

Malattia da reflusso gastroesofageo

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UO Gastroenterologia ed Endoscopia Digestiva Clinica Pediatrica Università di Brescia Ospedale dei Bambini, Brescia PEDIATRIC GERD – OUTLINE
1. DEFINITIONS
2. NATURAL HISTORY
3. CURRENT APPROACH
4. GERD AND EOE
5. INVESTIGATIONS
6. TREATMENT



Definitions

Gastro-esophageal reflux (GER)	Passage of gastric contents into the esophagus, with or without regurgitation and vomiting
Gastro-esophageal reflux disease (GERD)	GER leading to troublesome symptoms that affect daily functioning and/or complications
Pharyngo-laryngeal reflux (PLR)	Passage of gastro-esophageal refluxate into the larynx

GER vs. GERD: the challenges



- Wide variety of clinical presentations by age
- Manifestations are neither sensitive nor specific
- Cause-effect relationship between reflux events and clinical manifestations is often difficult to prove
- No 'gold standard' test

Infant regurgitation



Infants 3 weeks-12 months: •Regurgitation $\geq 2/day$ for \geq 3 weeks •No retching (vomiting!), hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

(Benninga MA, Nurko S, et al – Rome IV, Gastroenterology 2016)

Table II.Functional GI disorder prevalence in infants andtoddlers according to Rome III and Rome IV criteria

Diagnoses	Rome IV, N (%)	Rome III*
Infants (N = 58)		
Infant regurgitation	14 (24.10%)	25.90%
infant colic	3 (5.20%)	5.90%
Infant dyschezia	0 (0%)	2.40%
Cyclic vomiting syndrome	1 (1.70%)	0.00%
Rumination	1 (1.70%)	2.40%
Functional constipation	7 (12.10%)	4.70%
Functional diarrhea	0 (0%)	2.40%
At Least 1 functional GI disorder (infants)	22 (37.90%)	27.10%
Toddlers (N = 238)	. , ,	
Cyclic vomiting syndrome	5 (2.10%)	3.40%
Rumination	5 (2.10%)	1.90%
Functional constipation	44 (18.50%)	9.40%
Functional diarrhea	0 (0.00%)	6.40%
At least 1 functional GI disorder (toddlers)	51 (21.40%́)	Not reported

(Van Tilburg MAL, J Pediatr 2015; Robin SG, J Pediatr 2018)

Prevalence of regurgitation in infancy



(Nelson SP, Arch Pediatr Adolesc Med 1997; Martin AJ, Pediatrics 2002)

Symptoms and signs associated with GERD in infants and children (I)

- Gastrointestinal
 - Regurgitation/vomiting
 - Heartburn/chest pain
 - Epigastric pain
 - Dysphagia, odynophagia
 - Hematemesis
 - Esophagitis
 - Esophageal stricture
 - Barrett's esophagus



- General
 - Discomfort
 - Irritability
 - Feeding refusal
 - Failure to thrive
 - Sandifer syndrome
 - Dental erosions
 - Anemia

Symptoms and signs associated with GERD in infants and children (II)

- Respiratory
 - Wheezing
 - Asthma
 - Stridor
 - Cough
 - Hoarseness
 - Apnea spells, BRUE
 - Aspiration pneumonia
 - Recurrent otitis media



Alarm features in infants and children with regurgitation

- Late onset regurgitation
- Bilious vomiting
- Weight loss
- Hematemesis
- Rectal bleeding
- Chronic diarrhea
- Abdominal distension
- Dysuria

- Lethargy
- Fever
- Excessive irritability/pain
- Bulging fontanelle
- Macro/microcephaly
- Seizures
- Chronic forceful vomiting
- Nocturnal vomiting

(Hyams JS, Di Lorenzo C, et al – Rome IV, Gastroenterology 2016)

Is infantile regurgitation always a self-limiting condition?



Infant regurgitation: follow-up



- 693 Australian children with infant regurgitation
- 9 year follow-up
- 19.2% had ≥1 GERD symptom
- RR for \geq 3 months spilling
 - acid regurgitation 4.7
 - heartburn 4.6
 - vomiting 2.7

(Nelson SP, J Pediatr Gastroenterol Nutr1999; Martin AJ, Pediatrics 2002)

GERD from childhood to adult age

GERD No GERD



(Waring JP, J Pediatr Gastroenterol Nutr 2002)

Who is at risk?



Conditions predisposing to complications of GERD



- Neurological impairment
- Cystic fibrosis
- Repaired esophageal atresia
- Repaired achalasia
- Hiatus hernia
- Obesity
- Lung transplantation
- Family history

Erosive esophagitis in childhood as risk factor for chronic GERD

- 222 children 5-17 y.o. with erosive esophagitis
- Exclusion criteria
 - neurological impairment
 - cystic fibrosis
 - esophageal atresia \pm TEF
 - severe co-morbid illness
- Follow-up ≥ 5 years



(El-Serag HB, Am J Gastroenterol 2004)

Severe GERD in childhood



402 children with GERD

- Poor correlation between type/severity of symptoms and esophagitis/Barrett's
- Long duration of GERD symptoms is a strong risk factor for complications
 - Barrett's esophagus
 - esophageal adenocarcinoma

(Eisen JM, Am J Gastroenterol 1997; Niemantsverdriet EC, Eur J Gastroenterol Hepatol 1997; Lagergren J, N Engl J Med 1999; El-Serag HB, Am J Gastroenterol 2002) Society Paper

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

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Eosinophilic esophagitis (EoE)

Chronic, local, immunemediated esophageal disease, characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation. Clinical manifestations or pathologic data should not be interpreted in isolation

(Lucendo AJ, et al – EUREOS Guidelines on eosinophilic esophagitis, UEGJ 2017)

Evolutionary pattern of clinical symptoms in esophageal disease

Vomiting, Feeding problems

GERD

EOSINOPHILIC ESOPHAGITIS

ACHALASIA

Esophageal stricture

Eosinophilic esophagitis vs. GERD

	Eosinophilic esophagitis	GER disease
Sex	mostly male	$\mathbf{M} = \mathbf{F}$
Atopy	common	= controls
Regurgitation	common	common
Food impaction	common	rare
pH monitoring	normal	abnormal
Endoscopy	furrows, plaques, rings	normal or erosions
Eosinophils	≥15/HPF	<10/HPF
PPI's	ineffective	effective

EOSINOPHILI C ESOPHAGITIS

1993 ROESOPHA

EOSINOPHILIC ESOPHAGITIS RESPONSIVE TO ANTI-REFLUX THERAPY

2015

GASTROESOPHAGEAL REFLUX DISEASE NOT RESPONSIVE TO ANTI-REFLUX THERAPY

PPI-reversible allergic inflammation

Down-regulation of eotaxin-3 and Th2 cytokines overexpression (PPI-REE)

PPI-REE = EoE: CCL26 (eotaxin-3), DSG1 (barrier), MUC4 (IL-13), CPA3 (mast cells), POSTN (periostin)

(Molina-Infante J, Aliment Pharmacol Ther 2014; Wen T, J Allergy Clin Immunol 2015)

Major causes of esophageal dysphagia

Patients more likely to have EoE

- Infant with regurgitation and/or feeding problems not responsive to hydrolysate or anti-reflux therapy
- Child with GERD symptoms not responsive to PPI's
- Child and adolescent with dysphagia for solid foods, especially if atopic

Which test, when and for whom?

- The diagnosis of GERD is based on clinical suspicion
- The main tests are aimed to quantify and qualify GERD
- Other investigations may be utilized to rule out other conditions

(NASPGHAN/ESPGHAN Pediatric GER clinical practice guidelines, J Pediatr Gastroenterol Nutr 2009/2018)

Investigation of gastroesophageal reflux

Test	Advantages	Disadvantages
Endoscopy evidence (esophag	Visual and histological gitis)	Requires sedation Does not detect reflux
pH-impedance monitoring	Quantifies acid and non-acid reflux Correlation with clinical symptoms	Invasive. Poor reproducibility Normal values unclear
Manometry aspects and pathop	Information on functional physiology	Invasive and cumbersome Does not indicate reflux
Scintigraphy Measurement of g	Detects aspiration & non-acid reflux astric emptying	Study of short duration Lacks standardization
Barium meal	Information on GI anatomy	Low accuracy
Ultrasonography Measurement of g	Detects conditions mimicking GERD astric emptying	Very low specificity Does not indicate GERD

Therapy of GERD

Pharmacological therapy of GERD

PROLONGED CONTROL

OFACID SECRETION

AND PREVENTION OF

- Anti-secretory agents
 - PPI (OME 0.5-3.7 mg/kg/day)
 - 1-2 doses
 - H₂ receptor blockers (RAN 5-20 mg/kg/day)
 - 2-3 doses
- Alginate
- Sucralfate
- Prokinetic drugs
 - Domperidone (0.4-2 mg/kg/day)
 - 20-30 min. before meals

Efficacy of PPI's in infantile GERD (FDA review)

- Four blinded controlled trials
- Infants 1-12 mos.
 35-80 per arm
- Clinical diagnosis of GERD
- Assessment by parent/physician questionnaire

PI medication	Primary efficacy result relative to control
someprazole	Hazard ratio 0.69 (PPI/placebo)
54 C	95% CI 0.35-1.35
	(P = 0.275)
ansoprazole	Responder rate (PPI vs placebo)
2.52	54.3% (44/81) vs 54.3% (44/81)
	(P = 1.000)
antoprazole	Responder rate (PPI vs placebo)
	12% (6/52) vs 11% (6/54)
	(P = 1.000)
Omeprazole	Adjusted LS means (ANCOVA)*:
	0.5 mg/kg dose -4.34 (-8.5 to -0.15)
	1.0 mg/kg dose $-2.97 (-7.0 to 1.06)$
	1.5 mg/kg dose $-4.35 (-8.2 to -0.46)$
	(All pairwise comparisons to 0.5 mg/kg dose had $P > 0.50$)

(Chen IL, J Pediatr Gastroenterol Nutr 2012)

Infant irritability and GERD

- Rule out milk allergy, neurological problems, constipation, infection...
- GERD should not be considered in the absence of typical symptoms
- Trial with anti-secretory drugs unjustified
- Hydrolized or aminoacid-based formula reasonable in selected cases

(NASPGHAN/ESPGHAN Pediatric GER clinical practice guidelines, J Pediatr Gastroenterol Nutr 2009/2018)

Anti-secretory therapy and risk of community-acquired infections

Characteristics	Controls (a — 95)	GA inhibitors (a — 91)
Age, median, mo (IQR)	10 (8–15)	10 (8–16)
Viale, n (%)	50 (53)	48 (53)
Weight, median, kg (IQR)	9.3 (8–10)	9.1 (8–15)
ength, median, cm (IQR)	74 (70–78)	74 (70–80)
Patients presenting with	17 (18)	18 (20)
Acute gastroenteritis in the previous 4 mo, n (%)		
Acute gastroenteritis in the follow-up period, n (%)	19 (20)	43 (47) ^{a,b}
Pneumonta in the previous 4 mo, n (96)	1(1)	3 (3)
Pneumonia in the follow-up period, n (96)	2 (2)	11 (1 <i>2)</i> #/6
P < .05 GA inhibitor users versus control children.	2 (2)	11 (12)

Probiotics in pediatric GERD

128 children with GERD, randomized to *L. reuteri* or placebo during a 12 wk PPI course, evaluated with glucose hydrogen breath test to detect small bowel bacterial overgrowth

(Belei O, J Neurogastroenterol Motil 2018)

Anti-reflux surgery

• Indications:

- failure of optimized medical therapy
- dependence on long-term medical therapy
- non-compliance with medical therapy
- life-threatening complications (aspiration)
- established primary GERD!
- [↑] Morbidity, mortality, failure rate:
 - CNS disease, chronic lung disease, operated esophageal atresia, etc.

(NASPGHAN/ESPGHAN Pediatric GER clinical practice guidelines, J Pediatr Gastroenterol Nutr 2009/2018)

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Childhood GERD in perspective

- Identify children at risk for complications
- Continue to reassess the at-risk patients

 complications may be insidious
- Decide about the relevance of long-term therapy

 medical vs. surgical
- Transition to internist or adult gastroenterologist

i.e.: Treat (true) GERD as a lifelong disease

