Cow’s Milk Allergy

Subjects: Nutrition & Dietetics

Contributor: Yvan Vandenplas

Cow’s milk allergy (CMA) and gastro-esophageal reflux disease (GERD) may manifest with similar symptoms in infants making the diagnosis challenging. While immediate reaction to cow’s milk protein indicate CMA, regurgitation, vomiting, crying, fussiness, poor appetite, sleep disturbances have been reported in both CMA and GERD and in other conditions such as functional gastrointestinal disorders, eosinophilic esophagitis, anatomic abnormalities, metabolic and neurological diseases. Gastrointestinal manifestations of CMA are often non-IgE mediated and clinical response to cow’s milk free diet is not a proof of immune system involvement.

Keywords: reflux ; GER ; GERD ; cow’s milk allergy ; CMA ; eosinophilic esophagitis ; infants ; hydrolyzed formula ; alginate ; thickened formula

1. Introduction

Gastroesophageal reflux (GER) and cow milk allergy (CMA) occur frequently in the first year of life [1][2][3][4]. The pathogenesis of these two conditions is complex and involves multiple mechanisms of nutrition, motility, immunology and hypersensitivity. A number of papers discussed the overlapping symptoms or simultaneous occurrence of CMA and GERD [1][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29] Nonetheless, discrimination between both disorders is still challenging due to the similarity of the symptoms and the lack of accurate and handy diagnostic tests [1][27]). Although the response to a CM elimination diet and oral challenge are essential to confirm the diagnosis of CMA [30][31][32][33], a positive challenge test does not proof the involvement of the immune system. Moreover, delayed reactions as occurring in non-IgE mediated allergy, may be insufficiently recognized with an oral challenge test. Upper endoscopy and biopsies and esophageal pH-impedance are the recommended diagnostic investigations for GERD [34]. However, a normal endoscopy and histology does not rule out GERD, as is the case in non-erosive GERD. Normal ranges for pH-impedance are missing and parameters such as symptom association probability have not been validated in children. Performance of pH-impedance is also hampered by cost and investment of time [34][35]. As a consequence, under- or over-diagnosis of CMA and GERD are likely to occur. CM protein elimination diet and treatment with acid inhibitors are often empirically initiated and are, sometimes, excessively protracted.

2. CMA and GERD: A Pathogenic Twist

GER and other persistent gastrointestinal symptoms in allergic patients are predominantly associated with cellular immune mechanisms and delayed reactions. In non-IgE mediated CMA, activated mast-cells, eosinophils and Th2 lymphocytes, release histamine, tryptase, IL-4, IL-5, IL-13, eotaxin and other chemokines that lead to increased permeability, epithelial dysfunction, inflammatory infiltration in the mucosal, submucosal and, in some cases, muscle layers and nociception [25][27][28][36].

A migration of activated mast cells in proximity of enteric nervous system has been demonstrated in allergic children exposed to CM proteins and may determine gastrointestinal dysmotility and related symptoms [37].

GER and regurgitation are commonly related to overfeeding, short length of the (intra-abdominal) esophagus, obtuse His angle, horizontal position of the infant. Inappropriate relaxations of the lower esophageal sphincter (LES), ineffective clearance and the impaired resistance of the esophageal mucosa contribute to GERD [34].

Crying and pain in infants and children are determined by interplaying factors such as esophageal and gastrointestinal distension, dysmotility, visceral hyperalgesia, genetics, early life events, inflammatory and microbiota components, increased permeability, stress, parental and individual coping and perception [4][38][39].

GER and CMA can coexist in the same patient and it has been reported that CMA can induce GER and also be a predisposing factor for gastrointestinal functional disorders [22][27]. Conversely, treatment with acid inhibitors for GERD increase the risk of allergy later in life [40][41].

3. Functional Disorder, CMA or GERD: The Clinical Enigma

3.1. Definition and Epidemiological Data of Infant Regurgitation and Colic

Infant regurgitation and colic are defined by the Rome IV criteria as functional gastrointestinal disorders (FGIDs) of infancy [42]. Diagnostic criteria for infant regurgitation must include at least due episodes of regurgitation per day for at least three weeks in an otherwise healthy infant 3 weeks to 12 months of age without retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties or abnormal posturing [42]. Infant colic is defined by recurrent or prolonged periods of crying, fussing or irritability that occur without an obvious cause, that cannot be prevented or resolved by caregivers in an infant younger than 5 months with no failure to thrive, fever or illness [42]. For clinical research purposes, to fulfill the definition of colic these episodes of crying or fussiness should last at least 3 h per days, for a minimum of one day when measured by a prospectively kept 24 h behavior diary or 3 days per week according to a caregiver's interview [42]. They affect, alone or in combination and depending on selection and inclusion criteria around 20 to 25% of infants all over the world [4][39][43][44]. Neonates born preterm, small for gestational age or exposed to early life antibiotics have been recently reported to be at increased risk of infantile regurgitation and colic [45][46]. One fifth to one third of parents are concerned about their infant's health condition and consult health care providers because of regurgitation, fussiness and crying [3][4][39][41][47]. Regurgitation and infantile colic occur mostly during the first three to four months of life, with a natural resolution in the vast majority of cases around 4 to 5 months for colic and from 6 months onwards for regurgitation [3][42][48][49][50]. When the onset of regurgitation is in the first two weeks of life or when projectile vomiting is the predominant symptom, secondary GER related to anatomic malformations or conditions such as CMA are more likely [42].

3.2. Symptoms and Prevalence of GERD in Infants

When GER is associated with troublesome, persistent severe symptoms or complications (e.g., respiratory problems or esophagitis) it is referred to as GERD [34]. As the definition of troublesome is subjective, the distinction between GER and GERD is challenging in infants and the two terms are often misused interchangeably [34].

The most frequently reported symptom of GER in infants is regurgitation but the latter is neither sensitive nor specific to diagnose GERD, neither if associated with crying or fussiness [14][15][34][38][47][51][52][53]. Thus, acid inhibitors should not be started in these infants unless an investigation-based diagnosis of GERD is established [34]. The exact prevalence of GERD in infants is difficult to define because symptoms are not specific, empirical treatment is often started, many infants are not submitted to pH-impedance and/or endoscopy and prospective data are limited. The only report in which healthy infants (N = 509), screened for risk of sudden infant death syndrome, underwent pH-monitoring dates from 1991 [54]. Using a glass microelectrode to detect acid pH, the 95th percentile of esophageal acid exposure rate, during the first 12 months of life, was about 10% [54]. Hence, 5% of healthy infants, would present a pathological oesophageal acid exposure when the threshold is fixed to 10%. In the last 30 years, for ethical reasons, only symptomatic infants suspected to have GERD were investigated. When 151 infants with persistent crying underwent pH-monitoring, 17.9% infants had pathological acid exposure time (>10%) and no association with total crying duration was noted [15]. Regurgitation occurring more than 5 times daily was the most specific GERD symptom (specificity 70.9%) but had a poor positive predictive value (22%). In the absence of frequent regurgitation or feeding difficulties, pathological GERD according to pH monitoring results was unlikely (negative predictive value 87–90%) [15]. In another study evaluating 100 infants, suspected of having GERD, a pathological pH tracing was found in 21% of cases and esophagitis was identified in 17 out of 44 infants (39%) underwent endoscopy, with poor correlation between clinical symptoms, histology and pH results [51]. In a multicenter retrospective cross-sectional study in the United States using an Endoscopy Database System, emerged that 5.5% of children aged 0 to 1 year had erosive esophagitis [55]. In another cohort of 245 infants with symptoms of reflux submitted to endoscopy and esophageal biopsy, 62 cases (25%) had histological esophagitis [56]. In 8 out of 40 infants (20%) referred for persisting symptoms attributed to GERD (regurgitation and/or vomiting and inconsolable crying, fussiness, irritability, sleeping difficulties or respiratory problems for at least 2 weeks, in the absence of any other identifiable cause) a pathological acid exposure (defined as ≥7%, as measured by an antimony electrode) was found by pH-impedance [57]. More recently, our group analyzed impedance-pH tracings of 62 children (ages 15 days to 23 months, median age 3.5 months) with persistent unexplained fussiness or distress and 19% showed an acid reflux exposure time >7% [58].

3.3. Symptoms and Prevalence of CMA in Infants

The prevalence of hospital based diagnosed CMA in the first year of life ranges from 0.5% to 3% of infants, with the lowest rate when breast feeding and food challenge are considered [25][28][36][59]. Nonetheless, in a Finnish study, of the 824 exclusively breast-fed infants, 2.1% had CMA, verified by a CM elimination-challenge test [60].

In the EuroPrevall birth cohort study, 12,049 children with symptoms possibly related to CMA were enrolled and 77.5% were followed up to 2 years of age. Clinical evaluation included CM-specific IgE antibodies (IgE), skin prick test and double-blind, placebo-controlled food challenge. CMA was suspected in 358 (3%) children and confirmed by the food challenge in 55 cases (0.54%, 95% CI 0.41–0.70). Of all children with CMA, 23.6% had negative specific serum IgE and all of them tolerated CM one year after diagnosis compared to 57% of those children with IgE-associated CMA [59].

According to these epidemiological data, the expected casual coexistence of CMA and GERD would occur, by far, in less than 1% of the breastfed or formula fed infants. In breastfed infants, reflux and infantile colic as single manifestations are only seldom caused by CMA [61].

GERD may be the cause of regurgitation, vomiting, feeding disorders, day and night crying [34]. Similar symptoms may also be present in CMA and make it difficult to understand which condition is responsible for the clinical picture, especially in the absence of other signs of allergy, such as atopic dermatitis or otherwise unexplained rectal bleeding in the first months of life [1][4][30][31][61][62].

Prolonged crying during or after a meal or in the evening and night are often erroneously attributed to both CMA and GERD which seem to be responsible for only 5–10% of cases of infantile colic [25][27][38].

Repeated episodes of incoercible vomiting, with possible severe dehydration, lethargy and diarrhea occurring within a few hours from CM intake, can be classified as food protein induced enterocolitis syndrome (FPIES) [63][64]. Diarrhea, poor feeding, vomiting, failure to thrive and malabsorption are reported in food protein enteropathy. Food protein induced allergic proctocolitis typically shows he presence of blood and mucous in the stools and mild diarrhea in otherwise well-appearing, often breastfed infants [28][31][32][33][64].

3.4. Literature Data on the Association of CMA and GERD

A number of studies examined the presence of CMA in infants with symptoms attributed to GERD (Table 1).

Table 1. Summary of the studies evaluating the association of cow's milk allergy (CMA) and gastro-esophageal reflux disease (GERD) (modified from Ferreira 2014 [23]).

Author, Year	Population	Investigation	Main Results
Forget, 1985 [5]	15 children with recurrent vomiting	Contrast X-ray, small bowel biopsy	All children showed GER on X-ray. 3/15 (20%) had enteropathy with IgE plasmatocytes, reported no improvement with GER treatment but disappearance on symptoms on CM free diet
McLain, 1994 [6]	10 infants with GERD who failed to respond to reflux treatment	pH-monitoring	Symptoms improved in 2/10 (20%) infants on CM free diet. No infant showed significant improvement in pH monitoring indices
Staiano, 1995 [11]	25 infants with recurrent vomiting	Endoscopy and small bowel biopsies, permeability test	Primary GERD in 16/25 (64%), GERD + CMA in 4/25 (16%), CMA alone in 4/25 (16%). Enteropathy in 19% GERD, 67% CMA. Abnormal permeability test in 6% GERD, 100% CMA
Iacono, 1996 [9]	204 infants (median age, 6.3 months) with GERD	pH-monitoring, upper endoscopy, allergy tests, CM challenge	93 (45%) had positive allergy tests, 85 (42%) improved with hydrolyzed formula and reappeared on challenge. GER + CMA significantly associated with the presence of diarrhea or atopic dermatitis
Cavataio, 1996 [8]	96 infants with suspected GERD, CMA and controls	Serum specific IgE and IgG, blood eosinophils, pH-monitoring, endoscopy, CM challenge	14 out of 47 (30%) infants with GERD had CMA These infants had similar symptoms to those with primary GERD but significantly higher concentrations of total IgE, circulating eosinophils and IgG anti-beta lactoglobulin. A specific phasic pH pattern, with progressive decrease in pH tracing, occurred in 24/25 infants with CMA, 12/14 GERD + CMA and 0 controls. CM free diet improved only in the ones with CMA
Milocco, 1997 [10]	112 infants with GERD	pH-monitoring, CM challenge	18 infants (16%) had CMA, 10/18 had failure to thrive. A phasic pH-pattern was present in 1/18 with CMA and in 3 with only GERD

Author, Year	Population	Investigation	Main Results
Hill, 2000 [14]	19 infants with persistent distress and GER symptoms with no response to eHF and GERD treatment	Endoscopy, pH-monitoring, CM challenge	Nine infants had histologic evidence of esophagitis and 9 had inflammatory changes in the stomach and/or duodenum. Symptoms remitted in all infants within 2 weeks of starting AAF. On double blind challenge, after a median period of 3 months of AAF, 12 infants were still intolerant to CM
Ravelli, 2001 [21]	26 vomiting infants (7 CMA, 9, GER, 10 controls)	Electrogastrography electrical impedance tomography, CM challenge	Children with CMA showed more gastric dysrythmia (67% vs. 29.4% GER and 30.4% controls) and delayed gastric emptying (89 ± 26 min) compared to infants with GERD (54 ± 13 min) and controls (62 ± 13 min). 7/7 CMA patients had regurgitation and/or vomiting, colic and positive family history of allergy
Garzi, 2002 [12]	10 infants with GER symptoms, 10 controls	Ultrasonography to measure gastric emptying time-with CM formula and protein hydrolysate	All infants with a clinical diagnosis for GER showed delayed gastric emptying vs. normal subjects (205 vs. 124 min, $p = 0.000$). With eHF there was a significant improvement in gastric emptying time and symptoms especially in infants with positive skin-test and RAST
Nielsen, 2004 [17]	18 infants and children (median age 8.7 years; range 2 months to 14.8 years) with GERD	Endoscopy, 48-h pH-metry (Day 1-elimination diet, Day 2-challenge test), 2nd CM challenge	10 (56%) infants had CMA + GERD (higher acid exposure time vs. primary GERD), responded to CM free diet and had a positive challenge which was not associated with a significant increase in the esophageal acid exposure in the simultaneous pH monitoring
Nielsen, 2006 [18]	17 infants and children (aged 2–178 months) (mean age of 7.8 years) with GERD	Endoscopy and biopsies, pH-monitoring, allergy tests, CM challenge	10/17 (59%) were classified as CMA-GERD. Two patients showed >15 eosinophils at biopsies (=EoE) No differences in the number of eosinophils, mast cells or T cells were found between children with CMA and those with primary GERD
Semeniuk, 2007 [19] and 2008 [20]	264 children with suspected GERD (mean age 21 ± 17 months) or CMA	Esophageal manometry, pH-monitoring, allergy tests and CM challenge	138 children with GERD: 76 only GERD, 62 (23.5%) GER + CMA/FA, 32 only CMA/FA. No differences between primary GERD and GERD+ CMA in reflux parameters, in the mean values of resting LES pressure and LES length at baseline and during 2 years of follow-up
Farahmand, 2011 [13]	81 children (aged 1mo-2 yrs, median 12.5 mo) with supsected GERD.	Clinical study	54 (66%) responded to PPI, 27 (33%) to CM elimination diet
Borrelli, 2012 [22]	17 children (median age: 14 months) with proven f CMA and suspected GERD	48-h pH-impedance. Day 1-amino acid formula Day 2-challenge with cow's milk	The total reflux episodes and the number of weakly acidic episodes were higher during CM challenge compared with the amino acid-based formula period. No differences were found for either acid or weakly alkaline reflux
Vandenplas, 2014 [24]	72 Infants with suspected CMA	Clinical study comparing a thickened and non-thickened eHF casein formula: results after one month.	Regurgitation was reduced in all infants (from 6.4 ± 3.2 to 2.8 ± 2.9, $p < 0.001$) but fell more with the thickened hydrolyzed formula (−4.2 ± 3.2 regurgitations/day) vs. non thickened formula, especially in infants with a negative challenge (−3.9 ± 4.0 vs. −1.9 ± 3.4, ns). In the group with positive challenge the two formulas showed a similar decrease (−4.4 ± 2.6 vs. 4.7 ± 5.6). The global reduction of a symptom-based score was −7.4 points and the non-thickened hydrolysate was more effective in the group with a positive challenge (−9.2 vs. −5.7 points)

Author, Year	Population	Investigation	Main Results
Yukselen, 2016 [26]	151 children (aged 3–60 mo) with GERD resistant to 8 wks PPI treatment	skin prick test, specific serum IgE, eosinophil count, atopy patch test and CM challenge	58 children (38.4%) had positive CM challenge and 28 (48%) of them had positive skin prck tests or IgE, 16 (28%) had positive patch tests. Bloody stools, atopic dermatitis and recurrent wheezing episodes were significantly more common in these children Vomiting and diarrhea were more common in non-IgE children. Ten children who had positive challenge were finally diagnosed as EoE
Omari, 2020 [29]	50 infants with persistent crying, vomiting and/or food refusal (suspected to be GERD and or CMA related)	48 h cry-fuss chart, I-GERQ-R, allergy tests, blinded milk elimination-challenge sequence, pH-impedance before and after CM elimination, ^{13}C-octanoate breath test for gastric emptying, dual-sugar intestinal permeability, fecal calprotectin	14 (28%) were diagnosed as non-IgE-mediated CMA, 17 (34%) had negative challenge, 19 were excluded for equivocal findings or incomplete data. No baseline differences in any of the tests or GERD parameters between infants with and without CMA. In the CMA group, CM elimination significantly reduced reflux symptoms, esophageal acid exposure, acid clearance time and increased impedance baseline

The association of CMA-GERD was reported in 16–56% of cases with persistent gastrointestinal symptoms and suspicion of GERD, irrespective of breast or formula feeding [1][17][23][27][28][29][45][62]. The percentage of infants with persistent GER symptoms with clinical improvement on diet and worsening on challenge is extremely variable depending on the population recruited, design of the study and follow up data [27]. In one study, out of 19 infants with persistent distress and GER symptoms with no response to eHF and acid suppressive agents, 9 infants had esophagitis, 9 had inflammatory changes in the stomach and/or duodenum and all 19 improved on amino acid-based formula [14].

References

1. Salvatore, S.; Vandenplas, Y. Gastroesophageal reflux and cow milk allergy: Is there a link? Pediatrics 2002, 110, 972–984, doi:10.1542/peds.110.5.972.
2. Nwaru, B.I.; Hickstein, L.; Panesar, S.S.; Roberts, G.; Muraro, A.; Sheikh, A.; EAACI Food Allergy and Anaphylaxis Gui de-lines Group Prevalence of common food allergies in Europe: A systematic review and meta-analysis. Allergy 2014, 6 9, 992–1007, doi:10.1111/all.12423.
3. Vandenplas, Y.; Abkari, A.; Bellaiche, M.; A Benninga, M.; Chouraqui, J.P.; Çokuðraþ, F.; Harb, T.; Hegar, B.; Lifschitz, C.H.; Ludwig, T.; et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. J. Pediatr. Gastroenterol. Nutr. 2015, 61, 531–537, doi:10.1097/mpg.0000000000000949.
4. Vandenplas, Y.; Benninga, M.; Broekaert, I.; Falconer, J.; Gottrand, F.; Guarino, A.; Lifschitz, C.; Lionetti, P.; Orel, R.; Pa padopoulou, A.; et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. Acta Paediatr. 2015, 105, 244–252, doi:10.1111/apa.13270.
5. Forget, P.; Arends, J.W. Cow's milk protein allergy and gastro-oesophageal reflux. Eur. J. Pediatr. 1985, 144, 298–300.
6. McLain, B.I; Cameron, D.J.S; Barnes, G.L. Is cow's milk protein intolerance a cause of gastro-oesophageal reflux in inf ancy? J. Paediatr. Child. Health 1994, 30, 316–318.
7. Cavataio, F.; Iacono, G.; Montalto, G.; Soresi, M.; Tumminello, M.; Campagna, P.; Notarbartolo, A.; Carroccio, A. Gas-tr oesophageal reflux associated with cow's milk allergy in infants, which diagnostic examinations are useful? Am. J. Gast ro-enterol. 1996, 91, 1215–1220.
8. Cavataio, F.; Iacono, G.; Montalto, G.; Soresi, M.; Tumminello, M.; Carroccio, A. Clinical and pH-metric characteristics o f gastro-oesophageal reflux secondary to cows' milk protein allergy. Arch. Dis. Child. 1996, 75, 51–56.
9. Iacono, G.; Carroccio, A.; Cavataio, F.; Montalto, G.; Kazmierska, I.; Lorello, D.; Soresi, M.; Notarbartolo, A. Gastroesop hageal reflux and cow's milk allergy in infants, a prospective study. J. Allergy Clin. Immunol. 1996, 97, 822–827.
10. Milocco, C.; Torre, G.; Ventura, A. Gastro-oesophageal reflux and cows' milk protein allergy. Arch. Dis. Child. 1997, 77, 183, doi:10.1136/adc.77.2.183a.
11. Staiano, A.; Troncone, R.; Simeone, D.; Mayer, M.; Finelli, E.; Cella, A.; Auricchio, S. Differentiation of cows' milk intoler ance and gastro-oesophageal reflux. Arch. Dis. Child. 1995, 73, 439–442.
12. Garzi, A.; Messina, M.; Frati, F.; Carfagna, L.; Zagordo, L.; Belcastro, M.; Parmiani, S.; Sensi, L.; Marcucci, F. An exten sively hydrolysed cow's milk formula im-proves clinical symptoms of gastroesophageal reflux and reduces the gastric e mptying time in infants. Allergol. Immunopathol. 2002, 30, 36–41.

13. Farahmand, F.; Najafi, M.; Ataee, P.; Modarresi, V.; Shahraki, T.; Rezaei, N. Cow's milk allergy among children with gas -troesopha-geal reflux disease. Gut Liver. 2011, 5, 298–301.

14. Hill, D.J.; Heine, R.G.; Cameron, D.J.; Cairo-Smith, A.G.; Chow, C.W.; Francis, D.E.; Hosking, C.S. Role of food protein intol-erance in infants with persistent distress attributed to reflux esophagitis. J. Pediatr. 2000, 136, 641–647, doi:10.10 67/mpd.2000.104774.

15. Heine, R.G. Gastroesophageal reflux disease, colic and constipation in infants with food allergy. Curr. Opin. Allergy Cli n. Im-munol. 2006, 6, 220–225, doi:10.1097/01.all.0000225164.06016.5d.

16. Heine, R.G.; Jordan, B.; Lubitz, L.; Meehan, M.; Catto-Smith, A.G. Clinical predictors of pathological gastro-oesophage al re-flux in infants with persistent distress. J. Paediatr. Child. Health 2006, 42, 134–139, doi:10.1111/j.1440-1754.200 6.00812.x.

17. Nielsen, R.G.; Bindslev-Jensen, C.; Kruse-Andersen, S.; Husby, S. Severe Gastroesophageal Reflux Disease and Cow Milk Hypersensitivity in Infants and Children: Disease Association and Evaluation of a New Challenge Procedure. J. Pe diatr. Gas-troenterol. Nutr. 2004, 39, 383–391, doi:10.1097/00005176-200410000-00015.

18. Nielsen, R.G.; Fenger, C.; Bindslev-Jensen, C.; Husby, S. Eosinophilia in the upper gastrointestinal tract is not a charac teristic fea-ture in cow's milk sensitive gastro-oesophageal reflux disease Measurement by two methodologies. J. Clin. Pathol. 2006, 59, 89-94.

19. Semeniuk, J.; Kaczmarski, M. 24-hour esophageal pH monitoring in children with pathological acid gastroesophageal r eflux: Primary and secondary to food allergy. Part, I. Intraesophageal pH values in distal channel; preliminary study and control studies--after 1, 2, 4 and 9 years of clinical observation as well as dietary and pharmacological treatment. Adv. Med. Sci. 2007, 52, 199–205.

20. Semeniuk, J.; Kaczmarski, M.; Uścinowicz, M. Manometric study of lower esophageal sphincter in children with primary acid gastroesophageal reflux and acid gastroesophageal reflux secondary to food allergy. Adv. Med. Sci. 2008, 53, doi: 10.2478/v10039-008-0034-8.

21. Ravelli, A.M.; Tobanelli, P.; Volpi, S.; Ugazio, A.G. Vomiting and gastric motility in infants with cow's milk allergy. J. Pedi atr. Gastroenterol. Nutr. 2001, 32, 59–64.

22. Borrelli, O.; Mancini, V.; Thapar, N.; Giorgio, V.; Elawad, M.; Hill, S.; Shah, N.; Lindley, K.J. Cow's Milk Challenge Increa ses Weakly Acidic Reflux in Children with Cow's Milk Allergy and Gastroesophageal Reflux Disease. J. Pediatr. 2012, 1 61, 476–481.e1, doi:10.1016/j.jpeds.2012.03.002.

23. Ferreira, C.T.; de Carvalho, E.; Sdepanian, V.L.; Morais, M.B.; Vieira, M.C.; Silva, L.R. Gastroesophageal reflux diseas e, ex-aggerations, evidence and clinical practice. J. Pediatr. 2014, 90, 105-118.

24. Vandenplas, Y.; De Greef, E.; ALLAR Study Group. Extensive protein hydrolysate formula effectively reduces regurgitati on in infants with positive and negative challenge tests for cow's milk allergy. Acta Paediatr. 2014,103, e243–e250.

25. Nocerino, R.; Pezzella, V.; Cosenza, L.; Amoroso, A.; Di Scala, C.; Amato, F.; Iacono, G.; Canani, R.B. The Controversi al Role of Food Allergy in Infantile Colic: Evidence and Clinical Management. Nutrients 2015, 7, 2015–2025, doi:10.339 0/nu7032015.

26. Yukselen, A.; Celtik, C. Food allergy in children with refractory gastroesophageal reflux disease. Pediatr. Int. 2015, 58, 254–258, doi:10.1111/ped.12779.

27. Pensabene, L.; Salvatore, S.; D'Auria, E.; Parisi, F.; Concolino, D.; Borrelli, O.; Thapar, N.; Staiano, A.; Vandenplas, Y.; Saps, M. Cow's Milk Protein Allergy in Infancy: A Risk Factor for Functional Gastrointestinal Disorders in Children? Nutr ients 2018, 10, 1716, doi:10.3390/nu10111716.

28. D'Auria, E.; Salvatore, S.; Pozzi, E.; Mantegazza, C.; Sartorio, M.U.A.; Pensabene, L.; Baldassarre, M.E.; Agosti, M.; V anden-plas, Y.; Zuccotti, G.V. Cow's Milk Allergy: Immunomodulation by Dietary Intervention. Nutrients 2019, 11, 1399, doi:10.3390/nu11061399.

29. Omari, T.; Tobin, J.M.; McCall, L. Characterization of Upper Gastrointestinal Motility in Infants with Persistent Distress a nd Non-IgE-mediated Cow's Milk Protein Allergy. J. Pediatr. Gastroenterol. Nutr. 2020, 70, 489–496.

30. Koletzko, S.; Niggemann, B.; Arato, A.; Dias, J.A.; Heuschkel, R.; Husby, S.; Mearin, M.L.; Papadopoulou, A.; Ruemmel e, F.M.; Staiano, A.; et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children, E S-PGHAN gastrointestinal committee practical guidelines. J. Pediatr. Gastroenterol. Nutr. 2012, 55, 221-229.

31. Muraro, A.; Werfel, T.; Hoffmann-Sommergruber, K.; A.; Roberts, G.; Beyer, K.; Bindslev-Jensen, C.; Cardona, V.; Dubo is, A.; Dutoit, G.; Eigenmann, P.; et al. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and management of food aller-gy. Allergy 2014, 69, 1008–1025, doi:10.1111/all.12429.

32. Luyt, D.; Ball, H.; Makwana, N.; Green, M.R.; Bravin, K.; Nasser, S.M.; Clark, A. BSACI guideline for the diagnosis and management of cow's milk allergy. Clin. Exp. Allergy 2014, 44, 642–672, doi:10.1111/cea.12302.

33. Fiocchi, A.G.; Dahda, L.; Dupont, C.; Campoy, C.; Fierro, V.; Nieto, A. Cow's milk allergy: Towards an update of DRACMA guidelines. World Allergy Organ. J. 2016, 9, 35, doi:10.1186/s40413-016-0125-0.

34. Rosen, R.; Vandenplas, Y.; Singendonk, M.; Cabana, M.; Di Lorenzo, C.; Gottrand, F.; Gupta, S.; Langendam, M.; Staiano, A.; Thapar, N.; et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines, Joint Recommendations of the North Amer-ican Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J. Pediatr. Gastroenterol. Nutr. 2018, 66, 516–554.

35. Quitadamo, P.; Tambucci, R.; Mancini, V.; Cristofori, F.; Baldassarre, M.; Pensabene, L.; Francavilla, R.; Di Nardo, G.; Caldaro, T.; Rossi, P.; et al. Esophageal pH-impedance monitoring in children: Position paper on indications, methodology and interpretation by the SIGENP working group. Dig. Liver Dis. 2019, 51, 1522–1536, doi:10.1016/j.dld.2019.07.016.

36. Sicherer, S.H.; Sampson, H.A. Food allergy, A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J. Allergy Clin. Immunol. 2018, 141, 41–58.

37. Schäppi, M.G.; Borrelli, O.; Knafelz, D.; Williams, S.; Smith, V.V.; Milla, P.J.; Lindley, K.J. Mast Cell–Nerve Interactions in Children with Functional Dyspepsia. J. Pediatr. Gastroenterol. Nutr. 2008, 47, 472–480, doi:10.1097/mpg.0b013e318186008e.

38. Shamir, R.; St James-Roberts, I.; Di Lorenzo, C.; Burns, A.J.; Thapar, N.; Indrio, F.; Riezzo, G.; Raimondi, F.; Di Mauro, A.; Francavilla, R.; et al. Infant crying, colic, and gastrointestinal discomfort in early childhood, a review of the evidence and most plausible mechanisms. J. Pediatr. Gastroenterol. Nutr. 2013, 57, S1.

39. Salvatore, S.; Abkari, A.; Cai, W.; Catto-Smith, A.; Cruchet, S.; Gottrand, F.; Hegar, B.; Lifschitz, C.; Ludwig, T.; Shah, N.; et al. Review shows that parental reassurance and nutritional advice help to optimise the management of functional gastroin-testinal disorders in infants. Acta Paediatr. 2018, 107, 1512–1520, doi:10.1111/apa.14378.

40. Yadlapati, R.; Kahrilas P.J. The "dangers" of chronic proton pump inhibitor use. J. Allergy Clin. Immunol. 2018, 141, 79–81.

41. Levy, E.J.; Vandenplas, Y. Proton pump inhibitors, microbiota and micronutrients. Acta Paediatr. 2020, 109, 1531–1538.

42. Benninga, M.A.; Nurko, S.; Faure, C.; Hyman, P.E.; Roberts, I.S.J.; Schechter, N.L. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology 2016, 150, 1443–1455.e2, doi:10.1053/j.gastro.2016.02.016.

43. Wolke, D.; Bilgin, A.; Samara, M. Systematic review and meta-analysis, fussing and crying durations and prevalence of colic in infants. J. Pediatr. 2017, 185, 55–61.

44. Bellaiche, M.; Oozeer, R.; Gerardi-Temporel, G.; Faure, C.; Vandenplas, Y. Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life. Acta Paediatr. 2018, 107, 1276–1282, doi:10.1111/apa.14348.

45. Salvatore, S.; Baldassarre, M.E.; Di Mauro, A.; Laforgia, N.; Tafuri, S.; Bianchi, F.P.; Dattoli, E.; Morando, L.; Pensabene, L.; Meneghin, F.; et al. Neonatal Antibiotics and Prematurity Are Associated with an Increased Risk of Functional Gastrointesti-nal Disorders in the First Year of Life. J. Pediatr. 2019, 212, 44–51, doi:10.1016/j.jpeds.2019.04.061.

46. Baldassarre, M.E.; Di Mauro, A.; Salvatore, S.; Tafuri, S.; Bianchi, F.P.; Dattoli, E.; Morando, L.; Pensabene, L.; Meneghin, F.; DiLillo, D.; et al. Birth Weight and the Development of Functional Gastrointestinal Disorders in Infants. Pediatr. Gastroenterol. Hepatol. Nutr. 2020, 23, 366–376, doi:10.5223/pghn.2020.23.4.366.

47. Salvatore, S.; Barberi, S.; Borrelli, O.; Castellazzi, A.; Di Mauro, D.; Di Mauro, G.; Doria, M.; Francavilla, R.; Landi, M.; Martelli, A.; et al. Pharmacological interventions on early functional gastrointestinal disorders. Ital. J. Pediatr. 2016, 42, 1–8, doi:10.1186/s13052-016-0272-5.

48. Nelson, S.P.; Chen, E.H.; Syniar, G.M. Prevalence of symptoms of gastroesophageal reflux in infancy. Arch. Pediatr. Adolesc. Med. 1997, 151, 569–572.

49. Hegar, B.; Dewanti, N.R.; Kadim, M.; Alatas, S.; Firmansyah, A.; Vandenplas, Y. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009, 98, 1189–1193, doi:10.1111/j.1651-2227.2009.01306.x.

50. Salvatore, S.; Vandenplas, Y. Epidemiology. In Gastroesophageal Reflux in Children; Vandenplas, Y., Ed.; Springer: Cham, Switzerland, 2017, doi:10.1007/978-3-319-60678-1_1.

51. Salvatore, S.; Hauser, B.; Vandemaele, K.; Novario, R.; Vandenplas, Y. Gastroesophageal reflux disease in infants, how much is predictable with questionnaires, pH-metry, endoscopy and histology? J. Pediatr. Gastroenterol. Nutr. 2005, 40, 210–215.

52. Orenstein, S.R.; Hassall, E.; Furmaga-Jablonska, W.; Atkinson, S.; Raanan, M. Multicenter, double-blind, randomized, place-bo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gas-troesophageal reflux disease. J. Pediatr. 2009, 154, 514–520.

53. Salvatore, S.; Arrigo, S.; Luini, C.; Vandenplas, Y. Esophageal Impedance in Children: Symptom-Based Results. J. Pediatr. 2010, 157, 949–954.e2, doi:10.1016/j.jpeds.2010.07.029.

54. Vandenplas, Y.; Goyvaerts, H.; Helven, R.; Sacre, L. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. Pediatrics 1991, 88, 834–840.

55. A.; Gilger, M.; El-Serag, H.B.; Gold, B.D.; Dietrich, C.L.; Tsou, V.; McDuffie, A.; Shub, M.D. Prevalence of Endoscopic Find-ings of Erosive Esophagitis in Children: A Population-based Study. J. Pediatr. Gastroenterol. Nutr. 2008, 47, 141–146, doi:10.1097/mpg.0b013e31815eeabe.

56. Volonaki, E.; Sebire, N.J.; Borrelli, O.; Lindley, K.J.; Elawad, M.; Thapar, N.; Shah, N. Gastrointestinal endoscopy and muco-sal biopsy in the first year of life, indications and outcome. J. Pediatr. Gastroenterol. Nutr. 2012, 55, 62–65, doi:10.1097/mpg.0b013e3182478f83.

57. Salvatore, S.; Ripepi, A.; Huysentruyt, K.; Van De Maele, K.; Nosetti, L.; Agosti, M.; Salvatoni, A.; Vandenplas, Y. The Effect of Alginate in Gastroesophageal Reflux in Infants. Pediatr. Drugs 2018, 20, 575–583, doi:10.1007/s40272-018-0314-0.

58. Salvatore, S.; Pagliarin, F.; Huysentruyt, K.; Bosco, A.; Fumagalli, L.; Van De Maele, K.; Agosti, M.; Vandenplas, Y. Distress in Infants and Young Children, Don’t Blame Acid Reflux. J. Pediatr. Gastroenterol. Nutr. 2020, 71, 465–469, doi:10.1097/mpg.0000000000002841.

59. Schoemaker, A.A.; Sprikkelman, A.B.; Grimshaw, K.E.; Roberts, G.; Grabenhenrich, L.; Rosenfeld, L.; Siegert, S.; Dubakiene, R.; Rudzeviciene, O.; Reche, M.; et al. Incidence and natural history of challenge-proven cow’s milk allergy in European chil-dren—EuroPrevall birth cohort. Allergy 2015, 70, 963–972.

60. Saarinen, K.M.; Juntunen-Backman, K.; Järvenpää, A.-L.; Klemetti, P.; Kuitunen, P.; Lope, L.; Renlund, M.; Siivola, M.; Vaar-ala, O.; Savilahti, E. Breast-Feeding and the Development of Cows’ Milk Protein Allergy. Adv. Exp. Med. Biol. 2000, 478, 121–130, doi:10.1007/0-306-46830-1_10.

61. Meyer, R.; Chebar Lozinsky, A.; Fleischer, D.M.; Vieira, M.C.; Du Toit, G.; Vandenplas, Y.; Dupont, C.; Knibb, R.; Uysal, P.; Cavkaytar, O.; et al. Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants-An EAACI Position Paper. Allergy 2020, 75, 14–32.

62. Hait, E.J.; McDonald, D.R. Impact of Gastroesophageal Reflux Disease on Mucosal Immunity and Atopic Disorders. Clin. Rev. Allergy Immunol. 2019, 57, 213–225, doi:10.1007/s12016-018-8701-4.

63. Nowak-Wegrzyn, A.; Chehade, M.; Groetch, M.E.; Spergel, J.M.; Wood, R.A.; Allen, K.; Atkins, D.; Bahna, S.; Barad, A.V.; Berin, C.; et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome, executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Al-lergy, Asthma & Immunology. J. Allergy Clin. Immunol. 2017, 139, 1111–1126.

64. Labrosse, R.; Graham, F.; Caubert, J.C. Non-IgE-mediated gastrointestinal food allergies in children, an update. Nutrients 2020, 12, 2086.