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EDITORIAL

Prescription of acid inhibitors in infants: an addiction hard to break

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O'Reilly et al. report in this issue of the *European Journal of Pediatrics* an increase in prescriptions of proton pump inhibitors (PPIs) in infants [1] and confirm thereby an ongoing worldwide trend despite the guidelines not recommending the usage of this group of drugs beyond the indication of erosive oesophagitis or evidence of acid reflux symptom association demonstrated by pH-impedance monitoring [2, 3].

According to epidemiologic data, around 20–30% of parents consulting health care providers are concerned because their infant presents with frequent regurgitation, vomiting, and/or distress or crying [4–6]. Moreover, a recent French report showed that up to 75 % of these infants present with a combination of symptoms [7]. Particularly, colicky infants present other gastro-intestinal functional disorders two to four times more frequent than those who do not have colic [8]. For unclear reasons, because it is not supported by evidence, the concept that acid gastro-oesophageal reflux (GOR) predominantly causes infant distress has been and remains very popular among health care providers. It is hypothesized that this concept is derived from the feeling of heartburn or pyrosis in adults, as a consequence of acid GOR: the so-called "occult" GOR. Although infant colic occurs in up to 20 % of all babies, it resolves spontaneously when the infant reaches the age of 10 weeks [9]. However, the oesophagus of an infant is shorter than 10 cm and can contain a volume of fewer than 10 ml. As a consequence, given that the oesophagus is so short and can contain only so small volumes, it seems very unlikely that GOR can be so severe to cause so much pain without ever resulting in reflux coming out of the mouth of the baby. PPIs are frequently prescribed as a treatment for infant distress, despite the lack of clinical efficacy, endorsed by the absence of correlation between infant crying and oesophageal acid exposure measured by pH monitoring [10–12]. But the number of prescriptions of PPIs continues to increase as shown in the paper by O'Reilly in this issue of *European Journal of Pediatrics*. Similar figures have been reported in many other countries, such as Australia, New Zealand, Belgium, Denmark, and the USA [13–18]. Although at the time of the study, in 2014, no PPI was approved by the FDA for patients aged <1 year old, results indicate that PPIs were commonly prescribed for newborns and infants, mostly in the hospital, but also in outpatient settings [14]. In Denmark, the proportion of prevalent users increased from 0.1 in 2000 to 3.1 per 1000 children in 2015, while the rate of new users increased from 1.2 to 8.0 per 1000 child years [15]. According to the 2012 data from New Zealand, 71.6% of infants dispensed a PPI by 3 months of age, and 8.7% received a PPI within the first month of life [18]. Before starting PPI, only 7.0% of infants had a hospital-based diagnosis of GOR-disease (GORD), with or without oesophagitis, and only 4.7% of infants presented one or more known or suspected GORD risk factors [18]. Similarly, in a substantial cohort of American newborns, 24% of infants were treated with acid-suppressive drugs and more than 10% with PPI, with the median onset of treatment at ten days of life (25th–75th percentiles: 3–28 days) [19].

In the last decades, not one study could show a decreasing trend in the prescription rate of PPIs, despite guidelines discouraging the use of PPIs in infants. A Cochrane review [20], the NICE guideline[3], the ESPGHAN/NASPGHAN guideline [2], and numerous consensus papers by key opinion leaders all recommend reassurance, anticipatory guidance and nutritional treatment, and first-line intervention. However, it is understandable why health care providers prescribe acid-blocking medications. It is hard in the daily practice to resist the desperate "scream for help" of parents for

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Table 1 Examples of warning signals requiring investigation in infants with regurgitation or vomiting (adapted from Rosen et al. [2])

Bilious vomiting
GI bleeding
Hematemesis
Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Bulging fontanelle
Hepatosplenomegaly
Macro/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

their inconsolable infant. Moreover, while the ESPGHAN/NASPGHAN guidelines do not recommend PPIs without an objective diagnosis, the NICE guidelines propose a blind PPI-trial [3]. In 2015, the majority of the Italian general paediatricians was not aware of the 2009 ESPGHAN/NASPGHAN guidelines and often prescribes PPIs despite a lack of efficacy for the symptoms being treated [21]. The many adverse effects of PPI have been highlighted in recent reviews [22–24]; none of these mentions the association of PPI and microscopic colitis [25]. Since PPIs cause dysbiosis already within 1 week of usage, they are likely to harm the developing immune system of the infant. They should be considered as a risk factor for developing later allergy and auto-immune disease [23]. Chronic PPI use may also have a negative nutritional impact, as it increases the risk to develop iron and vitamin B12 deficiency [22–24]. The absorption of magnesium and calcium is also challenged, resulting in an increased risk for bone fractures [22–24].

PPIs inhibit acid secretion and are therefore recommended in the management of acid GORD, causing erosive oesophagitis. However, PPIs do not decrease GOR incidence: they change acid GOR to non-acid GOR [26]. Our group recently showed that non-acid GOR causes more distress and crying than acid GOR in infants [27]. This explains why many infants with frequent regurgitation also suffer distress and crying and did not benefit from acid-suppressive treatment. From the pharmacological point of view, PPIs are best administered 30–60 min before a feeding, which is not realistic in young infants considering their feed and sleep cycle [23]. Further, the dose-related effects of PPIs in newborns have not been validated yet and the enzymes like cytochrome P450 2C19, P3A4 that clear PPIs, have only a mature activity about the age of 5 to 6 months of life [28]. In summary, the acid-blocking medication should be prescribed and should only be prescribed, when acid GORD has been diagnosed [2].

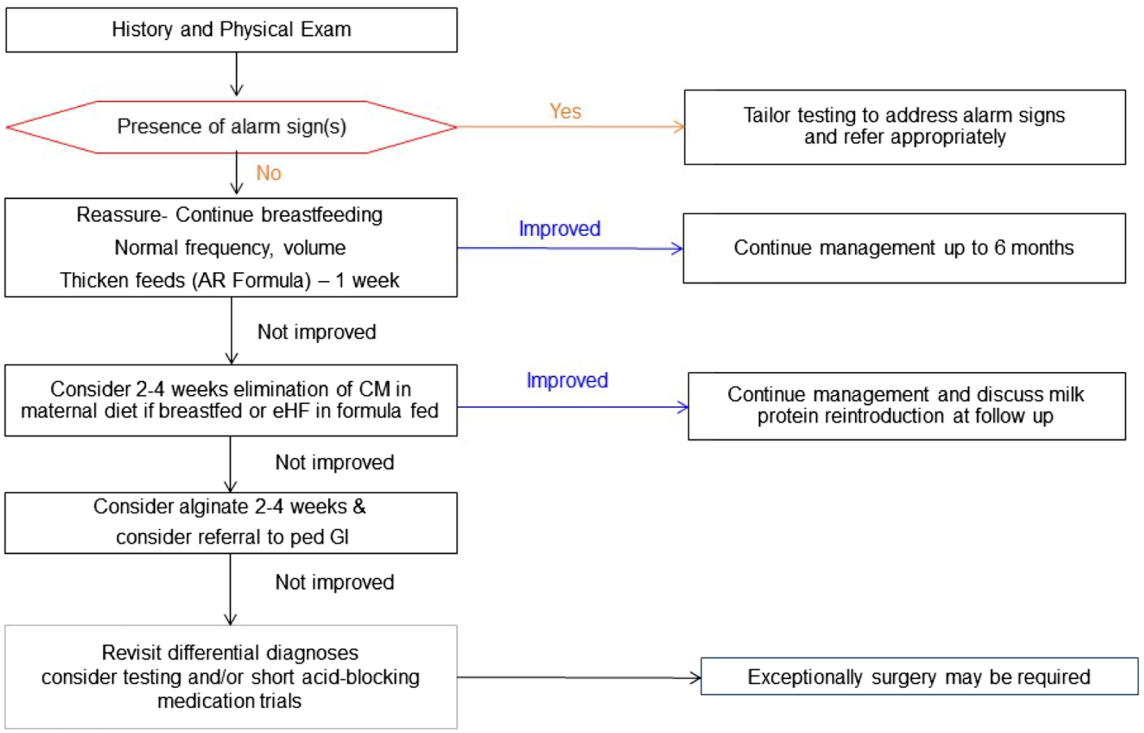

Fig. 1 Algorithm for the management of GORD in infants (adapted from O'Reilly et al. [1]). Legend: AR, anti-regurgitation; eHF, extensively hydrolysed formula; ped GI, pediatric gastroenterologist; CMA, cow milk allergy

Although less effective in acid-blocking power compared to PPI, histamine-2-receptor antagonists (H2RAs) have represented for many years a popular alternative to PPIs, mainly because H2RAs were commercially available as a syrup. H2RAS also cause dysbiosis [29]. Moreover, ranitidine syrup was withdrawn from the market in Europe and the USA in April 2020 due to a carcinogen component, nitrosamines. Further, the syrup did also contain alcohol at 7.5%, or 405 mg per 5 ml syrup. At a recommended dosage of 10 mg/kg/day and a concentration of 150 mg/10 ml, a 10-kg weighing infant received daily an equivalent amount of alcohol per day of around 6 ml wine.

Prokinetic drugs such as domperidone and metoclopramide are not recommended because of the lack of demonstrated efficacy [2]. However, concerning cisapride, the European Agency for the Evaluation of Medicinal Products concluded that it might have a beneficial effect on children with reflux [30]. Domperidone and cisapride have also been taken out of the market because of cardiac adverse effects. Other drugs such as baclofen and erythromycin are as well not recommended in the first-line management of GORD in infants [2].

Regarding the use of alginate, the recommendations of ESPGHAN/NASPGHAN [2] differ from those of the NICE [3] guidelines and the Cochrane analysis [20]. While the ESPGHAN/NASPGHAN [2] guidelines do not recommend alginates for usage because of their lack of evidence, NICE [3] and Cochrane do recommend to give this drug an empirical try during 2 weeks. Data supporting the efficacy of this drug is obtained from two studies without showing long-term outcomes [31, 32]. Further, two other studies were published after the guideline release favouring alginates [33–34]. However, a major shortcoming of alginate is the recommendation—according to the information provided by the company—to not combine alginate with thickened feedings to avoid bezoar formation [35] and obstruction [36, 37]. This dietary advice has received limited attention and is not considered in any of the guidelines. However, data are restricted to less than 10 cases reported in the literature, and all are dating from before 2000 with the threshold of a thickening agent in the milk formula yet not well defined. Nevertheless, because of the warning by the company, the combination with thickened feeds should be discouraged.

Nutritional treatment with thickened milk formulas [16, 20, 26] at normal volume and normal frequency according to the weight and age of the infant is recommended in the management of troublesome GORD during infancy [26]. Up to now, there is insufficient evidence from comparative trials to recommend one type of thickened commercial formula or thickeners over another. Other components such as kind of protein source, intact of hydrolysed prebiotics, or probiotics may also influence the clinical effect. Evidence from literature shows that thickened formula decreases regurgitation and infant distress caused by GOR [38, 39]. Data suggest that improvement occurs with a couple of days [38–40]. In case of failure, (non-IgE-mediated) cow's milk protein allergy should be considered [2], and management should be adapted accordingly.

The algorithm proposed (Fig. 1) attempts to consider the arguments as mentioned earlier. The health care provider should know warning signs in infants presented by the parents because of frequent regurgitation and vomiting and/or distress and crying (Table 1). If frequent regurgitation in infants starts before the age of 2 weeks or after the age of 6 months, the health care provider should first consider other diagnoses. Failure to thrive, neurological abnormalities, and hematemesis are other warning signs. Infection is another frequent cause of vomiting and distress in infants and should be promptly recognized. In the absence of warning signs, management should start with reassurance and dietary advice. If dietary treatment fails, the infant should be referred for appropriate investigations, and in the meantime, alginate can be given a chance. The over-diagnosis of GORD places undue burden on both families and national health system despite the publication of international guidelines [21].

In summary:

- Acid inhibitors keep on being over-prescribed in infants
- Occult GOR(D) is seldom in infants.
- The majority of GOR episodes in infants are non-acid.
- Non-acid reflux may cause more distress in infants than acid reflux
- Therefore, nutritional management should be used more often because of demonstrated efficacy and safety.

References

1. O'Reilly D, Conway R, O'Connor L, Fitzpatrick P (2020) Use of anti-reflux medications in infants under 1 year of age: a retrospective drug utilisation study using national prescription reimbursement data. Eur J Pediatr. https://doi.org/10.1007/s00431-020-03837-8
2. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M (2018) Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 66(3): 516–554. https://doi.org/10.1097/mpg.0000000000001889
3. National Institute for Health and Care Excellence (2018) Gastro-oesophageal reflux disease in children and young people: diagnosis and management. London: United Kingdom
4. Hegar B, Boediarso A, Firmansyah A, Vandenplas Y (2004) Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. World J Gastroenterol 10(12): 1795–1797. https://doi.org/10.3748/wjg.v10.i12.1795
5. Orenstein SR, Shalaby TM, Cohn JF (1996) Reflux symptoms in 100 normal infants: diagnostic validity of the infant

gastroesophageal reflux questionnaire. Clin Pediatr (Phila) 35(12): 607–614. https://doi.org/10.1177/000992289603501201
6. Nelson SP, Chen EH, Syniar GM, Christoffel KK (1997) Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 151(6):569–572. https://doi.org/10.1001/archpedi.1997.02170430035007
7. Bellaiche M, Oozeer R, Gerardi-Temporel G, Faure C, Vandenplas Y (2018) Multiple functional gastro-intestinal disorders are frequent in formula-fed infants and decrease their quality of life. Acta Paediatr 107(7):1276–1282. https://doi.org/10.1111/apa.14348
8. Vandenplas YLT, Bouritius H, Alliet P, Forde D, Peeters S et al (2017) Infant distress and occult gastro-oesophageal reflux. Acta Paediatr 106(7):1150–1158
9. Wolke D, Bilgin A, Samara M (2017) Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in Infants. J Pediatr 185:55–61.e4. https://doi.org/10.1016/j.jpeds.2017.02.020
10. Heine RG, Jordan B, Lubitz L, Meehan M, Catto-Smith AG (2006) Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. J Paediatr Child Health 42(3):134–139. https://doi.org/10.1111/j.1440-1754.2006.00812.x
11. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M (2009) 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 (4):514-520.e514. https://doi.org/10.1016/j.jpeds.2008.09.054
12. Gieruszczak-Białek D, Konarska Z, Skórka A, Vandenplas Y, Szajewska H (2015) No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. J Pediatr 166(3):767–770.e763. https://doi.org/10.1016/j.jpeds.2014.11.030
13. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D (2012) Trends of outpatient prescription drug utilization in US children, 2002-2010. Pediatrics 130(1):23–31. https://doi.org/10.1542/peds.2011-2879
14. Illueca M, Alemayehu B, Shoetan N, Yang H (2014) Proton pump inhibitor prescribing patterns in newborns and infants. J Pediatr Pharmacol Ther 19(4):283–287. https://doi.org/10.5863/1551-6776-19.4.283
15. De Bruyne P, Christiaens T, Vander Stichele R, Van Winckel M (2014) Changes in prescription patterns of acid-suppressant medications by Belgian pediatricians: analysis of the national database, [1997-2009]. J Pediatr Gastroenterol Nutr 58(2):220–225. https://doi.org/10.1097/MPG.0b013e3182a3b04e
16. Aznar-Lou I, Reilev M, Lødrup AB, Rubio-Valera M, Haastrup PF, Pottegård A (2019) Use of proton pump inhibitors among Danish children: a 16-year register-based nationwide study. Basic Clin Pharmacol Toxicol 124(6):704–710. https://doi.org/10.1111/bcpt.13191
17. Bell JC, Schneuer FJ, Harrison C, Trevena L, Hiscock H, Elshaug AG, Nassar N (2018) Acid suppressants for managing gastro-oesophageal reflux and gastro-oesophageal reflux disease in infants: a national survey. Arch Dis Child 103(7):660–664. https://doi.org/10.1136/archdischild-2017-314161
18. Blank ML, Parkin L (2017) National study of off-label proton pump inhibitor use among New Zealand infants in the first year of life (2005-2012). J Pediatr Gastroenterol Nutr 65(2):179–184. https://doi.org/10.1097/mpg.0000000000001596
19. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR (2016) Neonatal histamine-2 receptor antagonist and proton pump inhibitor treatment at United States children's hospitals. J Pediatr 174:63–70.e63. https://doi.org/10.1016/j.jpeds.2016.03.059
20. Kwok TC, Ojha S, Dorling J (2017) Feed thickener for infants up to six months of age with gastro-oesophageal reflux. Cochrane Database Syst Rev 12(12):Cd003211. https://doi.org/10.1002/14651858.CD003211.pub2
21. Quitadamo P, Miele E, Alongi A, Brunese FP, Di Cosimo ME, Ferrara D, Gambotto S, Lamborghini A, Mercuri M, Pasinato A, Sansone R, Vitale C, Villani A, Staiano A (2015) Italian survey on general pediatricians' approach to children with gastroesophageal reflux symptoms. Eur J Pediatr 174(1):91–96. https://doi.org/10.1007/s00431-014-2369-4
22. Corsonello A, Lattanzio F, Bustacchini S, Garasto S, Cozza A, Schepisi R, Lenci F, Luciani F, Maggio MG, Ticinesi A, Butto V, Tagliaferri S, Corica F (2018) Adverse events of proton pump inhibitors: potential mechanisms. Curr Drug Metab 19(2):142–154. https://doi.org/10.2174/1389200219666171207125351
23. Levy EI, Hoang DM, Vandenplas Y (2020) The effects of proton pump inhibitors on the microbiome in young children. Acta Paediatr 109(8):1531–1538. https://doi.org/10.1111/apa.15213
24. Yadlapati R, Kahrilas PJ (2018) The "dangers" of chronic proton pump inhibitor use. J Allergy Clin Immunol 141(1):79–81. https://doi.org/10.1016/j.jaci.2017.06.017
25. Bonderup OK, Nielsen GL, Dall M, Pottegård A, Hallas J (2018) Significant association between the use of different proton pump inhibitors and microscopic colitis: a nationwide Danish case-control study. Aliment Pharmacol Ther 48(6):618–625. https://doi.org/10.1111/apt.14916
26. Turk H, Hauser B, Brecelj J, Vandenplas Y, Orel R (2013) Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children. World J Pediatr 9(1):36–41. https://doi.org/10.1007/s12519-013-0405-5
27. Salvatore SPF, Huysentruyt K, Bosco A, Fumagalli L, Van De Maele K et al (2020) Distress in infants and young children: dont blame acid reflux. J Pediatr Gastroenterol Nutr 71(4):465–469
28. Ward R, Kearns G (2013) Proton pump inhibitors in pediatrics : mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. Paediatr Drugs 15:119–131. https://doi.org/10.1007/s40272-013-0012-x
29. Gupta RW, Tran L, Norori J, Ferris MJ, Eren AM, Taylor CM, Dowd SE, Penn D (2013) Histamine-2 receptor blockers alter the fecal microbiota in premature infants. J Pediatr Gastroenterol Nutr 56(4):397–400. https://doi.org/10.1097/MPG.0b013e318282a8c2
30. EMA (2002) Opinion following an article 31 referral: cisapride. https://www.ema.europa.eu/en/documents/referral/opinion-following-article-31-referral-cisapride-international-non-proprietary-name-inn-cisapride_en.pdf
31. Del Buono R, Wenzl TG, Ball G, Keady S, Thomson M (2005) Effect of gaviscon infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. Arch Dis Child 90(5):460–463. https://doi.org/10.1136/adc.2002.024463
32. Miller S (1999) Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. Curr Med Res Opin 15(3):160–168. https://doi.org/10.1185/03007999909114087
33. Salvatore S, Ripepi A, Huysentruyt K, van de Maele K, Nosetti L, Agosti M, Salvatoni A, Vandenplas Y (2018) The effect of alginate in gastroesophageal reflux in infants. Paediatr Drugs 20(6):575–583. https://doi.org/10.1007/s40272-018-0314-0
34. Baldassarre ME, Di Mauro A, Pignatelli MC, Fanelli M, Salvatore S, Di Nardo G, Chiaro A, Pensabene L, Laforgia N (2019) Magnesium alginate in gastro-esophageal reflux: a randomized multicenter cross-over study in infants. Int J Environ Res Public Health 17(1). https://doi.org/10.3390/ijerph17010083
35. Sorbie AL, Symon DN, Stockdale EJ (1984) Gaviscon bezoars. Arch Dis Child 59(9):905–906. https://doi.org/10.1136/adc.59.9.905-a

36. Keady S (2007) Update on drugs for gastrooesophageal reflux disease. Arch Dis Child Educ Pract Ed 92:ep114–ep118. https://doi.org/10.1136/adc.2006.106328
37. British Medical Association., Royal Pharmaceutical Society of Great Britain., Royal College of Paediatrics and Child Health., & Neonatal and Paediatric Pharmacists Group (2012) BNF for children: 2012-2013. BMJ Group, London
38. Chevallier B, Fournier V, Logre B, Beck L, Ceccato F, Hui Bon Hoa G, Lachambre E, Van Egroo LD, Sznajder M (2009) Value of a new thickened formula in infants with regurgitations. Arch Pediatr 16(4):343–352. https://doi.org/10.1016/j.arcped.2009.01.001
39. Hegar B, Rantos R, Firmansyah A, De Schepper J, Vandenplas Y (2008) Natural evolution of infantile regurgitation versus the efficacy of thickened formula. J Pediatr Gastroenterol Nutr 47(1):26–30. https://doi.org/10.1097/MPG.0b013e31815eeae9
40. Gatcheco F, Sales MIV, Battad G, Tan M, Gloria MCD, Kudla U, Muhardi L (2019) Nutritional management of gastroesophageal reflux among infants in the Philippines: insights from real-world evidence. Int J Clin Pediatr 8 (1):1–7. https://doi.org/10.14740/ijcp338