Acid suppressing drugs in children (to include zantac, prilosec, pantoprazole, lansoprazole, omeprazole); Clinical trials and some reviews.
July 22, 2010
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 H(2) 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 (Cmax), were lower in the younger age group, when the AUC and Cmax 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 Bhave, 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, amoxycillin 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 Makipernaa, 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 amoxycillin. 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, amoxicilin 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. Cadranel, S., Bontemps, P., Van Biervliet, S., Alliet, P., Lauvau, D., Vandenhoven, G., and Vandenplas, 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 omperazole 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., Dodero, 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., Shaghaghi, E.K., Popon, M., Laurence, M., Mougenot, 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., Shaghaghi, 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 < 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., Amoruso, 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 (chi2: 3.6, $p<0.05$); 1 patient in group A [8.3%) and 7 in group B (30.5%) remained unchanged (chi2: 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 use 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 >or=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 >or=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 < or = 2.5 and volume > or = 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., Mougenot, 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 T1/2 values of 0.68 hours and 0.71 hours were

observed in the < or = 30 kg and > 30 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 an 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 ($P < or = 0.05$) 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 fundoplications. 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 to 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 1 h(-1); t1/2,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., Iito, 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 Iinuma, 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: tmax (2.1 +/- 1.2, 1-6 h), Cmax (331.1 +/- 333.6, 20.8-885.8 ng/mL), AUC0-->infinity (809.5 +/- 893.8, 236.9-1330.9 ng/mL.h), t1/2 (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 AUC0-->infinity 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 (lambda z) for omeprazole were not significantly different for subjects with one versus two functional CYP2C19 alleles. No association between age and CL/F, t1/2, or lambda z was observed. The range of t1/2 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 Cmax 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 CmaX 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 (Vandenplas classification). The efficacy of pantoprazole to reduce esophageal acid exposure time (pH < 4), reduce the number and duration of reflux episodes, and to increase the percentage of time with gastric 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 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 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 fourty-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 >or=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 AUC0-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 Cmax 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 >or= 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 >or= 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 (> or =10,000 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. prylori-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 in tractable 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. Sevvel, 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. Intragastric/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 intragastric 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 intragastric 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*

Pediatr Gastroenterol Nutr 35 Suppl 4**:** S308-318, 2002.

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 < or = 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. Dilation 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. Dilation 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 < or = 4 had increased to > 5. Intragastric pH remained > 4 for a minimum of 15 hours. Mean +/- 1 standard deviation elimination half-life was 6.61 +/- 2.75 hours, and 41.5 +/- 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 <or=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 <or=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 <or=10 weeks showing higher plasma exposure and lower plasma clearance than those aged >10 weeks-1 year. Thus, pediatric patients aged <or=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 kg 1], 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 hyperserotonaemia 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 (periactin) 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 preformed 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 flunarezine 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. Wanasuwankul, 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.