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# Clinical efficacy of proton pump inhibitor therapy in neurologically impaired children with gastroesophageal reflux: prospective study

## 質子泵抑制劑治療患有胃食管逆流的神經受損兒童的臨床功效：預期研究

**Objective.** To study the effects of proton pump inhibitors in reducing vomiting, gastrointestinal bleeding, and chest infections in institutionalised neurologically impaired children with gastroesophageal reflux.

**Design.** Prospective study.

**Setting.** A regional hospital, Hong Kong.

**Patients.** Neurologically impaired children with refractory gastroesophageal reflux.

**Main outcome measures.** Episodes of vomiting, gastrointestinal bleeding, and pneumonia in the baseline and proton pump inhibitor treatment periods.

**Results.** Nine children received proton pump inhibitor therapy for a median duration of 81 days. Mean reflux index was 9.3% (standard deviation, 5%). Dosage of omeprazole used was 1.0-2.3 mg/kg/d. Vomiting was reduced significantly with proton pump inhibitor treatment (median vomiting index [baseline]=0.4, median vomiting index [proton pump inhibitors]=0.2;  $P<0.05$ ). No significant decrease in gastrointestinal bleeding or chest infection was observed.

**Conclusion.** Proton pump inhibitors significantly reduced vomiting episodes in neurologically impaired children with gastroesophageal reflux.

### Key words:

Child;  
 Gastroesophageal reflux;  
 Omeprazole;  
 Vomiting

### 關鍵詞：

兒童；  
 胃食管逆流；  
 奧美拉唑；  
 嘔吐

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**目的：**研究質子泵抑制劑對於患有胃食管逆流而長期住院的神經受損的兒童，在減少嘔吐，腸胃出血及胸部感染方面的作用。

**設計：**預期研究。

**安排：**香港地區醫院。

**患者：**患有難治的胃食管逆流的神經受損的兒童。

**主要結果測量：**起始和抑制劑治療期的嘔吐發作、腸胃出血、肺炎情況。

**結果：**9名接受了質子泵抑制劑治療的兒童，其治療期中值為81天。平均逆流指數為9.3%（標準差，5%）。奧美拉唑使用劑量為1.0-2.3毫克/公斤/天。用質子泵抑制劑治療使嘔吐大為減少（中值嘔吐指數【起始】=0.4，中值嘔吐指數【質子泵抑制劑】=0.2； $P<0.05$ ）。但並未觀察到腸胃出血或胸部感染狀況有明顯減少。

**結論：**質子泵抑制劑大大減少患有胃食管逆流神經受損兒童的嘔吐發作。

### Introduction

Gastroesophageal reflux (GOR) refers to a condition arising from pathological acid reflux. It is highly prevalent in neurologically impaired

children.<sup>1,2</sup> Patients present with various symptoms: vomiting, regurgitation, rumination, recurrent chest infection, apnoea, gastrointestinal bleeding (GIB), and failure to thrive.<sup>3</sup> Recurrent vomiting not only results in nutritional loss but also increases the risk of aspiration pneumonia. Previous studies have shown that children with neurological impairment respond poorly to conventional medical therapy, such as milk thickeners, prokinetic agents, and histamine type 2 receptor blockers.<sup>4,5</sup> Vomiting symptoms have been seen to persist despite these treatments.

Proton pump inhibitors (PPIs) have been shown to be superior to other antireflux medications in the treatment of reflux oesophagitis and reflux symptoms. The efficacy of PPIs in the paediatric population has been the subject of limited clinical research to date.<sup>6</sup> Two studies have shown, however, that 3 to 6 months of PPI treatment can lead to resolution of reflux oesophagitis and other reflux symptoms including vomiting, GIB, and pneumonia.<sup>7,8</sup> Although oesophagogastroduodenoscopy (OGD) is a widely available service, it is still a stressful procedure for severely brain-damaged children. Moreover, the absence of oesophagitis does not preclude GOR.<sup>9</sup> Bohmer et al<sup>10</sup> have proposed that endoscopic evidence of GOR need not be a prerequisite for use of PPI in neurologically impaired children with severe GOR symptoms. In this study, the clinical efficacy of PPI was investigated in a small group of institutionalised children with severe neurological impairment. All had previously failed to respond to conventional antireflux therapy.

## Methods

The Developmental Disabilities Unit of the Caritas Medical Centre in Hong Kong is a residential and rehabilitation centre for children with severe neurological impairment. All patients with GOR symptoms receive 24-hour oesophageal pH studies as part of routine management. Oesophageal pH measurements were carried out using Medical Measurement Systems, MMS UPS-2020 (NL, ORION, Medical Measurement Systems BV, Enschede, Netherlands) with a flexible glass electrode 7440-M3/6/2.5m/F300,250 stomach probe (Medical Instruments Corporation, Champagne d'Or, France). Antireflux medications were ceased at least 48 hours before monitoring. The pH probe was calibrated and positioned perinasally, with its tip placed at 87% of the distance from the nares to the gastroesophageal junction as determined by a length-based normogram.<sup>11</sup> Proxy height was used if patients had contractures such that actual height could not be measured.<sup>12</sup> The correct position of the probe was confirmed by withdrawal

from the stomach after having obtained an acid reading. Chest X-rays were taken to confirm the probe was within the thorax. The period of time with an oesophageal pH below 4.0 was expressed as a percentage of the total study duration (reflux index, RI). An RI of greater than 5% was considered pathological.

Patients who were refractory to conventional medical therapy or surgical treatment were eligible for the study. Endoscopic evidence of oesophagitis was not sought as OGD was considered too stressful for the patients, either by their parents or their physicians. Patients were excluded if other causes of recurrent vomiting were present such as gastrointestinal obstruction, metabolic disease, and recurrent urinary tract infections or otitis media. Patients with frequent infectious diseases who received nil by mouth for more than 25% of the study period were excluded. The clinical history, physical findings, and results of investigation for GOR were obtained from patient records.

The patients were followed prospectively for symptoms of GOR for at least 28 days before commencing treatment with the PPI. The total number of vomiting episodes per 4-week period was recorded. The frequency of vomiting in the period before PPI treatment was defined as the baseline vomiting index ( $VI_{\text{baseline}}$ ). The VI was expressed as the number of vomiting episodes per day, with a denominator of at least 28 days. For example, if the patient had 24 episodes of vomiting over 28 days, the VI was equal to 0.86 (24/28). Patients were treated with omeprazole 20 mg daily as a suspension (Losec mups, AstraZeneca, Mississauga, Canada). The frequency of vomiting during the treatment period was also recorded. At the end of the study, the VI for the treatment period ( $VI_{\text{ppi}}$ ) was determined. The incidence of GIB and chest infection were also represented as the GIB index and pneumonia index, respectively. Body weight was measured monthly during the baseline and treatment periods.

## Statistical analysis

The VI, GIB index, and pneumonia index for the baseline and treatment periods were compared using the Wilcoxon signed ranks test. The body weight at study entry, at commencement of treatment, and at the end of the study were compared using the Friedman test. Intention-to-treat analysis was used to assess all parameters.

## Results

Ten children (six girls and four boys) were recruited into the study. The aetiology of their neurological

impairment was recorded as due to birth asphyxia (four patients), hypoxic-ischaemic encephalopathy secondary to pulmonary atresia (one patient), and idiopathic in the remaining four patients, with one having arylthroglyposis multiplex congenita. All children received nasogastric tube feeding, in two cases given via milk drip. One child had already undergone fundoplication and gastrostomy. One patient was withdrawn from the study because of recurrent chest infections requiring nil by mouth for more than 30% of the baseline observation period.

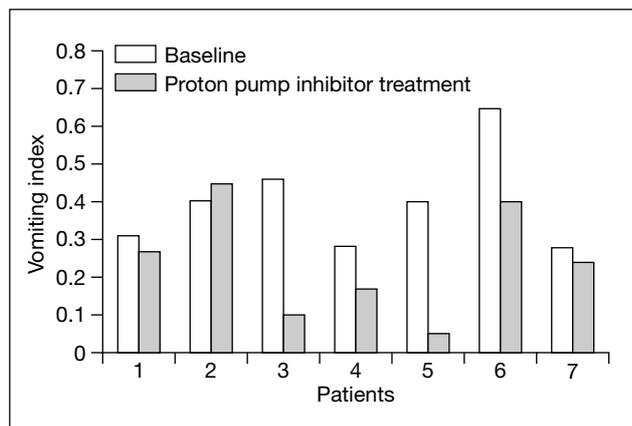
The mean age of the children was 6.2 years (standard deviation [SD], 4.8 years). The mean RI was 9.35% (SD, 5.0%). The median longest reflux period was 30.1 minutes (SD, 16.8 minutes). The mean number of reflux periods longer than 5 minutes was 6.2 episodes (SD, 4.8 episodes). The median baseline duration was 62 days (range, 28-356 days) and the median duration of treatment 81 days (range, 42-157 days) [not significant]. The PPI dose used ranged from 1.0 to 2.3 mg/kg/d. The  $VI_{baseline}$  was 0.40 (range, 0.26-0.63), while the  $VI_{PPI}$  was 0.20 (range, 0.06-0.26). A significant reduction in  $VI_{PPI}$  compared with  $VI_{baseline}$  was seen ( $P < 0.05$ , Wilcoxon signed rank test) [Fig, Table]. The incidence of GIB did not decrease significantly with treatment (median GIB index<sub>baseline</sub>=0.014 [range, 0-0.026], median GIB index<sub>PPI</sub>=0 [range, 0-0.05]). The incidence of pneumonia was also similar before and with treatment (median pneumonia index<sub>baseline</sub>=0 [range, 0-0.04],

median pneumonia index<sub>PPI</sub>=0 [range, 0-0.04]). Mean body weight did not differ significantly with treatment—mean body weight at the start of PPI treatment was 13.4 kg (SD, 4.1 kg) and mean weight at the end of PPI treatment was 14.2 kg (SD, 4.7 kg).

Two children were not included in the statistical analysis of the VI. However, remarkable clinical improvements were observed in these cases within 2 months of PPI treatment. One patient treated with ranitidine during the baseline period, could only tolerate feeding by a milk pump at the rate of up to 25 mL/h. She repeatedly developed severe milk regurgitation during and after feeding when the rate was increased further. The child also had recurrent chest infections (six episodes per year) and recurrent GIB (47 episodes per year). In the PPI treatment period, the milk drip rate was increased up to 60 mL/h and she remained free of chest infection and GIB. Weight gain of 2.6 kg over 3 months was noted following PPI treatment. The second patient presented with continuous naso-regurgitation and recurrent chest infections (36 episodes in 26 months). After receiving PPI treatment, the child experienced fewer episodes of naso-regurgitation and chest infection (two episodes in 5 months). No change in weight was observed in this patient with treatment.

**Discussion**

The results of this study provide quantitative evidence that the use of PPI therapy can significantly reduce vomiting in neurologically impaired children with GOR. A remarkable clinical reduction in the incidence of GIB and pneumonia was observed in two patients, although a statistically significant benefit for the patient group as a whole was not seen. The baseline incidence of GIB and chest infections in the selected sample was low, however. A considerably larger sample size is indicated to further investigate the effect of PPI treatment in reducing the incidence of GIB and chest infection in this population. Similarly, a research design incorporating a longer period of treatment is indicated to determine whether nutritional condition in this population could improve with PPI treatment.



**Fig. Vomiting index during baseline measurement and proton pump inhibitor treatment**

**Table. Vomiting, gastrointestinal bleeding, and pneumonia index during the baseline and proton pump inhibitor treatment periods**

	Baseline*	Proton pump inhibitors*	P value
Duration (days)	62 (28-356)	81 (42-157)	Not significant
Vomiting index†	0.4 (0.26-0.63)	0.2 (0.06-0.26)	<0.05
Gastrointestinal bleeding index†	0.014 (0-0.026)	0 (0-0.05)	Not significant
Pneumonia index†	0 (0-0.04)	0 (0-0.04)	Not significant

\* The range is expressed in brackets

† Episode of event per day

The treatment response was monitored by counting the actual episodes of vomiting, GIB, and chest infection. These monitoring tools were expressed as the VI, GIB index, and the pneumonia index. The use of such indexes provides more objective data than the scoring system of GOR symptoms used in a previous study,<sup>10</sup> and can be used for the longitudinal monitoring of GOR. Although 24-hour oesophageal pH monitoring and OGD are well-accepted tools for monitoring the effect of treatment, these can only provide cross-sectional results.

Both methods are expensive and laborious. In addition, many children with severe neurological impairment have poor respiratory effort due to spinal deformity and recurrent chest infections. Many consequently cannot tolerate general anaesthesia and even mild sedation may not be well tolerated, making a thorough endoscopic examination difficult. In the treatment of children with severe neurological impairment, the main concern is whether the treatment can lead to symptom improvement. The VI is therefore recommended by the authors as an adjunct in quantitative monitoring of the severity of GOR and the response to antireflux treatment in this population.

Poorly controlled GOR renders neurologically impaired children at higher risk of aspiration pneumonia, frequently requiring the use of potent antibiotics, oxygen therapy, and in some cases mechanical ventilation. Comparing the cost of antibiotic and PPI therapies, a year's treatment with omeprazole 20 mg/d is less expensive than 4 weeks of treatment with a third generation cephalosporin. Fundoplication has been recommended in this group of patients as the preferred surgical treatment for GOR disease. In neurologically impaired children, the operative failure rate is 25% to 28% and the complication rate is 59%.<sup>2</sup> Due to the failure of conventional antireflux medications and the high risk of undesirable complications with antireflux surgery in this patient group, the use of PPI treatment appears to be an appropriate and cost-effective means of managing GOR disease in neurologically impaired children.

Evidence is accumulating that long-term therapy with PPIs is safe.<sup>13</sup> In neurologically impaired children with refractory GOR disease, recurrent vomiting, GIB, and chest infection, are more serious and potentially life-threatening events than those potentially arising from PPI treatment. Further studies of long-term PPI treatment are needed, however, to assess the value of maintenance treatment, as an alternative to surgery, in children with severe GOR disease.

## Conclusions

The results in this study indicate that short-term use of PPI treatment can decrease vomiting in brain-damaged children with GOR refractory to conventional medical therapy. The long-term efficacy of PPIs in preventing GIB and pneumonia in this population requires investigation through further prospective studies.

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## References

1. Booth IW. Silent gastro-oesophageal reflux: how much do we miss? *Arch Dis Child* 1992;67:1325-7.
2. Sullivan PB. Gastrostomy feeding in the disabled child: when is an antireflux procedure required? *Arch Dis Child* 1999;81:463-4.
3. Vandenplas Y, Ashkenazi A, Belli D, et al. A proposition for the diagnosis and treatment of gastro-oesophageal reflux disease in children: a report from a working group on gastro-oesophageal reflux disease. Working Group of the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN). *Eur J Pediatr* 1993;152:704-11.
4. Ravelli AM, Milla PJ. Vomiting and gastroesophageal motor activity in children with disorders of the central nervous system. *J Pediatr Gastroenterol Nutr* 1998;26:56-63.
5. Byrne WJ, Euler AR, Ashcraft E, Nash DG, Seibert JJ, Golladay ES. Gastroesophageal reflux in the severely retarded who vomit: criteria for and results of surgical intervention in twenty-two patients. *Surgery* 1982;91:95-8.
6. Ulsben M. Gastroesophageal reflux. In: Behrman RE, Kliegman RM, Arvin AM, editors. *Nelson textbooks of pediatrics*. Philadelphia: W.B. Saunders Co.; 1996:1055-6.
7. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 1993;123:148-54.
8. De Giacomo C, Bawa P, Franceschi M, Luinetti O, Fiocca R. Omeprazole for severe reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 1997;24:528-32.
9. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. *Gastroenterology* 1997;113:399-408.
10. Bohmer CJ, Niezen-de Boer RC, Klinkenberg-Knol EC, Meuwissen SG. Omeprazole: therapy of choice in intellectually disabled children. *Arch Pediatr Adolesc Med* 1998;152:1113-8.
11. Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. *J Pediatr* 1979;94:81-4.
12. Cheng JC, Leung SS, Chiu BS, et al. Can we predict body height from segmental bone length measurements? A study of 3,647 children. *J Pediatr Orthop* 1998;18:387-93.
13. Falk GW. Gastroesophageal reflux disease. *Curr Opin Gastroenterol* 1999;15:333-8.