesthetizing children for emergency operations. Unfortunately, metoclopramide is associated with extrapyramidal side effects. Erythromycin, a motilin receptor agonist, is a prokinetic agent but its use has been little investigated in children. This randomized double-blind study compared the effects of premedication with oral metoclopramide 0.15 mg kg⁻¹ or erythromycin 1 mg kg⁻¹ on gastric emptying in 80 children undergoing tonsillectomy. Pre-operative fluids, premedication and anaesthetic technique were standardized and gastric volume was measured with an orogastric tube. Post-operative nausea and vomiting was recorded. Metoclopramide and erythromycin produced similar gastric volumes (0.29 and

0.24 ml kg(-1)) and there was no difference in post-operative vomiting. In the erythromycin group there were more patients with negative aspirates (45.9%) than in the metoclopramide group (35.1%), but the difference was not statistically significant. These results indicate that erythromycin may be as effective as metoclopramide as a prokinetic agent.

1. Calhoun, A.W., and Sullivan, J.E. Omegeaven for the treatment of parenteral nutrition associated liver disease: a case study. *J Ky Med Assoc* 107: 55-57, 2009.

A 17-month-old infant diagnosed with Short Gut Syndrome developed severe cholestasis and hepatopathy due to chronic parenteral nutrition (PN). In an effort to prevent multivisceral organ transplantation, he was started on Omegeaven, an experimental alternative form of parenteral lipid. Within six months, his cholestasis had resolved and his hepatopathy had significantly improved. Omegeaven uses Omega-3 rather than Omega-6 triglycerides as its primary fat source, improving fat absorption and modulating the systemic inflammatory response. It has also shown promise as a means of alleviating PN-induced cholestasis in several small trials. Omegeaven is only available in the United States on compassionate use basis.

2. Cheung, H.M., Lam, H.S., Tam, Y.H., Lee, K.H., and Ng, P.C. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. *Clin Nutr* 28: 209-212, 2009.

Four preterm infants with intestinal failure and severe parenteral nutrition-associated cholestasis (PNAC) received fish-oil-based parenteral lipid as rescue treatment in substitution for the standard soybean-based lipid preparation. The progression of liver disease was halted in 3 infants and they recovered with complete resolution of PNAC. The condition in two of these infants would almost certainly have progressed to end-stage hepatic failure if they had continued to receive long-term parenteral nutrition and <30% of total nutrition enterally. The remaining infant with residual inflamed bowel, protracted feeding intolerance and repeated episodes of sepsis did not respond. Our findings suggest that fish-oil-based parenteral lipid emulsion may contribute to effective treatment of PNAC in selected patients, which should be further evaluated in randomized controlled trials.

3. de Meijer, V.E., Gura, K.M., Le, H.D., Meisel, J.A., and Puder, M. Fish oil-based lipid emulsions prevent and reverse parenteral nutrition-associated liver disease: the Boston experience. *JPEN J Parenter Enteral Nutr* 33: 541-547, 2009.

Parenteral nutrition-associated liver disease (PNALD) is the most prevalent and most severe complication of long-term parenteral nutrition. Its underlying pathophysiology, however, largely remains to be elucidated. The currently approved parenteral lipid emulsions in the United States contain safflower or soybean oils, both rich in omega-6 polyunsaturated fatty acids (PUFAs). Mounting evidence indicates that the omega-6 PUFAs originating from plant oils in these lipid emulsions may play a role in the onset of liver injury. Fish oil-based

lipid emulsions, in contrast, are primarily composed of omega-3 PUFAs, thus providing a promising alternative. The authors review the literature on the role of lipid emulsions in the onset of PNALD and discuss prevention and treatment strategies using a fish oil-based lipid emulsion. They conclude that a fish oil-based emulsion is hepatoprotective in a murine model of PNALD, and it appears to be safe and efficacious for the treatment of this type of liver disease in children. A prospective randomized trial that is currently under way at the authors' institution will objectively determine the place of fish oil monotherapy in the prevention of PNALD.

4. de Meijer, V.E., Gura, K.M., Meisel, J.A., Le, H.D., and Puder, M. Parenteral fish oil as monotherapy for patients with parenteral nutrition-associated liver disease. *Pediatr Surg Int* 25: 123-124, 2009.

Keywords:

Child

Fat Emulsions, Intravenous/therapeutic use

Fatty Acids, Omega-3/ therapeutic use

Humans

Linoleic Acid/ therapeutic use

Liver Diseases/etiology/ therapy

Parenteral Nutrition

Short Bowel Syndrome/complications/ therapy

5. de Meijer, V.E., Le, H.D., Meisel, J.A., Gura, K.M., and Puder, M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr* 50: 212-218, 2010.

OBJECTIVE: The use of fish oil-based emulsions as the sole source of fat for patients receiving parenteral nutrition (PN) has raised concerns for the development of essential fatty acid deficiency (EFAD), hindering its adoption into clinical practice. The purpose of the present study was to examine fatty acid profiles of patients receiving no enteral energy, while completely dependent on PN and an intravenous fish oil-based lipid emulsion, for onset of EFAD and maintenance of growth. **PATIENTS AND METHODS:** Prospectively collected data from 10 patients were reviewed for evidence of EFAD, defined as a triene:tetraene ratio >0.2. Gestational age-adjusted z scores for length, growth, and head circumference at baseline were compared with the corresponding z scores at time of censoring. All of the patients received PN with a fish oil-based lipid emulsion at 1 g . kg . day as the sole source of fat energy for at least 1 month. The fish oil monotherapy was used under a compassionate use protocol. **RESULTS:** Median gestational age at the time of birth was 35 weeks, and median age at the start of treatment was 3.5 months. After a median time of 3.8 months on exclusive PN and fish oil-based lipid emulsion, none of the patients developed biochemical or clinical evidence of EFAD. z scores were not

statistically different, indicating no growth impairment. Median direct bilirubin levels improved in 9 patients from 6.8 to 0.9 mg/dL (P = 0.009).

CONCLUSIONS: When dosed appropriately, fish oil-based lipid emulsions contain sufficient amounts of essential fatty acids to prevent EFAD and sustain growth in patients who are completely dependent on PN.

6. Diamond, I.R., Pencharz, P.B., and Wales, P.W. Omega-3 lipids for intestinal failure associated liver disease. *Semin Pediatr Surg* 18: 239-245, 2009.

Intestinal failure associated liver disease (IFALD) is one of the most common and devastating complications in infants with intestinal failure. Although multifactorial, its pathophysiology is clearly related to the administration of parenteral nutrition (PN), with a recent focus on the role of PN lipid emulsions. This paper will review the evidence for the use of omega-3 fatty acid PN lipid emulsions, which are proposed to have efficacy in the treatment of IFALD. Mechanisms explaining their effects will be considered as will future research directions.

7. Diamond, I.R., Pencharz, P.B., and Wales, P.W. What is the current role for parenteral lipid emulsions containing omega-3 fatty acids in infants with short bowel syndrome? *Minerva Pediatr* 61: 263-272, 2009.

Parenteral nutrition associated liver disease is the most common complication of pediatric short bowel syndrome (SBS). There is emerging evidence that the disease may be reversed with the use of parenteral lipid emulsions derived from fish-oils, which contain significant concentrations of omega-3 fatty acids (w3FA). This paper will review the rationale for the use of parenteral lipid emulsions containing w3FA in SBS and the evidence for their efficacy. Given the promising results and apparent safety of these emulsions, we shall also consider what the current role for PN lipid emulsions containing w3FA in children with SBS should be.

8. Diamond, I.R., Sterescu, A., Pencharz, P.B., Kim, J.H., and Wales, P.W. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. *J Pediatr Gastroenterol Nutr* 48: 209-215, 2009.

BACKGROUND: Parenteral omega-3 fatty acids, such as Omegaven, may benefit patients with pediatric short bowel syndrome (SBS) who develop parenteral nutrition-associated liver disease (PNALD). PATIENTS AND METHODS: Retrospective cohort describing the outcome of all 12 children with SBS and advanced PNALD who were treated with Omegaven (target omega-6 to omega-3 fatty acid ratio = 1:1 to 2:1). RESULTS: The median age was 7.5 (range 3.6-46) months, and median parenteral nutrition duration before starting Omegaven was 28.4 (range 15.3-55.3) weeks. Median initial serum conjugated bilirubin was 137 (range 54-203) micromol/L (8.06 [3.18-11.94] mg/dL). Of the 12 patients, 9 had complete and sustained resolution of hyperbilirubinemia within a median of 24 (range 7-37) weeks, and all are no longer being considered for liver

transplantation. Improvements in markers of hepatic inflammation as well as nutritional status also were noted in these patients. Three patients received a liver-intestine transplant while taking Omegaven. There were no complications attributable to Omegaven. CONCLUSIONS: Omegaven is associated with restoration of liver function in patients with SBS and advanced liver disease. Parenteral omega-3 fatty acids, such as Omegaven, have the potential to fundamentally alter the paradigm of neonatal SBS from one of early death or transplantation from liver failure to a more chronic disease. More children with SBS should achieve full enteral tolerance and those who do not have the capacity for intestinal adaptation should be able to survive and receive an intestinal graft when older.

9. Diamond, I.R., Sterescu, A., Pencharz, P.B., and Wales, P.W. The rationale for the use of parenteral omega-3 lipids in children with short bowel syndrome and liver disease. *Pediatr Surg Int* 24: 773-778, 2008.

Parenteral nutrition associated liver disease (PNALD) is the major source of morbidity and mortality in children with short bowel syndrome (SBS). There is emerging evidence that omega-6 fatty acids (omega6FA) within the parenteral solution play a major role in PNALD and their effects may be reversed or ameliorated by substitution with omega-3 fatty acids (omega3FA). This paper reviews the mechanisms whereby omega3FAs may influence PNALD by improving bile flow, inhibiting steatosis, and having immunomodulatory effects. The early clinical experience with omega3FAs in SBS and PNALD is briefly reviewed and the implications of such, and future directions are considered.

10. Ekema, G., Milianti, S., and Boroni, G. Total parenteral nutrition in patients with short bowel syndrome. *Minerva Pediatr* 61: 283-291, 2009.

Nowadays short bowel syndrome (SBS) is quite frequent, because of more aggressive surgical and medical approaches to the management of neonatal intra-addominal catastrophes. Intestinal rehabilitation can be reached in case of SBS with a strategy that merges nutritional, pharmacologic and surgical approaches to achieve the ultimate goal of enteral nutrition. Long-term clinical nutrition which combines total parenteral nutrition (TPN) and enteral nutrition is required for the adaptation process. Long-term TPN can, however, be associated with mechanical, septic and metabolic complications, most of which have been consistently reduced by a better understanding of the prerequisites for its application and by improvements in parenteral solutions. Parenteral nutrition associated cholestasis (PNAC) and liver disease (PNALD) remain indeed the most worrisome complications and bear with them a high mortality rate. Their prevention will further improve the role of TPN in patients with SBS. The etiology of PNAC and PNALD, although elusive, is thought to be multifactorial and proposed theories also include problems arising from lipid emulsions. Parenteral nutrition, that includes n-3 fatty acids, appear to diminish the extent of the inflammatory response thought to be responsible for PNAC and PNALD. This

article will attempt to review the role of TPN in the rehabilitation process and discuss energy and macronutrients requirements.

11. Goulet, O., Joly, F., Corriol, O., and Colomb-Jung, V. Some new insights in intestinal failure-associated liver disease. *Curr Opin Organ Transplant* 14: 256-261, 2009.

PURPOSE OF REVIEW: To point new insights in the cholestasis that is a complication of both intestinal failure and parenteral nutrition. View on liver disease has recently evolved with the onset of fish oil-based intravenous lipid emulsions (ILE). **RECENT FINDINGS:** Focused on the role of ILE in causing liver disease. Reversal of cholestasis was recently achieved in infants with short bowel syndrome, by replacing the 'reference' soybean oil-based ILE by fish oil-based ILE. **SUMMARY:** It is likely that this reversal involves several factors such as the change in n-6: n-3 ratio, the reduction in phytosterol load, the increased provision of alpha-tocopherol as antioxidant agent. Alternative issue might be based on the use of a new generation of ILE aiming to provide n-3 and to reduce n-6 fatty acids load while enhancing alpha-tocopherol intake. New data are based on the use of an ILE containing a balanced proportion of four types of oil as a physical mixture of 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil and 15% fish oil with amounts of alpha-tocopherol calculated according to the number of double bonds. This new emulsion was reported to be beneficial in reversing or preventing liver disease.

12. Gura, K.M., Duggan, C.P., Collier, S.B., Jennings, R.W., Folkman, J., Bistran, B.R., and Puder, M. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics* 118: e197-201, 2006.

Here we report the reversal of cholestasis in 2 infants with intestinal failure and parenteral nutrition-associated liver disease. Treatment involved the substitution of a conventional intravenous fat emulsion with one containing primarily omega-3 fatty acids. Biochemical tests of liver function improved significantly. One child was removed from the liver transplantation list because of improved hepatic function, and the second child had complete resolution of cholestasis while solely on parenteral nutrition. This suggests that fat emulsions made from fish oils may be an effective means of treating and preventing this often-fatal condition. A randomized, controlled trial is necessary to study the efficacy of this new approach to parenteral nutrition-associated liver disease.

13. Gura, K.M., Lee, S., Valim, C., Zhou, J., Kim, S., Modi, B.P., Arsenault, D.A., Strijbosch, R.A., Lopes, S., Duggan, C., and Puder, M. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 121: e678-686, 2008.

BACKGROUND: Parenteral nutrition-associated liver disease can be a

progressive and fatal entity in children with short-bowel syndrome. Soybean-fat emulsions provided as part of standard parenteral nutrition may contribute to its pathophysiology. METHODS: We compared safety and efficacy outcomes of a fish-oil-based fat emulsion in 18 infants with short-bowel syndrome who developed cholestasis (serum direct bilirubin level of > 2 mg/dL) while receiving soybean emulsions with those from a historical cohort of 21 infants with short-bowel syndrome who also developed cholestasis while receiving soybean emulsions. The primary end point was time to reversal of cholestasis (3 consecutive measurements of serum direct bilirubin level of < or = 2 mg/dL). RESULTS: Among survivors, the median time to reversal of cholestasis was 9.4 and 44.1 weeks in the fish-oil and historical cohorts, respectively. Subjects who received fish-oil-based emulsion experienced reversal of cholestasis 4.8 times faster than those who received soybean emulsions and 6.8 times faster in analysis adjusted for baseline bilirubin concentration, gestational age, and the diagnosis of necrotizing enterocolitis. A total of 2 deaths and 0 liver transplantations were recorded in the fish-oil cohort and 7 deaths and 2 transplantations in the historical cohort. The provision of fish-oil-based fat emulsion was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, infections, or growth delay. CONCLUSIONS: Parenteral fish-oil-based fat emulsions are safe and may be effective in the treatment of parenteral nutrition-associated liver disease.

14. Hardy, G., and Puzovic, M. Formulation, stability, and administration of parenteral nutrition with new lipid emulsions. *Nutr Clin Pract* 24: 616-625, 2009.

Intravenous lipid emulsions (IVLE) are an important source of energy and essential fatty acids and their incorporation into pediatric and adult parenteral nutrition (PN) regimens has revolutionized nutrition therapy. However, their clinical use has not been without risk, and will continue to remain so because of the intravenous route of administration. Pharmaceutical and microbiological concerns are centered around the methods of compounding all-in-one (AIO) admixtures, but these can be largely minimized with today's technologies and advanced understanding of aseptic principles. Modern lipid products, based on olive, coconut, and/or fish oils, have demonstrable formulation and clinical benefits over traditional soybean and safflower IVLE and, when combined in the new multi-chamber bags, can also offer improvements in stability and safety. This review outlines the rationale for different lipid formulations in PN admixtures, reviews the factors influencing stability and efficacy of lipid-based AIO regimens and evaluates some technologies for minimizing peroxidation and maximizing stability of AIO admixtures.

15. Lee, S.I., Valim, C., Johnston, P., Le, H.D., Meisel, J., Arsenault, D.A., Gura, K.M., and Puder, M. Impact of fish oil-based lipid emulsion on serum triglyceride, bilirubin, and albumin levels in children with parenteral nutrition-associated liver disease. *Pediatr Res* 66: 698-703, 2009.

Parenteral nutrition is known to cause liver injury in babies. The aim of this study is to investigate the effects of different lipid emulsions on parenteral nutrition-associated cholestasis in infants. In addition, there may be a relationship between the lipid emulsion and triglyceride levels. Furthermore, triglyceride levels may correlate with direct bilirubin and albumin, as markers of liver impairment and nutritional status. Patients with parenteral nutrition-associated cholestasis who were treated with a fish oil-based lipid emulsion (n = 18) were prospectively followed for triglyceride, direct bilirubin, and albumin levels and compared with patients who were maintained on a soy-based lipid emulsion (n = 59). Triglyceride levels decreased in the fish oil cohort from a mean of 140 mg/dL at wk 0 to 40 mg/dL at wk 20 but remained unchanged at approximately 140 mg/dL in the soybean cohort. Triglyceride levels of patients treated with fish oil declined over time, while those receiving soybean oil did not. Also, changes in triglyceride levels over time were directly correlated with direct bilirubin and inversely related to albumin levels. These findings may indicate an added benefit of reduced triglyceride levels for patients treated with fish oil and this effect coincides with markers for improved liver function and nutritional status.

16. Mallah, H.S., Brown, M.R., Rossi, T.M., and Block, R.C. Parenteral fish oil-associated burr cell anemia. *J Pediatr* 156: 324-326 e321, 2010.

We report the development of burr cell anemia in an infant with short bowel syndrome who received parenteral fish oil (Omegaven, Fresenius-Kabi, Graz, Austria) after development of total parenteral nutrition-associated liver disease. Parenteral fish oil was discontinued, and the burr cell anemia disappeared, suggesting that parenteral fish oil might be associated with hemolytic anemia.

17. Puder, M., Valim, C., Meisel, J.A., Le, H.D., de Meijer, V.E., Robinson, E.M., Zhou, J., Duggan, C., and Gura, K.M. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 250: 395-402, 2009.

OBJECTIVE: The objective was to determine the safety and efficacy of a fish oil-based intravenous lipid emulsion (ILE) in the treatment of parenteral nutrition-associated liver disease (PNALD). **SUMMARY AND BACKGROUND DATA:** PNALD can be a lethal complication in children with short bowel syndrome (SBS). ILE based on soybean oil administered with parenteral nutrition (PN) may contribute to its etiology. **METHODS:** We performed an open-labeled trial of a fish oil-based ILE in 42 infants with SBS who developed cholestasis (serum direct bilirubin >2 mg/dL) while receiving soybean oil-based ILE. Safety and efficacy outcomes were compared with those from a contemporary cohort of 49 infants with SBS and cholestasis whose PN course included soybean ILE only. The primary efficacy end-point was time to reversal of cholestasis (direct bilirubin ≤2 mg/dL). **RESULTS:** Three deaths and 1 liver transplantation occurred in the fish oil cohort, compared with 12 deaths and 6 transplants in the soybean oil cohort (P = 0.005). Among survivors not transplanted during PN, cholestasis

reversed while receiving PN in 19 of 38 patients in the fish oil cohort versus 2 of 36 patients in the soybean oil cohort. Based on Cox models, subjects receiving fish oil-based ILE experienced reversal of cholestasis 6 times faster (95% CI: 2.0-37.3) than those receiving soybean oil-based ILE. The provision of fish oil-based ILE was not associated with hypertriglyceridemia, coagulopathy, or essential fatty acid deficiency. Moreover, hypertriglyceridemic events and abnormal international normalized ratio levels were more common among controls. CONCLUSIONS: Fish oil-based ILE is safe, may be effective in treating PNALD, and may reduce mortality and organ transplantation rates in children with SBS.

18. Soden, J.S., Lovell, M.A., Brown, K., Partrick, D.A., and Sokol, R.J. Failure of resolution of portal fibrosis during omega-3 fatty acid lipid emulsion therapy in two patients with irreversible intestinal failure. *J Pediatr* 156: 327-331, 2010.

Parenteral omega-3 fatty acid lipid emulsions have been evaluated for their potential role in reversing intestinal failure-associated liver disease. We report our experience using Omegaven in 2 patients with irreversible intestinal failure and intestinal failure-associated liver disease. Despite biochemical and histologic improvement in cholestasis, both patients had persisting, significant portal fibrosis on liver biopsy.

Miralax (Polyethylene Glycol 3350) for chronic constipation in pediatric population
07/21/2010
20 citations

1. Bekkali, N.L., van den Berg, M.M., Dijkgraaf, M.G., van Wijk, M.P., Bongers, M.E., Liem, O., and Benninga, M.A. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics* 124: e1108-1115, 2009.

OBJECTIVE: We hypothesized that enemas and polyethylene glycol (PEG) would be equally effective in treating rectal fecal impaction (RFI) but enemas would be less well tolerated and colonic transit time (CTT) would improve during disimpaction. METHODS: Children (4-16 years) with functional constipation and RFI participated. One week before disimpaction, a rectal examination was performed, symptoms of constipation were recorded, and the first CTT measurement was started. If RFI was determined, then patients were assigned randomly to receive enemas once daily or PEG (1.5 g/kg per day) for 6 consecutive days. During this period, the second CTT measurement was started and a child's behavior questionnaire was administered. Successful rectal disimpaction, defecation and fecal incontinence frequencies, occurrence of abdominal pain and watery stools, CTTs (before and after disimpaction), and behavior scores were assessed. RESULTS: Ninety-five patients were eligible, of whom 90 participated (male, n = 60; mean age: 7.5 +/- 2.8 years). Forty-six patients received enemas and 44 PEG, with 5 dropouts in each group. Successful disimpaction was achieved with enemas (80%) and PEG (68%; P = .28). Fecal incontinence and watery stools were reported more frequently with PEG (P < .01), but defecation frequency (P = .64), abdominal pain (P = .33), and behavior scores were comparable between groups. CTT normalized equally (P = .85) in the 2 groups. CONCLUSION: Enemas and PEG were equally effective in treating RFI in children. Compared with enemas, PEG caused more fecal incontinence, with comparable behavior scores. The treatments should be considered equally as first-line therapy for RFI.

2. Bell, E.A., and Wall, G.C. Pediatric constipation therapy using guidelines and polyethylene glycol 3350. *Ann Pharmacother* 38: 686-693, 2004.

OBJECTIVE: To review current guidelines on the treatment of functional constipation in pediatric patients, with an emphasis on the role of polyethylene glycol 3350 (PEG 3350). DATA SOURCES: Primary medical literature published in English was identified by MEDLINE search (1980-May 2003). STUDY SELECTION AND DATA EXTRACTION: Recently published treatment guidelines relating to pediatric functional constipation and its pharmacotherapy are assessed and compared. Published trials evaluating PEG 3350 in pediatric subjects are discussed and their results applied to the clinical role and use of this new agent. DATA SYNTHESIS: Constipation is a common disorder among

children. A number of factors may play a role. A variety of medications are commonly used for this disorder, although few treatments have undergone evaluation by controlled clinical trials. Consensus guidelines recommend either osmotic laxatives, mineral oil, or their combination for maintenance treatment in concert with patient and parental education and behavioral training. PEG 3350 solution (MiraLax) has been shown in recent clinical studies to be an effective maintenance treatment for pediatric constipation. CONCLUSIONS: PEG 3350 is an effective and well-tolerated treatment choice for pediatric constipation, especially as an adjunct to education and behavioral training. PEG 3350 is an option for children with constipation who have failed or are intolerant of other pharmacotherapies.

3. Candy, D.C., Edwards, D., and Geraint, M. Treatment of faecal impaction with polyethylene glycol plus electrolytes (PEG + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy. *J Pediatr Gastroenterol Nutr* 43: 65-70, 2006.

OBJECTIVES: To assess the efficacy of polyethylene glycol 3350 plus electrolytes (PEG + E; Movicol) as oral monotherapy in the treatment of faecal impaction in children, and to compare PEG + E with lactulose as maintenance therapy in a randomised trial. PATIENTS AND METHODS: An initial open-label study of PEG + E in the inpatient treatment of faecal impaction (phase 1), followed by a randomised, double-blind comparison between PEG + E and lactulose for maintenance treatment of constipation over a 3-month period (phase 2) in children aged 2 to 11 years with a clinical diagnosis of faecal impaction. RESULTS: Disimpaction on PEG + E was achieved in 58 (92%) of 63 of children (89% of 2-4 year olds and 94% of 5-11 year olds) without additional interventions. A maximum dose of 4 sachets (for 2-4 year olds) or 6 sachets (for 5-11 year olds) was required; median time to disimpaction was 6 days (range, 3-7 days). Seven children (23%) reimpacted whilst taking lactulose, whereas no children reimpacted while taking PEG + E ($P = 0.011$). The total incidence rate of adverse events seen was higher in the lactulose group (83%) than in the PEG + E group (64%). CONCLUSIONS: PEG + E is safe and highly effective in the management of childhood constipation. It allows a single orally administered laxative to be used for disimpaction without recourse to invasive interventions. It is significantly more effective than lactulose as maintenance therapy, both in efficacy in treating constipation and efficacy in preventing the recurrence of faecal impaction.

4. Chung, S., Cheng, A., and Goldman, R.D. Polyethylene glycol 3350 without electrolytes for treatment of childhood constipation. *Can Fam Physician* 55: 481-482, 2009.

ABSTRACT QUESTION: I have come across many pediatric patients with functional constipation. Is polyethylene glycol 3350 without electrolytes a safe and effective long-term treatment option for these patients? ANSWER:

Functional constipation is a common and often difficult problem for parents and families to deal with. Polyethylene glycol 3350 is a safe and effective long-term laxative in pediatric populations, but there are limited studies for its use in children younger than 2 years of age.

5. Erickson, B.A., Austin, J.C., Cooper, C.S., and Boyt, M.A. Polyethylene glycol 3350 for constipation in children with dysfunctional elimination. *J Urol* 170: 1518-1520, 2003.

PURPOSE: Children with daytime wetting often have constipation, and treatment of constipation helps children become dry. Polyethylene glycol 3350 (Miralax, Braintree Laboratories, Braintree, Massachusetts) is a nonaddictive, tasteless powder that can be mixed with any liquid for treatment of constipation.

MATERIALS AND METHODS: We review our use of polyethylene glycol 3350 in 35 girls and 11 boys with dysfunctional elimination. Noninvasive urodynamic studies and post-void residual measurement were performed before and during treatment. **RESULTS:** A significant increase in frequency of bowel movements occurred while taking polyethylene glycol 3350 ($p = 0.0001$). Average final dose was 0.63 gm/kg. The only reported adverse effect was diarrhea (9 patients). Of the children 18 became dry, 26 had decreased wetting and 2 had no improvement. Voided volume increased (146 vs 210 ml, $p < 0.0001$) and post-void residual decreased significantly (92 vs 48 ml, $p < 0.0001$) while on polyethylene glycol 3350. Ten children were still considered constipated including both patients who experienced no change in wetting. Average final dose in this group (0.69 gm/kg) did not differ significantly from those in whom constipation resolved (0.61 gm/kg). Patients in whom constipation resolved had a significantly lower post-void residual than those who remained constipated (11.8% vs 30.6%, $p < 0.01$) and were significantly more likely to become dry or improved ($p = 0.045$). **CONCLUSIONS:** The efficacy, compliance and lack of significant side effects make polyethylene glycol 3350 an ideal substance for treatment of constipation in children with dysfunctional elimination. Persistent constipation was associated with decreased resolution of voiding symptoms and significantly increased post-void residuals.

6. Gremse, D.A., Hixon, J., and Crutchfield, A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. *Clin Pediatr (Phila)* 41: 225-229, 2002.

Polyethylene glycol (PEG) 3350 and lactulose were compared in an unblinded, randomized, crossover design for treatment of constipation in 37 children aged 2 to 16 years. Subjects received lactulose (1.3 g/kg/d divided twice daily up to 20 g) or PEG 3350 (10 g/m²/day) for 2 weeks. PEG 3350 significantly decreased the total colonic transit time compared to lactulose (47.6 \pm 2.7 vs 55.3 \pm 2.4 hours, mean \pm SE, PEG 3350 vs lactulose, respectively, $p = 0.038$). The stool frequency, form, and the ease of passage were similar for each laxative. Polyethylene glycol 3350 is an effective laxative for the treatment of chronic

constipation in children.

7. Hanson, S., and Bansal, N. The clinical effectiveness of Movicol in children with severe constipation: an outcome audit. *Paediatr Nurs* 18: 24-28, 2006.

This audit reviewed the clinical effectiveness of polyethylene glycol 3350 plus electrolytes (PEG+E, Movicol) in the management of severe paediatric constipation. A seven-day disimpaction regimen was initiated followed by a maintenance dose as appropriate. An information and support service was provided by the community children's nursing team (CCNT) at Darent Valley Hospital. Twenty-three parents completed questionnaires on their children's experiences with previous and current laxative treatments, bowel movement status, in-patient admissions or home visits required and the perceived value of the back up service. The mean age of children studied was 6.7 years. Prior to PEG+E treatment, 57 per cent of children were admitted to hospital and 26 per cent required home visits for constipation treatment. After treatment, no child needed either intervention. Thirty-nine percent of parents used the support service, of which 96 per cent rated the information it provided as adequate. When asked about their satisfaction with the control of their children's constipation, 96 per cent of parents were 'more than happy' after treatment with PEG+E. The treatment of severe paediatric constipation with PEG+E in conjunction with a support and advice service was both clinically and economically effective.

8. Kinservik, M.A., and Friedhoff, M.M. The efficacy and safety of polyethylene glycol 3350 in the treatment of constipation in children. *Pediatr Nurs* 30: 232-237, 2004.

Keywords:

Adolescent

Age Factors

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Child, Preschool

Constipation/ drug therapy

Evidence-Based Medicine/organization & administration

Humans

Infant

Patient Education as Topic

Pediatrics/methods/standards

Polyethylene Glycols/ therapeutic use

Practice Guidelines as Topic

Research Design

Safety

Treatment Outcome

9. Loening-Baucke, V. Polyethylene glycol without electrolytes for children with

constipation and encopresis. *J Pediatr Gastroenterol Nutr* 34: 372-377, 2002.

BACKGROUND: Children with functional constipation and encopresis benefit from behavior modification and from long-term laxative medication. Polyethylene glycol without electrolytes has become the first option for many pediatric gastroenterologists. **METHODS:** Twenty-eight children treated with polyethylene glycol without electrolytes were compared with 21 children treated with milk of magnesia to evaluate the efficiency, acceptability, side effects, and treatment dosage of polyethylene glycol in long-term treatment of functional constipation and encopresis. Children were rated as "doing well," "improved," or "not doing well," depending on resolution of constipation and encopresis. **RESULTS:** At the 1-, 3-, 6-, and 12-month follow-ups, bowel movement frequency increased and soiling frequency decreased significantly in both groups. At the 1-month follow-up, children on polyethylene glycol were soiling more frequently ($P < 0.01$) and fewer were improved ($P < 0.01$). At the 3- and 6-month follow-ups, both groups had similarly improved. At the 12-month visit, 61% of children on polyethylene glycol and 67% of children on milk of magnesia were doing well. Children on polyethylene glycol soiled more frequently ($P < 0.01$). None refused polyethylene glycol, but 33% refused to take milk of magnesia. The mean initial treatment dosage of polyethylene glycol was 0.6 ± 0.2 g/kg daily. Polyethylene glycol had no taste, and no loss of efficacy occurred. Polyethylene glycol did not cause clinically significant side effects. **CONCLUSIONS:** Polyethylene glycol without electrolytes is an alternative for long-term management of children with constipation and encopresis.

10. Loening-Baucke, V. Prevalence, symptoms and outcome of constipation in infants and toddlers. *J Pediatr* 146: 359-363, 2005.

OBJECTIVE: To determine the prevalence of constipation in children ≤ 2 years, describe the symptoms of constipation, and review how often specific interventions were effective. **STUDY DESIGN:** Retrospective chart review. **RESULTS:** Of 4,157 children < 2 years of age, 185 children had constipation. The prevalence rate for constipation in the first year of life was 2.9%, and in the second year of life, the rate was 10.1%. Functional constipation was the cause in 97% of the children. Boys and girls were affected with equal frequency. Constipation was caused by an underlying organic disease in 1.6% of cases, and 97% of the children had functional constipation. Dietary changes and corn syrup were the initial treatment suggestions for 116 children; 93% of these children underwent follow-up examinations, and the constipation resolved in 25% of the children. Of 100 children treated with milk of magnesia or polyethylene glycol 3350 without electrolytes, 93 children underwent follow-up examinations, and the constipation was resolved with treatment in 92% of the children. **CONCLUSIONS:** Dietary changes, corn syrup, or both resolved constipation in 25% of children, and laxatives resolved constipation in 92% of children. Both milk of magnesia and polyethylene glycol were efficient and safe in infants and toddlers.

11. Loening-Baucke, V., and Pashankar, D.S. A randomized, prospective, comparison study of polyethylene glycol 3350 without electrolytes and milk of magnesia for children with constipation and fecal incontinence. *Pediatrics* 118: 528-535, 2006.

OBJECTIVE: Our aim was to compare 2 laxatives, namely, polyethylene glycol 3350 without electrolytes and milk of magnesia, evaluating the efficacy, safety, acceptance, and 1-year outcomes. METHODS: Seventy-nine children with chronic constipation and fecal incontinence were assigned randomly to receive polyethylene glycol or milk of magnesia and were treated for 12 months in tertiary care pediatric clinics. Children were counted as improved or recovered depending on resolution of constipation, fecal incontinence, and abdominal pain after 1, 3, 6, and 12 months. An intent-to-treat analysis was used. Safety was assessed with evaluation of clinical adverse effects and blood tests. RESULTS: Thirty-nine children were assigned randomly to receive polyethylene glycol and 40 to receive milk of magnesia. At each follow-up visit, significant improvement was seen in both groups, with significant increases in the frequency of bowel movements, decreases in the frequency of incontinence episodes, and resolution of abdominal pain. Compliance rates were 95% for polyethylene glycol and 65% for milk of magnesia. After 12 months, 62% of polyethylene glycol-treated children and 43% of milk of magnesia-treated children exhibited improvement, and 33% of polyethylene glycol-treated children and 23% of milk of magnesia-treated children had recovered. Polyethylene glycol and milk of magnesia did not cause clinically significant side effects or blood abnormalities, except that 1 child was allergic to polyethylene glycol. CONCLUSIONS: In this randomized study, polyethylene glycol and milk of magnesia were equally effective in the long-term treatment of children with constipation and fecal incontinence. Polyethylene glycol was safe for the long-term treatment of these children and was better accepted by the children than milk of magnesia.

12. Nurko, S., Youssef, N.N., Sabri, M., Langseder, A., McGowan, J., Cleveland, M., and Di Lorenzo, C. PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial. *J Pediatr* 153: 254-261, 261 e251, 2008.

OBJECTIVE: To establish the efficacy and best starting dose of polyethylene glycol (PEG)3350 in the short-term treatment of children with functional constipation. STUDY DESIGN: Prospective, randomized, multicenter, double-blinded, placebo-controlled, dose-ranging study of PEG3350 in children with functional constipation. Patients were randomly assigned to either placebo or 0.2 g/kg per day, 0.4 g/kg per day, or 0.8 g/kg per day of PEG3350 after a 1 week run-in period, followed by 2 weeks of treatment. All received behavior modification. The primary outcome was the proportion of patients with a successful treatment response: ≥ 3 bowel movements (BM) in the second week. RESULTS: 103 children (mean, 8.5 +/- 3.1 years) were enrolled. 77%,

74%, and 73% of the 0.2, 0.4, and 0.8 g/kg groups were successfully treated, as compared with 42% receiving placebo ($P < .04$). There was a significant increase in BM ($P < .001$) and straining improvement ($P < .05$) with the different PEG3350 doses. Stool consistency improved significantly for doses 0.4 g/kg or higher ($P < .001$). There was more abdominal pain and fecal incontinence in patients receiving 0.8 g/kg. PEG3350 was well tolerated. CONCLUSIONS: This placebo-controlled study confirms the efficacy and safety of PEG3350 for the short-term treatment of children with functional constipation. We recommend a starting dose of 0.4 g/kg per day.

13. O'Connor, J. Polyethylene glycol 3350 without electrolytes: a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr Gastroenterol Nutr* 39: 105-106, 2004.
14. Pashankar, D.S. Childhood constipation: evaluation and management. *Clin Colon Rectal Surg* 18: 120-127, 2005.

Constipation is a common problem in children. It is also a long-term problem persisting for many months to years in children. Approximately 95% of childhood constipation is functional in nature without any obvious cause. Evaluation of a child with constipation requires a thorough history and physical examination. Hirschsprung's disease is an important cause of constipation arising in infancy and requires a thorough diagnostic evaluation and surgical treatment. Treatment of functional constipation in children requires a well-designed plan and a team approach involving the child, parents, and a health care provider. Treatment involves education of the family about constipation and encopresis, fecal disimpaction, and long-term maintenance therapy of laxatives and behavioral modification. Laxatives such as magnesium hydroxide, lactulose, and mineral oil have been used in children for a long time. A new laxative, polyethylene glycol 3350, has been used successfully in children with constipation and encopresis. Several novel therapeutic interventions have been tried for children presenting with intractable constipation, refractory to conventional treatment.

15. Pashankar, D.S., and Bishop, W.P. Efficacy and optimal dose of daily polyethylene glycol 3350 for treatment of constipation and encopresis in children. *J Pediatr* 139: 428-432, 2001.

OBJECTIVE: To determine efficacy, safety, and optimal dose of a laxative, polyethylene glycol (PEG) 3350, in children with chronic constipation. STUDY DESIGN: Children with chronic constipation ($n = 24$) were treated with PEG for 8 weeks at an initial dose of 1 g/kg/d. The dose was adjusted every 3 days as required to achieve 2 soft stools per day. A diary was kept to monitor dose, stool frequency and consistency, soiling, and other symptoms. Stool consistency was rated from 1 (hard) to 5 (watery). Subjects were examined for fecal retention. The

Student t test and the Fisher exact test were used for data analysis. RESULTS: All 20 children who completed the study found PEG to be palatable and were satisfied with the treatment. There were no significant adverse effects. Weekly stool frequency increased from 2.3 +/- 0.4 to 16.9 +/- 1.6 (P <.0001) during treatment and stool consistency from 1.2 +/- 0.1 to 3.3 +/- 0.1 (P <.0001). In 9 children with soiling, weekly soiling events declined from 10.0 +/- 2.4 to 1.3 +/- 0.7 (P =.003). The mean effective dose was 0.84 g/kg/d (range, 0.27-1.42 g/kg/d). CONCLUSION: Daily administration of PEG at a mean dose of 0.8 g/kg is an effective, safe, and palatable treatment for constipation.

16. Pashankar, D.S., Bishop, W.P., and Loening-Baucke, V. Long-term efficacy of polyethylene glycol 3350 for the treatment of chronic constipation in children with and without encopresis. *Clin Pediatr (Phila)* 42: 815-819, 2003.

Seventy-four children (43 with chronic constipation, 31 with constipation and encopresis) treated with polyethylene glycol 3350 (PEG) for longer than 3 months were studied to assess long-term efficacy. The mean duration of PEG therapy was 8.4 months (range, 3-30). Weekly stool frequency, stool consistency, and symptoms associated with constipation improved significantly with PEG therapy in all 74 patients. In 31 children with encopresis, soiling ceased completely in 16 patients and frequency of soiling decreased significantly in all others. The average effective long-term dose of PEG was 0.7 g/kg/day. Long-term PEG therapy is effective for the treatment of chronic constipation with and without encopresis in children.

17. Pashankar, D.S., Loening-Baucke, V., and Bishop, W.P. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. *Arch Pediatr Adolesc Med* 157: 661-664, 2003.

OBJECTIVES: To assess the clinical and biochemical safety profile of long-term polyethylene glycol 3350 (PEG) therapy in children with chronic constipation and to assess pediatric patient acceptance of PEG therapy. DESIGN: Prospective observational study. SETTING: Pediatric clinics at a referral center. Patients Eighty-three children (44 with chronic constipation, 39 with constipation and encopresis) receiving PEG therapy for more than 3 months. MAIN OUTCOME MEASURES: Clinical adverse effects related to PEG therapy and acceptance and compliance with PEG therapy. Serum electrolyte levels, osmolality, albumin levels, and liver and renal function test results were measured. RESULTS: At the time of evaluation, the mean duration of PEG therapy was 8.7 months, and the mean PEG dose was 0.75 g/kg daily. There were no major clinical adverse effects. All blood test results were normal, except for transient minimal alanine aminotransferase elevation unrelated to therapy in 9 patients. All children preferred PEG to previously used laxatives, and daily compliance was measured as good in 90% of children. CONCLUSIONS: Long-term PEG therapy is safe and is well accepted by children with chronic constipation with and without encopresis.

18. Thomson, M.A., Jenkins, H.R., Bisset, W.M., Heuschkel, R., Kalra, D.S., Green, M.R., Wilson, D.C., and Geraint, M. Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study. *Arch Dis Child* 92: 996-1000, 2007.

OBJECTIVES: To assess the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG+E) for the treatment of chronic constipation in children. **DESIGN:** Randomised, double blind, placebo controlled crossover trial, with two 2-week treatment periods separated by a 2-week placebo washout. **SETTING:** Six UK paediatric departments. **PARTICIPANTS:** 51 children (29 girls, 22 boys) aged 24 months to 11 years with chronic constipation (lasting > or =3 months), defined as < or =2 complete bowel movements per week and one of the following: pain on defaecation on 25% of days; > or =25% of bowel movements with straining; > or =25% of bowel movements with hard/lumpy stools. 47 children completed the double blind treatment. **MAIN OUTCOME MEASURES:** Number of complete defaecations per week (primary efficacy variable), total number of complete and incomplete defaecations per week, pain on defaecation, straining on defaecation, faecal incontinence, stool consistency, global assessment of treatment, adverse events and physical examination. **RESULTS:** The mean number of complete defaecations per week was significantly higher for children on PEG+E than on placebo (3.12 (SD 2.05) v 1.45 (SD 1.20), respectively; $p < 0.001$). Further significant differences in favour of PEG+E were observed for total number of defaecations per week ($p = 0.003$), pain on defaecation ($p = 0.041$), straining on defaecation ($p < 0.001$), stool consistency ($p < 0.001$) and percentage of hard stools ($p = 0.001$). Treatment related adverse events (all mild or moderate) occurred in similar numbers of children on PEG+E (41%) and placebo during treatment (45%). **CONCLUSIONS:** PEG+E is significantly more effective than placebo, and appears to be safe and well tolerated in the treatment of chronic constipation in children.

19. Voskuijl, W., de Lorijn, F., Verwijs, W., Hogeman, P., Heijmans, J., Makel, W., Taminiau, J., and Benninga, M. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut* 53: 1590-1594, 2004.

BACKGROUND: Recently, polyethylene glycol (PEG 3350) has been suggested as a good alternative laxative to lactulose as a treatment option in paediatric constipation. However, no large randomised controlled trials exist evaluating the efficacy of either laxative. **AIMS:** To compare PEG 3350 (Transipeg: polyethylene glycol with electrolytes) with lactulose in paediatric constipation and evaluate clinical efficacy/side effects. **PATIENTS:** One hundred patients (aged 6 months-15 years) with paediatric constipation were included in an eight week double blinded, randomised, controlled trial. **METHODS:** After faecal disimpaction, patients <6 years of age received PEG 3350 (2.95 g/sachet) or lactulose (6 g/sachet) while children > or =6 years started with 2 sachets/day. Primary

outcome measures were: defecation and encopresis frequency/week and successful treatment after eight weeks. Success was defined as a defecation frequency ≥ 3 /week and encopresis ≤ 1 every two weeks. Secondary outcome measures were side effects after eight weeks of treatment. RESULTS: A total of 91 patients (49 male) completed the study. A significant increase in defecation frequency (PEG 3350: 3 pre v 7 post treatment/week; lactulose: 3 pre v 6 post/week) and a significant decrease in encopresis frequency (PEG 3350: 10 pre v 3 post/week; lactulose: 8 pre v 3 post/week) was found in both groups (NS). However, success was significantly higher in the PEG group (56%) compared with the lactulose group (29%). PEG 3350 patients reported less abdominal pain, straining, and pain at defecation than children using lactulose. However, bad taste was reported significantly more often in the PEG group. CONCLUSIONS: PEG 3350 (0.26 (0.11) g/kg), compared with lactulose (0.66 (0.32) g/kg), provided a higher success rate with fewer side effects. PEG 3350 should be the laxative of first choice in childhood constipation.

20. Youssef, N.N., Peters, J.M., Henderson, W., Shultz-Peters, S., Lockhart, D.K., and Di Lorenzo, C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. *J Pediatr* 141: 410-414, 2002.

OBJECTIVE: To investigate the efficacy and safety of polyethylene glycol (PEG) 3350 in the treatment of childhood fecal impaction. METHODS: This was a prospective, double-blind, parallel, randomized study of 4 doses of PEG 3350; 0.25 g/kg per day, 0.5 g/kg per day, 1 g/kg per day, 1.5 g/kg per day, given for 3 days in children with constipation for >3 months and evidence of fecal impaction. RESULTS: Forty patients completed the study (27 boys, median age 7.5, range 3.3-13.1 years). Disimpaction occurred in 75% of children, with a significant difference between the two higher doses and the lower doses (95% vs 55%, $P < .005$). All groups had an increased number of bowel movements during the 5-day study versus baseline, respectively: 6.5 versus 1.1 ($P < .005$), 8.0 versus 1.3 ($P < .005$), 10.9 versus 1.7 ($P < .005$), and 12.3 versus 1.4 ($P < .005$). Adverse effects included nausea (5%), vomiting (5%), bloating (18%), cramping (5%), and diarrhea (13%). Diarrhea and bloating were more prevalent ($P < .02$) in the higher-dose than in the lower-dose group. No clinically significant changes in electrolytes were noted. CONCLUSIONS: The 3-day administration of PEG 3350 is safe and effective in the treatment of childhood fecal impaction at doses of 1 and 1.5 g/kg per day.

Treatments for irritable and inflammatory bowel diseases (pediatric);
Clinical trials and reviews;
July 23, 2010
108 citations with abstracts

1. Ament, M.E., and Vargas, J.H. Medical therapy for ulcerative colitis in childhood. *Semin Pediatr Surg* 3: 28-32, 1994.

Corticosteroids remain the primary therapeutic agent to induce remission in moderate to severe ulcerative colitis (UC) and Crohn's disease because of their rapidity of action in comparison to other agents. Mild UC and/or Crohn's disease of the colon and terminal small bowel may be treated with azulfidine first. However, if patients are intolerant of these medications, dipentum or asacol may be used. Occasionally, patients with Crohn's colitis but not UC may respond to metronidazole. Immunosuppressive agents such as 6-mercaptopurine are very useful for steroid-dependent inflammatory bowel disease, as a substitute for long-term corticosteroids. Cyclosporine, although it has been proposed as an alternative to other antimetabolite or immunosuppressive therapy, is of benefit in fewer than 25% of cases of UC or Crohn's disease. Rowasa enemas are useful for left-sided disease in UC or Crohn's disease of the colon; however, use in children may be difficult in view of psychosocial issues that must be considered.

2. Baldassano, R., Braegger, C.P., Escher, J.C., DeWoody, K., Hendricks, D.F., Keenan, G.F., and Winter, H.S. Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol* 98: 833-838, 2003.

OBJECTIVE: The aim of this study was to assess the efficacy and safety of a single infusion of infliximab in the treatment of pediatric Crohn's disease (CD).
METHODS: A total of 21 pediatric CD patients were enrolled at seven study centers and randomized to receive a single infusion of infliximab 1 mg/kg (n = 6), 5 mg/kg (n = 7), or 10 mg/kg (n = 8) over at least 2 hrs at week 0 in this multicenter, open-label, dose-blinded trial. Efficacy assessments, including the Pediatric Crohn's Disease Activity Index (PCDAI), modified CDAI, C-reactive protein concentration (CRP), and erythrocyte sedimentation rate (ESR) determinations, were made at screening and at weeks 1, 2, 4, 8, and 12. Adverse events were assessed throughout study participation. **RESULTS:** Improvements in the PCDAI, modified CDAI, ESR, and CRP were observed with all infliximab doses, beginning at week 1. On average, all treated patients experienced approximately 50% improvement in the PCDAI by week 2. By week 12, the PCDAI remained approximately 30% improved from baseline. During the study, all 21 patients (100%) achieved a clinical response, and 10 patients (48%) achieved clinical remission. There were no infusion reactions in any of the treatment arms. **CONCLUSIONS:** The results of this trial suggest that infliximab may be safe and effective as short-term therapy of medically refractory moderate to severe CD in a pediatric population.

3. Barabino, A., Torrente, F., Castellano, E., Gandullia, P., Calvi, A., Cucchiara, S., De, G.L., Fontana, M., Lionetti, P., De Giacomo, C., and Gissi, A. The use of ciclosporin in paediatric inflammatory bowel disease: an Italian experience. *Aliment Pharmacol Ther* 16: 1503-1507, 2002.

AIM: To assess the efficacy and safety of ciclosporin in a paediatric population with inflammatory bowel disease. PATIENTS AND METHODS: Twenty-three Italian children treated with ciclosporin were studied retrospectively. The indications for treatment were severe unresponsive colitis, chronic active colitis or severe fistulizing Crohn's disease. The treatment duration, follow-up and causes of drug discontinuation were assessed. RESULTS: Sixteen patients were treated intravenously for a mean time of 10 +/- 7 days (1-24 days) and 19 orally for a mean time of 133 days (17-660 days). The mean follow-up of all patients was 13.2 months. Ciclosporin was totally ineffective, being discontinued for surgery, in nine of 23 patients (39%); it was discontinued for partial response in three patients (13%). During treatment, clinical remission was achieved in eight children (35%) and maintained after drug withdrawal in four (17%). In severe unresponsive colitis, urgent colectomy was avoided in 12 (85%) of 14 patients who tolerated the drug. Side-effects appeared in six of 23 patients (26%), and three (13%) required ciclosporin to be discontinued due to neurotoxicity. CONCLUSIONS: Ciclosporin shows disappointing long-term results in the treatment of refractory inflammatory bowel disease, but can play an important role in preventing urgent surgery in unresponsive severe colitis. Severe side-effects can occur.

4. Biancone, L., Orlando, A., Kohn, A., Colombo, E., Sostegni, R., Angelucci, E., Rizzello, F., Castiglione, F., Benazzato, L., Papi, C., Meucci, G., Riegler, G., Petruzzello, C., Mocciaro, F., Geremia, A., Calabrese, E., Cottone, M., and Pallone, F. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 55: 228-233, 2006.

BACKGROUND AND AIMS: The widespread use of anti-tumour necrosis factor alpha antibody (Infliximab) in Crohn's disease (CD) raises concerns about a possible cancer risk in the long term. In a matched pair study, we assessed whether Infliximab is associated with an increased risk of neoplasia. METHODS: In a multicentre matched pair study, 404 CD patients treated with Infliximab (CD-IFX) were matched with 404 CD patients who had never received Infliximab (CD-C). Cases and controls were matched for sex, age (+/-5 years), site of CD, age at diagnosis (+/-5 years), immunosuppressant use, and follow up. New diagnoses of neoplasia from April 1999 to October 2004 were recorded. RESULTS: Among the 404 CD-IFX, neoplasia was diagnosed in nine patients (2.22%) while among the 404 CD-C, seven patients developed neoplasia (1.73%) (odds ratio 1.33 (95% confidence interval 0.46-3.84); p=0.40). The survival curve adjusted for patient year of follow up showed no differences between CD-IFX and CD-C (p=0.90; log rank test). In the CD-IFX group, there was one cholangiocarcinoma,

three breast cancers, one skin cancer, one leukaemia, one laryngeal cancer, and two anal carcinomas. Among the 7/404 (1.73%) CD-C, there were three intestinal adenocarcinomas (two caecum, one rectum), one basalioma, one spinalioma, one non-Hodgkin's lymphoma, and one breast cancer. Age at diagnosis of neoplasia did not differ between groups (CD-IFX v CD-C: median 50 (range 40-70 years) v 45 (27-72); $p=0.50$). CONCLUSION: In our multicentre matched pair study, the frequency of a new diagnosis of neoplasia in CD patients treated with Infliximab was comparable with CD patients who had never received Infliximab.

5. Borrelli, O., Bascietto, C., Viola, F., Bueno de Mesquita, M., Barbato, M., Mancini, V., Bosco, S., and Cucchiara, S. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig Liver Dis* 36: 342-347, 2004.

BACKGROUND: Infliximab has recently emerged as an efficacious agent for patients with severe Crohn's disease. There are only few studies on the use of infliximab in children with Crohn's disease: most of them are retrospective and deal only with the clinical response to the drug. **AIM:** We aimed at assessing the efficacy of infliximab in children and adolescents with severe Crohn's disease recruited consecutively and followed up prospectively at a single centre. Clinical response, intestinal inflammation and growth pattern were evaluated. **PATIENTS:** Eighteen patients entered into the trial (median age: 13 years, range: 6-18). They were referred because of severe symptoms with unsatisfactory response to conventional drugs. **METHODS:** All patients received a baseline schedule of three intravenous infusions of infliximab (0, 2 and 6 weeks), 5 mg/kg. Paediatric Crohn's Disease Activity Index, nutritional and activity serum variables, and ileocolonoscopy (with histology) were evaluated before and 8 weeks after beginning the therapy. All patients had long-term administration of azathioprine (2 mg/kg per day). After the baseline schedule, eight patients had a retreatment infusion of infliximab (5 mg/kg) every 8 weeks. Weight and height Z scores were measured before starting the baseline infusion programme and after 6 months. **RESULTS:** After 8 weeks of therapy, there was a dramatic improvement in Paediatric Crohn's Disease Activity Index, in nutritional and activity blood parameters, as well as in endoscopic and histological scores; 10 patients had a clinical remission (Paediatric Crohn's Disease Activity Index ≤ 10), 12 patients had an inflammatory remission (decrease in both endoscopic and histological scores for $\geq 50\%$ as compared to baseline values). In all patients corticosteroids were stopped within 4 weeks after beginning infliximab therapy. After 6 months of therapy, Paediatric Crohn's Disease Activity Index was markedly lower than the pre-treatment value; however, it was significantly lower in patients on retreatment than in those who received only three infusions of infliximab. Furthermore, a significant increase in both weight and height Z scores was observed 6 months after beginning of the baseline infusion programme. Moreover, weight and height gain was significantly higher in patients on retreatment rather than in those treated only with three baseline infusions of infliximab. Mild infusion reactions controlled by slowing infusion rate were

observed in four patients. No delayed hypersensitivity-like reactions were seen. CONCLUSIONS: In children with severe Crohn's disease, infliximab is a safe and valuable treatment in inducing remission, in healing inflammatory lesions of the gut, as documented by endoscopy and histology, and in promoting growth. Retreatment infusions of infliximab may be suggested in childhood-onset Crohn's disease to maintain remission and reverse growth failure.

6. Borrelli, O., Cordischi, L., Cirulli, M., Paganelli, M., Labalestra, V., Uccini, S., Russo, P.M., and Cucchiara, S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 4: 744-753, 2006.

BACKGROUND & AIMS: Nutritional therapy has been reported to have an almost equivalent efficacy of corticosteroids in achieving clinical remission in active Crohn's disease (CD). However, the effects of both treatments on intestinal mucosal inflammation rarely are reported. In a randomized controlled trial in children with active CD we compared the efficacy of nutritional therapy alone or corticosteroids on clinical variables and intestinal mucosal healing. METHODS: In a prospective, 10-week open-label trial, children with active, naive CD were randomized to orally polymeric formula alone or oral corticosteroids. The clinical activity index and nutritional and activity serum variables were evaluated at week 0 and then every 2 weeks; intestinal mucosal inflammation was assessed through endoscopy and histology at weeks 0 and 10. Primary efficacy outcomes were clinical remission and mucosal healing. RESULTS: Of the 37 children randomized, 19 received polymeric formula and 18 received corticosteroids. At week 10, on an intention-to-treat basis, the proportion of patients achieving clinical remission was comparable between the 2 groups (polymeric formula: 15/19 [79%; 95% confidence interval (CI), 56%-92%]; corticosteroid group: 12/18 [67%; 95% CI, 44%-84%]; $P = .4$; not significant). On the contrary, the proportion of children showing mucosa healing was significantly higher in the polymeric (14/19; 74%; 95% CI, 51%-89%) than the corticosteroid group (6/18 [33%; 95% CI, 16%-57%]; $P < .05$). At week 10 both endoscopic and histologic scores significantly decreased only in the polymeric group ($P < .001$). CONCLUSIONS: In children with active and recently diagnosed CD, a short course of polymeric diet is more effective than corticosteroids in inducing healing of gut inflammatory lesions.

7. Bousvaros, A., Guandalini, S., Baldassano, R.N., Botelho, C., Evans, J., Ferry, G.D., Goldin, B., Hartigan, L., Kugathasan, S., Levy, J., Murray, K.F., Oliva-Hemker, M., Rosh, J.R., Tolia, V., Zholudev, A., Vanderhoof, J.A., and Hibberd, P.L. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis* 11: 833-839, 2005.

Probiotics are widely used by patients with Crohn's disease (CD) in an attempt to improve their health, but few controlled studies have been done to evaluate the

efficacy of these therapies. We conducted a randomized, placebo-controlled trial of the probiotic *Lactobacillus rhamnosus* strain GG (LGG) to see if the addition of LGG to standard therapy prolonged remission in children with CD. Concomitant medications allowed in the study included aminosalicylates, 6-mercaptopurine, azathioprine, and low-dose alternate day corticosteroids. Seventy-five children (age range, 5-21 yr) with CD in remission were randomized to either LGG (n=39) or placebo (n=36) and followed for up to 2 years. The median time to relapse was 9.8 months in the LGG group and 11.0 months in the placebo group (P=0.24); 31% (12/39) of patients in the LGG group developed a relapse compared with 6/36 (17%) of the placebo group (P=0.18). The LGG was well tolerated, with a side effect profile comparable with placebo. This study suggests that LGG does not prolong time to relapse in children with CD when given as an adjunct to standard therapy.

8. Bousvaros, A., Kirschner, B.S., Werlin, S.L., Parker-Hartigan, L., Daum, F., Freeman, K.B., Balint, J.P., Day, A.S., Griffiths, A.M., Zurakowski, D., Ferry, G.D., and Leichtner, A.M. Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 137: 794-799, 2000.

OBJECTIVE: To evaluate the efficacy of oral tacrolimus as an induction agent in steroid-refractory severe colitis. **STUDY DESIGN:** Open-label, multicenter trial of oral tacrolimus in patients with severe colitis. Patients not responding to conventional therapy received tacrolimus, 0.1 mg/kg/dose given twice a day, and the dosage was adjusted to achieve blood levels between 10 and 15 ng/mL. Response was defined as improvement in a number of clinical parameters (including abdominal pain, diarrhea, rectal bleeding, and cessation of transfusions). Patients who responded by 14 days continued to receive tacrolimus, and 6-mercaptopurine or azathioprine was added as a steroid-sparing agent 4 to 6 weeks after the tacrolimus was instituted. **RESULTS:** Fourteen patients were enrolled in the study. One patient elected to withdraw after 48 hours. Of the 13 remaining, 9 (69%) responded and were discharged. Tacrolimus was continued for 2 to 3 months in the responders, except for 1 patient who was given tacrolimus for 11 months. After 1 year of follow-up, only 5 (38%) patients were receiving maintenance therapy; the other 4 responders had undergone colectomy. **CONCLUSION:** Although tacrolimus is effective induction therapy for severe ulcerative or Crohn's colitis, fewer than 50% of patients treated will successfully achieve a long-term remission.

9. Breese, E.J., Michie, C.A., Nicholls, S.W., Williams, C.B., Domizio, P., Walker-Smith, J.A., and MacDonald, T.T. The effect of treatment on lymphokine-secreting cells in the intestinal mucosa of children with Crohn's disease. *Aliment Pharmacol Ther* 9: 547-552, 1995.

BACKGROUND: Recent studies have shown both interleukin 2 (IL-2) and interferon gamma (IFN) to be elevated in patients with active Crohn's disease compared to ulcerative colitis or non-inflammatory bowel disease controls.

However the effect of treatment on these lymphokines has not been studied. PATIENTS AND METHODS: Using a reverse haemolytic plaque assay the percentage of lymphokine-secreting cells was determined in the intestinal mucosa of children with Crohn's disease before and after 8 weeks of treatment with either enteral nutrition, cyclosporin or steroids. RESULTS: Before treatment, a high percentage of cells isolated from mucosal biopsies secreted IL-2 or interferon-gamma. Eight weeks' treatment with the immunosuppressive agents cyclosporin, or with corticosteroids, produced a significant reduction in the percentage of IL-2 secreting cells, although only for the former was there also a reduction in interferon-gamma secreting cells. Enteral nutrition however, produced a reduction in lymphokine-secreting cells equivalent to cyclosporin and produced the best histological and clinical improvement. CONCLUSION: Enteral nutrition and cyclosporin can down-regulate lymphokine secretion in the gut in Crohn's disease.

10. Buckell, N.A., Gould, S.R., Day, D.W., Lennard-Jones, J.E., and Edwards, A.M. Controlled trial of disodium cromoglycate in chronic persistent ulcerative colitis. *Gut* 19: 1140-1143, 1978.

Oral disodium cromoglycate (200 mg qds) has been tested in 26 patients with ulcerative colitis that was resistant to medical treatment. In a double-blind crossover trial disodium cromoglycate and placebo were added to conventional treatment in random order, each for four weeks. There was no significant difference in therapeutic effect between disodium cromoglycate and placebo.

11. Buderus, S., Boone, J., Lyerly, D., and Lentze, M.J. Fecal lactoferrin: a new parameter to monitor infliximab therapy. *Dig Dis Sci* 49: 1036-1039, 2004.

The glycoprotein lactoferrin is found in many body fluids but also in the granules of neutrophilic granulocytes. Fecal lactoferrin levels increase quickly with the influx of leukocytes into the intestinal lumen during inflammation. This biomarker has recently been shown to be a sensitive and specific marker of disease activity in chronic inflammatory bowel disease. Our aim was the determination of fecal lactoferrin as a marker of intestinal inflammation and therapeutic response following infliximab therapy in pediatric patients with Crohn's disease (CD). A total of five patients (ages 10-15 years) with severe Crohn's disease as defined by the Pediatric Crohn's Disease Activity Index (PCDAI) was enrolled in the study. The fecal lactoferrin levels were determined before and after therapy with infliximab by a quantitative lactoferrin ELISA (IBD-SCAN; TechLab, Inc.). Of the five patients on infliximab therapy, three received a single infusion and the remaining two underwent a regime with three maintenance infusions. All five patients responded to infliximab clinically after the first infusion, and in all patients, fecal lactoferrin levels significantly and rapidly decreased from elevated to near baseline in parallel to clinical assessment and the PCDAI. The reduction in fecal lactoferrin at days 7-10 was 93.43 +/- 4.49%, in comparison with the level before infliximab therapy, and correlated with a mean decrease in the PCDAI

from 48.50 to 14.0. For the patients followed during multiple infusions, one remained with mild disease and the other reached remission (subjective and PCDAI). Fecal lactoferrin is a sensitive and specific biomarker representing intestinal inflammation and response to therapy in pediatric patients with Crohn's disease. It may be a helpful noninvasive diagnostic tool for monitoring therapeutic efficiency in pediatric IBD patients. Future studies are needed to further establish the relationship between endoscopic changes and the level of fecal lactoferrin as well as the possible role of lactoferrin as being an early and preclinical indicator of relapse.

12. Cezard, J.P., Munck, A., Mouterde, O., Morali, A., Lenaerts, C., Lachaux, A., Turck, D., Schmitz, J., Maurage, C., Girardet, J.P., Belli, D., Lamireau, T., Sarles, J., Chouraqui, J.P., Descos, B., Dabadi, A., Meyer, M., Olives, J.P., and Mary, J.Y. Prevention of relapse by mesalazine (Pentasa) in pediatric Crohn's disease: a multicenter, double-blind, randomized, placebo-controlled trial. *Gastroenterol Clin Biol* 33: 31-40, 2009.

AIM: This study aimed to test the efficacy of mesalazine in maintaining remission in pediatric Crohn's disease (CD) following successful flare-up treatment.

METHODS: In this double-blind, randomized, placebo-controlled trial, 122 patients received either mesalazine 50mg/kg per day (n=60) or placebo (n=62) for one year. Treatment allocation was stratified according to flare-up treatment (nutrition or medication alone). Recruitment was carried out over two periods, as the first period's results showed a trend favoring mesalazine. Relapse was defined as a Harvey-Bradshaw score more than or equal to 5. Time to relapse was analyzed using the Cox model. RESULTS: The one-year relapse rate was 57% (n=29) and 63% (n=35) in the mesalazine and placebo groups, respectively. We demonstrated a twofold lower relapse risk ($P<0.02$) in patients taking mesalazine in the medication stratum (first recruitment period), and a twofold higher risk in patients taking mesalazine in the nutrition stratum (second recruitment period), compared with the other groups. None of the children's characteristics, which differed across the two recruitment periods, accounted for the between-period variation in mesalazine efficacy. One serious adverse event was reported in each treatment group. CONCLUSION: Overall, mesalazine does not appear to be an effective maintenance treatment in pediatric CD.

13. Crandall, W., Hyams, J., Kugathasan, S., Griffiths, A., Zrubek, J., Olson, A., Liu, G., Heuschkel, R., Markowitz, J., Cohen, S., Winter, H., Veereman-Wauters, G., Ferry, G., and Baldassano, R.N. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. *J Pediatr Gastroenterol Nutr* 49: 183-190, 2009.

OBJECTIVE: Post hoc analyses evaluated the effect of infliximab upon concurrent perianal Crohn disease (CD) in a subpopulation of 31 patients from REACH, a randomized trial of 112 children with moderately to severely active luminal CD. MATERIALS AND METHODS: The Pediatric Crohn Disease Activity

Index perirectal subscore was used to assess perianal symptom activity and therapeutic response. Patients with no symptoms or asymptomatic tags received a score of 0; those with "1-2 indolent fistula, scant drainage, no tenderness" received a score of 5; and those with "active fistula, drainage, tenderness or abscess" received a score of 10. Initial perirectal subscores of 10 or 5 decreasing to 0 were considered complete response. Subscores of 10 decreasing to 5 were considered partial response. All patients were followed for efficacy and safety through week 54. RESULTS: Twenty-two patients with baseline perianal disease were randomized at week 10 following a 3-dose infliximab induction regimen. At week 2, 40.9% (9/22) of patients with signs and symptoms of perianal disease at baseline attained response (4 partial and 5 complete). At week 54, 72.7% (16/22) of patients with signs and symptoms of perianal disease attained response (1 partial and 15 complete). Nine patients developed perianal signs and symptoms during treatment; 7 had complete response and 2 had no response at week 54. The incidence of adverse events for patients with perianal symptoms at baseline and for those in the overall REACH population was similar (95.7% vs 94.6%). CONCLUSIONS: Infliximab rapidly reduced concurrent perianal disease signs and symptoms in this REACH cohort.

14. Cucchiara, S., Escher, J.C., Hildebrand, H., Amil-Dias, J., Stronati, L., and Ruemmele, F.M. Pediatric inflammatory bowel diseases and the risk of lymphoma: should we revise our treatment strategies? *J Pediatr Gastroenterol Nutr* 48: 257-267, 2009.

Inflammatory bowel diseases (IBDs) are lifelong inflammatory gastrointestinal diseases starting in about one third of patients during childhood. Treatment strategies aim to control this chronic inflammatory process. Owing to recent advances in the understanding of IBD, immunosuppressive agents (mainly against TNFalpha directed) as well as biological drugs are more and more often used. This therapeutic approach clearly improved the clinical condition of the majority of patients with IBD. However, with this more aggressive treatment strategy, safety concerns clearly arise. Recently, the description of a series of a particularly severe form of T cell lymphoma in pediatric and young adult patients with IBD under immunomodulator and biological combination therapy raised the question of the risks of treatment-induced side effects or complications. As reviewed in the present article, there is a slightly increased risk of not only lymphoma development in IBD patients, potentially related to the inflammatory process, but also to the use of immunosuppressive therapies. On the basis of the literature data, we analyzed current treatment strategies for children with moderate-to-severe IBD, who are candidates to receive immunomodulator and/or biological agents potentially accelerating the risk of lymphoma development. Comparative clinical studies in IBD are still missing; however, it is prudent to think about adapting immunosuppressive therapies to the inflammatory process of the underlying disorder and if possible to reduce them to monotherapy. Alternative treatment strategies for heavy immunosuppression exist (eg, enteral nutrition in Crohn disease or colectomy in patients with ulcerative colitis) and

should be considered whenever appropriate. There is a major need for comparative studies before evidence-based guidelines can be established for safest and best treatment strategies of pediatric patients with IBD.

15. Cucchiara, S., Romeo, E., Viola, F., Cottone, M., Fontana, M., Lombardi, G., Rutigliano, V., de'Angelis, G.L., and Federici, T. Infliximab for pediatric ulcerative colitis: a retrospective Italian multicenter study. *Dig Liver Dis* 40 Suppl 2: S260-264, 2008.

BACKGROUND: Infliximab (IFX), the chimeric anti TNFalpha antibody, an established treatment for Crohn's disease in adults and in children, is used less frequently in ulcerative colitis (UC). **AIM OF THE STUDY:** To report the clinical course of pediatric patients with active UC receiving IFX. **PATIENTS AND METHODS:** Charts of 22 patients were reviewed (13 male, 9 female): 4 with a severe UC attack refractory to systemic corticosteroids (CS); 18 with a protracted course, of which 16 CS-dependent and 2 CS-resistant. The baseline therapeutic program consisted of 3 consecutive intravenous infusions (0, 2, 6 weeks) of IFX (5 mg/kg), followed by a retreatment schedule (infusion every 8 weeks); azathioprine (AZA) was administered chronically in all. Clinical evaluation was done with the Lichtiger Colitis Activity Index (LCAI). Follow-up was performed until week 54. LCAI ≥ 9 was considered treatment failure; a LCAI ≤ 2 was consistent with remission. **RESULTS:** All 22 patients began the study with a LCAI > 9 : 12 had a full response and were on remission at week 54 and did not receive CS (8 on IFX re-treatment and AZA, 4 on AZA alone); 6 had a partial response; 4 were non responders. Colectomy was performed in 7 patients, beyond the period of the acute attack in all but one. **CONCLUSIONS:** In children with severe ulcerative colitis IFX is a valuable treatment for inducing remission, avoiding emergency colectomy; retreatment may be offered to maintain remission.

16. Cuffari, C., Theoret, Y., Latour, S., and Seidman, G. 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. *Gut* 39: 401-406, 1996.

BACKGROUND: 6-Mercaptopurine (6-MP) has confirmed short and longterm efficacy in the treatment of IBD. However, the relation between its metabolism, efficacy, and side effects is not well understood. **AIMS:** To assay 6-MP metabolites and to correlate levels with drug compliance, disease activity, and adverse effects of treatment. **PATIENTS:** Heparinised blood was obtained prior to daily administration of 6-MP in 25 adolescent Crohn's disease patients (14 ileocolitis, 11 colitis) receiving 1.2 (range 0.4-1.6) mg/kg/day for a mean of 17 (range 4-65) months. **METHODS:** Erythrocyte free bases 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) were measured (pmol/ 8×10^8 red blood cells) using reverse phase high performance liquid chromatography. **RESULTS:** Disease activity (modified Harvey-Bradshaw index) improved significantly with 6-MP ($p = 0.001$). Clinical remission was achieved in 72% of patients, who stopped taking prednisone, or were successfully weaned to a low alternate day dose ($<$

0.4 mg/kg/OD). Remission correlated well with erythrocyte 6-TG ($p < 0.05$), but not 6-MMP levels. Neutropenia was associated with 6-MP use ($p < 0.005$), but did not correlate with erythrocyte 6-MP metabolite levels. One patient refractory to 6-MP had 6-TG, but no measurable 6-MMP production, suggesting deficient thiopurine methyl-transferase activity or poor compliance. 6-MP induced complications (hepatitis, pancreatitis, and marrow suppression) were generally associated with increased 6-MMP levels. CONCLUSIONS: These results suggest that high performance liquid chromatography measurement of erythrocyte 6-MP metabolites may provide a quantitative assessment of patient responsiveness and compliance to treatment. The data support an immunosuppressive role for 6-TG, and potential cytotoxicity of raised 6-MMP levels.

17. de Ridder, L., Benninga, M.A., Taminiau, J.A., Hommes, D.W., and van Deventer, S.J. Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 45: 3-14, 2007.

Infliximab is a chimeric monoclonal antibody (75% human, 25% murine) against tumor necrosis factor-alpha, a cytokine with a central role in the pathogenesis of inflammatory bowel disease. Large randomized controlled trials have shown the efficacy and safety of infliximab for the induction and maintenance of remission in adult patients with active Crohn disease (CD). In children and adolescents, mostly small, nonrandomized, non-placebo-controlled studies have supported the notion that infliximab is a potent drug in a population that does not respond to standard therapies. The safety of infliximab is of major concern, and the most frequent severe adverse events are related to severe infections and reactivation of tuberculosis. Non-life-threatening infusion reactions occur rather frequently and seem to be related to the formation of antibodies. The indications for infliximab treatment are therapy-resistant luminal CD (no efficacy or insufficient efficacy of conventional treatment) and therapy-resistant fistulas. An efficient remission induction strategy consists of 3 initial infliximab infusions at 0, 2, and 6 weeks in a dosage of 5 mg/kg to sustain remission. Patients needing maintenance therapy are subsequently treated with an infliximab infusion every 8 weeks. There are indications that the early stages of CD may be more susceptible to immunomodulation, and the natural history of CD may be altered by the introduction of infliximab early in the disease process instead of waiting until conventional therapy has failed. Major points of discussion are whether infliximab maintenance treatment should be episodic (on demand) or scheduled and when infliximab therapy can be discontinued.

18. de Ridder, L., Rings, E.H., Damen, G.M., Kneepkens, C.M., Schweizer, J.J., Kokke, F.T., Benninga, M.A., Norbruis, O.F., Hoekstra, J.H., Gijsbers, C.F., and Escher, J.C. Infliximab dependency in pediatric Crohn's disease: long-term follow-up of an unselected cohort. *Inflamm Bowel Dis* 14: 353-358, 2008.

BACKGROUND: Infliximab is effective for induction and maintenance of

remission in Crohn's disease. It is unknown how long patients should be kept on infliximab therapy. The primary aim of this study was to assess duration of effective maintenance therapy and infliximab dependency in pediatric CD patients initially responding to infliximab therapy. **METHODS:** All pediatric patients treated with infliximab by pediatric gastroenterologists in the Netherlands because of severe luminal or fistulizing CD with initial response to infliximab therapy were reviewed. Duration of therapy, clinical response and adverse events were recorded. **RESULTS:** Sixty-six CD patients (37 boys) in 10 hospitals were initially responding to infliximab therapy. Mean age at the start of infliximab therapy was 14.5 years (range, 8.1-18.5 years). Mean follow-up since infliximab was started was 41.3 months (range 12-165). In total, 991 infusions were administered. Analysis demonstrates that 15.2% of patients had prolonged response, while 56.1% were infliximab dependent and 28.8% lost response. In total, 10 patients (15.2%) developed an infection during infliximab therapy and 8 (12.1%) had an immediate allergic reaction. **CONCLUSIONS:** Good clinical response to maintenance infliximab therapy was seen in 70% of patients. Infliximab maintenance therapy seems very effective and safe in pediatric CD. However, more than half of the patients in this cohort is dependent on repeated infliximab infusions. The number of infliximab infusions received when patients lost response to infliximab was diverse. There was no statistical difference regarding response to infliximab therapy when started early as compared to later in the course of Crohn's disease.

19. Dohil, R., Hassall, E., Wadsworth, L.D., and Israel, D.M. Recombinant human erythropoietin for treatment of anemia of chronic disease in children with Crohn's disease. *J Pediatr* 132: 155-159, 1998.

We evaluated the efficacy and safety of and compliance with rH-EPO (150 U/kg three times a week subcutaneously for up to 12 weeks) for treatment of anemia in childhood Crohn's disease (n = 4). The mean hemoglobin level before rH-EPO therapy was 109 gm/L (10.9 gm/dl) (range, 103 to 115 gm/L). The mean hemoglobin level in the three compliant children increased to 138 gm/L (13.8 gm/dl) after treatment. Response time for the correction of anemia ranged from 6 to 12 weeks (mean, 9.5 weeks). Resolution of symptoms of lethargy, poor appetite, and irritability occurred with correction of the anemia. The only adverse effect observed was transient local pain at the injection site.

20. Domenech, E., Manosa, M., and Cabre, E. Top-down therapy: is the evidence strong enough? *Dig Dis* 27: 306-311, 2009.

Crohn's disease (CD) has usually been managed in an escalation manner, introducing more powerful (and toxic) drugs only once those with a better safety profile had failed. However, the natural history of CD under conventional therapeutic strategies results in high intestinal resection requirements and high rates of clinical relapse and steroid dependence. Indirect data seem to point at an improved efficacy of drugs when they are introduced early after disease

diagnosis. The spreading use of immunomodulators and the appearance of biological agents prompted the idea of their early introduction in order to change the natural history of the disease. By now, only thiopurines have been shown to reduce steroid requirements, relapse rates, and even surgical requirements, at least in pediatric CD. However, many other 'top-down' treatment strategies have not yet been evaluated. In addition, there is a risk of overtreating those 10-30% of patients that will have a benign course of the disease; that's the reason why the implementation of top-down strategies remains as a matter of debate.

21. Dubinsky, M.C. Azathioprine, 6-mercaptopurine in inflammatory bowel disease: pharmacology, efficacy, and safety. *Clin Gastroenterol Hepatol* 2: 731-743, 2004.

6-Mercaptopurine and its prodrug azathioprine remain the mainstay of immunomodulator therapy for the maintenance of a steroid-free remission in patients with IBD. Recent evidence suggests that the cytotoxic and immunosuppressive effects of azathioprine might be mediated via the induction of lymphocyte apoptosis by its active metabolites, 6-thioguanine nucleotides. The therapeutic benefits of thiopurines have been shown to correlate with the concentration of 6-thioguanine nucleotides. Inherited differences in drug metabolism and disposition can significantly impact the safety and efficacy of these drugs. The thiopurine methyltransferase enzyme plays an important role in the metabolism of 6-mercaptopurine and azathioprine and in the determination of thiopurine cytotoxicity. By gaining an understanding of the pharmacology and metabolism of thiopurine therapy and putting it into the clinical context, clinicians will be able to optimize thiopurine therapy in IBD.

22. Dubinsky, M.C. New patients: should children be treated differently? *Colorectal Dis* 8 Suppl 1: 15-19, 2006.

Inflammatory bowel disease (IBD) in childhood is often diagnosed at a vulnerable time of growth and development, and is recognized as one of the most significant chronic gastrointestinal diseases to affect children. Children and adolescents with IBD are at increased risk of complications as a result of malnutrition secondary to reduced appetite, increased metabolism and decreased absorptive capacity. The most common and serious complications are growth failure, bone demineralization and impaired psychosocial development. These issues add to the complexity of childhood IBD management and it is essential that adequate medical management is in place to prevent these long-term complications. Current treatment options include 5-aminosalicylic acid, antibiotics, corticosteroids, nutritional therapy and immunomodulators used to induce and maintain remission; some are specifically employed to maintain a steroid free long-term remission. As a general rule, long-term corticosteroid use should be avoided to reduce the risk of bone demineralization and growth failure. Newer treatment options such as infliximab have been shown to be effective for inducing and prolonging remission of Crohn's disease in children and paediatric use of infliximab is likely to increase in the near future. A recent case report, involving a

15-year old boy presenting with abdominal pain and bloody diarrhoea, illustrates the difficulty in correctly diagnosing IBD in children and the need for optimizing therapy to achieve treatment success.

23. Dubinsky, M.C. Clinical perspectives in Crohn's disease. Serologic and prognostic biomarkers: who, when, and how? *Rev Gastroenterol Disord* 7 Suppl 2: S3-7, 2007.

The introduction of anti-tumor necrosis factor- α therapies has significantly expanded the armamentarium for patients with inflammatory bowel disease (IBD). Clinical experience has shown that not all patients respond to therapies in this class, which emphasizes the hypothesis that there are different pathways involved in the inflammatory cascade characteristic of the spectrum of IBD phenotypes. The broadening of therapeutics with different mechanisms of action and targets is important for patients with IBD. Based on evidence gathered in recent studies, the key to success with these therapies may lie in targeting the right patients based on knowledge of their underlying genetic defects and resultant immune reactivity. Determining the factors that can predict the progression from uncomplicated to complicated disease states may stratify patients into at-risk populations and have an impact on their ultimate therapeutic management.

24. Dubinsky, M.C., Hassard, P.V., Seidman, E.G., Kam, L.Y., Abreu, M.T., Targan, S.R., and Vasiliauskas, E.A. An open-label pilot study using thioguanine as a therapeutic alternative in Crohn's disease patients resistant to 6-mercaptopurine therapy. *Inflamm Bowel Dis* 7: 181-189, 2001.

BACKGROUND AND AIMS: A substantial number of patients with inflammatory bowel disease (IBD) fail to achieve a complete clinical response with 6-mercaptopurine (6-MP) and azathioprine (AZA). Inability to achieve therapeutic 6-thioguanine nucleotide (6-TGN) levels due to the preferential overproduction of 6-methylmercaptopurine ribonucleotides (6-MMPR) upon dose escalation characterizes a newly described subgroup of IBD patients resistant to 6-MP/AZA therapy. Treatment with 6-thioguanine (6-TG), a related thiopurine, which forms 6-TGNs more directly may be beneficial in such patients. This pilot study evaluated the safety, tolerance, and efficacy of 6-TG in the subgroup of Crohn's disease (CD) patients failing to attain adequate disease control with traditional 6-MP/AZA therapy. **METHODS:** Ten CD patients with preferential 6-MMPR production upon 6-MP/AZA dose escalation were enrolled in an open-label pilot study. Seven of 10 patients had experienced dose-related 6-MP toxicities. **RESULTS:** Seventy percent of the patients (7 of 10) responded or were in remission at week 16. Clinical response was evident by week 4 in most. 6-TGN levels were nine-fold higher with 6-TG treatment than with 6-MP, whereas 6-MMPR levels were undetectable. No patient developed a recurrence of hepatic or hematological toxicity. **CONCLUSIONS:** 6-TG was a safer and more efficacious thiopurine in this subgroup of IBD patients resistant to 6-MP therapy.

Larger controlled trials are warranted to further evaluate both the short- and long-term safety and efficacy in this subgroup of patients as well as a broader spectrum of IBD patients.

25. Dubinsky, M.C., Lamothe, S., Yang, H.Y., Targan, S.R., Sinnett, D., Theoret, Y., and Seidman, E.G. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 118: 705-713, 2000.

BACKGROUND & AIMS: The effects of 6-mercaptopurine (6-MP) are mediated via its intracellular conversion to 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) nucleotide metabolites, the latter genetically controlled by thiopurine methyltransferase (TPMT). We sought to determine optimal therapeutic 6-MP metabolite levels and their correlation with medication-induced toxicity and TPMT genotype. **METHODS:** Therapeutic response was determined in 92 pediatric patients with inflammatory bowel disease coincidentally with hematologic, pancreatic, and hepatic laboratory parameters, and compared with erythrocyte metabolite levels and TPMT genotype. **RESULTS:** Clinical response was highly correlated with 6-TG levels ($P < 0.0001$) but not with any other variable, including 6-MMP levels, drug dose, gender, and concurrent medications. The frequency of therapeutic response increased at 6-TG levels $> 235 \text{ pmol}/8 \times 10^8$ erythrocytes ($P < 0.001$). Hepatotoxicity correlated with elevated 6-MMP levels ($> 5700 \text{ pmol}/8 \times 10^8$ erythrocytes; $P < 0.05$). Although leukopenia was associated with higher 6-TG levels ($P < 0.03$), it was observed in only 8% of responders. Patients heterozygous for TPMT (8/92) had higher 6-TG levels ($P < 0.0001$), and all responded to therapy. **CONCLUSIONS:** 6-MP metabolite levels and TPMT genotyping may assist clinicians in optimizing therapeutic response to 6-MP and identifying individuals at increased risk for drug-induced toxicity.

26. Dubinsky, M.C., and Seidman, E.G. Novel immunosuppressive therapies for intestinal and hepatic diseases. *Curr Opin Pediatr* 11: 390-395, 1999.

Recent advances in the understanding of the pathogenesis of immune-mediated hepatic and intestinal diseases have led to major therapeutic advances. The introduction of genetically engineered biologic agents specifically designed to target inflammatory mediators responsible for the perpetuation of chronic inflammatory processes is a novel example. Although corticosteroids remain important as a first-line therapeutic option for active inflammatory bowel disease, approximately one third and one fifth of patients develop steroid dependence and resistance, respectively. From a pediatric perspective, a major advance has thus been the advocacy of prolonged immunosuppressive therapy with 6-mercaptopurine or azathioprine for children with inflammatory bowel disease. The introduction of effective steroid-sparing agents for the induction and maintenance of remission is a key management issue. The past year has also witnessed the increased utilization of powerful immunosuppressive agents with

rapid onset of action, such as cyclosporine and tacrolimus, in patients resistant to conventional therapies. This review will afford pediatricians a sense of what to expect for the management of hepatic and intestinal disorders with immunosuppression as we advance into the new millennium.

27. Eidelwein, A.P., Cuffari, C., Abadom, V., and Oliva-Hemker, M. Infliximab efficacy in pediatric ulcerative colitis. *Inflamm Bowel Dis* 11: 213-218, 2005.

BACKGROUND: The effects of infliximab, a tumor necrosis factor-alpha (TNF-alpha) antibody, have been well established in adult patients with inflammatory and fistulizing Crohn's disease. This study evaluates short- and long-term efficacy of infliximab in children with ulcerative colitis. **METHODS:** All pediatric patients with ulcerative colitis who received infliximab between July 2001 and November 2003 at the Johns Hopkins Children's Center were identified. Short- and long-term outcomes and adverse reactions were evaluated. **RESULTS:** Twelve pediatric patients with ulcerative colitis received infliximab for treatment of fulminant colitis (3 patients), acute exacerbation of colitis (3), steroid-dependent colitis (5), and steroid-refractory colitis (1). Nine patients had a complete short-term response, and 3 had partial improvement. The mean per patient dose of corticosteroid after the first infliximab infusion decreased from 45 mg/day at the first infusion to 22.2 mg/day at 4 weeks ($P = 0.02$) and 7.8 mg/day at 8 weeks ($P = 0.008$). Eight patients were classified as long-term responders with a median follow-up time of 10.4 months. Of the 4 long-term nonresponders, 3 underwent colectomy, and the fourth has ongoing chronic symptoms. Three of 4 long-term nonresponders were steroid-refractory compared with 1 of 8 long-term responders. Patients receiving 6-mercaptopurine had a better response to infliximab. **CONCLUSION:** Infliximab should be considered in the treatment of children with symptoms of acute moderate to severe ulcerative colitis.

28. El-Matary, W., Vandermeer, B., and Griffiths, A.M. Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*: CD007560, 2009.

BACKGROUND: Methotrexate, a folate antagonist, is an immunosuppressant drug that is effective for treating several inflammatory disorders including Crohn's disease. Ulcerative colitis, a related chronic inflammatory bowel disease, can be challenging to treat. This review was performed to examine the efficacy of methotrexate for maintenance of remission in ulcerative colitis. **OBJECTIVES:** To systematically review randomized controlled trials examining the efficacy and safety of methotrexate for maintenance of remission in patients with ulcerative colitis. **SEARCH STRATEGY:** The Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane IBD/FBD Review Group Specialized Trials Register, MEDLINE (PUBMED), EMBASE (1984 to November 2008), Web of Science, Scopus, Database of Abstracts of Reviews of Effects (DARE), and Clinical trials database (ClinicalTrials.gov) were searched. In addition, references from selected papers and abstracts from Digestive Disease Week were also examined. **SELECTION CRITERIA:** Only randomized controlled trials (RCT)

evaluating the efficacy of methotrexate for maintaining remission in patients with ulcerative colitis compared to placebo or any other intervention were considered for inclusion in this review. DATA COLLECTION AND ANALYSIS: Data were extracted independently by each author. The odds ratio of relapse, 95% confidence interval and P-value were calculated using the Mantel-Haenszel method. An intention to treat analysis was used. MAIN RESULTS: Only one trial fulfilled the inclusion criteria. This trial randomized 30 patients to methotrexate and 37 to placebo. Methotrexate was given orally in a dose of 12.5 mg/week. Fourteen patients in the methotrexate group and 18 patients in the placebo group who entered remission were followed for 9 months or to the time of first relapse. Sixty-four per cent of methotrexate patients relapsed compared to 44% of placebo patients (OR 2.25; 95% CI 0.54 to 9.45; P = 0.27). AUTHORS' CONCLUSIONS: The available evidence is not sufficient to recommend the use of methotrexate to maintain remission in patients with ulcerative colitis. A large scale methodologically rigorous randomized controlled trial is needed. Such a study should investigate higher doses of methotrexate and parenteral administration.

29. Escher, J.C. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled, multicentre trial. *Eur J Gastroenterol Hepatol* 16: 47-54, 2004.

OBJECTIVES: Budesonide is a corticosteroid with low systemic bioavailability because of its high first-pass metabolism in the liver. In this paediatric, randomized, double-blind, double-dummy, controlled, multicentre trial, the safety and efficacy of budesonide versus prednisolone were evaluated in children with active Crohn's disease. METHODS: Forty-eight children, aged 6-16 years, with active Crohn's disease (Crohn's Disease Activity Index > 200) involving ileum and/or ascending colon were randomized to receive budesonide (9 mg/day for 8 weeks, 6 mg/day for 4 weeks) or prednisolone (1 mg/kg/day for 4 weeks, tapering for 8 weeks). RESULTS: The groups were comparable for age, sex, pubertal stage, disease activity and disease duration. Mean morning plasma cortisol concentration was significantly higher in the budesonide group (200 nmol/l) than in the prednisolone group (98 nmol/l) after 8 weeks, reflecting less adrenal suppression by budesonide (difference -102 nmol/l; 95% CI -226, -52; P = 0.0028). Glucocorticosteroid side effects such as moon face and acne occurred significantly less frequently in the budesonide group. Remission (Crohn's Disease Activity Index < or = 150) was seen at 8 weeks in 12/22 (55%) patients treated with budesonide and in 17/24 (71%) patients receiving prednisolone (difference -16%; 95% CI -45,13; P = 0.25). CONCLUSIONS: Significantly fewer side effects and less adrenal suppression were observed in the children receiving budesonide. Remission rates were not significantly different in the two groups. However, there was a trend for prednisolone to be more effective for inducing remission.

30. Escher, J.C., Taminiu, J.A., Nieuwenhuis, E.E., Buller, H.A., and Grand, R.J.

Treatment of inflammatory bowel disease in childhood: best available evidence. *Inflamm Bowel Dis* 9: 34-58, 2003.

The physician treating children with inflammatory bowel disease is confronted with a number of specific problems, one of them being the lack of randomized, controlled drug trials in children. In this review, the role of nutritional therapy is discussed with a focus on primary treatment, especially for children with Crohn's disease. Then, the available medical therapies are highlighted, reviewing the evidence of effectiveness and side effects in children, as compared with what is known in adults. Nutritional therapy has proven to be effective in inducing and maintaining remission in Crohn's disease while promoting linear growth. Conventional treatment consists of aminosalicylates and corticosteroids, whereas the early introduction of immunosuppressives (such as azathioprine or 6-mercaptopurine) is advocated as maintenance treatment. If these drugs are not tolerated or are ineffective, methotrexate may serve as an alternative in Crohn's disease. Cyclosporine is an effective rescue therapy in severe ulcerative colitis, but only will postpone surgery. A novel strategy to treat Crohn's disease is offered by infliximab, a monoclonal antibody to the proinflammatory cytokine tumor necrosis factor (TNF)-alpha. Based on the best-available evidence, suggested usage is provided for separate drugs with respect to dosage and monitoring of side effects in children.

31. Etchevers, M.J., Aceituno, M., and Sans, M. Are we giving azathioprine too late? The case for early immunomodulation in inflammatory bowel disease. *World J Gastroenterol* 14: 5512-5518, 2008.

Inflammatory bowel disease (IBD) includes two entities, Crohn's disease and ulcerative colitis. Both are chronic conditions with frequent complications and surgical procedures and a great impact on patient's quality of life. The thiopurine antimetabolites azathioprine and 6-mercaptopurine are widely used in IBD patients. Current indications include maintenance therapy, steroid-dependent disease, fistula closure, prevention of infliximab immunogenicity and prevention of Crohn's disease recurrence. Surprisingly, the wide use of immunosuppressants in the last decades has not decreased the need of surgery, probably because these treatments are introduced at too late stages in disease course. An earlier use of immunosuppressants is now advocated by some authors. The rationale includes: (1) failure to modify IBD natural history of present therapeutic approach, (2) demonstration that azathioprine can induce mucosal healing, a relevant prognostic factor for Crohn's disease and ulcerative colitis, and (3) demonstration that early immunosuppression has a very positive impact on pediatric, recently diagnosed Crohn's disease patients. We are now awaiting the results of new studies, to clarify the contribution of azathioprine, as compared to infliximab (SONIC Study), and to demonstrate the usefulness of azathioprine in recently diagnosed adult Crohn's disease patients (AZTEC study).

32. Faubion, W.A., Jr., and Bousvaros, A. Medical therapy for refractory pediatric

Crohn's disease. *Clin Gastroenterol Hepatol* 4: 1199-1213, 2006.

Crohn's disease is a common indication for referral to pediatric gastroenterology. While most patients with Crohn's disease respond to standard induction therapy, steroid-refractory or steroid-dependent disease is a frequently encountered problem. This review discusses the data existing in both the adult and pediatric literature for medical therapy of refractory pediatric Crohn's disease.

33. Ferrante, M., Vermeire, S., Katsanos, K.H., Noman, M., Van Assche, G., Schnitzler, F., Arijis, I., De Hertogh, G., Hoffman, I., Geboes, J.K., and Rutgeerts, P. Predictors of early response to infliximab in patients with ulcerative colitis. *Inflamm Bowel Dis* 13: 123-128, 2007.

BACKGROUND: Our objective is to report the outcome of infliximab (IFX) in ulcerative colitis (UC) patients from a single center and to identify predictors of early clinical response. **METHODS:** The first 100 UC patients (45 female; median age, 37.9 years) who received IFX at a single center were included. Eighty-four patients received 5 mg/kg IFX, and 37 patients received a 3-dose IFX induction at weeks 0, 2, and 6. The Mayo endoscopic subscore, assessed by sigmoidoscopy before inclusion, was 1, 2, and 3 in 5%, 52%, and 43% of patients, respectively. Sixty percent had pancolitis, 63% were on concomitant immunosuppressive therapy, 9% were active smokers, 64% had C-reactive protein $>$ or $=$ 5 mg/dL, and 44% were pANCA+/ASCA-. Five patients received IFX because of severe acute colitis refractory to intravenous corticosteroids. **RESULTS:** Early complete and partial clinical responses were observed in 41% and 24% of patients. Patients with early clinical response were significantly younger than nonresponders (median age, 35.7 versus 41.6 years, $P = 0.041$). Patients who were pANCA+/ASCA- had a significantly lower early clinical response (55% versus 76%; odds ratio [OR] = 0.40 (0.16-0.99), $P = 0.049$). Concomitant immunosuppressive therapy and the use of an IFX induction scheme did not influence early clinical response. Only 1 of 5 patients who received IFX for acute steroid-refractory colitis required colectomy within 2 months. **CONCLUSIONS:** IFX is an efficient therapy in UC, as shown by 65% early clinical response. A pANCA+/ASCA- serotype and an older age at first IFX infusion are associated with a suboptimal early clinical response.

34. Ferry, G.D., Kirschner, B.S., Grand, R.J., Issenman, R.M., Griffiths, A.M., Vanderhoof, J.A., Fiedorek, S.C., Winter, H.S., Hassall, E.G., Watkins, J.B., and et al. Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. *J Pediatr Gastroenterol Nutr* 17: 32-38, 1993.

The safety and efficacy of olsalazine sodium was compared to sulfasalazine over 3 months in a multicenter, randomized, double-blind study of 56 children with mild to moderate ulcerative colitis. Twenty-eight children received 30 mg/kg/day of olsalazine (maximum, 2 g/day) and 28 received 60 mg/kg/day of sulfasalazine

(maximum, 4 g/day). Side effects were frequent in both groups. Eleven of 28 patients (39%) on olsalazine reported headache, nausea, vomiting, rash, pruritus, increased diarrhea, and/or fever. Thirteen of 28 on sulfasalazine (46%) reported similar side effects and/or neutropenia, and four patients had the drug stopped because of an adverse reaction. After 3 months, 11 of 28 (39%) on olsalazine were asymptomatic or clinically improved, compared to 22 of 28 (79%) on sulfasalazine ($p = 0.006$). In addition, 10 of 28 patients on olsalazine versus one on sulfasalazine required prednisone because of lack of response or worsening of colitis ($p = 0.005$). The dose of olsalazine used in this clinical trial was thought to be equivalent to a standard dose of sulfasalazine, but fewer patients on olsalazine improved and a greater number had progression of symptoms when compared to sulfasalazine. Although side effects were slightly less frequent for olsalazine, the number of patients was too small to detect a clinically significant difference.

35. Grand, R.J., Ramakrishna, J., and Calenda, K.A. Therapeutic strategies for pediatric Crohn disease. *Clin Invest Med* 19: 373-380, 1996.

The main aims of therapy for inflammatory bowel disease (Crohn disease) in children and adolescents are (1) the induction and maintenance of remission, (2) the correction of nutrient deficits and (3) the restoration of growth and maturation. These goals are reached with the use of a combination of therapeutic methods, including pharmacologic agents, nutritional and psychological support, and surgical intervention. The commonly used drugs sulfasalazine, corticosteroids and metronidazole have all been shown to be safe and efficacious when given to children. Newer steroid preparations that are rapidly degraded either in the target tissue or elsewhere are being studied. Of these, budesonide currently shows promise as an efficacious drug with few side effects, but its use in children needs further study. Newer 5-amino-salicylate preparations such as Asacol have been shown to be effective in children, but the number of patients studied is small. Immunomodulatory drugs such as azathioprine and 6-mercaptopurine appear to be safe and efficacious for children; cyclosporine has been used infrequently to treat refractory Crohn disease in children. The use of other agents such as methotrexate, tacrolimus, monoclonal antibodies to cytokines, antibiotics and specific dietary products such as fish oils have not been intensively studied in children with Crohn disease. Nutritional therapy remains a mainstay of treatment because it corrects nutritional deficits, replaces losses and stimulates growth.

36. Greifer, M.K., and Markowitz, J.F. Update in the treatment of paediatric ulcerative colitis. *Expert Opin Pharmacother* 7: 1907-1918, 2006.

Ulcerative colitis is an important disease in the paediatric population. Ulcerative colitis is one of the chronic inflammatory bowel diseases, and is medically incurable. However, the arsenal of medications has grown as knowledge of the pathogenesis of this disease advances. This review looks at the classical treatments for children with ulcerative colitis, including the 5-aminosalicylates,

corticosteroids and immunomodulators, as well as biological therapy and other, newer modalities.

37. Gremse, D.A., and Crissinger, K.D. Ulcerative colitis in children: medical management. *Paediatr Drugs* 4: 807-815, 2002.

Ulcerative colitis is a chronic relapsing inflammatory disorder of the colonic mucosa of unknown etiology. The inflammatory process involves the mucosa and submucosa in a continuous segment of bowel with rectal involvement in almost all cases. Since its etiology is unknown, therapy is directed at modulating the inflammatory response in order to control symptoms and to prevent relapses. 5-aminosalicylates and corticosteroids have been the most widely used therapeutic agents for treatment of ulcerative colitis. Recently, experience has been gained with the use of other immunomodulators, such as mercaptopurine, azathioprine, methotrexate, cyclosporine, and tacrolimus, in pediatric patients. Colectomy is indicated in patients with severe colitis who do not respond to intensive medical therapy. The care of children with ulcerative colitis not only involves control of symptoms from gastrointestinal and extraintestinal manifestations, but also optimizing growth and development. The complications of chronic inflammation and long-term medical therapy must be weighed against the risks and benefits of surgery for children and adolescents with this condition.

38. Griffiths, A., Koletzko, S., Sylvester, F., Marcon, M., and Sherman, P. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. *J Pediatr Gastroenterol Nutr* 17: 186-192, 1993.

Pharmacologic agents effective in the treatment of Crohn's disease confined to the small intestine are limited. The therapeutic efficacy of oral mesalazine in small bowel inflammation, although theoretically promising, remains unproven. In an open-labeled initial trial, timed-release 5-aminosalicylic acid (5-ASA), administered at a daily dosage of 30.6 +/- 9.0 mg/kg (mean +/- SEM) to children with active Crohn's disease involving the small intestine, was associated with improvement on the Harvey index in six of 12 patients treated for 8.1 +/- 3.9 weeks. In a subsequent prospective, double-blind study 14 children, ages 9.3 to 16.1 years, with active Crohn's disease limited radiologically in the small intestine were randomized to receive either timed-release 5-ASA [50 mg/kg/day (maximum 3 g/day)] or placebo for 8 weeks. Following a 4-week washout period, patients crossed over to receive the other study drug for a further 8 weeks. Six children completed the entire 20-week trial. The van Hees index improved among patients receiving 5-ASA for 8 weeks (delta = -18 +/- 6.4) but deteriorated among patients given placebo (delta = +14 +/- 4.1) (p < 0.05). Mean Crohn's Disease Activity Index (CDAI) decreased marginally after 8 weeks of 5-ASA treatment (delta = -48 +/- 38.2) but not with placebo (delta = -3.0 +/- 7.9) (p = 0.31). Of the eight noncompleters, more patients dropped out of the study because of lack of therapeutic response to placebo (n = 5) than to 5-ASA (n = 2).(ABSTRACT TRUNCATED AT 250 WORDS)

39. Gulati, A.S., and Dubinsky, M.C. Probiotics in pediatric inflammatory bowel diseases. *Curr Gastroenterol Rep* 11: 238-247, 2009.

The intestinal microbiota plays a key role in the initiation and perpetuation of inflammatory bowel diseases (IBD). As such, there is a strong rationale to use agents such as probiotics to modulate the gut microbiome as a treatment strategy for these disorders. Furthermore, the potential toxicities of current IBD therapies make probiotics attractive medications for patients and physicians. However, although much attention is being placed on probiotic therapy, relatively few well-designed trials have evaluated its efficacy in the management of IBD, particularly in the pediatric population. This article examines the currently available published trials studying probiotics for the treatment of IBD, with particular emphasis on their role in pediatric IBD patients.

40. Gupta, I., Parihar, A., Malhotra, P., Singh, G.B., Ludtke, R., Safayhi, H., and Ammon, H.P. Effects of *Boswellia serrata* gum resin in patients with ulcerative colitis. *Eur J Med Res* 2: 37-43, 1997.

Ulcerative colitis is a chronic inflammatory disease of the colon where leukotrienes are suggested to play an important role for keeping inflammation active. Boswellic acids, the biologically active ingredients of the gum resin of *Boswellia serrata* (Sallai guggal), have been shown to be specific, nonredox and noncompetitive inhibitors of 5-lipoxygenase, the key enzyme of leukotriene biosynthesis. In patients suffering from ulcerative colitis grade II and III the effect of *Boswellia serrata* gum resin preparation (350 mg thrice daily for 6 weeks) on stool properties, histopathology and scan microscopy of rectal biopsies, blood parameters including Hb, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils was studied. Patients receiving sulfasalazine (1 g thrice daily) served as controls. All parameters tested improved after treatment with *Boswellia serrata* gum resin, the results being similar compared to controls: 82% out of treated patients went into remission; in case of sulfasalazine remission rate was 75%.

41. Haller, C.A., and Markowitz, J. IBD in children: lessons for adults. *Curr Gastroenterol Rep* 9: 528-532, 2007.

When children develop inflammatory bowel disease (IBD), physicians and researchers are presented with a singular opportunity to understand the nature of these chronic, idiopathic illnesses in the earliest stages. Genetic susceptibility factors tend to be common, whereas complicating environmental factors such as cigarette smoking are generally not an issue. As opposed to the case in adult patients, Crohn's disease is usually diagnosed in children at an early, inflammatory phase of the disease. Pediatric ulcerative colitis tends to present with more severe and more extensive involvement than in adults. In both forms of IBD, the severity of disease activity often dictates the need for early aggressive

nutritional, immunomodulatory, and biologic therapy. As a result, the lessons learned from the evaluation and treatment of children with IBD are critically important to the clinician caring for adults with the same disorders.

42. Hande, S., Wilson-Rich, N., Bousvaros, A., Zholudev, A., Maurer, R., Banks, P., Makrauer, F., Reddy, S., Burakoff, R., and Friedman, S. 5-aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. *Inflamm Bowel Dis* 12: 251-257, 2006.

BACKGROUND: Small uncontrolled trials have suggested that 5-aminosalicylate (5-ASA) medications increase 6-thioguanine nucleotide (6-TGn) levels in adults with Crohn's disease (CD) on azathioprine (AZA) or 6-mercaptopurine (6-MP), presumably through the inhibition of thiopurine methyltransferase (TPMT). We tested the theory that coadministration of 5-ASA agents with AZA/6-MP results in higher 6-TGn levels in a large cohort of children and adults with CD or ulcerative colitis (UC). **METHODS:** A retrospective cohort study identified all children and adults treated for IBD with AZA/6-MP at 2 tertiary medical centers. Patients were included if their TPMT genotype was known and 6-TGn and 6-methylmercaptopurine (6-MMP) levels had been obtained after 3 months of clinical remission at a stable dose of AZA/6-MP. 6-TGn and 6-MMP levels were compared between patients taking and those not taking 5-ASA medications through the use of linear regression models to identify and adjust for potentially confounding variables. **RESULTS:** Of the 126 patients included, 88 were taking 5-ASA medications. Patients on 5-ASA agents had higher mean 6-TGn levels after adjustment for confounding variables (Delta6-TGn, 47.6 +/- 21.8 pmol/8 x 10 red blood cells; P = 0.03). CD and TPMT heterozygosity was independently associated with higher 6-TGn levels (P = 0.01 and P = 0.03, respectively). 5-ASA exposure was not associated with a change in 6-MMP levels. **CONCLUSIONS:** We found that 5-ASA therapy is associated with higher 6-TGn levels in children and adults with IBD on 6-MP/AZA. TPMT inhibition may not explain this effect because 5-ASA exposure did not affect 6-MMP levels. The observed association of CD with higher 6-TGn levels is novel and needs to be verified in prospective studies.

43. Hoffman, I., Vermeire, S., Van Assche, G., and Rutgeerts, P. Infliximab for pediatric Crohn's disease. *Drugs Today (Barc)* 44: 615-628, 2008.

The natural history of Crohn's disease (CD) is characterized by recurrent flares combined with periods of inactive disease. The goal of therapy should be to induce and maintain clinical remission, to strive for endoscopic healing of the intestinal mucosa and to improve the quality of life. The nineties have been characterized by the introduction of biological therapies designed to block or neutralize pro-inflammatory cytokines which play a role in the pathogenesis of the disease. Biologic treatment with the anti-human tumor necrosis factor alpha antibody infliximab has dramatically changed the therapeutic approach even in

pediatric patients. Numerous studies are available and report the beneficial effect of infliximab in pediatric CD patients with moderate to severe disease, refractory and steroid-dependent patients. The safety profile of infliximab is overall favorable although continued vigilance, especially for the occurrence of infrequent but serious events, including opportunistic infection and lymphomas, remains necessary.

44. Holland, N., Harmatz, P., Golden, D., Hubbard, A., Wu, Y.Y., Bae, J., Chen, C., Huen, K., and Heyman, M.B. Cytogenetic damage in blood lymphocytes and exfoliated epithelial cells of children with inflammatory bowel disease. *Pediatr Res* 61: 209-214, 2007.

This longitudinal, prospective study sought to establish whether pediatric Crohn's disease (CD) and ulcerative colitis (UC) are associated with increased levels of cytogenetic damage and whether folate supplementation in combination with other treatments mitigates cytogenetic damage in children with inflammatory bowel disease (IBD). After a 1-mo treatment and folate supplementation, all clinical tests in CD (n = 24) and UC (n = 17) patients improved. Patients with CD were comparable in the cytogenetic response with controls (n = 28) assessed by micronucleus (MN) assay, but both groups differed from the UC group. While the MN frequency in epithelial cells slightly decreased from first to second observations in CD patients (p = 0.05) and controls (p = 0.11), an increase was observed in UC patients (p = 0.001). Similar changes were observed in blood lymphocytes resulting in significantly higher levels of the MNs and chromosome bridges in UC patients. These preliminary findings of a difference in chromosome damage between pediatric UC patients compared with CD patients and healthy controls warrant confirmation and expansion to determine (1) the role of cytogenetic damage in the pathogenesis of these diseases, (2) relative contribution of treatment and folate supplementation, and (3) potential links to the eventual development of cancer in some patients.

45. Homan, M., Baldassano, R.N., and Mamula, P. Managing complicated Crohn's disease in children and adolescents. *Nat Clin Pract Gastroenterol Hepatol* 2: 572-579, 2005.

The natural history of Crohn's disease is characterized by recurrent exacerbations. A small, but significant, number of pediatric patients with Crohn's disease are resistant to standard medical therapies. The goal of therapy in pediatric patients is not only to achieve and maintain clinical remission, but also to promote growth, development and improve quality of life. All of this needs to be achieved within a relatively short window of opportunity, before growth and development deficiencies become permanent. The standard therapy for pediatric patients with Crohn's disease consists of 5-aminosalicylic-acid compounds, antibiotics and enteral nutrition. Enteral nutrition has an excellent adverse-effect profile and, in addition to its therapeutic effect, positively impacts growth and nutritional status. Immunomodulating medications, such as azathioprine, 6-

mercaptopurine and methotrexate, are frequently used to maintain remission, and to treat corticosteroid-dependent and perianal disease. Recently, biologic treatment with the anti-tumor-necrosis-factor-alpha antibody infliximab has dramatically changed the therapeutic approach. The long-term safety of this therapy still needs to be established. Limited data are available on other biologic therapies, which, at this point in time, are considered experimental and are only available through clinical trials.

46. Hyams, J., Crandall, W., Kugathasan, S., Griffiths, A., Olson, A., Johanns, J., Liu, G., Travers, S., Heuschkel, R., Markowitz, J., Cohen, S., Winter, H., Veereman-Wauters, G., Ferry, G., and Baldassano, R. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 132: 863-873; quiz 1165-1166, 2007.

BACKGROUND AND AIMS: The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active Crohn's disease. **METHODS:** Patients (n = 112) with a Pediatric Crohn's Disease Activity Index (PCDAI) score >30 received infliximab 5 mg/kg at weeks 0, 2, and 6. Patients responding to treatment at week 10 were randomized to infliximab 5 mg/kg every 8 or 12 weeks through week 46. A concurrent immunomodulator was required. Clinical response (decrease from baseline in the PCDAI score > or =15 points; total score < or =30) and clinical remission (PCDAI score < or =10 points) were evaluated at weeks 10, 30, and 54. **RESULTS:** At week 10, 99 of 112 (88.4%) patients responded to infliximab (95% confidence interval: [82.5%, 94.3%]) and 66 of 112 (58.9%) patients achieved clinical remission (95% confidence interval: [49.8%, 68.0%]). At week 54, 33 of 52 (63.5%) and 29 of 52 (55.8%) patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 17 of 51 (33.3%) and 12 of 51 (23.5%) patients receiving treatment every 12 weeks (P = .002 and P < .001, respectively). **CONCLUSIONS:** Pediatric patients responding to an induction regimen of infliximab were more likely to be in clinical response and remission at week 54 without dose adjustment when their maintenance therapy was given every 8 weeks rather than every 12 weeks. Allowing for dose intensification in the case of relapse, remission rates, but not response rates, at week 54 were superior with every 8-week dosing compared with every 12-week dosing.

47. Hyams, J., Markowitz, J., Lerer, T., Griffiths, A., Mack, D., Bousvaros, A., Otley, A., Evans, J., Pfefferkorn, M., Rosh, J., Rothbaum, R., Kugathasan, S., Mezoff, A., Wyllie, R., Tolia, V., delRosario, J.F., Moyer, M.S., Oliva-Hemker, M., and Leleiko, N. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol* 4: 1118-1123, 2006.

BACKGROUND & AIMS: The aim of this study was to determine the clinical outcome after corticosteroid therapy in children who are newly diagnosed with ulcerative colitis (UC). **METHODS:** Data were gathered prospectively from the

Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry database between January 2002 and March 2005. All children who were newly diagnosed with inflammatory bowel disease younger than the age of 16 years were managed according to the dictates of their respective physicians. Demographic, clinical, and laboratory data were collected at diagnosis, at 30 days, and then quarterly. Patients were classified as corticosteroid responsive, corticosteroid dependent, or refractory, and outcomes were determined at 3 months and at 1 year. RESULTS: Ninety-seven patients had a diagnosis of UC and a minimum of 1 year of follow-up evaluation; 77 (79%) received corticosteroids (62 within 30 days of diagnosis [early] and 15 between 31 days and 6 months [late]). At diagnosis, 81% of corticosteroid-treated patients (age, 11.3 +/- 3.5 y) had moderate/severe disease, and 81% had pancolitis. For those treated early with corticosteroids, disease activity at 3 months was inactive in 60%, mild in 27%, and moderate/severe in 11%. At 1 year, 31 of 62 (50%) of the early corticosteroid-treated patients were considered corticosteroid responsive and 28 (45%) were corticosteroid dependent. A total of 4 patients receiving corticosteroids (5%) required colectomy in the first year. Immunomodulators were used in 61% of all corticosteroid-treated patients. CONCLUSIONS: Although short-term clinical response to corticosteroids in children with newly diagnosed UC is excellent, even with the common use of immunomodulators corticosteroid dependence is seen in 45% of patients.

48. Hyams, J.S., Lerer, T., Griffiths, A., Pfefferkorn, M., Kugathasan, S., Evans, J., Otley, A., Carvalho, R., Mack, D., Bousvaros, A., Rosh, J., Mamula, P., Kay, M., Crandall, W., Oliva-Hemker, M., Keljo, D., LeLeiko, N., and Markowitz, J. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis* 15: 816-822, 2009.

BACKGROUND: Infliximab therapy has short-term benefits in children with moderate-to-severe Crohn's disease (CD). We assessed the long-term outcome of infliximab maintenance therapy in children with CD. METHODS: We performed a multicenter cohort study of 729 pediatric patients with CD enrolled in the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Children younger than 16 years and newly diagnosed with CD were eligible for this study. Disease and medication information were collected prospectively from the treating physician at diagnosis, 30 days, and quarterly thereafter. No interventions were specified, per protocol. RESULTS: In all, 202 of 729 patients received infliximab: 62%, 23%, and 15% within 1, 1-2, and >2 years of diagnosis, respectively. The mean age at infliximab initiation was 12.7 years. A total of 158 infliximab-treated patients received maintenance therapy, 29 episodic (8 converted to maintenance), and 15 had incomplete follow-up. Among 128 patients administered maintenance infliximab and followed for ≥ 1 year, concomitant medications at infliximab initiation included corticosteroids (52%) and immunomodulators (90%). By 1, 2, and 3 years, <10% of patients continuing on maintenance infliximab were receiving corticosteroids ($P < 0.001$). Following maintenance therapy initiation, 26%, 44%, and 33% of patients continuing on

maintenance infliximab over 0-1, 1-2, and 2-3 years, respectively, had clinically inactive disease not requiring corticosteroids or surgery. The likelihood of continuing maintenance infliximab at 1, 2, and 3 years was 93%, 78%, and 67%, respectively. CONCLUSIONS: Infliximab maintenance therapy was a durable and effective treatment that was associated with prolonged corticosteroid withdrawal over a 3-year period in children with CD.

49. Hyams, J.S., Lerer, T., Griffiths, A., Pfefferkorn, M., Stephens, M., Evans, J., Otley, A., Carvalho, R., Mack, D., Bousvaros, A., Rosh, J., Grossman, A., Tomer, G., Kay, M., Crandall, W., Oliva-Hemker, M., Keljo, D., LeLeiko, N., and Markowitz, J. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 105: 1430-1436, 2010.

OBJECTIVES: Infliximab is effective in treating moderate/severe ulcerative colitis (UC) in adults. The aim of this study was to determine the outcome after treatment with infliximab in pediatric UC. METHODS: We performed a multicenter cohort study of 332 pediatric patients with UC enrolled in the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Children \leq 16 years of age and newly diagnosed with UC are enrolled in the registry. Disease and medication information are collected prospectively from the treating physician at diagnosis, 30 days, and quarterly thereafter. No interventions were specified, per protocol. RESULTS: Of 332 patients, 52 (16%) received infliximab (23% $<$ 3 months from diagnosis, 38% 3-12 months, 38% $>$ 12 months). Mean age at infliximab initiation was 13.3 \pm 2.6 (range 6-17) years; 87% of patients had pancolitis. Median follow-up was 30 months. Continuous maintenance (CM) therapy was given in 65%, episodic in 21%, episodic converted to CM in 6%, and insufficient data in 8% of patients. Sixty-three percent of patients were corticosteroid refractory, and 35% were corticosteroid dependent. Concomitant medications at first infliximab infusion included corticosteroids (87%), thiopurines (63%), and 5-aminosalicylates (51%). Corticosteroid-free inactive disease by physician global assessment was noted in 12/44 (27%), 15/39 (38%), and 6/28 (21%) patients at 6, 12, and 24 months, respectively. Kaplan-Meier analysis showed that the likelihood of remaining colectomy free after treatment with infliximab was 75% at 6 months, 72% at 12 months, and 61% at 2 years. CONCLUSIONS: In this cohort of children with UC receiving infliximab, corticosteroid-free inactive disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy.

50. Hyams, J.S., Markowitz, J., and Wyllie, R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. *J Pediatr* 137: 192-196, 2000.

BACKGROUND: Crohn's disease is often poorly responsive to conventional therapy with corticosteroids and immunomodulators. A novel chimeric antibody to tumor necrosis factor-alpha, infliximab, has shown utility in the treatment of refractory Crohn's disease in adults. PURPOSE: To evaluate the efficacy of

open-label administration of infliximab in children and adolescents with active intestinal Crohn's disease. METHODS: Chart review of the experience with 19 subjects (mean age 14.4 years, range 9 to 19 years) receiving 1 to 3 infusions of infliximab (5 mg/kg/dose) over a 12-week period for corticosteroid-resistant disease (n = 7) or corticosteroid dependence (n = 12). Disease activity was monitored by physician global assessment and the Pediatric Crohn's Disease Activity Index. RESULTS: Significant initial improvement (first 4 weeks after infusion) was noted in all subjects, with Pediatric Crohn's Disease Activity Index values decreasing significantly (mean +/- SD, 42.1 +/- 13.7 to 10.0 +/- 5.6, P <.0001). Over the subsequent 8-week period, 8 of 19 treated subjects had worsening of symptoms, although none deteriorated to severe activity. The mean Pediatric Crohn's Disease Activity Index at 12 weeks was 26.8 +/- 16.4. The mean daily prednisone dosages at baseline, 4 weeks, and 12 weeks were 28 +/- 14 mg, 20 +/- 12 mg, and 8 +/- 12 mg, respectively (P <.01). Adverse effects were noted in 3 patients during infusion (dyspnea, rash) and were self-limited. CONCLUSIONS: Infliximab is associated with short-term clinical improvement in children and adolescents with severe Crohn's disease. The rapid return of disease activity in some patients suggests that additional dosing strategies may be required. Long-term safety necessitates close monitoring.

51. Hyams, J.S., Wilson, D.C., Thomas, A., Heuschkel, R., Mitton, S., Mitchell, B., Daniels, R., Libonati, M.A., Zanker, S., and Kugathasan, S. Natalizumab therapy for moderate to severe Crohn disease in adolescents. *J Pediatr Gastroenterol Nutr* 44: 185-191, 2007.

OBJECTIVES: This study evaluated the safety, tolerability, and efficacy of natalizumab, a humanized monoclonal immunoglobulin-G4 antibody to [alpha]4 integrin, in adolescent patients with moderately to severely active Crohn disease (CD). PATIENTS AND METHODS: In a single-arm study, 38 adolescent patients (ages 12-17 y) with active CD (Pediatric Crohn Disease Activity Index [PCDAI] >30) received 3 intravenous infusions of natalizumab (3 mg/kg) at 0, 4 and 8 weeks. The primary analysis was safety, assessed by adverse events, laboratory results, and vital signs. Pharmacokinetic and pharmacodynamic measurements and formation of anti-natalizumab antibodies also were analyzed. Efficacy outcomes were assessed by changes in PCDAI, quality of life (IMPACT III), and levels of C-reactive protein and serum albumin. RESULTS: Thirty-one patients (82%) received 3 natalizumab infusions. The most common adverse events were headache (26%), pyrexia (21%) and CD exacerbation (24%). Clinical response (> or =15-point decrease from baseline PCDAI) and remission (PCDAI < or =10) rates were greatest at week 10 (55% and 29%, respectively). Three patients (8%) tested positive for anti-natalizumab antibodies. The peak level (61.0 and 66.3 microg/mL) and half-life (92.3 and 96.3 h) of natalizumab were comparable after the first and third infusions. Mean [alpha]4 integrin receptor saturation was 93% at 2 hours and <40% at 4 weeks after the first and third infusions. Increase from baseline in circulating lymphocytes ranged from 106% to 122% at 2 weeks and 45% to 65% at 4 weeks after each infusion. CONCLUSION: Natalizumab (3

mg/kg) was well tolerated in these adolescent patients with active CD, with a safety and efficacy profile similar to that of adult natalizumab-treated CD patients. Future studies should evaluate long-term safety and efficacy.

52. Jaspers, G.J., Verkade, H.J., Escher, J.C., de Ridder, L., Taminiou, J.A., and Rings, E.H. Azathioprine maintains first remission in newly diagnosed pediatric Crohn's disease. *Inflamm Bowel Dis* 12: 831-836, 2006.

6-Mercaptopurine (6-MP) maintains remission in pediatric Crohn's disease (CD). Azathioprine, a prodrug of 6-MP, is used for maintenance of remission of CD in Europe. We evaluated to what extent azathioprine is used in newly diagnosed pediatric CD patients and whether maintenance of remission differed between patients using azathioprine or not. Charts of children (diagnosed 1998-2003, follow-up > or = 18 mo) were reviewed. Active disease was defined as Pediatric Crohn's Disease Activity Index (PCDAI) greater than 10 or systemic corticosteroid use. Remission was defined as PCDAI 10 or less without use of corticosteroids. Eighty-eight children (55M/33F, age 12 +/- 3 yr) were included. Seventy-two (82%) patients received azathioprine during the follow-up period (38 +/- 17 mo). Patients diagnosed after 2000 received azathioprine significantly earlier during the course of disease compared with those diagnosed earlier (median, at 233 vs. 686 days; $P < 0.05$). At initial presentation, moderate-severe disease activity and prescription of corticosteroids were more prevalent in patients using azathioprine compared with nonazathioprine patients (75% vs. 52%; $P < 0.05$; and 89% vs. 58%; $P < 0.005$, respectively). Duration of corticosteroid use was longer in patients receiving azathioprine (232 vs. 168 days; $P < 0.005$). Median maintenance of first remission in patients who initially used corticosteroids, however, was longer in patients receiving azathioprine compared with nonazathioprine patients (PCDAI, 544 vs. 254 days, $P = 0.08$; corticosteroid free, 575 vs. 259 days, $P < 0.05$, respectively). We conclude that, since 2000, azathioprine is being introduced earlier in the treatment of newly diagnosed pediatric CD patients. The use of azathioprine is associated with prolonged maintenance of the first remission.

53. Jones, N.L., Roifman, C.M., Griffiths, A.M., and Sherman, P. Ketotifen therapy for acute ulcerative colitis in children: a pilot study. *Dig Dis Sci* 43: 609-615, 1998.

Eosinophils contribute to the inflammatory process in a variety of chronic inflammatory bowel diseases. Ketotifen is beneficial in experimental models of colitis and in patients with eosinophilic gastroenteritis. Therefore, we investigated the efficacy of ketotifen therapy for the treatment of active ulcerative colitis. Children with newly or previously diagnosed ulcerative colitis with mild-moderate disease activity were treated with ketotifen at a dosage of 4 mg daily for eight weeks. Efficacy was determined by a physician disease severity index and by endoscopic and histologic examinations. Ten patients were enrolled. Symptoms improved in four patients and resolved completely in one patient. There was endoscopic improvement in three patients and histologic improvement in one.

Increased eosinophils on rectal biopsy at entry were present in two of the responders. Five patients withdrew due to a lack of symptomatic improvement. No adverse events were identified. Low-dose ketotifen offers a limited therapeutic advantage in active ulcerative colitis that may be enhanced in the subgroup of patients with a high eosinophil count in the colonic mucosa. Further study of therapeutic efficacy with increased dosages of the mast cell stabilizer for acute and maintenance therapy is warranted.

54. Kappelman, M.D., Bousvaros, A., Hyams, J., Markowitz, J., Pfefferkorn, M., Kugathasan, S., Rosh, J., Otley, A., Mack, D., Griffiths, A., Evans, J., Grand, R., Langton, C., Kleinman, K., and Finkelstein, J.A. Intercenter variation in initial management of children with Crohn's disease. *Inflamm Bowel Dis* 13: 890-895, 2007.

BACKGROUND: Variation in care is a ubiquitous feature of medical practice and may lead to significant differences in health care costs, quality, and outcomes. We undertook this study to determine the extent of intercenter variation in the initial management of children newly diagnosed with Crohn's disease.

METHODS: We analyzed the utilization of 5 classes of medication (immunomodulators, prednisone, antibiotics, 5-aminosalicylates, and infliximab) among 311 children with newly diagnosed Crohn's disease followed at 10 North American pediatric gastroenterology centers. Multivariate logistic regression was used to compare the utilization rate of each class of medication at each of the 10 centers, adjusting for potential confounders including patient age, sex, race, disease severity, and anatomic location of disease. **RESULTS:** Median utilization of each class of medication was: immunomodulators, 56% (range 29%-97%); prednisone, 78% (range 32%-88%); antibiotics, 29% (range 11%-68%); 5-aminosalicylates, 63.5% (range 18%-92%); and infliximab, 7.5% (range 3%-21%). Each of these treatments showed statistically significant intercenter variation in utilization ($P < 0.001$ for immunomodulators, prednisone, antibiotics, and 5-ASA; $P = 0.02$ for infliximab). After adjusting for the demographic and clinical factors listed above, intercenter variation remained significant; however, the low utilization of infliximab precluded multivariate analysis. **CONCLUSIONS:** Widespread intercenter variation in the medical management of newly diagnosed children with Crohn's disease was observed, even after adjusting for possible differences in case mix between institutions. This variation may lead to unintended differences in health care costs and outcomes.

55. Kugathasan, S., Werlin, S.L., Martinez, A., Rivera, M.T., Heikenen, J.B., and Binion, D.G. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. *Am J Gastroenterol* 95: 3189-3194, 2000.

OBJECTIVES: Tumor necrosis factor-alpha plays a central role in chronic intestinal inflammation of Crohn's disease. Targeting this cytokine with the chimeric monoclonal antibody infliximab has emerged as an effective form of therapy in adult Crohn's disease patients. We sought to determine whether

infliximab treatment would benefit pediatric patients with medically refractory Crohn's disease. We also assessed the duration of response, comparing children with early disease to children with long-standing (late) Crohn's disease. METHODS: Fifteen consecutive children (mean age 12.8 +/- 3.2 yr) with medically refractory Crohn's disease were enrolled in a prospective, open-label trial of a single, 5-mg/kg infliximab intravenous infusion. Medically refractory disease was defined as an inability to taper steroids, lack of response to immunomodulator therapy over 4 months, and active disease as measured by the Pediatric Crohn's Disease Activity Index (PCDAI). Primary endpoints included measurements of disease activity (PCDAI), steroid use, and duration of clinical response. RESULTS: In all, 14/15 children (94%) improved after infliximab infusion, with a significant decrease of both PCDAI and daily steroid use by 4 wk. Ten patients (67%) achieved complete remission by 10 wk. Among the 14 patients who responded, three of six children (50%) with early disease maintained clinical response through the 12-month trial period, compared to none of eight children with late disease. There were no serious complications associated with the use of infliximab in any of the patients. CONCLUSIONS: Infliximab is safe and effective in the short-term treatment of medically refractory pediatric Crohn's disease. More importantly, there is a remarkably prolonged duration of response after infliximab therapy in children with early compared to late Crohn's disease.

56. Lamireau, T., Cezard, J.P., Dabadie, A., Goulet, O., Lachaux, A., Turck, D., Maurage, C., Morali, A., Sokal, E., Belli, D., Stoller, J., Cadranel, S., Ginies, J.L., Viola, S., Huet, F., Languépin, J., Lenaerts, C., Bury, F., and Sarles, J. Efficacy and tolerance of infliximab in children and adolescents with Crohn's disease. *Inflamm Bowel Dis* 10: 745-750, 2004.

Infliximab, a monoclonal antibody against tumor necrosis factor-alpha, has been shown to be effective for the treatment of refractory Crohn's disease in adult patients, but experience in pediatrics is limited. This retrospective study included 88 children and adolescents, 39 girls and 49 boys, with a median age of 14 years (range 3.3-17.9). Infliximab was indicated for active disease (66%) and/or fistulas (42%) that were refractory to corticosteroids (70%), and/or other immunosuppressive (82%) agents, and/or parenteral nutrition (20%). Patients received 1 to 17 infusions (median 4) of 5 mg/kg (range 3.8-7.3) of infliximab during a median time period of 4 months (1-17 months). Infusion reaction was noted in 13 patients (15%), with a total of 16 reactions in 450 infusions (4%). At Day 90 after the first infusion of infliximab, symptoms improved in 49% of patients, whereas 29% of patients were in remission and 13% of patients relapsed. From Day 0 to Day 90, Harvey-Bradshaw score decreased from 7.5 to 2.8 ($P < 0.001$), C-reactive protein from 36 to 16 mg/L ($P < 0.01$), and 1-hour erythrocyte sedimentation rate from 35 to 17 mm ($P < 0.01$). Dosage of corticosteroids decreased from 0.59 to 0.17 mg/kg/d ($P < 0.001$); 53% of patients could be weaned of corticosteroids and 92% of parenteral nutrition. Treatment with infliximab is well tolerated and effective in most children and

adolescents with Crohn's disease that is refractory to conventional immunosuppressive therapy. Nevertheless, long-term efficacy remains to be shown, and further studies are urgently needed to precisely determine the best modality of continuing treatment.

57. Levine, A., Kori, M., Dinari, G., Broide, E., Shaoul, R., Yerushalmi, B., On, A., Bujanover, Y., Prots, M., and Greinwald, R. Comparison of two dosing methods for induction of response and remission with oral budesonide in active pediatric Crohn's disease: a randomized placebo-controlled trial. *Inflamm Bowel Dis* 15: 1055-1061, 2009.

BACKGROUND: Oral budesonide has been found to be comparable to systemic corticosteroids in mild to moderately active Crohn's disease (CD). Remission rates in pediatric studies to date have been suboptimal (47%-55%), even though patients with colonic involvement were excluded in some studies. In addition, the optimal pediatric dosing regimen has never been evaluated before. **METHODS:** This was a randomized, controlled, double-blind study in 70 children with mild or moderately active CD randomized to 1 of 2 groups: Group 1: Standard dose budesonide (9 mg/day) for 7 weeks followed by 6 mg budesonide daily for an additional 3 weeks. Group 2: Induction with 12 mg/day for the first month followed by the same regimen as Group 1. Outcome measures included a decrease in Pediatric Crohn's Disease Activity Index and remission rates. Patients with colonic disease were not excluded. **RESULTS:** At week 7 a clinical response was obtained in 51.4% in Group 1 versus 74.3% in Group 2. A significant decrease in C-reactive protein was seen only in Group 2. At the end of treatment, remission was obtained in 42.9% in Group 1 versus 65.7% in Group 2 ($P = 0.054$). There was no significant difference in adverse events or serum cortisol. **CONCLUSIONS:** Use of an induction dose of budesonide followed by a budesonide taper resulted in a trend to higher rates of clinical remission and a decrease in inflammation, without an increase in steroid-associated side effects. Budesonide was also useful for patients with ileocolonic disease.

58. Levine, A., Weizman, Z., Broide, E., Shamir, R., Shaoul, R., Pacht, A., Dinari, G., On, A., Weiss, B., and Bujanover, Y. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 36: 248-252, 2003.

OBJECTIVES: Budesonide has been found effective in patients with mild and moderate Crohn disease and has been found to cause fewer side effects than prednisone. The use of oral budesonide has not been prospectively evaluated in children with Crohn disease. Therefore, the authors initiated a trial to compare remission and tolerance to budesonide and prednisone in children with mild or moderately active Crohn disease. **METHODS:** A prospective randomized open controlled 12-week trial was carried out comparing pH modified release budesonide, 9 mg, versus prednisone, 40 mg, in children with active mild to moderate pediatric Crohn disease. **RESULTS:** Thirty-three patients (20 boys and

13 girls; mean age, 14.3 years) enrolled and completed the study. The groups treated with budesonide and prednisone did not differ by age, onset of disease, location of disease, or disease activity. The remission rate at 12 weeks was 47% in the budesonide treatment group and 50% in the prednisone treatment group. Side effects occurred in 32% and 71% of patients treated with budesonide and prednisone, respectively ($P < 0.05$). Severity of cosmetic side effects was significantly lower in patients treated with budesonide ($P < 0.01$).

CONCLUSIONS: Remission rates for Crohn disease with budesonide and prednisone treatment in this study were similar. Pediatric patients treated with budesonide had significantly fewer side effects than patients treated with prednisone. Budesonide should be considered an alternative to prednisone in pediatric patients with mild to moderate disease activity.

59. Lionetti, P., Bronzini, F., Salvestrini, C., Bascietto, C., Canani, R.B., De Angelis, G.L., Guariso, G., Martellosi, S., Papadatou, B., and Barabino, A. Response to infliximab is related to disease duration in paediatric Crohn's disease. *Aliment Pharmacol Ther* 18: 425-431, 2003.

BACKGROUND: Infliximab is an effective therapy in adult patients with refractory and fistulizing Crohn's disease. Experience in children is still limited. **AIM:** : To evaluate the experience in 22 children and adolescents treated with infliximab with refractory and/or fistulizing Crohn's disease, and to compare duration of response in children between early Crohn's disease and late Crohn's disease. **METHODS:** The experience in 22 children and adolescents treated with a total of 73 infusions was evaluated retrospectively. Treatment indication was refractory Crohn's disease in 9/22 patients, fistulizing Crohn's disease in 7/22 patients and both these conditions in 6/22. All patients with refractory Crohn's disease had late Crohn's disease (> 1 year), whereas 6/13 patients with fistulas had early disease (< 1 year). **RESULTS:** Mean Paediatric Crohn's Disease Activity Index (PCDAI) decreased from 41.2 to 16.2 at 4 weeks ($P < 0.01$), and to 15.4 at 18 weeks ($P < 0.01$). Mean PCDAI at 18 weeks in children with early Crohn's disease and late Crohn's disease was 5.5 and 18.1, respectively ($P < 0.05$). Complete closure of fistulas was obtained in 5/6 children with early Crohn's disease and in 2/7 children with late Crohn's disease. Immediate adverse reactions were observed in two children. **CONCLUSIONS:** Infliximab is a highly effective treatment in children and adolescents with both severe refractory or fistulizing Crohn's disease. Children with early Crohn's disease have a higher chance of prolonged response to infliximab than children with late Crohn's disease.

60. Lyckegaard, E., Hakansson, K., and Bengtsson, B. Budesonide in Crohn's disease: findings of a compassionate-use program. *Hepatogastroenterology* 54: 2024-2027, 2007.

BACKGROUND/AIMS: Budesonide controlled-release (CR) capsules are effective for inducing remission of Crohn's disease (CD) and are associated with fewer side effects than conventional corticosteroids. A compassionate-use

program was implemented in countries where this treatment was unavailable. This paper reports the findings of this program. **METHODOLOGY:** Physicians were allowed to apply to AstraZeneca for a supply of budesonide CR capsules primarily for patients with CD who had experienced unacceptable side effects from conventional steroids or were unresponsive to other drugs. Physicians were requested to record adverse events (AEs) and patient response (1 = 'moderate'; 2 = 'well'; 3 = 'very well'). **RESULTS:** Four thousand and ninety-two patients were enrolled. There were 232 AE reports involving 326 different symptoms. There were 138 serious AEs (mainly gastrointestinal), and four deaths. Ten serious AEs were considered related to budesonide (no deaths). Budesonide was discontinued as a result of AEs in 147 patients (75 due to serious AEs, mainly gastrointestinal). Efficacy data were obtained from 1188 patients, with 943 (79%) responding 'well' or 'very well'. In the subgroups of patients that were young, elderly, or had unsuccessfully received immunosuppressants previously, the mean patient response score was >2. **CONCLUSIONS:** In a normal clinical setting, budesonide CR capsules were well tolerated by patients with ileocecal CD.

61. Mack, D.R., Young, R., Kaufman, S.S., Ramey, L., and Vanderhoof, J.A. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. *J Pediatr* 132: 830-835, 1998.

OBJECTIVE: The objective of this study was to describe the clinical outcome of children with Crohn's disease treated with subcutaneous methotrexate. **SUBJECTS/METHODS:** Fourteen patients (10 boys) with extensive Crohn's disease diagnosed at a mean age of 10.6 +/- 3.6 years had previously received various medical therapies for 4.3 +/- 4.0 years. Because of the severity of their disease, 6-mercaptopurine had been introduced but discontinued because of the patients' failure to respond (n = 11) or the development of pancreatitis (n = 3). Subsequently, low-dose, weekly, subcutaneous methotrexate was initiated. Pediatric Crohn's Disease Activity Index scores and prednisone requirement were followed as outcome measures. **RESULTS:** Overall, 9 (64%) of the 14 patients showed improvement, including 6 (55%) of 11 patients who had previously received an adequate trial of 6-mercaptopurine and all three patients who were intolerant of 6-mercaptopurine. Improvement in clinical and laboratory measures occurred by 4 weeks and were similar whether (n = 8) or not (n = 6) the dose of corticosteroids was increased before the start of subcutaneous methotrexate. Three patients were tapered from their initial methotrexate dose after the minimization of corticosteroids and remain well. One patient receiving daily corticosteroids died suddenly after acute onset of illness. Among patients responding, methotrexate was discontinued because of side effects (n = 2) or electively (n = 2). Of the latter two patients, one has resumed methotrexate after disease relapse, whereas the other patient has had a sustained remission. **CONCLUSIONS:** Low-dose, weekly, subcutaneous methotrexate can induce remission in some pediatric patients with Crohn's disease who fail to adequately respond to other immunomodulator medications.

62. Mahadevan, U., Kane, S., Sandborn, W.J., Cohen, R.D., Hanson, K., Terdiman, J.P., and Binion, D.G. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 21: 733-738, 2005.

AIM: To study the effects of infliximab on pregnancy and foetal outcome.

METHODS: We conducted a retrospective chart review of women with Crohn's disease treated intentionally with infliximab during pregnancy. The primary outcome measure was the occurrence of congenital malformations. Secondary outcome measures were the rate of premature birth, low-birth weight, small for gestational age infants, intrauterine growth retardation and caesarean section.

RESULTS: Ten women were identified. Eight women received maintenance infliximab infusions throughout their pregnancy and two women received their initial infliximab infusions during pregnancy. All 10 pregnancies ended in live births. No infants had congenital malformations, intrauterine growth retardation or small for gestational age parameters. Three infants were premature and one had low-birth weight. Eight women had a caesarean section. CONCLUSIONS: This is the first reported series of intentional infliximab use throughout pregnancy. These data, combined with other studies of inadvertent use of infliximab during pregnancy, suggest that the benefits of infliximab in achieving response and maintaining remission in mothers with Crohn's disease may outweigh the risk to the foetus of exposure to the drug. Further prospective data collection will be helpful to confirm these findings.

63. Mahadevan, U., and Sandborn, W.J. Evolving medical therapies for Crohn's disease. *Curr Gastroenterol Rep* 3: 471-476, 2001.

Medical therapy for Crohn's disease has changed dramatically over the past few years. Physicians have become increasingly willing to use traditional immunosuppressive agents such as azathioprine/6-mercaptopurine (6-MP) and methotrexate as well as new biologic therapies such as infliximab. Azathioprine, 6-MP, and methotrexate have demonstrated efficacy in induction and maintenance of remission in Crohn's disease. 6-MP has also demonstrated efficacy in the pediatric population and possibly as first-line therapy. As use of the purine metabolites grows, therapeutic drug monitoring for efficacy and toxicity will become an emerging area of interest. With respect to the biologic therapies, infliximab is increasingly used to treat patients with difficult disease; however, knowledge is still evolving regarding optimal dosing schedules and the significance of immune reactions to the compound. A humanized anti-tumor necrosis factor antibody, CDP571, may be less immunogenic. Interleukin-10 did not consistently demonstrate benefit in Crohn's disease. Similarly, antisense to intracellular adhesion molecule 1 (ISIS 2302) was not efficacious when administered either subcutaneously or intravenously. Finally, growth hormone has shown promising results in a small trial.

64. Mahdi, G., Israel, D.M., and Hassall, E. Cyclosporine and 6-mercaptopurine for active, refractory Crohn's colitis in children. *Am J Gastroenterol* 91: 1355-1359, 1996.

OBJECTIVES: This prospective, open trial of treatment was conducted to determine whether cyclosporine A (CSA) is effective in inducing remission in children with severe, active Crohn's colitis refractory to other medical treatment and if remission may be maintained by 6-mercaptopurine (6-MP) and 5-aminosalicylic acid (5-ASA) after discontinuing CSA. METHODS: Ten children (five males, five females), ages 1.2-16 yr (mean 11), all had failed to respond to 4 wk of treatment with i.v. methylprednisolone and total parenteral nutrition/elemental diet; three were already receiving 6-mercaptopurine. CSA was initially given as a twice daily i.v. dosage and was switched to oral CSA when a clinical response was observed. At the same time, corticosteroids were switched to the oral route and tapered over the next 3 months. Patients were grouped by treatment outcome. "Responders" were those who achieved remission with i.v. CSA therapy, "relapsers" were those who achieved remission with i.v. CSA but relapsed later, and nonresponders had not achieved remission after 4 wk of i.v. CSA. Responders were given 6-MP with intent to discontinue CSA after 6 months and maintain remission by 6-MP and 5-ASA. RESULTS: There were seven responders to CSA. For all patients, the Pediatric Crohn's Disease Activity Index (PCDAI) (score range 0-100) had a mean value of 55 (range 40-65) just before treatment; PCDAI improved to a mean of 19 (range 5-42.5) after 2 wk of CSA therapy. Four of the seven responders discontinued CSA after 6 months and remain well on 6-MP and 5ASA alone for 22, 13, 8, and 3 months. One patient had massive GI bleeding (from active Crohn's colitis), which stopped within 48 h of CSA treatment. There were three relapsers (at 2-6 months of CSA), and three were nonresponders. Three patients who were already receiving 6-MP before CSA therapy either did not respond to CSA or relapsed while receiving it. The six nonresponders and relapsers required surgical resection. Transient side effects included hypertension responding to nifedipine in one child and hirsutism and tremors in another. CONCLUSIONS: We conclude that CSA offers a good remission rate for children with severe Crohn's colitis failing other medical treatment, although relapse was common especially if the child was already on 6-MP. In addition, CSA may offer "temporizing" therapy in severe, active Crohn's colitis; this may allow surgery to be performed electively, with time for psychosocial and nutritional preparation before surgery.

65. Mamula, P., Cohen, S.A., Ferry, G.D., Kirschner, B.S., Winter, H.S., Innes, A., Patel, J., and Baldassano, R.N. CDP571, a humanized anti-tumor necrosis factor-alpha monoclonal antibody in pediatric Crohn's disease. *Inflamm Bowel Dis* 10: 723-730, 2004.

OBJECTIVES: The objectives of this study were to evaluate the safety, pharmacokinetics, and immunogenicity of CDP571 in pediatric patients with Crohn's disease. METHODS: A single dose of CDP571, 10 mg/kg, was

administered by infusion to pediatric patients (aged 6-17 years) with Crohn's disease in a 12-week open-label study. Adverse events were monitored during infusion and throughout the study. Plasma concentrations of CDP571 and standard clinical and laboratory values were assessed. Changes in disease activity were monitored using the Pediatric Crohn's Disease Activity Index (PCDAI). RESULTS: Twenty patients were enrolled and stratified by age: 6 to 13 (n = 9) and 14 to 17 years (n = 11). Fourteen patients experienced adverse events, which were mainly mild or moderate in intensity. The plasma concentration profile was consistent with a half-life of approximately 2 weeks. At Week 4, 4 patients in the 6- to 13-year-old group and 2 patients in the 14- to 17-year-old group had detectable anti-CDP571 antibodies. By Week 2, 7 patients in the 6- to 13-year-old group and 6 patients in the 14- to 17-year-old group had responded to treatment (reduction in PCDAI score >10 points). CONCLUSION: In conclusion, CDP571 was well tolerated among pediatric patients with Crohn's disease.

66. Markowitz, J. Early inflammatory bowel disease: different treatment response to specific or all medications? *Dig Dis* 27: 358-365, 2009.

BACKGROUND: The literature suggests that medications prescribed for the treatment of inflammatory bowel disease may be more efficacious in children than adults. Care must be exercised in comparing these data, however, as significant differences in disease duration and concomitant therapy are present among studies. METHODS: Review of key clinical trials, meta-analyses and observational registries for which there are treatment response data from both pediatric and adult Crohn's disease (CD) populations. RESULTS: Acute response to corticosteroids is similar in children (84-89%) and adults (80-84%), but prolonged response may be better in children (50-61 vs. 32-44%). Differences in duration of CD among the various studies' subjects and the proportion of subjects receiving concomitant immunomodulators probably explain much of these differences. CD remission rates with thiopurines appear higher in children at both 6 months (85 vs. 31%) and 15-18 months (81 vs. 42%), but the reported outcomes are likely influenced by very short duration of CD in the pediatric populations studied. Similarly, remission of CD 1 year following initiation of infliximab also appears higher in children (56%) than adults (28%), but again differences in study populations' durations of CD and use of concomitant immunomodulators likely are responsible for the observed differences. CONCLUSION: Differences between pediatric and adult responses to a variety of IBD treatments appear to be due more to study design than the age of the subjects evaluated. As published pediatric trials have generally evaluated subjects with potent treatments at or shortly after diagnosis, the consistently higher rates of responses seen in children lend weight to the argument that some form of 'top-down' therapy offers the best option to maximize remission rates in all patients with IBD.

67. Markowitz, J., Grancher, K., Kohn, N., Lesser, M., and Daum, F. A multicenter

trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 119: 895-902, 2000.

BACKGROUND & AIMS: Clinical experience suggests that 6-mercaptopurine (6-MP) is effective therapy for children with active steroid-dependent Crohn's disease (CD). We report the results of a prospective, placebo-controlled, multicenter trial evaluating the combination of 6-MP and prednisone as therapy for children with newly diagnosed moderate-to-severe CD. **METHODS:** Fifty-five children (age, 13+/-2 years) were randomized to treatment with 6-MP (1.5 mg x kg(-1) x day(-1)) or placebo within 8 weeks of initial diagnosis. Both groups also received prednisone (40 mg/day). Prednisone dosage adjustments were based on a defined schedule determined by the change in a subject's disease activity score, and steroid administration was discontinued as remission was achieved. Study treatment with 6-MP or placebo continued for 18 months. **RESULTS:** Groups were comparable for age, sex, and site and activity of disease. In the 6-MP group, the duration of steroid use was shorter ($P < 0.001$) and the cumulative steroid dose lower at 6, 12, and 18 months ($P < 0.01$). Although remission was induced in 89% of both groups, only 9% of the remitters in the 6-MP group relapsed compared with 47% of controls ($P = 0.007$). Growth was comparable in both groups. No clinically significant adverse events occurred, although mild leukopenia and increases in aminotransferase activity were noted in the 6-MP group. **CONCLUSIONS:** Addition of 6-MP to a regimen of corticosteroids significantly lessens the need for prednisone and improves maintenance of remission. 6-MP should be part of the initial treatment regimen for children with newly diagnosed moderate-to-severe CD.

68. Markowitz, J., Hyams, J., Mack, D., Leleiko, N., Evans, J., Kugathasan, S., Pfefferkorn, M., Mezoff, A., Rosh, J., Tolia, V., Otley, A., Griffiths, A., Moyer, M.S., Oliva-Hemker, M., Wyllie, R., Rothbaum, R., Bousvaros, A., Del Rosario, J.F., Hale, S., and Lerer, T. Corticosteroid therapy in the age of infliximab: acute and 1-year outcomes in newly diagnosed children with Crohn's disease. *Clin Gastroenterol Hepatol* 4: 1124-1129, 2006.

BACKGROUND & AIMS: The aim of this study was to describe 3-month and 1-year outcomes of children with Crohn's disease (CD) treated with corticosteroids within 30 days of diagnosis, with particular emphasis on the influence of infliximab on these outcomes. We also aimed to determine whether there are clinical or laboratory characteristics associated with corticosteroid therapy outcomes. **METHODS:** Data from 109 children were drawn from a multicenter observational registry that was started in 2002. Clinical characteristics and data on corticosteroid and other therapies were recorded prospectively. Corticosteroid therapy outcomes at 3 months were defined as complete acute response, partial response, or corticosteroid resistance. At 1 year, corticosteroid responsiveness, dependence, and surgical rates were determined. Infliximab's influence on short- and long-term outcomes also was investigated. **RESULTS:** At 3 months, 65 of 109 (60%) patients had a complete acute response to corticosteroids, 26 (24%)

had a partial response, and 18 (17%) were corticosteroid resistant. At 1 year, 61% were corticosteroid responsive, 31% were corticosteroid dependent, and 8% required surgery. Irrespective of the duration of corticosteroid treatment, 16 of 24 of corticosteroid-dependent/resistant patients rapidly discontinued corticosteroids after starting infliximab. No clinical or laboratory characteristics at diagnosis predicted short-term outcome. Growth impairment at diagnosis increased risk for corticosteroid dependence or surgery at 1 year. CONCLUSIONS: At 3 months, 84% of children had a complete or partial response to corticosteroids. However, despite concomitant immunomodulators, at 1 year 31% were corticosteroid dependent and 8% required surgery. Infliximab improves outcomes of corticosteroid-dependent/resistant patients because the duration of corticosteroid use can be controlled by initiating treatment with infliximab.

69. Mesker, T., van Rheenen, P.F., Norbruis, O.F., Uitentuis, J., Waalkens, H.J., Gonera, G., van Overbeek, L.A., Butler, J., and Rings, E.H. Pediatric Crohn's disease activity at diagnosis, its influence on pediatrician's prescribing behavior, and clinical outcome 5 years later. *Inflamm Bowel Dis* 15: 1670-1677, 2009.

BACKGROUND: No studies have been performed in which therapeutic regimens have been compared between mild and moderate-to-severe pediatric Crohn's disease (CD) at diagnosis. The aim was to analyze pediatric CD activity at diagnosis, its influence on pediatrician's prescribing behavior, and clinical outcome 5 years later. METHODS: In a retrospective multicenter study we divided pediatric CD patients at diagnosis into mild or moderate-severe disease. We compared initial therapies, duration of first remission, number of exacerbations, height-for-age and weight-for-height evolvment, and cumulative duration of systemic steroid use in a 5-year follow-up period. RESULTS: Forty-three children were included (25 with mild and 18 with moderate-severe disease). Aminosalicylate monotherapy was more frequently prescribed in the mild group (40% versus 17%; $P < 0.01$). The median duration of systemic steroid use was 18.3 months in the mild group and 10.4 months in the moderate-severe group ($P = 0.09$). Duration of first remission was 15.0 months in the mild group and 23.4 months in the moderate-severe group ($P = 0.16$). The mean number of exacerbations was 2.2 in the mild group and 1.8 in the moderate-severe group ($P = 0.28$). CONCLUSIONS: CD patients with mild disease were treated with aminosalicylate monotherapy more frequently. These patients, however, tend to have more exacerbations, shorter duration of first remission, and longer total duration of systemic steroid use. Our data support the concept that severity of disease at diagnosis does not reliably predict subsequent clinical course. This study suggests that there is no indication that children with mild CD should be treated differently compared to children with moderate-severe disease.

70. Naftali, T., Novis, B., Pomeranz, I., Leichtman, G., Maor, Y., Shapiro, R., Moskowitz, M., Avidan, B., Avni, Y., Bujanover, Y., and Fireman, Z. Cyclosporin for severe ulcerative colitis. *Isr Med Assoc J* 2: 588-591, 2000.

BACKGROUND: About one-third of patients with severe ulcerative colitis do not respond to conventional therapy and require urgent colectomy. It was recently shown that cyclosporin is effective in some of these patients. **OBJECTIVES:** To review the current experience of six hospitals in central Israel that used cyclosporin in patients with severe ulcerative colitis. **METHODS:** The files of all 32 patients treated with cyclosporin for corticosteroid-resistant ulcerative colitis were reviewed. Activity of disease was measured by a clinical activity, index colonoscopy and laboratory tests. **RESULTS:** The average duration of treatment with intravenous cyclosporin was 12.7 days (range 9-28) after which the disease activity index dropped from an average of 14.22 to 4.74. The mean time for response was 7.5 days (4-14). Twelve patients (40%) required surgery within 6 months and another 6 patients (18.8%) were operated on after more than 6 months. Twelve patients (37%) maintained remission for at least 6 months and did not require surgery. In one patient treatment was stopped because of non-compliance and one was lost to follow-up. There were numerous side effects, but in only one case with neurotoxicity was treatment withdrawn. **CONCLUSIONS:** Cyclosporin is a relatively safe and effective treatment for severe ulcerative colitis. It induced long-term remission in 37% of the patients, and in those who required surgery the treatment resulted in an improved clinical condition before the operation.

71. Nicholls, S., Domizio, P., Williams, C.B., Dawnay, A., Braegger, C.P., MacDonald, T.T., and Walker-Smith, J.A. Cyclosporin as initial treatment for Crohn's disease. *Arch Dis Child* 71: 243-247, 1994.

Childhood Crohn's disease may cause significant morbidity. T cell activation is considered to be central to Crohn's disease pathology, and as cyclosporin is a powerful inhibitor of T cell activation, and has been used in adult Crohn's disease with encouraging results, it may offer the prospect of remission if given early in the course of disease. Children with newly diagnosed Crohn's disease or those relapsing off treatment were therefore given cyclosporin or conventional treatment (enteral nutrition or corticosteroids) by random allocation. Evaluation was performed initially and at two months. Twenty four children were studied (10 on cyclosporin and 14 on conventional treatment; one child on cyclosporin withdrew). Significant clinical improvement occurred in the group on conventional treatment, but not in the cyclosporin group. Colonoscopic improvement was noted in 5/9 on cyclosporin and 8/14 on conventional treatment, but neither group produced a significant fall in median colonoscopic index. Histological improvement was seen in 7/8 on cyclosporin and 8/13 on conventional treatment, but cyclosporin was not significantly better. Cyclosporin produced improved clinical and histological appearance without matched improvement in blood disease indices. It was not better than conventional treatment, and simple oral administration is probably not suitable for newly diagnosed patients with Crohn's disease.

72. Otley, A., and Steinhart, A.H. Budesonide for induction of remission in Crohn's

disease. *Cochrane Database Syst Rev*: CD000296, 2005.

BACKGROUND: Corticosteroids continue to play a central role in induction of remission in active Crohn's disease. However, their use comes at a price of significant adverse effects when used repeatedly or for extended periods. Newer corticosteroid agents with limited systemic bioavailability offer a tantalizing option, if they can be shown to be efficacious and safer than conventional corticosteroids. Budesonide is the main alternative corticosteroid currently available in an enteric formulation. **OBJECTIVES:** To evaluate the effectiveness of oral budesonide for the treatment of acute flares of Crohn's disease. A secondary but important endpoint was to evaluate the adverse effect profile. **SEARCH STRATEGY:** The following sources were used to search the literature for potentially relevant papers and trials. 1. A computer-assisted search of the on-line bibliographic database MEDLINE from 1986 onwards. 2. Hand searching the reference lists of trials and review articles identified by means of the computer-assisted search. 3. Proceedings from major gastrointestinal meetings were manually searched from 1990 onwards. 4. Contact with the relevant pharmaceutical companies that have been involved in the development of budesonide. **SELECTION CRITERIA:** Potentially relevant articles were reviewed in an independent unblinded fashion by two authors to determine if they met the criteria specified below: 1) Study population: Patients of any age with acutely active Crohn's disease, as defined by a CDAI > 150. 2) Methodology: Randomized double blind controlled trials comparing budesonide to a control treatment. Patients in the control arm may have received placebo, conventional corticosteroids, 5-aminosalicylic acid or sulfasalazine. 3) Outcome measures: Clinical remission was the outcome measure of interest. The definition of remission was usually a CDAI < 150 by 8 to 16 weeks of therapy. **DATA COLLECTION AND ANALYSIS:** Eligible articles were reviewed in duplicate and the results of the primary research trials were abstracted onto specially designed data extraction forms. The proportion of patients achieving remission in the active treatment and control groups of each study were derived from the data provided in the original research papers. Where possible, data were broken down based on site of disease or other strata used by the individual trials. **STATISTICAL ANALYSIS:** Data extracted from the original research articles were converted, where necessary, into individual 2 x 2 tables (remission versus no remission x budesonide versus control) for each of the individual studies. Where available, individual 2 x 2 tables for strata within studies were also used. The presence of significant heterogeneity among studies was tested for using the chi-square test. Because this is a relatively insensitive test for the presence of heterogeneity, a p-value of 0.10 was regarded as statistically significant. Where $p < 0.10$ the data from the individual studies were still combined but the pooled results were interpreted with caution. The 2 x 2 tables were synthesized into a summary test statistic using the pooled odds ratio and 95% confidence intervals as described by Cochran and Mantel and Haenszel. A fixed effects model was used for the pooling of data. The analysis was performed initially by combining data from all trials to estimate the response rate to budesonide therapy. The analysis was also

performed by combining only studies with comparable control groups. MAIN RESULTS: Eight studies were deemed eligible for review. EFFICACY: Budesonide was superior to placebo for induction of remission with a pooled odds ratio for the two placebo-controlled trials of 2.85 (95% CI 1.67 - 4.87). A single trial comparing budesonide with mesalamine demonstrated an odds ratio of 2.80 (95% CI 1.50 - 5.20) in favour of budesonide over mesalamine for induction of remission in active Crohn's disease. However, budesonide was inferior to conventional corticosteroids (prednisone or prednisolone) for induction of remission with a pooled odds ratio for the five trials of 0.69 (95% CI 0.51 - 0.95). SAFETY: The two trials comparing budesonide versus placebo (Greenberg 1994; Tremaine 2002) showed no difference between study groups for proportion of reported corticosteroid-related adverse effects with the pooled odds ratio for both trials of 0.98 (95% CI 0.58 - 1.67). Five trials comparing budesonide versus prednisone showed the budesonide study group had fewer reported corticosteroid-related adverse effects than the prednisone study group (pooled odds ratio was 0.38 (95% CI 0.28 - 0.53). AUTHORS' CONCLUSIONS: With disease in the ileum or ascending colon, budesonide offers an effective therapy which is somewhat less efficacious but with fewer adverse effects than conventional corticosteroids (e.g. prednisone, prednisolone, or 6-methylprednisolone).

73. Oussalah, A., Danese, S., and Peyrin-Biroulet, L. Efficacy of TNF antagonists beyond one year in adult and pediatric inflammatory bowel diseases: a systematic review. *Curr Drug Targets* 11: 156-175, 2010.

The introduction in the mid-1990s of tumor necrosis factor (TNF) antagonists changed the treatment of inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis (UC) refractory to conventional medications (corticosteroids, immunomodulators). This review summarizes current data on the long-term efficacy and safety of anti-TNF therapy in IBD beyond 1 year. We searched Medline, the Cochrane Library, Embase, and Ovid Medliner for relevant studies. Infliximab, adalimumab and certolizumab are effective in maintaining clinical remission in luminal Crohn's disease. Infliximab and adalimumab are also effective in maintaining long-term fistula closure in Crohn's disease. Only infliximab has been evaluated in UC in the long term, with similar data on its effectiveness than in CD. In addition to the maintenance of clinical remission, TNF antagonists have the ability to maintain long-term mucosal healing, resulting in a reduced risk of surgery. With 2010 on the horizon, we have no good reasons to stop anti-TNF therapy in IBD patients because of its efficacy in maintaining remission and a risk-benefit ratio that remains in its favor. It is now clear that patients in deep remission, comprising clinical, biological, and endoscopic remission, are at lower risk of relapse after withdrawal of anti-TNF therapy.

74. Pescatori, M., Interisano, A., Basso, L., Arcana, F., Buffatti, P., Di Bella, F., Doldi, A., Forcheri, V., Gaetini, R., Pera, A., and et al. Management of perianal Crohn's disease. Results of a multicenter study in Italy. *Dis Colon Rectum* 38: 121-124,

1995.

PURPOSE: Management of perianal Crohn's disease is still controversial, and reports on large series are very few in the literature. The aim of this multicenter study was to investigate the outcome of both medical and surgical treatment in 225 patients. **METHODS:** Patients cared for at different institutions were followed up for a median of six years. Most of them had either anal fistula or an abscess (86 percent and 43 percent, respectively), but fissures were also present in 26 percent of the cases. Diarrhea and anal pain were the most common symptoms. Anal lesions preceded the onset of intestinal symptoms in 19 percent of cases. **RESULTS:** Medical treatment was curative only in 21 of 123 patients. Overall, medical and surgical treatment either cured or improved 62 percent of the cases. Fifty percent had an intestinal resection. Abscess drainage and fistulotomy were the most common anal surgeries. Rectovaginal fistulas (n = 30) required intestinal surgery in 36 percent and anal surgery in 20 percent of the cases, 50 percent with good results. Of 166 patients who had anal surgery, 97 (58 percent) had a positive outcome. Recurrence of anal disease requiring further surgery occurred in 24.5 percent of the cases. **CONCLUSIONS:** Limited surgeries seem to achieve satisfactory results in more than one-half of the patients affected by perianal Crohn's lesions, whereas medical treatment alone is curative in a small portion of them.

75. Pettersson, B., Almer, S., Albertioni, F., Soderhall, S., and Peterson, C. Differences between children and adults in thiopurine methyltransferase activity and metabolite formation during thiopurine therapy: possible role of concomitant methotrexate. *The Drug Monit* 24: 351-358, 2002.

This study examined the role of thiopurine methyltransferase (TPMT) polymorphism in the metabolism and clinical effects of azathioprine and 6-mercaptopurine in the treatment of inflammatory bowel disease and childhood leukemia. The current hypothesis is that the cytotoxic effects of thiopurines are caused by the incorporation of thioguanine nucleotides into DNA. In this context, S-methylation catalyzed by TPMT can be regarded as a competing metabolic pathway. The authors assayed the TPMT activity in red blood cells from 122 patients treated with azathioprine or 6-mercaptopurine (83 adults with inflammatory bowel disease and 39 children with acute lymphoblastic leukemia) and in 290 untreated controls (219 adult blood donors and 71 children). The concentrations of thioguanine nucleotides and methylthioinosine monophosphate were also assayed in red blood cells from the patients. The TPMT activity and the concentrations of methylthioinosine monophosphate and thioguanine nucleotides were higher in children than in adults. All children but no adult patient received concomitant methotrexate. Interaction between methotrexate and 6-mercaptopurine has been described, and may explain the results. Low TPMT activity in adult patients with inflammatory bowel disease correlated to an increased incidence of adverse drug reactions. However, there was no correlation between TPMT activity and the red blood cell concentrations of

methylthioinosine monophosphate or thioguanine nucleotides, or between the concentrations of these metabolites and the occurrence of adverse effects. The results show that the role of thiopurine metabolism for drug effects is complex.

76. Pressman, A.R., Hutfless, S., Velayos, F., Fireman, B., Lewis, J.D., Allison, J., Abramson, O., and Herrinton, L.J. Patterns of infliximab use among Crohn's disease patients in a community setting. *Inflamm Bowel Dis* 14: 1265-1272, 2008.

BACKGROUND: Information on infliximab use in a community setting is important to understand patterns of medication use and to anticipate and plan for costs associated with the drug. We sought to understand predictors of initiation and discontinuation of infliximab in the community-based setting of Kaiser Permanente, Northern California, which provides integrated care to its members. **METHODS:** The cohort study was set during 1998-2006. Predictors of initiation were assessed among 494 Crohn's disease (CD) patients who initiated infliximab and 2470 CD patients who did not initiate infliximab (controls). Data were obtained through linkage of computerized clinical information and were analyzed using logistic regression and Cox survival analysis. **RESULTS:** Infliximab infusions have increased rapidly since 2001, with no evidence of leveling off. Initiators were appreciably younger than controls ($P < 0.001$), but were similar to controls with respect to sex and race/ethnicity. The presence of at least 1 comorbidity was related to a modest increase in the risk of initiating (compared with none: 1 comorbidity, odds ratio [OR] = 1.52 with 95% confidence interval [CI] 1.16-2.00; 2 comorbidities, OR = 1.38 with CI 0.89-2.13). By 3 years after initiating, only 20% of patients remained on infliximab. **CONCLUSIONS:** In a community-based setting infliximab use has steadily increased. Age and comorbidity are associated with initiation, but sex and race/ethnicity are not. More information is needed to determine why, in this community-based setting, a large number of patients on infliximab discontinued their treatment. (*Inflamm Bowel Dis* 2008).

77. Pruitt, R., Hanson, J., Safdi, M., Wruble, L., Hardi, R., Johanson, J., Koval, G., Riff, D., Winston, B., Cross, A., Doty, P., and Johnson, L.K. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. *Am J Gastroenterol* 97: 3078-3086, 2002.

OBJECTIVE: Balsalazide is a novel azo-bonded 5-aminosalicylic acid treatment for mild-to-moderate ulcerative colitis. The study objective was to compare symptomatic remission rates with balsalazide and mesalamine while controlling for extent of disease and time since diagnosis in patients with active, mild-to-moderate ulcerative colitis. **METHODS:** A total of 173 patients with sigmoidoscopically verified ulcerative colitis were randomized to 8 wk of double-blind treatment with balsalazide 6.75 g/day or mesalamine 2.4 g/day. Both treatments provided 2.4 g/day of oral 5-aminosalicylic acid. Patients maintained

symptom diaries throughout the treatment period. RESULTS: Overall, 46% of balsalazide- and 44% of mesalamine-treated patients achieved symptomatic remission. Higher response rates were noted in newly diagnosed patients with ≤ 40 cm of disease (68% vs 61%) than in recently relapsed patients with >40 cm of disease (36% vs 25%). The median time to symptomatic remission was 12 days shorter with balsalazide (25 days) than with mesalamine (37 days). Significantly more balsalazide patients showed sigmoidoscopic ($p = 0.002$), stool frequency ($p = 0.006$), rectal bleeding ($p = 0.006$), and physician's global assessment score ($p = 0.013$) improvement by 14 days than did mesalamine patients. Similar proportions of patients reported adverse events (54% vs 64%), which were most commonly related to the gastrointestinal and central and peripheral nervous systems. CONCLUSIONS: Balsalazide is an effective and safe treatment for mild-to-moderate ulcerative colitis. Improvement of symptoms occurs considerably earlier with balsalazide than with mesalamine.

78. Punati, J., Markowitz, J., Lerer, T., Hyams, J., Kugathasan, S., Griffiths, A., Otley, A., Rosh, J., Pfefferkorn, M., Mack, D., Evans, J., Bousvaros, A., Moyer, M.S., Wyllie, R., Oliva-Hemker, M., Mezoff, A., Leleiko, N., Keljo, D., and Crandall, W. Effect of early immunomodulator use in moderate to severe pediatric Crohn disease. *Inflamm Bowel Dis* 14: 949-954, 2008.

BACKGROUND: The immunomodulators (IMs) 6-mercaptopurine and azathioprine decrease corticosteroid dependence and maintain remission in Crohn's disease (CD). We describe IM use in newly diagnosed pediatric CD, comparing outcomes of "early" versus "late" initiation of therapy. METHODS: Data were obtained from pediatric CD patients enrolled in a prospective, multicenter observational study. Moderate/severe disease patients treated with IM were compared for outcomes of remission, corticosteroid use, infliximab therapy, hospitalizations, and CD-related surgery based on timing of initiation of IM therapy. RESULTS: In all, 247 children met the criteria (60% male, mean age 11.9 years); 199 were treated with IM within 1 year of diagnosis; 150 between 0-3 months (early), 49 between 3-12 months (late). Both groups showed a decrease in corticosteroid use by 12 months, at which time proportionately fewer early group patients had received corticosteroids in the preceding quarter (22%) than late groups patients (41%)($P = 0.013$). The number of hospitalizations per patient was also noted to be significantly lower in the early group over the 2-year follow-up ($P = 0.03$). No difference was noted in the rates of remission, infliximab use over time, or surgery. CONCLUSIONS: 80% of children with newly diagnosed moderate to severe CD are treated with IM within 1 year. Early IM use is associated with reduced corticosteroid exposure and possibly fewer hospitalizations per patient.

79. Quiros, J.A., Heyman, M.B., Pohl, J.F., Attard, T.M., Pieniaszek, H.J., Bortey, E., Walker, K., and Forbes, W.P. Safety, efficacy, and pharmacokinetics of balsalazide in pediatric patients with mild-to-moderate active ulcerative colitis: results of a randomized, double-blind study. *J Pediatr Gastroenterol Nutr* 49:

571-579, 2009.

OBJECTIVES:: A multicenter, double-blind study was conducted to evaluate the safety, efficacy, and pharmacokinetics of balsalazide in pediatric patients with mild-to-moderate ulcerative colitis (UC). **PATIENTS AND METHODS::** Sixty-eight patients, 5 to 17 years of age, with mild-to-moderate active UC based on the modified Sutherland UC activity index (MUCAI) were randomized to receive oral balsalazide 2.25 or 6.75 g/day for 8 weeks. The primary endpoint was clinical improvement (reduction of the MUCAI score by > or =3 points from baseline). Clinical remission (MUCAI score of 0 or 1 for stool frequency) and histological improvement after 8 weeks were also assessed. Pharmacokinetic parameters for balsalazide, 5-aminosalicylic acid, and N-acetyl-5-aminosalicylic acid were determined at 2 weeks. Adverse events and laboratory changes were monitored throughout the study. **RESULTS::** Clinical improvement was achieved by 45% and 37% of patients and clinical remission by 12% and 9% of patients receiving 6.75 and 2.25 g/day, respectively. Improvement in histologic grade was achieved by 8 of 16 (50%) and 3 of 10 (30%) patients receiving 6.75 and 2.25 g/day, respectively. No significant differences were seen in efficacy. Pharmacokinetics in 12 patients were characterized by large interpatient variability and low systemic exposure. Adverse events were similar between the treatment groups, the most common being headache and abdominal pain. No clinically significant changes were observed in laboratory values, including those indicative of hepatic or renal toxicity. **CONCLUSIONS::** Balsalazide is well tolerated and improves the signs and symptoms of mild-to-moderate active UC in pediatric patients 5 to 17 years of age.

80. Ramakrishna, J., Langhans, N., Calenda, K., Grand, R.J., and Verhave, M. Combined use of cyclosporine and azathioprine or 6-mercaptopurine in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 22: 296-302, 1996.

The aim of this study was to assess whether in steroid-resistant patients with pediatric inflammatory bowel disease (IBD) a combination of cyclosporine and azathioprine (or 6-mercaptopurine) could induce remission and subsequently permit maintenance on azathioprine/6-mercaptopurine as the sole immunosuppressive agent. Two boys and six girls (six with ulcerative colitis and two with Crohn's disease; ages 3-17 years) received 100-200 micrograms/kg/day cyclosporine intravenously and then 4-10 mg/kg/day orally. Doses were adjusted to achieve trough serum cyclosporine levels of 100-200 mu/L (Abbott's TDX assay). Seven of the eight patients received azathioprine/6-mercaptopurine, and all were given a 5-aminosalicylate preparation and corticosteroids. The latter drugs were continued and then tapered off as clinical status allowed. Cyclosporine was continued for 3-10 months in those who responded. In seven of eight patients, there was a rapid clinical response; one patient showed a transient response, but recurrent bleeding led to total colectomy 9 days after starting cyclosporine. Of the seven responders, three were able to discontinue prednisone and cyclosporine and are doing well on azathioprine at long-term

follow-up (2-5 years). One who did not receive azathioprine/6-mercaptopurine maintained remission for 2 years after cyclosporine was stopped, one experienced a disease flare-up 5 months after start of cyclosporine treatment and required colectomy, one who did not tolerate 6-mercaptopurine had a flare-up during cyclosporine tapering and underwent surgery at 6 months, and one started to flare up with cyclosporine tapering at 6 months and was scheduled for surgery. No significant complications of treatment were observed. Seven patients had an initial response and four of them have so far not required surgery. These preliminary findings suggest that azathioprine/6-mercaptopurine can be used safely to maintain cyclosporine-induced remission in children with IBD.

81. Rangwalla, S.C., Waljee, A.K., and Higgins, P.D. Voting With their Feet (VWF) endpoint: a meta-analysis of an alternative endpoint in clinical trials, using 5-ASA induction studies in ulcerative colitis. *Inflamm Bowel Dis* 15: 422-428, 2009.

BACKGROUND: Strict clinical remission endpoints in ulcerative colitis (UC) trials produce low remission rates and do not reflect the good outcomes of UC therapy. We proposed the use of the VWF (Voting With their Feet) endpoint, the percentage of subjects leaving a randomized controlled trial (RCT) arm for lack of efficacy). The aims were 1) to determine if the VWF endpoint can be extracted from 5-aminosalicylate (5-ASA) RCTs in UC; 2) to perform meta-analyses of VWF and clinical remission (CR) endpoints; and 3) to determine the statistical power of the VWF endpoint. **METHODS:** Fixed effects meta-analysis and power calculations were used. **RESULTS:** In 5 studies, including 1048 subjects, 9.5% of patients left 5-ASA study arms for lack of efficacy, versus 28.3% leaving placebo. The rate of failure to achieve CR was 68.2% with 5-ASA, versus 86.9% with placebo. The relative risk (RR) of treatment failure for 5-ASA using the VWF endpoint was 0.33 (95% confidence interval [CI] 0.24-0.44), which was significantly smaller than with the CR endpoint (RR 0.81, 95% CI 0.76-0.88). The statistical power of VWF was slightly greater than CR. **CONCLUSIONS:** VWF is inexpensive, intuitive, and has similar statistical power to CR. The VWF endpoint can confirm the validity of outcome measures in clinical trials, and estimate real-world clinical efficacy.

82. Romano, C., Cucchiara, S., Barabino, A., Annese, V., and Sferlazzas, C. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. *World J Gastroenterol* 11: 7118-7121, 2005.

AIM: To assess the value of long-chain omega-3 fatty acids (FAs) supplementation in addition to amino-salicylic-acid (5-ASA) in pediatric patients with Crohn's disease (CD). **METHODS:** Thirty-eight patients (20 males and 18 females, mean age 10.13 years, range 5-16 years) with CD in remission were randomized into two groups and treated for 12 mo. Group I (18 patients) received 5-ASA (50 mg/kg/d)+ omega-3 FAs as triglycerides in gastro-resistant capsules, 3 g/d (eicosapentanoic acid, EPA, 400 mg/g, docosahexaenoic acid, DHA, 200

mg/g). Group II (20 patients) received 5-ASA (50 mg/kg/d)+olive oil placebo capsules. Patients were evaluated for fatty acid incorporation in red blood cell membranes by gas chromatography at baseline 6 and 12 mo after the treatment. RESULTS: The number of patients who relapsed at 1 year was significantly lower in group I than in group II ($P<0.001$). Patients in group I had a significant increase in the incorporation of EPA and DHA ($P<0.001$) and a decrease in the presence of arachidonic acids. CONCLUSION: Enteric-coated omega-3 FAs in addition to treatment with 5-ASA are effective in maintaining remission of pediatric CD.

83. Rosh, J.R. Alternative strategies for the use of infliximab in pediatric inflammatory bowel disease. *Curr Gastroenterol Rep* 10: 302-307, 2008.

Infliximab is approved for the induction and 1-year maintenance of remission in pediatric Crohn's disease unresponsive to conventional therapy. Despite significant experience with the use of this agent in children and adolescents who have inflammatory bowel disease, many questions about its optimal use remain. Recent safety concerns raised debate over the common practice of using infliximab in combination with conventional immunomodulatory agents. Additionally, although regularly scheduled administration maintains remission more effectively than episodic therapy, it is not known whether all patients who start infliximab must continue it for maintenance. Some patients may be able to use infliximab for induction and another agent for maintenance. Finally, the optimal placement of infliximab in the algorithm for the medical treatment of pediatric inflammatory bowel disease remains an open question.

84. Rosh, J.R. Use of biologic agents in pediatric inflammatory bowel disease. *Curr Opin Pediatr* 21: 646-650, 2009.

PURPOSE OF REVIEW: Owing to its aggressive clinical course and associated immunologic abnormalities, pediatric inflammatory bowel disease (IBD) is increasingly managed with immunomodulators and biologic agents. Clinical experience with therapy targeted against tumor necrosis factor-alpha has raised important questions about these agents, which will be addressed in this review. RECENT FINDINGS: Pediatric IBD is increasingly appreciated to have a variety of recognized clinical phenotypes that are associated with particular genotypes and serologic responses. These observations may ultimately allow individualized therapy that could change the natural history of pediatric IBD and reverse its severe metabolic and growth effects. Several new studies suggest that antitumor necrosis factor therapy could be an important part of this therapeutic vista. In addition to shedding light on who could best benefit from such agents, optimization of such therapy and its safety have been active areas of recent research. SUMMARY: Biologic therapy for pediatric IBD is an increasingly employed strategy. The aggressive nature of the disease and its consequent metabolic effects make this an attractive option for many patients. Recent research is helping guide the clinician to identify who could best benefit from

such therapy while also exploring its safety and ideal dosing strategy.

85. Rosh, J.R., Lerer, T., Markowitz, J., Goli, S.R., Mamula, P., Noe, J.D., Pfefferkorn, M.D., Kelleher, K.T., Griffiths, A.M., Kugathasan, S., Keljo, D., Oliva-Hemker, M., Crandall, W., Carvalho, R.S., Mack, D.R., and Hyams, J.S. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease. *Am J Gastroenterol* 104: 3042-3049, 2009.

OBJECTIVES: Adalimumab, an anti-tumor necrosis factor immunoglobulin-1 antibody, is increasingly being reported as a potential treatment option for children with moderate-to-severe Crohn's disease (CD). The aim of this study was to characterize common indications, safety, tolerability, and clinical response to adalimumab in pediatric CD in a large, multicenter, patient cohort. **METHODS:** Data were obtained using a retrospective, uncontrolled chart review at 12 sites of the Pediatric Inflammatory Bowel Disease Collaborative Research Group. Clinical, laboratory, and demographic data were obtained for CD patients who received at least one dose of adalimumab. Indication for adalimumab, concomitant medications, and clinical outcome at 3, 6, and 12 months for each patient were recorded using physician global assessment (PGA) and Pediatric CD Activity Index scores. Serious adverse events were identified. **RESULTS:** A total of 115 patients (54% female) received at least one dose of adalimumab. The mean age at the diagnosis of CD was 11.1+/-3.1 years, with the first adalimumab dose administered at 4.7+/-2.8 years after diagnosis. The most common dosing frequency was every other week with induction doses of 160/80 mg in 19%, 80/40 mg in 44%, and 40/40 mg in 15% of patients. Maintenance dosing was 40 mg every other week in 88% of patients. Mean follow-up after initial adalimumab dose was 10+/-8.6 months. Infliximab treatment preceded adalimumab in 95% of patients, with a mean of 12 infliximab infusions (range: 1-44). Infliximab discontinuation was due to loss of response (47%), infusion reaction or infliximab intolerance (45%), or preference for a subcutaneous medication (9%). Concomitant medications at the commencement of adalimumab were corticosteroids (38%), azathioprine/6-mercaptopurine (41%), and methotrexate (23%). Clinical response measured by PGA at 3, 6, and 12 months was 65, 71, and 70%, respectively, with steroid-free remission at 3, 6, and 12 months of 22, 33, and 42%, respectively. There were no malignancies, serious infections, or deaths in the study subjects. **CONCLUSIONS:** Adalimumab was a well-tolerated and effective rescue therapy for moderate-to-severe pediatric CD patients previously treated with infliximab. Adalimumab demonstrated a steroid-sparing effect, and >70% of patients achieved rapid response that was sustained through 12 months.

86. Ruemmele, F.M., Lachaux, A., Cezard, J.P., Morali, A., Maurage, C., Ginies, J.L., Viola, S., Goulet, O., Lamireau, T., Scaillon, M., Breton, A., and Sarles, J. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy.

Inflamm Bowel Dis 15: 388-394, 2009.

BACKGROUND: Infliximab (IFX) is efficacious in inducing remission in severe forms of pediatric Crohn's disease (CD). Adult studies indicate that IFX is also safe and well tolerated as maintenance therapy. The present study aimed to evaluate in a prospective manner the efficacy and safety of IFX as maintenance therapy of severe pediatric CD comparing scheduled and "on demand" treatment strategies. **METHODS:** Forty children with CD (nonpenetrating, nonstricturing as well as penetrating forms, mean age: 13.9 +/- 2.2 years) with a severe flare-up (Harvey-Bradshaw Index [HBI] > or =5, erythrocyte sedimentation rate [ESR] >20 mm/h) despite well-conducted immunomodulator therapy (n = 36 azathioprine, n = 1 mercaptopurine, n = 3 methotrexate) combined with steroids were included in this randomized, multicenter, open-label study. Three IFX infusions (5 mg/kg) were administered at week (W)0/W2/W6. At W10, clinical remission (HBI <5) and steroid withdrawal were analyzed and IFX responders were randomized to maintenance therapy over 1 year: group A, scheduled every 2 months; group B, "on demand" on relapse. **RESULTS:** In all, 34/40 children came into remission during IFX induction therapy (HBI: 6.7 +/- 2.5 (WO) vs. 1.1 +/- 1.5 (W10); P < 0.001). At the end of phase 2, 15/18 (83%) patients were in remission in group A compared to 8/13 (61%) children in group B (P < 0.01), with a mean HBI of 0.5 versus 3.2 points (group A versus B, P = 0.011). In group A, 3/13 (23.1%) children experienced a relapse compared to 11/12 (92%) children in group B. No severe adverse event occurred during this trial. **CONCLUSIONS:** IFX is well tolerated and safe as maintenance therapy for pediatric CD, with a clear advantage when used on a scheduled 2-month basis compared to an "on demand" basis.

87. Sack, D.M., and Peppercorn, M.A. Drug therapy of inflammatory bowel disease. *Pharmacotherapy* 3: 158-176, 1983.

Although the etiology of inflammatory bowel disease is unknown and specific therapy is unavailable, enough information on existing empiric agents is available to allow rational therapy. These agents include sulfasalazine, steroids, immunosuppressive drugs, metronidazole and cholestyramine. Sulfasalazine is a two-part molecule that depends on bacterial cleavage in the colon to deliver locally acting 5-aminosalicylate, whose mechanism of action may relate to inhibition of prostaglandin synthesis. The other half of the molecule, sulfapyridine, is responsible for most of the side effects of the drug. While the efficacy of sulfasalazine in the treatment and prevention of attacks of ulcerative colitis is well established, its use in Crohn's disease appears to be limited to patients with active colitis and ileo-colitis. Sulfasalazine is of major benefit in preventing relapses in patients with ulcerative colitis in remission. New formulations of 5-aminosalicylate may allow delivery of the apparently active moiety to the small bowel and colon without concomitant sulfapyridine toxicity. Corticosteroids are highly effective in acute attacks of ulcerative colitis and Crohn's ileitis and ileo-colitis; the mechanism of antiinflammatory action remains

speculative. However, maintenance therapy with steroids is ineffective in preventing relapses or recurrent attacks of either ulcerative colitis or Crohn's disease. Steroid enemas allow topical administration to patients with distal colitis and proctitis with few systemic side effects. In children with growth failure associated with active Crohn's disease, amelioration by steroid therapy may actually restore normal growth. Immunosuppressive agents such as azathioprine and 6-mercaptopurine are of little value in active Crohn's disease when administered alone; however, in combination with other agents they may help diminish steroid dose, close fistulae and prevent relapse. Their mode of action likely depends on long-term cytostatic effects on immune effector cells. Concern for leukopenia and the development of late malignancy has limited their use to patients not responding to other therapies. Metronidazole, an antimicrobial agent that is effective against anaerobes, has recently been shown useful in Crohn's disease involving the colon and perianal area. Its mechanism of action is uncertain, but may be related to its antibacterial actions on anaerobes. Cholestyramine can be successfully used to control bile salt-induced diarrhea in Crohn's patients with terminal ileal resections. Effective drug therapy of inflammatory bowel disease is only part of a total program of management including reassurance, frequent explanation, well-timed use of surgery, and an understanding physician.

88. Saeed, S.A., and Crandall, W.V. Managing Crohn disease in children and adolescents : focus on tumor necrosis factor antagonists. *Paediatr Drugs* 10: 31-38, 2008.

Crohn disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by a relapsing course and variable presentation that often includes abdominal pain, diarrhea, and fatigue. CD frequently presents during childhood, resulting in pediatric-specific complications, such as growth failure and delayed puberty. Conventional drug therapy for moderate to severe pediatric CD includes induction of remission with corticosteroids, and maintenance of remission with immunomodulators. Patients who have an inadequate response to standard therapy are being increasingly treated with anti-tumor necrosis factor-alpha (TNFalpha) agents. Infliximab has been the most widely studied anti-TNFalpha agent in pediatric CD, and has been shown to be efficacious in this condition. Adalimumab has been proven to be efficacious in adults with CD, but there has been only a single case report in children. CDP571 has been tested in 20 children with CD, showing some efficacy. Finally, thalidomide therapy has been associated with improvement in two small case series. Toxicities of these agents include infusion reactions, infections, malignancies, neurologic disorders, and hematologic derangements.

89. Sandberg-Gertzen, H., Jarnerot, G., and Kraaz, W. Azodisal sodium in the treatment of ulcerative colitis. A study of tolerance and relapse-prevention properties. *Gastroenterology* 90: 1024-1030, 1986.

One hundred sixty patients intolerant of or allergic to sulfasalazine (Salazopyrin, Azulfidine) participated in an open tolerance study of azodisal sodium (Dipentum). More than 4 of every 5 patients tolerated azodisal sodium well, but 12.5% of patients stopped medication because of diarrhea. Even after 7 patients who had also experienced diarrhea when taking sulfasalazine were excluded, there still remained a group of patients (9.8%) who had to discontinue azodisal sodium because of diarrhea. Apart from this, only minor side effects occurred. No serious drug-related changes were seen in hematologic or biochemical parameters. Male fertility appeared to be unaffected. One hundred two patients, who were in clinical and sigmoidoscopic remission, took part in a double-blind, placebo-controlled maintenance trial. Of these, 23.1% of the patients treated with azodisal sodium and 44.9% of the patients treated with placebo had a clinical and sigmoidoscopic relapse during a 6-mo trial period ($p = 0.02$). Azodisal sodium appears to be an effective agent for the maintenance treatment of ulcerative colitis.

90. Sandborn, W.J., Present, D.H., Isaacs, K.L., Wolf, D.C., Greenberg, E., Hanauer, S.B., Feagan, B.G., Mayer, L., Johnson, T., Galanko, J., Martin, C., and Sandler, R.S. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* 125: 380-388, 2003.

BACKGROUND & AIMS: This study determined the effectiveness of tacrolimus for the treatment of Crohn's disease fistulas. **METHODS:** The study was a randomized, double-blind, placebo-controlled, multicenter clinical trial. Forty-eight patients with Crohn's disease and draining perianal or enterocutaneous fistulas were randomized to treatment with oral tacrolimus 0.2 mg. kg⁻¹. day⁻¹ or placebo for 10 weeks. The primary outcome measure was fistula improvement as defined by closure of $\geq 50\%$ of particular fistulas that were draining at baseline and maintenance of that closure for at least 4 weeks. A secondary outcome measure was fistula remission as defined by closure of all fistulas and maintenance of that closure for at least 4 weeks. **RESULTS:** Forty-three percent of tacrolimus-treated patients had fistula improvement compared with 8% of placebo-treated patients ($P = 0.004$). Ten percent of tacrolimus-treated patients had fistula remission compared with 8% of placebo-treated patients ($P = 0.86$). Adverse events significantly associated with tacrolimus, including headache, increased serum creatinine level, insomnia, leg cramps, paresthesias, and tremor, were managed with dose reduction. **CONCLUSIONS:** Oral tacrolimus 0.2 mg. kg⁻¹. day⁻¹ is effective for fistula improvement, but not fistula remission, in patients with perianal Crohn's disease. Adverse events associated with tacrolimus can be managed by dose reduction. Lower doses of tacrolimus should be evaluated.

91. Sayani, F.A., Prosser, C., Bailey, R.J., Jacobs, P., and Fedorak, R.N. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. *Can J Gastroenterol* 19: 147-151, 2005.

BACKGROUND: Azathioprine (AZA), used to treat inflammatory bowel disease (IBD), is metabolized by thiopurine methyltransferase (TPMT). The accumulation of individual metabolites varies because humans display genetic polymorphism for TPMT expression. Deficiencies in TPMT result in accumulation of toxic metabolites, followed by neutropenia and hepatic inflammation. Concern over acute toxicity frequently leads to under dosing and frequent monitoring tests and visits. **OBJECTIVE:** To determine whether assessment of TPMT activity before the administration of AZA would predict acute toxicity and, thus, allow for reductions in health care costs related to biochemical screening for, and management of, AZA-induced adverse events. **METHODS:** Before AZA treatment, 29 patients with IBD were prospectively randomized to one of two groups: group 1, in which no TPMT assay was performed, was started on AZA at 1 mg/kg/day and then titrated every two weeks to a target dose of 2.5 mg/kg/day; and group 2, in which TPMT assays were performed, was started on AZA at the target dose of 2.5 mg/kg/day. For both groups, complete blood count and liver enzymes were monitored weekly for six weeks and at monthly intervals thereafter. Additional tests and health care interventions were undertaken at the discretion of the attending physicians. **RESULTS:** Of the 29 patients in the study, 15 were randomly assigned to group 1 and 14 to group 2. Demographics and disease activity were similar for both groups. Mean follow-up time was 7.1 months (range 3.5 to 10.7 months). Eight patients from group 1 and six patients from group 2 withdrew as a result of AZA-induced adverse events. There was no correlation between the TPMT activity and the development of AZA-induced adverse events. The direct health care costs for group 1 (300.11 dollars per patient) were lower than in group 2 (348.87 dollars per patient). **CONCLUSION:** The prospective assessment of TPMT enzyme activity before initiating AZA therapy in IBD patients incurred additional cost and did not predict AZA-induced toxicity.

92. Shteyer, E., and Wilschanski, M. Novel therapeutic modalities in pediatric inflammatory bowel disease. *Isr Med Assoc J* 10: 816-820, 2008.

Management of inflammatory bowel disease in childhood poses great challenges. Apart from the disease complications, the drugs' adverse affects, especially corticosteroids, are significant. In the past decade major progress was made in elucidating the pathogenesis of IBD, which led to new treatment options aiming to achieve better control of the disease and decrease the various complications of current therapy. In this review we provide an overview of novel therapies for IBD, their efficacy, safety and their current use in children.

93. Silbermintz, A., and Markowitz, J. Inflammatory bowel diseases. *Pediatr Ann* 35: 268-274, 2006.

The inflammatory bowel diseases remain at the forefront of clinical investigation. Immunologic and genetic advances are fueling an explosion of novel diagnostic

and therapeutic modalities. With further breakthroughs, there is hope that in the near future, these illnesses will no longer be considered either idiopathic or chronic.

94. Teml, A., Kratzer, V., Schneider, B., Lochs, H., Norman, G.L., Gangl, A., Vogelsang, H., and Reinisch, W. Anti-Saccharomyces cerevisiae antibodies: a stable marker for Crohn's disease during steroid and 5-aminosalicylic acid treatment. *Am J Gastroenterol* 98: 2226-2231, 2003.

OBJECTIVES: An increased prevalence of elevated serum anti-Saccharomyces cerevisiae antibody (ASCA) levels in patients with Crohn's disease (CD) has been described. The aim of the present work was to investigate serum ASCA levels during the courses of prednisolone and mesalamine therapy in CD patients. **METHODS:** Serum samples of 25 patients with active CD were studied for ASCA levels before as well as 2 and 9 wk after initiation of a prednisolone tapering regimen. The influence of mesalamine (4 g o.d.) on serum ASCA levels compared to that of placebo was tested over 1 yr in 38 patients (20 mesalamine and 18 placebo) participating in a postoperative prophylaxis study. Serum IgG and IgA ASCA levels were measured by ELISA. Sera of 91 CD and 40 ulcerative colitis (UC) patients as well as 334 healthy donors were tested for ASCA to recalculate new cut-off values. **RESULTS:** For IgG ASCA cut-off values were determined to be 17.0 U and 25.0 U, and for IgA ASCA 9.3 U and 14.0 U. At baseline visit, 73.0% (46/63) of patients displayed serum ASCA positivity. During prednisolone therapy, a decrease in serum IgG and IgA ASCA levels from baseline to wk 2 ($p < 0.0001$ and $p < 0.001$, respectively) as well as to wk 9 ($p < 0.001$ and $p = 0.01$, respectively) was observed. A trend toward an association of ASCA positivity and steroid responsiveness was calculated ($p = 0.07$). During mesalamine treatment, no differences in changes of ASCA levels were observed compared to placebo at any time point. **CONCLUSIONS:** ASCA are stable markers during steroid and mesalamine treatment, highlighting their reliability for use in diagnosis of CD.

95. Teml, A., Schwab, M., Hommes, D.W., Almer, S., Lukas, M., Feichtenschlager, T., Florin, T., Seiderer, J., Petritsch, W., Bokemeyer, B., Kreisel, W., Herrlinger, K.R., Knoflach, P., Bonaz, B., Klugmann, T., Herfarth, H., Pedarnig, N., and Reinisch, W. A systematic survey evaluating 6-thioguanine-related hepatotoxicity in patients with inflammatory bowel disease. *Wien Klin Wochenschr* 119: 519-526, 2007.

OBJECTIVE: Drug-induced liver injury was recently reported as a major complication leading to hepatic nodular regenerative hyperplasia (NRH) in patients with inflammatory bowel disease (IBD) and 6-thioguanine (6-TG) therapy. The aim of the study was to evaluate the prevalence of 6-TG-related hepatotoxicity in a large multi-centered IBD population by means of a systematic online survey. **METHODS:** Clinical and laboratory data, imaging techniques (sonography, CT, MRI) and histology of liver biopsies were surveyed in IBD

patients treated with 6-TG. The decision on whether liver imaging and/or liver biopsy were performed was exclusively at the discretion of the investigator. RESULTS: 6-TG use was fully documented in 296 patients (median treatment duration 56 weeks, range < 1-207). Laboratory signs of drug-induced liver injury were found in 43 patients (14.5%). Liver imaging revealed pathologic results in 68/176 patients (38.6%). Liver biopsy was performed in a subset of 60 patients; using silver-reticulin staining (n = 59), NRH was considered in 16 patients (27.1%). Age was the only independent, albeit weak, risk factor for development of NRH. CONCLUSION: This large online survey confirms the strong association between 6-TG treatment and the significant risk of development of NRH in patients with IBD. The definitive diagnosis of NRH depends solely upon liver biopsy.

96. Thayu, M., Leonard, M.B., Hyams, J.S., Crandall, W.V., Kugathasan, S., Otley, A.R., Olson, A., Johanns, J., Marano, C.W., Heuschkel, R.B., Veereman-Wauters, G., Griffiths, A.M., and Baldassano, R.N. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol* 6: 1378-1384, 2008.

BACKGROUND & AIMS: Crohn's disease (CD) is associated with altered bone metabolism. This study examined changes in bone formation and resorption after infliximab induction and associations between bone biomarkers, linear growth, and disease activity (Pediatric Crohn's Disease Activity Index [PCDAI]) after 54 weeks of infliximab therapy. METHODS: One hundred twelve subjects ages 6-17 years with moderate to severe CD received infliximab induction (5 mg/kg/dose) at weeks 0, 2, and 6; week-10 responders were randomized to infliximab every 8 or every 12 weeks maintenance therapy. Serum bone-specific alkaline phosphatase (BSAP), N-terminal propeptide of type 1 collagen (P1NP), urine C-telopeptide of collagen cross-links (CTX-1), and deoxypyridinoline (DPD) were collected at baseline and 10 weeks. PCDAI and height z-scores were assessed at baseline and at 10 and 54 weeks. RESULTS: Models were adjusted for bone age, gender, height, and steroid use. Baseline BSAP and P1NP levels were negatively associated with PCDAI (both $P = .01$). BSAP and P1NP increased during induction (both $P < .001$) and were associated with 54-week increases in height z-score ($P < .05$ and $P < .001$, respectively). Improvements in P1NP were associated with 54-week decreases in PCDAI ($P = .01$). CTX-1 and DPD also increased during induction ($P < .001$ and $P = .01$, respectively) but were not associated with changes in PCDAI. Changes in CTX-1 were associated with improvements in height z-score ($P < .002$). CONCLUSIONS: Infliximab therapy is associated with dramatic increases in BSAP and P1NP, consistent with inhibition of tumor necrosis factor-alpha effects on osteoblasts. The increases in CTX-1 and DPD likely reflect coupling of bone formation and resorption and increases in linear growth.

97. Travis, S.P., Stange, E.F., Lemann, M., Oresland, T., Chowers, Y., Forbes, A., D'Haens, G., Kitis, G., Cortot, A., Prantera, C., Marteau, P., Colombel, J.F.,

Gionchetti, P., Bouhnik, Y., Turet, E., Kroesen, J., Starlinger, M., and Mortensen, N.J. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 55 Suppl 1: i16-35, 2006.

This second section of the European Crohn's and Colitis Organisation (ECCO) Consensus on the management of Crohn's disease concerns treatment of active disease, maintenance of medically induced remission, and surgery. The first section on definitions and diagnosis includes the aims and methods of the consensus, as well as sections on diagnosis, pathology, and classification of Crohn's disease. The third section on special situations in Crohn's disease includes postoperative recurrence, fistulating disease, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations, and alternative therapy for Crohn's disease.

98. Turner, D., Grossman, A.B., Rosh, J., Kugathasan, S., Gilman, A.R., Baldassano, R., and Griffiths, A.M. Methotrexate following unsuccessful thiopurine therapy in pediatric Crohn's disease. *Am J Gastroenterol* 102: 2804-2812; quiz 2803, 2813, 2007.

BACKGROUND: The thiopurines, azathioprine and 6-mercaptopurine, are traditional first-line immunomodulatory agents in adult and pediatric Crohn's disease, but the comparative efficacy and safety of methotrexate have seldom been examined. We report outcomes with methotrexate treatment in pediatric patients previously refractory to or intolerant of thiopurines. **METHODS:** In a four-center, retrospective cohort study, efficacy of methotrexate in maintaining remission was assessed by PCDAI measurements, steroid use, and height velocity. Patients served as their own historical controls. Multivariable analysis controlled for route of methotrexate administration, reason for thiopurine discontinuation, baseline disease activity, and disease duration. **RESULTS:** Forty-two percent of 60 children treated with methotrexate were in clinical remission without steroids at both 6 and 12 months. A strong steroid sparing effect was observed compared with the year prior to methotrexate ($P < 0.001$). Success rates were similar in previously thiopurine-intolerant and refractory patients. Height velocity increased from -1.9 SDS to -0.14 SDS ($P = 0.004$) in the year following therapy. In a median 3-yr follow-up, a third of the patients did not require escalation of therapy; the others required step-up therapy with infliximab or surgery. Eight children (13%) stopped methotrexate due to adverse events, including, most commonly, elevated liver enzymes, and one serious episode of sepsis. **CONCLUSION:** Methotrexate appears effective in maintaining remission in pediatric Crohn's disease, when thiopurines have failed. Consideration should be given to its use earlier in pediatric treatment algorithms.

99. Turner, D., Kolho, K.L., Mack, D.R., Raivio, T., Leleiko, N., Crandall, W., Markowitz, J., Silverberg, M.S., Janne, O.A., Stempak, J., Hyams, J., and Griffiths, A.M. Glucocorticoid bioactivity does not predict response to steroid therapy in severe pediatric ulcerative colitis. *Inflamm Bowel Dis* 16: 469-473,

2010.

BACKGROUND: The pathophysiological basis for corticosteroid (CS) failure in ulcerative colitis (UC) is unknown. A transactivation glucocorticoid bioassay (GBA) was developed to measure the biological activity of CS by quantifying glucocorticoid response elements. This approach eliminates differences in bioavailability, chemistry, affinity, and other potential differences between the various steroids regarding their ability to activate the glucocorticoid receptor. In this multicenter prospective study, we aimed to evaluate whether CS bioavailability plays a role in CS refractoriness in severe pediatric UC.

METHODS: GBA (using COS-1 transfected cells) was measured in the serum of 50 children (52% males, age 13.4 +/- 3.5 years) admitted for acute severe UC on the third day of CS treatment. Demographic, clinical, and laboratory data were prospectively recorded. **RESULTS:** Of the children enrolled, 16 (32%) failed CS therapy and required infliximab (n = 14) or colectomy (n = 2) within a median of 10 days (interquartile range [IQR] 6.5-14.5). Reflecting internal validity of the assay, GBA was highly correlated with the last CS dose and the time interval to bloodletting (r = -0.41 and r = -0.54, respectively; P < 0.001). There was no statistically significant difference in the GBA levels between responders and nonresponders (249 nM versus 200 nM cortisol equivalent, P = 0.18). In a multivariate regression model adjusted for time elapsed from CS and the administered dose, GBA did not predict response to CS (P = 0.34).

CONCLUSIONS: The lack of correlation of GBA level and treatment outcome lends support to the hypothesis that the bioavailability, type, and dosing of intravenous CS are not associated with response or failure to the drug.

100. Turner, D., Mack, D., Leleiko, N., Walters, T.D., Uusoue, K., Leach, S.T., Day, A.S., Crandall, W., Silverberg, M.S., Markowitz, J., Otley, A.R., Keljo, D., Mamula, P., Kugathasan, S., Hyams, J., and Griffiths, A.M. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology* 138: 2282-2291, 2010.

BACKGROUND & AIMS: In a prospective study of children with severe ulcerative colitis (UC), we aimed to assess outcomes and to identify predictors of nonresponse to intravenous corticosteroids. **METHODS:** A total of 128 children (47% males; 12.9 +/- 3.9 y) hospitalized for severe UC were enrolled from 10 pediatric centers. Clinical and laboratory data and the Pediatric UC Activity Index (PUCAI) were recorded throughout the admission. Patients were followed up for 1 year postdischarge. **RESULTS:** Thirty-seven (29%; 95% confidence interval [CI], 22%-37%) children failed intravenous corticosteroids and received, within 10.5 +/- 6.4 days, cyclosporine (n = 1; 3%), colectomy (n = 3; 8%), or infliximab (n = 33; 89%). Several predictors were associated with intravenous corticosteroids failure, but the best model included number of stools, amount of blood, age, and new-onset disease (odds ratio [OR], 1.9; 95% CI, 1.1-3.5; OR, 2.5; 95% CI, 1.3-4.6; OR, 1.2; 95% CI, 1.04-1.36; and OR, 0.27; 95% CI, 0.1-0.7, respectively). The PUCAI, followed closely by the Travis rule, strongly predicted

response when compared with other measures (Seo and Lindgren indices, C-reactive protein level, and fecal calprotectin level) ($P < .001$). Aiming for sensitivity on day 3, a PUCAI greater than 45 screened for patients likely to fail intravenous corticosteroids (negative predictive value, 94%; positive predictive value, 43%; $P < .001$). Aiming for specificity on day 5, a PUCAI score greater than 70 optimally guided implementation of salvage therapy (positive predictive value, 100%; negative predictive value, 79%; $P < .001$). Twenty-five of 33 children treated with infliximab responded. The overall cumulative colectomy rate was 9% and 19% by discharge and 1-year, respectively. The day 3 PUCAI score predicted response up to 1 year postdischarge ($P < .001$; time to salvage therapy). **CONCLUSIONS:** The PUCAI, calculated on days 3 and 5 of steroid therapy, can identify patients requiring salvage therapy. Infliximab is an effective therapy in steroid-refractory pediatric UC.

101. Uhlen, S., Belbouab, R., Narebski, K., Goulet, O., Schmitz, J., Cezard, J.P., Turck, D., and Ruemmele, F.M. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. *Inflamm Bowel Dis* 12: 1053-1057, 2006.

BACKGROUND: Immunosuppressors play a major role in maintaining remission in Crohn's disease (CD). In patients who do not tolerate or escape therapy with azathioprine (AZA)/6-mercaptopurine, there is a marked need for other immunosuppressive drugs. The aim of the present study was to evaluate the efficacy and safety of methotrexate (MTX) in children with active CD. **METHODS:** In a retrospective multicenter ($n = 3$) study, the efficacy of MTX to induce complete remission or a clinical improvement was analyzed in 61 children with active CD. **RESULTS:** CD was diagnosed at a mean age of 11.1 \pm 2.3 years, and MTX was introduced 3.1 \pm 2.2 years after diagnosis. Indications to use MTX were a nonresponse to or relapse under AZA ($n = 42$) or AZA intolerance/toxicity ($n = 19$). MTX improved or induced complete remission in 49 patients (80%), of whom 18 (29.5%) relapsed after 13 \pm 10 months of treatment. Under MTX medication, complete remission was observed in 39%, 49%, and 45% at 3, 6, and 12 months, respectively. Follow-up over at least 24 months in 11 children confirmed a sustained remission on MTX monotherapy up to 40 months. Adverse reactions were observed in 14 patients (24%), requiring discontinuation of MTX in 6 children (10%) (liver enzyme elevation, $n = 2$; varicella-zoster, $n = 1$; nausea, $n = 3$). MTX allowed corticosteroid discontinuation in 36 patients. **CONCLUSIONS:** MTX improved the clinical course in most pediatric CD patients who escaped or did not tolerate AZA. Short-time toxicity of MTX resulted in drug discontinuation in $<10\%$. These data point to a beneficial and safe use of MTX in the treatment of pediatric CD.

102. Van Assche, G., Sandborn, W.J., Feagan, B.G., Salzberg, B.A., Silvers, D., Monroe, P.S., Pandak, W.M., Anderson, F.H., Valentine, J.F., Wild, G.E., Geenen, D.J., Sprague, R., Targan, S.R., Rutgeerts, P., Vexler, V., Young, D., and Shames, R.S. Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active

ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. *Gut* 55: 1568-1574, 2006.

BACKGROUND: An uncontrolled pilot study demonstrated that daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), might be effective for the treatment of active ulcerative colitis. **METHODS:** A randomised, double blind, placebo controlled trial was conducted to evaluate the efficacy of daclizumab induction therapy in patients with active ulcerative colitis. A total of 159 patients with moderate ulcerative colitis were randomised to receive induction therapy with daclizumab 1 mg/kg intravenously at weeks 0 and 4, or 2 mg/kg intravenously at weeks 0, 2, 4, and 6, or placebo. The primary end point was induction of remission at week 8. Remission was defined as a Mayo score of 0 on both endoscopy and rectal bleeding components and a score of 0 or 1 on stool frequency and physician's global assessment components. Response was defined as a decrease from baseline in the Mayo score of at least 3 points. **RESULTS:** Two per cent of patients receiving daclizumab 1 mg/kg ($p = 0.11$ v placebo) and 7% of patients receiving 2 mg/kg ($p = 0.73$) were in remission at week 8, compared with 10% of those who received placebo. Response occurred at week 8 in 25% of patients receiving daclizumab 1 mg/kg ($p = 0.04$) and in 33% of patients receiving 2 mg/kg ($p = 0.30$) versus 44% of those receiving placebo. Daclizumab was well tolerated. The most frequently reported adverse events in daclizumab treated patients compared with placebo treated patients were nasopharyngitis (14.6%) and pyrexia (10.7%). **CONCLUSION:** Patients with moderate ulcerative colitis who are treated with daclizumab are not more likely to be in remission or response at eight weeks than patients treated with placebo.

103. Veres, G., Baldassano, R.N., and Mamula, P. Infliximab therapy for pediatric Crohn's disease. *Expert Opin Biol Ther* 7: 1869-1880, 2007.

Crohn's disease (CD) is a chronic inflammatory disease that may involve any part of the gastrointestinal tract, characterized by transmural intestinal lesion in a genetically susceptible host. Anti-TNF-alpha neutralising agent, infliximab, the chimeric monoclonal IgG1 antibody, is indicated for pediatric patients with CD and medically refractory luminal and fistulising disease. The present clinical practice for infliximab use is induction sequence of 5 mg/kg at 0, 2 and 6 weeks administered intravenously and followed by infusion every 8 weeks thereafter. Careful attention should be paid to the potential adverse events, especially infections and malignancy. Recently, fatal cases in young patients with hepatosplenic T-cell lymphoma treated with infliximab and concomitant purine analogs were reported. In this review the authors summarize the present knowledge of infliximab therapy in children with CD based on the available published literature.

104. Veres, G., Baldassano, R.N., and Mamula, P. Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 67: 1703-1723, 2007.

This review summarises the present knowledge of infliximab therapy in children with inflammatory bowel disease (IBD) based on the available published literature. Infliximab, the chimeric monoclonal IgG(1) antibody to tumour necrosis factor-alpha, is indicated for medically refractory luminal and fistulising paediatric Crohn's disease. Recently, ulcerative colitis case series in children and adolescents suggested that infliximab might also be effective for treatment of ulcerative colitis resistant to standard medical therapy. Induction therapy with infliximab 5 mg/kg at weeks 0, 2 and 6 is routinely used. Since the majority of patients will relapse if not re-treated, a long-term approach with systematic re-treatment with 5 mg/kg every 8-12 weeks is recommended. Maintenance therapy every 8 weeks was superior to 12 weeks' administration in maintaining response and remission in the largest-to-date paediatric randomised trial. Concomitant immunosuppressive therapy reduces the risk of infliximab antibody formation and infusion reactions, and prolongs the duration of treatment success. Severe reactions may not be an absolute contraindication to future infliximab therapy. Premedication does not prevent the development of infusion reactions; however, it is indicated for prevention of subsequent infusion reactions. Adverse events and safety findings in children are comparable to those observed in adults. Latent tuberculosis needs to be screened for. Malignancy rates in paediatric patients treated with infliximab do not seem to be increased. However, newly reported cases of hepatosplenic T-cell lymphoma in young patients with IBD treated with infliximab and mercaptopurine therapy raise concern, and long-term follow-up studies are necessary to determine the true malignancy risk.

105. Vernier-Massouille, G., Cosnes, J., Lemann, M., Marteau, P., Reinisch, W., Laharie, D., Cadiot, G., Bouhnik, Y., De Vos, M., Boureille, A., Duclos, B., Seksik, P., Mary, J.Y., and Colombel, J.F. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. *Gut* 56: 1404-1409, 2007.

AIM: To assess the characteristics and clinical course of nodular regenerative hyperplasia (NRH) in patients with inflammatory bowel disease treated with azathioprine, so as to estimate the frequency of this complication and search for risk factors. METHODS: Cases were identified through a systematic survey of patients followed at 11 centres. At one centre, the cumulative risk of NRH was estimated and a case-control study was undertaken to identify risk factors. RESULTS: 37 cases of NRH (30 male, 7 female) were identified between 1994 and 2005. The median dose of azathioprine was 2 mg/kg/d (range 1.5 to 3.0). The median time between the start of azathioprine and the diagnosis of NRH was 48 months (range 6 to 187). After a median follow up period of 16 months (range 1 to 138), 14 patients developed complications of portal hypertension. Using multivariate analysis, male sex and stricturing behaviour were the two risk factors associated with NRH in patients treated with azathioprine. The cumulative risk calculated from the database (one centre) was 0.5% at 5 years (95% confidence interval, 0.11 to 0.89) and 1.25% at 10 years (0.29 to 2.21). CONCLUSIONS: NRH is a rare but potentially severe complication of azathioprine in patients with

inflammatory bowel disease. Clinicians should be aware of this complication, and should monitor liver function tests and platelet counts closely in their patients.

106. Vihinen, M.K., Raivio, T., Verkasalo, M., Janne, O.A., and Kolho, K.L. Circulating glucocorticoid bioactivity during peroral glucocorticoid treatment in children and adolescents with inflammatory bowel disease. *J Clin Gastroenterol* 42: 1017-1024, 2008.

GOALS: Our objective was to investigate the changes in circulating glucocorticoid bioactivity (GBA) at the onset of systemic glucocorticoid therapy in pediatric patients with inflammatory bowel disease. **STUDY:** Prednisolone (1 mg/kg/d) or budesonide (9 mg/d) was introduced as a single daily dose, and the patients (n=22) were subsequently followed up at 2 to 4 week intervals. The limit for a raised value of serum GBA was defined in pediatric patients (mean+2 SD; 118 nM cortisol equivalents; n=142). **RESULTS:** Two weeks of prednisolone brought about an increase in serum GBA from 84+/-14 to 336+/-38 nM cortisol equivalents (mean+/-SE; P<0.001). Young patients (<10 y) had similar GBA values to older patients, even though their prednisolone dose was higher (1.3 vs. 0.79 mg/kg; P<0.05). Patients treated with budesonide displayed a minor increase in GBA (151+/-20 vs. 267+/-21 nM cortisol equivalents after 4 wk of treatment; P<0.05; n=3), and when switched to prednisolone (n=2), their GBA level increased 3-fold. GBA levels did not predict the development of glucocorticoid-related side effects. **CONCLUSIONS:** Prednisolone doses used in the treatment of pediatric inflammatory bowel disease patients elicit a 4-fold increase in serum GBA that is significantly higher than the increase induced by budesonide. The GBA measurement is an additional tool for assessing steroid therapy at an individual level during systemic glucocorticoid treatment.

107. Weiss, B., Lerner, A., Shapiro, R., Broide, E., Levine, A., Fradkin, A., and Bujanover, Y. Methotrexate treatment in pediatric Crohn disease patients intolerant or resistant to purine analogues. *J Pediatr Gastroenterol Nutr* 48: 526-530, 2009.

BACKGROUND: Immunomodulatory drugs play a major role in maintaining remission and steroid sparing in children with Crohn disease. Although thiopurine agents are commonly used, unresponsiveness or intolerance to these drugs is common. The efficacy of methotrexate in maintenance of remission has been shown in adult Crohn disease; however, pediatric data are limited. Our goal was to evaluate the efficacy and safety of methotrexate in induction and maintenance of clinical remission in children with active Crohn disease who failed thiopurine treatment. **PATIENTS AND METHODS:** In a retrospective multicenter study, efficacy of methotrexate in inducing and maintaining remission or response was assessed by Harvey-Bradshaw activity index, paediatric Crohn disease activity index and steroid use, in 25 children with Crohn disease, refractory or intolerant to thiopurine analogues. **RESULTS:** Crohn disease was diagnosed at a mean age of 11.1 +/- 3.1 years and methotrexate was initiated at age 14.5 +/- 3.1

years. The median methotrexate dose was 12.5 mg/m². Remission was achieved in 16 patients (64%), and response in 6 patients (24%). Out of 18 patients treated for longer than 6 months, 83% were in remission or response after 12 months of treatment. The mean duration of remission and response was 10.8 +/- 8.8 months. Steroid withdrawal was possible in 12/16 patients (75%) receiving steroids at methotrexate introduction. Adverse effects were observed in 6 patients (24%) including nausea and vomiting in 3, elevation of liver enzymes in 2 and pancreatitis in 1 patient. CONCLUSIONS: Methotrexate is beneficial in maintaining remission and steroid-sparing treatment in children with Crohn disease following failure of thiopurine therapy.

108. Wiersma, H., Escher, J.C., Dilger, K., Trenk, D., Benninga, M.A., van Boxtel, C.J., and Taminiau, J. Pharmacokinetics of mesalazine pellets in children with inflammatory bowel disease. *Inflamm Bowel Dis* 10: 626-631, 2004.

Mesalazine is a first-line drug in pediatric inflammatory bowel disease (IBD), and is customarily used to induce and maintain remission in mild to moderate disease. In children, pharmacokinetic data are scarce, and dosage recommendations are largely extrapolated from studies in adults. Aim of the study was to obtain the pharmacokinetic profile of a new mesalazine pellet formulation in children with ulcerative colitis and Crohn's colitis. A single oral dose of 20 mg/kg mesalazine was administered to 13 patients (age 6-16 years). Serial blood and urine sampling for determination of mesalazine and acetylmесalazine was performed before and during 24 hours following ingestion. Maximum plasma concentration of mesalazine (C_{max}) was 1332 ng/mL (geometric mean, geometric coefficient of variation [CV]: 0.57), obtained 3.7 hours (t_{max}; CV: 0.31) after drug administration. Systemic exposure as determined by area under the plasma concentration-time curve (AUC(0-infinity)) was 8712 ng/ml*h (CV: 0.44). Terminal half-life of elimination of mesalazine was 3.5 hours (t(1/2); CV: 1.43). This study presents extensive pharmacokinetic data on mesalazine in children with mild-moderately active ulcerative colitis and Crohn's colitis. In comparison with previous experience in adults, pharmacokinetics of mesalazine administered as pellets appear to be similar in both populations.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
Best Pharmaceuticals for Children Act (BPCA)

Parenteral Fish Oil (Omegaven) in the Treatment of TPN-Associated Liver Disease in Infants (<2 years), PK, Safety and Efficacy

PK-PD	Number of studies:	0	Lack of information specific to age group: All
Efficacy	Number of studies:	12	Lack of information specific to age group: < 2 months
Safety	Number of studies:	7	Lack of information specific to age group: <2 months

Type of study	Number of trials
Randomized Clinical trials	0
Clinical trials not randomized	4
Case reports series	8

Reference	Study Type	Indication	Patients No.	Age	Results and Authors Comments
Diamond, I.R., Sterescu, A., et al. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 48: 209-215, 2009	Case Reports Series	A retrospective cohort describing the outcome of children with short bowel syndrome (SBS) and advanced parenteral nutrition-associated liver disease (PNALD) who were treated with Omegaven (target omega-6 to omega-3 fattyacid ratio 1:1 to 2:1) between April 2006 until November 2007 at the Hospital for Sick Children, Toronto. Omegaven 1g/kg/day + Intralipid 1g/kg/day	12	3.6– 46 months, median age 7.5 months.	Median parenteral nutrition duration before starting Omegaven was 28.4 (range 15.3–55.3) weeks. Median initial serum conjugated bilirubin was 137 (range 54–203) µmol/L (8.06 [3.18–11.94] mg/dL). Of the 12 patients, 9 had complete and sustained resolution of hyperbilirubinemia within a median of 24 (range 7–37) weeks, and all are no longer being considered for

					liver transplantation. Improvements in markers of hepatic inflammation as well as nutritional status also were noted in these patients. Three patients received a liver-intestine transplant while taking Omegaven. There were no complications attributable to Omegaven.
de Meijer, V.E., Le, H.D et al. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. <i>J Pediatr Gastroenterol Nutr</i> 50: 212-218, 2010.	A prospective study	Prospective collection of data from April 2005 to February 2009 on the fatty acid profile and growth parameters of infants who were exclusively administered PN and a fish oil-based lipid emulsion (Omegaven 1 g/kg/day) for the onset of essential fatty acid deficiency (EFAD).	10	Median age at the start of study treatment was 3.5 months (range 0.8–37 months).	Median gestational age at the time of birth was 35 weeks. After a median time of 3.8 months on exclusive PN and fish oil-based lipid emulsion, none of the patients developed biochemical or clinical evidence of EFAD. Z scores were not statistically different, indicating no growth impairment. Median direct bilirubin levels improved in 9 patients from 6.8 to 0.9 mg/dL (P<0.009).
Gura, K.M., Duggan, C.P., et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. <i>Pediatrics</i> 118: e197-201, 2006.	Case report	Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome. Omegaven 1g/kg/day.	2	Start age of Omegaven not indicated. <15 months	Patient 1: male born at 34 weeks gestation (birth weight =2.8 kg) had intractable feeding difficulties and required PN since birth. At 6 weeks of age evidence of PNALD. Because of his intractable feeding difficulties and evidence of rapidly progressive PNALD, he was listed for a liver/small bowel transplant at 5 months of age. Patient 2: male born at 25 weeks gestation (birth weight 850 g). At 7th weeks of age developed feeding intolerance and was maintained exclusively on PN and Intralipid and developed worsening elevations in his hepatic enzymes,

					<p>serum bilirubin, and prothrombin time (PT) and thrombocytopenia. Both patients tolerated the infusion of Omegaven without incident. Cholestasis resolved in both infants within 60 days despite their continuing PN requirement. In both cases, the AST and ALT values also normalized.</p> <p>Patient one was removed from the liver/small bowel transplantation list, is now 15 months old and remains on PN and Omegaven. His direct bilirubin remains within the reference range. He has continued to grow and achieve his developmental milestones appropriately.</p> <p>Patient 2 is now 4 months old and has continued to be exclusively parenterally fed. His ALT, AST, PT, and platelet counts have normalized, and his cholestasis has resolved.</p>
Gura, K.M., Lee, S., et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. <i>Pediatrics</i> 121: e678-686, 2008.	Interventional Clinical trial in comparison with historical cohort	Comparing safety and efficacy outcomes of a fish-oil-based fat emulsion (Omegaven 1/g/kg per day) in 18 infants with short-bowel syndrome (SBS) (between Sept 2004 and August 2006 at Children's Hospital Boston) who developed cholestasis (serum direct bilirubin level of >2 mg/dL) while receiving soybean emulsions with those from a historical cohort of 21 infants with SBS who also developed cholestasis while receiving soybean emulsions.	18	Mean age: 14 weeks	Among survivors, the median time to PN cessation was 13.8 weeks in the fish-oil cohort and 22.9 weeks in the historical cohort. Also, the median time to reversal of cholestasis was 9.4 and 44.1 weeks in the fish-oil and historical cohorts, respectively. Subjects who received fish-oil-based emulsion experienced reversal of cholestasis 4.8 times faster than those who received soybean emulsions and 6.8 times faster in analysis adjusted for

		The primary end point was time to reversal of cholestasis (3 consecutive measurements of serum direct bilirubin level of ≤ 2 mg/dL).			baseline bilirubin concentration, gestational age, and the diagnosis of necrotizing enterocolitis. Seven children in the fish-oil cohort and 14 children in the historical cohort never reversed cholestasis. A total of 2 deaths and 0 liver transplantations were recorded in the fish-oil cohort and 7 deaths and 2 transplantations in the historical cohort. The provision of fish-oil-based fat emulsion was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, infections, or growth delay.
Lee, S.I., Valim, C., et al. Impact of fish oil-based lipid emulsion on serum triglyceride, bilirubin, and albumin levels in children with parenteral nutrition-associated liver disease. <i>Pediatr Res</i> 66: 698-703, 2009.	Interventional Clinical trial in comparison with historical cohort	Investigate the effects of Omegaven on parenteral nutrition-associated cholestasis and on triglycerides levels in infants (between Sept 2004 and August 2006 at Children's Hospital Boston), in comparison with a historical cohort of infants maintained on soy-based lipid emulsion (n=59).	18 (?Same cohort as above (Gura KM 2008))	Median age 13 weeks (fish-oil treated)	Triglyceride levels decreased in the fish oil cohort from a mean of 140 mg/dL at wk 0 to 40 mg/dL at wk 20 but remained unchanged at ~140 mg/dL in the soybean cohort. Also, changes in triglyceride levels over time were directly correlated with direct bilirubin and inversely related to albumin levels.
Calhoun, A.W., and Sullivan, J.E. Omegaven for the treatment of parenteral nutrition associated liver disease: a case study. <i>J Ky Med Assoc</i> 107: 55-57, 2009.	Case Report	An infant with SBS who developed severe cholestasis and hepatopathy due to chronic parenteral nutrition was started with Omegaven therapy in an effort to prevent multivisceral organ transplantation.	1	17 months	At 6 months of age, was started on Omegaven. Within six months of treatment, his cholestasis had resolved and his hepatopathy had significantly improved. At 7 months of therapy he reached the goal of oral feeding and his PN was discontinued.

<p>Wales PW, Diamond IR Changing the paradigm: Omegaven for the treatment of liver failure in pediatric short bowel syndrome. 39th Annual meeting of the Canadian Association of Pediatric Surgeons. St Johns, Newfoundland, 2007.</p>	<p>Case Reports Series</p>	<p>Substitution of parenteral nutrition (PN) Omega-6 fatty acids for Omega-3 fatty acids, such as Omegaven in patients with pediatric SBS who develop liver failure.</p>	<p>9</p>	<p>Median age 7.7 (range: 3.5 – 45.8) months</p>	<p>Retrospective review of 9 infants with SBS and advanced liver disease who were started on Omegaven during 2006. Mean PN duration prior to Omegaven was 218 days, and mean initial conjugated bilirubin was 180 mmol/L. Of the 9 patients, 6 had complete and sustained resolution of hyperbilirubinemia within a median of 118 days, and all were de-listed for transplantation. Two have had a mean bilirubin reduction of 30% with a mean of 76 days of therapy, with ongoing improvement. One patient was transplanted while on Omegaven. Enteral tolerance didn't change meaningfully. There were no complications, and no deaths. The author concluded that Omegaven has the ability to restore liver function in SBS patients with advanced liver disease. This provides time for ongoing gut adaptation, or in patients with no adaptive potential it permits survival until an intestinal transplant is possible.</p>
<p>Cheung, H.M., Lam, H.S., et al. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. Clin Nutr 28: 209-212, 2009.</p>	<p>Case Reports Series</p>	<p>Preterm infants with intestinal failure and severe parenteral nutrition-associated cholestasis (PNAC) between January 2007 and March 2008.</p>	<p>4</p>	<p>Gestational ages (weeks): 31.4 28.6 29 36.6</p>	<p>Infants were switched to fish-oil-based preparation, which was increased in a stepwise fashion to a maximum of 1 g/kg/day. The progression of liver disease was halted in 3 infants and they recovered with complete resolution of PNAC. The remaining infant</p>

					with residual inflamed bowel, protracted feeding intolerance and repeated episodes of sepsis did not respond.
Mallah, H.S., Brown, M.R., et al. Parenteral fish oil-associated burr cell anemia. J Pediatr 156: 324-326 e321, 2010.	Case Report	Preterm female infant with SBS who developed TPN-associated cholestasis.	1	34 weeks gestational age, was started on Omegaven at 2 months of age.	<p>The infant was started on TPN on the first day of life (Intralipid). Due to TPN-associated cholestasis, In an attempt to halt the progression of the liver disease, parenteral fish oil (Omegaven) was started at 2 months of age. Gradually increasing the dose from 0.5 g/kg/day to 1g/kg/day. The hepatic biochemical profile normalized by age 3 months.</p> <p>Burr cell anemia was developed, requiring a total of 8 red blood cell transfusions throughout the 5 months of administration. Parenteral fish oil was discontinued, and the burr cell anemia disappeared, suggesting that parenteral fish oil might be associated with hemolytic anemia.</p>
Puder, M., Valim, C., et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg 250: 395-402, 2009.	Clinical trail. Open label study	Safety and efficacy of a fish oil-based intravenous lipid emulsion (ILE) in the treatment of parenteral nutrition-associated liver disease (PNALD) in infants with SBS.	42	Median age cohort at Fish Oil start was 12 weeks, median gestational age of 30±5 weeks.	<p>Safety and efficacy outcomes were compared with those from a contemporary cohort of 49 infants with SBS and cholestasis whose PN course included soybean ILE only. The primary efficacy end-point was time to reversal of cholestasis (direct bilirubin \leq2 mg/dL).</p> <p>Three deaths and 1 liver transplantation occurred in the fish</p>

					oil cohort, compared with 12 deaths and 6 transplants in the soybean oil cohort (P = 0.005). Among survivors not transplanted during PN, cholestasis reversed while receiving PN in 19 of 38 patients in the fish oil cohort versus 2 of 36 patients in the soybean oil cohort. Based on Cox models, subjects receiving fish oil-based ILE experienced reversal of cholestasis 6 times faster (95% CI: 2.0-37.3) than those receiving soybean oil-based ILE. The provision of fish oil-based ILE was not associated with hypertriglyceridemia, coagulopathy, or essential fatty acid deficiency. The authors concluded that Fish oil-based ILE is safe, may be effective in treating PNALD, and may reduce mortality and organ transplantation rates in children with SBS.
Soden, J.S., Lovell, M.A., et al. Failure of resolution of portal fibrosis during omega-3 fatty acid lipid emulsion therapy in two patients with irreversible intestinal failure. J Pediatr 156: 327-331, 2010.	Case Report	Intestinal failure-associated liver disease in two infants.	2	Infant 1: 38- week gestational age , male. Was switched from Intralipid to Omegaven at 6 months. Infant 2: 32-week	Despite biochemical and histologic improvement in cholestasis, both patients had persisting, significant portal fibrosis on liver biopsy.

				gestational age female. Was switched from Intralipid to Omegaven at 9 months of age.	
Ekema, G., D. Falchetti, et al. (2008). "Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (Omega-3 fatty acids)." J Pediatr Surg 43(6): 1191-5	Case Report	Full term male with SBS secondary to a midgut volvulus and severe parenteral nutrition-associated liver disease.	1	~ 7 months of age started on Omegaven	Omegaven was well tolerated, there was a constant and progressive amelioration of all functional hepatic indexes monitored. Cholestasis, defined as a direct bilirubin level more than 2 mg/dL, resolved after 8 months of therapy despite continuing cyclic PN requirements. The child is still on Omegaven therapy, and at present there are no clinical signs of fatty acid deficiency or evidence of bleeding.

PNAC- Parenteral nutrition-associated cholestasis

PNALD- Parenteral nutrition-associated liver disease

IFALD- Intestinal failure associated liver disease

PN- Parenteral nutrition

EFAD- Essential fatty acid deficiency

SBS- Short bowel syndrome

ILE- Intravenous lipid emulsion

TPN- Total parenteral nutrition

Pending Clinical Trials (from Clinicaltrials.gov)

Efficacy of an Omega-3 Enriched Intravenous Fat Emulsion in the Prevention of PN Induced Injury in Infants (NCT00512629); Estimated enrollment: 84; Ages eligible: up to 3 months. Principal Investigator: Mark Puder, MD, PhD Children's Hospital Boston

Efficacy of an Omega-3 Enriched Intravenous Fat Emulsion in the Treatment of Parenteral Nutrition Associated Liver Disease in Infants (Reversal) (NCT00910104); Estimated enrollment:200; Ages: up to 17 years. Contact: Mark Puder, MD, PhD

A Safety and Efficacy Study to Determine if Giving Intravenous Fish Oil Helps Children With Liver Disease (FO) (NCT00969332); Estimated enrollment:15; Ages: up to 12 months. Principal Investigator: Kara L Calkins, MD University of California, Los Angeles

Compassionate Use of Omegaven IV Fat Emulsion (NCT00816348); Estimated enrollment:5; Ages: up to 6 months. Principal Investigator: Richard J Schanler, MD Schneider Children's Hospital at North Shore.

Use of Omega-3 Fat Emulsion (Omegaven) in Infants With Parenteral Nutrition Associated Liver Disease (NCT00862446); Estimated enrollment:20. Ages: up to 24 months. Sponsor: Vanderbilt University

Compassionate Use of an Intravenous Fish Oil Emulsion in the Treatment of Liver Injury in Infants (NCT00738101); Estimated enrollment:15; Ages: up to 5 years. Principal Investigator: Steve A Abrams, MD Baylor College of Medicine

Completed Clinical Trials (from Clinicaltrials.gov)

There are no completed trials with Omegaven in pediatrics