



Gastro-esophageal reflux disease (GERD) Consensus and Controversies

IPS 2011



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Universitair
Kinderziekenhuis
Brussel



- Introduction
- Symptoms and age
- Diagnostic investigations
- Management
 - The infant and young child
 - The older child
- Special groups
- Conclusion

NASPGHAN-ESPGHAN Guidelines for Evaluation and Treatment of Gastro-Esophageal Reflux in Infants and Children

*Y. Vandenplas, C. Rudolph, G. Liptak, M. Lynette, C. Di Lorenzo, E. Hassall,
J. Sondheimer, M. Thomson, A. Staiano, G. Veereman, T. Wenzl
J Pediatr Gastroenterol Nutr 2009;49:498-547*

*R. Rosen, Y. Vandenplas, C. Di Lorenzo, A. Staiano, N. Thapar, M. Tabbers, M. Singendonck,
M. Langendam, F. Gottrand, TA Neelesh , SK Gupta, M. Cabana
J Pediatr Gastroenterol Nutr 2017*

Gastroesophageal reflux: management guidance for the pediatrician.

*Lightdale JR, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition.
Pediatrics. 2013;131:e1684-95*

*This clinical report endorses the rigorously developed,
well-referenced North American Society for Pediatric Gastroenterology,
Hepatology, and Nutrition guidelines and
likewise emphasizes important concepts for the general pediatrician.*

European pediatricians' approach to children with GER symptoms: survey on the implementation of 2009 NASPGHAN-ESPGHAN Guidelines. Quitadamo P. JPGN. 2014;59:356-9.

*The overall results of our survey show that the **majority of pediatricians are unaware of 2009 NASPGHAN-ESPGHAN guidelines** and often prescribe PPIs despite a lack of efficacy for the symptoms being treated.*

The over diagnosis of GERD places undue burden on both families and national health systems which has not been impacted by the publication of international guidelines.

*Influence of "GERD" label on parents' decision to medicate infants.
Scherer LD. Pediatrics 2013;131:839-45*

Parents who received a GERD diagnosis were interested in medicating their infant, even when they were told that the medications are likely ineffective. However, parents not given a disease label were interested in medication only when medication effectiveness was not discussed (and hence likely assumed)

Labeling an otherwise healthy infant as having a "disease" increased parents' interest in medicating their infant . Also when they were told that medications are ineffective.

These findings suggest that use of disease labels may promote overtreatment by causing people to believe that ineffective medications are both useful and necessary



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Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy

Nelson SP. J Med Eco 2009;12:348-55.

- *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	1999	31.5%
	2005	62.6%

when compared with H²RA-initiated patients

- associated with 30% less discontinuation
- 90% less therapy switching in 1st month
- higher comorbidity burden
- pre-treatment total HCU
- costs when diagnosed

Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(3)

Martigne L. Eur J Pediatr 2012;171:1767-73.

Prevalence of GER in France according to age

	0-23 month	2-11 year	12-17 year	Total
Extrapolation to French population	24.4%	7.2%	10.7%	10.3%
GER symptoms				
	0-23 month	2-11 year	12-17 year	
Mean duration (month)	4.4	20.9	21.8	
Typical symptoms				
Regurgitation	85% ^{BC}	36%	33%	
Vomiting	26% ^C	32% ^C	13%	
Crying	45% ^{BC}	-	-	
Heartburn	-	37% ^A	86% ^{AB}	
Atypical symptoms				
Feeding difficulties, anorexia	42% ^{BC}	-	-	
Failure to thrive	6% ^{BC}	-	-	
Postural defects	8% ^{BC}	-	-	
Stridor	10% ^{BC}	4% ^C	<1%	
Chronic cough	6% ^{BC}	68% ^{AC}	33% ^A	
Laryngitis, otitis	-	35% ^{AC}	12% ^A	
Asthma	-	24% ^{AC}	15% ^A	
Sinusitis	-	2% ^{AC}	6% ^A	

Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of NASPGHAN and ESPGHAN

Vandenplas Y. J Pediatr Gastroenterol Nutr 2009;49:498-547

‘Typical Reflux Syndrome’ cannot be diagnosed
in infants and children who lack
the cognitive ability to reliably report symptoms.

*Children < 8 (... up to 11) years old
cannot report symptoms
in a reliable / reproducible way*



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Statement 4 (2017 Guidelines)

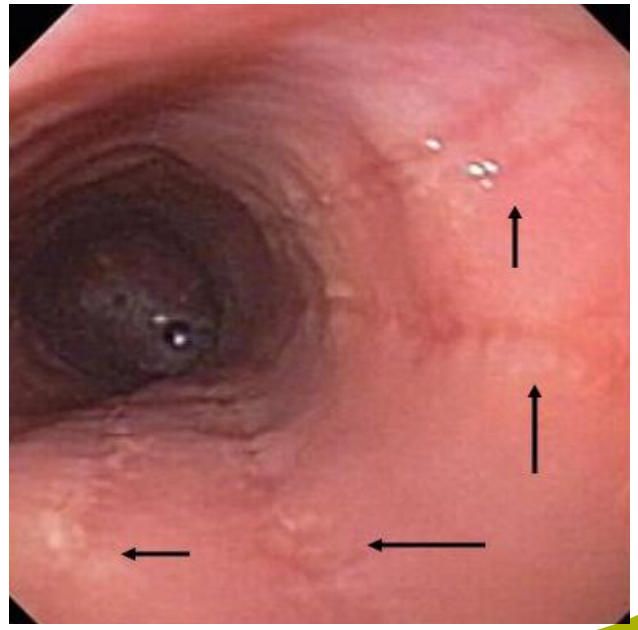
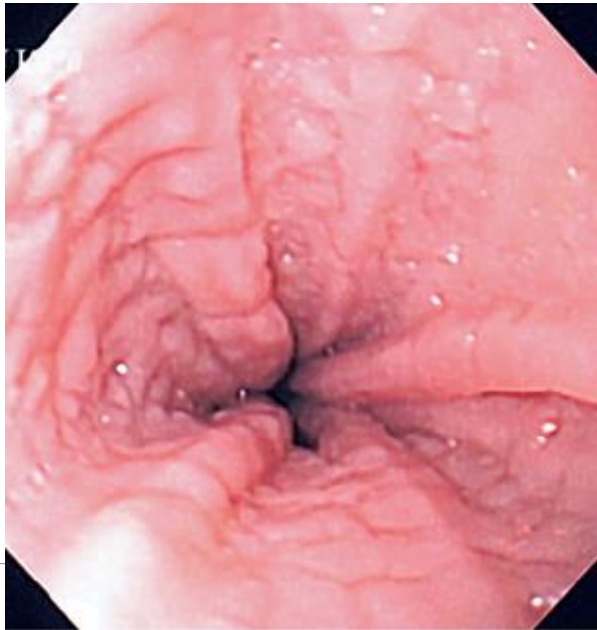
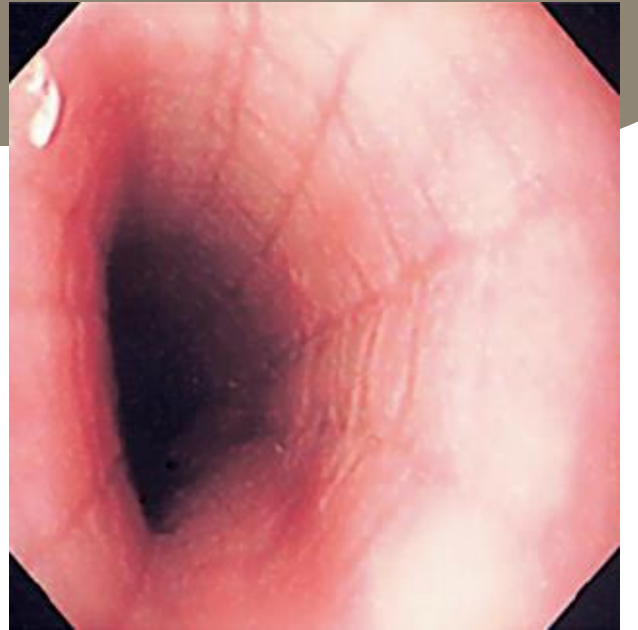
Esophago-Gastro-Duodenoscopy :

*The working group suggests **not** to use EGD for diagnosing GERD in infants and children.*

VOTING: 7, 8, 8, 8, 9, 9, 9, 9, 9, 9

Based on expert opinion, the working group suggests to use EGD with biopsies to assess complications of GERD, in case an underlying mucosal disease is suspected and prior to escalation of therapy.

VOTING: 6, 8, 8, 9, 9, 9, 9, 9, 9, 9



*Comparison of **UGI contrast studies** and pH/impedance tests for the diagnosis of childhood GER.*

Macharia EW. Pediatr Radiol. 2012;42:946-51

retrospective, compared

*UGI studies
pH/impedance tests.*

*GER UGIS: 116 / 579 children (20%)
66 also underwent a pH/impedance test*

Using pH/impedance tests as the reference for GER,

UGIS sensitivity of 42.8%

negative predictive value of 24%

No significant correlation ($P > 0.05$) between the reflux index and the number of reflux episodes in the pH/impedance tests and height of reflux in the UGI study

pH < 4 why ??

pH < 4: corresponds best with “pyrosis”

pH monitoring:

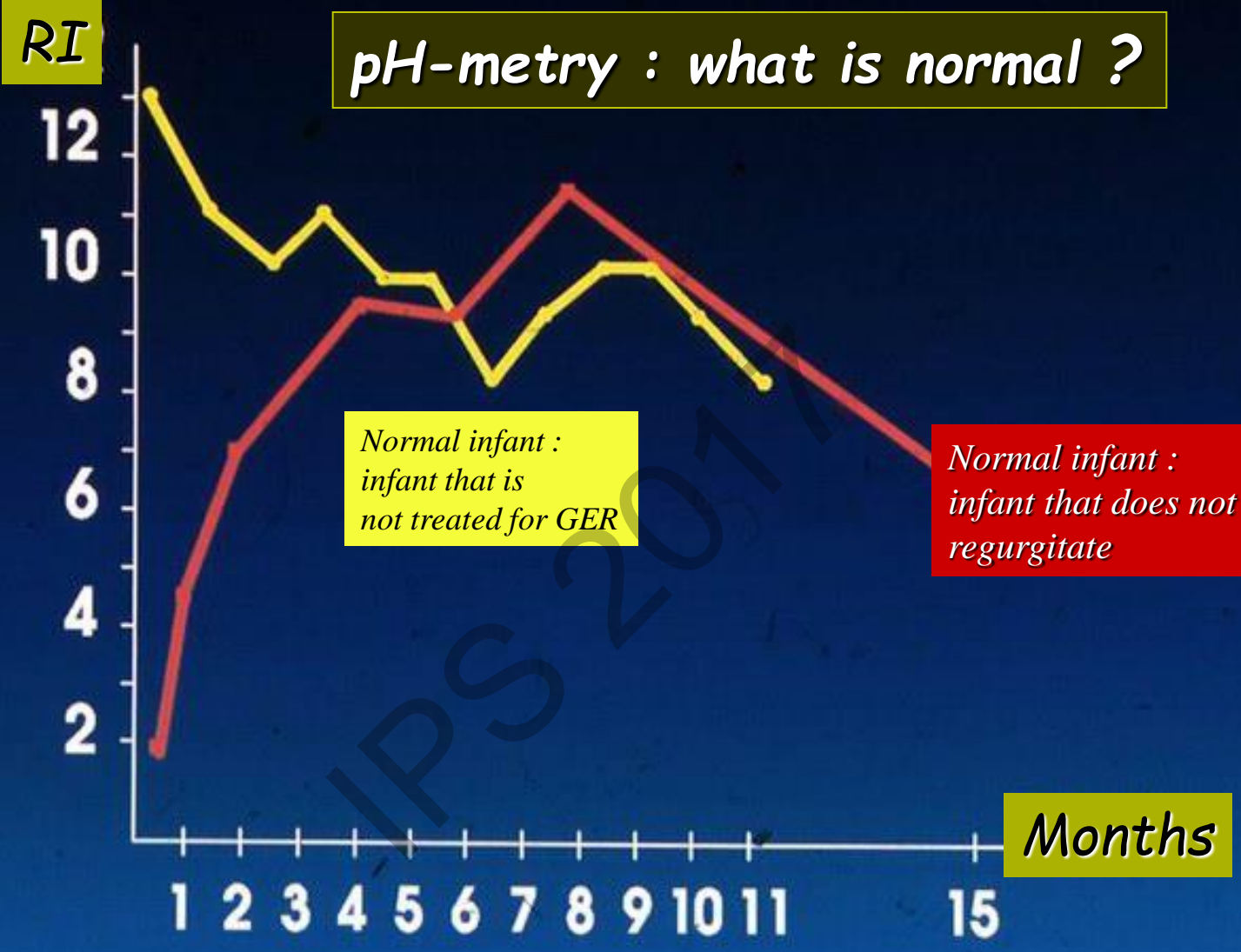
developed to diagnose GER(D)

in adults with “heartburn”

without cardiac reason for the heartburn

⇒ to diagnose “Non-Erosive Reflux Disease”

.... The technique has been used in many indications for which it was not developed



Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old.
 Vandenoop Y.J *Pediatr Gastroenterol Nutr.* 1987;6:220-4

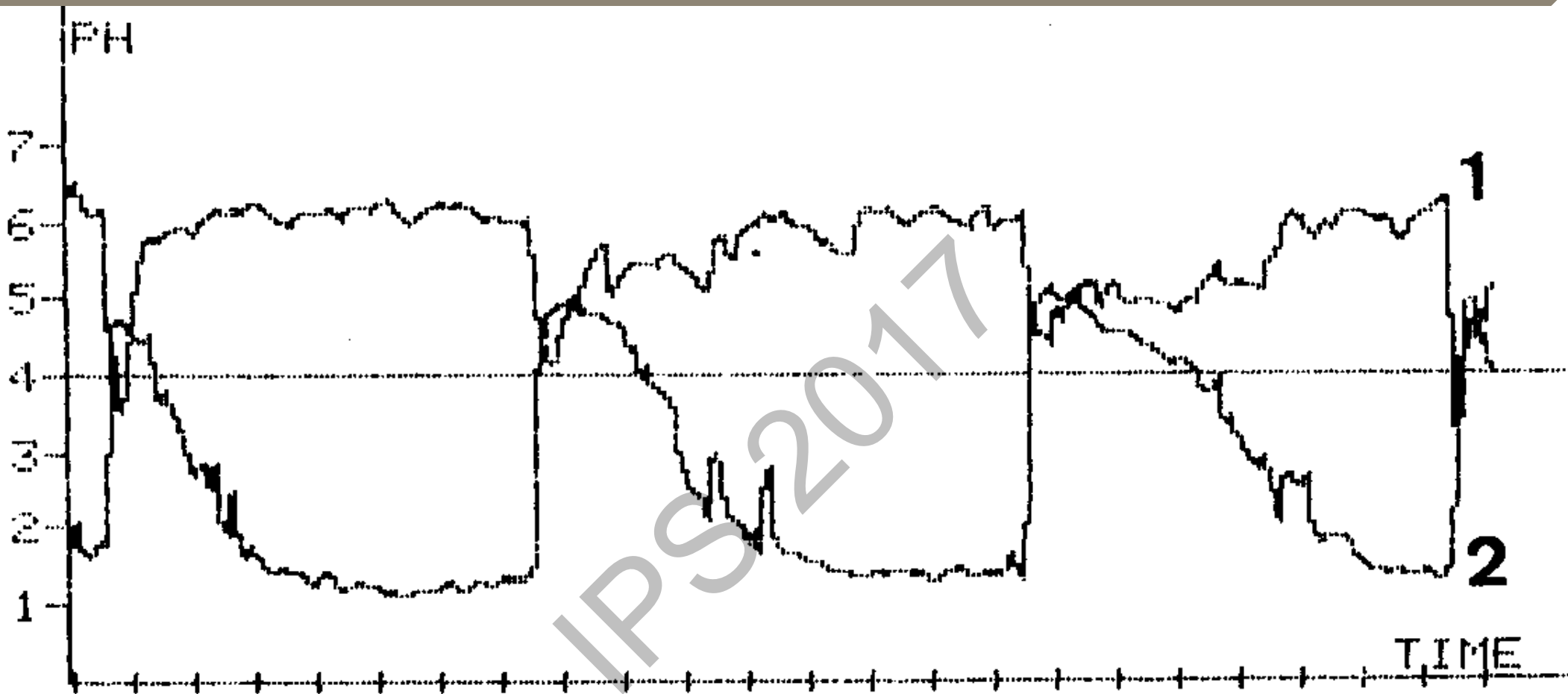
Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of SIDS
 Vandenoop Y. *Pediatrics.* 1991;88:834-40

*Ambulatory oesophageal pH monitoring:
a comparison between antimony, ISFET, and glass pH electrodes.
Hemmink GJ. Eur J Gastroenterol Hepatol. 2010;22:572-7*

*During in-vivo experiments,
significant differences were found
in acid exposure times derived from*

<i>antimony</i>	<i>4.0 +/- 0.8%</i>
<i>ISFET</i>	<i>5.7 +/- 1.1%</i>
<i>glass pH electrodes</i>	<i>9.0 +/- 1.7%</i>

*A comparative study between glass and antimony electrodes
for continuous oesophageal pH monitoring.
Vandenplas Y. Gut 1991;32:708-712*



IMPEDANCE: more data ...more useful ?

MII vs pH-study :
It is more than graph*ic* difference !

- *All kind of reflux - acid, non-acid
- liquid, gas, mixed*
- *Number and % of time of reflux episodes*
- *(Height of) proximal migration of reflux*
- *time of bolus exposure*
- *reflux and bolus clearance time*
- *Symptom-reflux correlation*

Low mean impedance in 24-hour tracings and esophagitis in children: a strong connection.

Salvatore S. Dis Esophagus. 2016;29:10-4

Data adjusted for age through z-score transformation using percentiles normalized by the LMS (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation) method.

298 impedance tracings were analyzed.

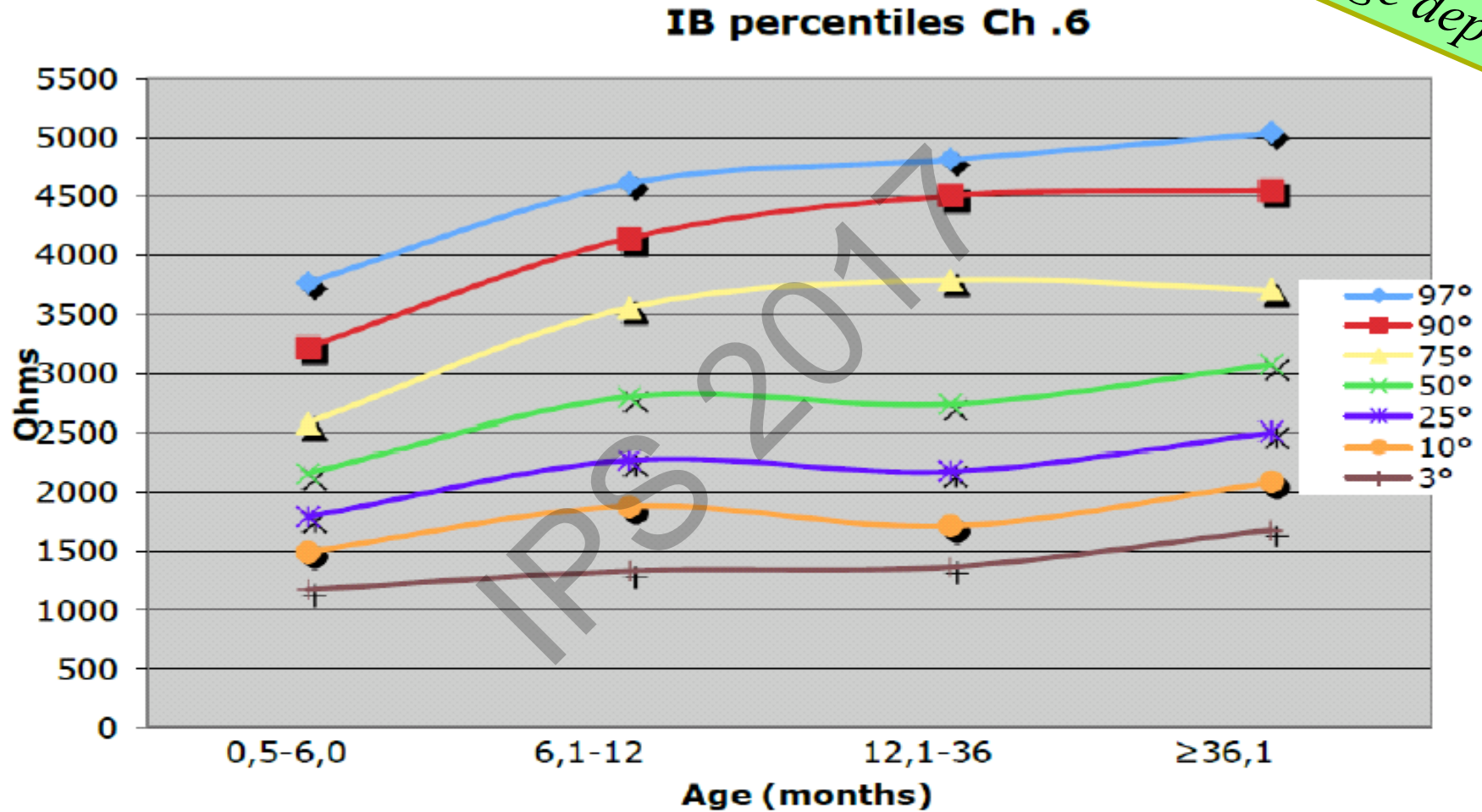
*Esophagitis endoscopic 30%
 histological 29%*

- *Median baseline z-score was significantly decreased both in proximal ($P = 0.02$) and distal ($P = 0.01$) esophagus in patients with endoscopic (but not histological) esophagitis.*
- *Patients with more severe esophagitis showed the lowest z-score.*
- *Bolus exposure index and the number of reflux episodes were the variables that were significantly associated with the baseline z-score.*

Esophageal impedance baseline is age-dependent

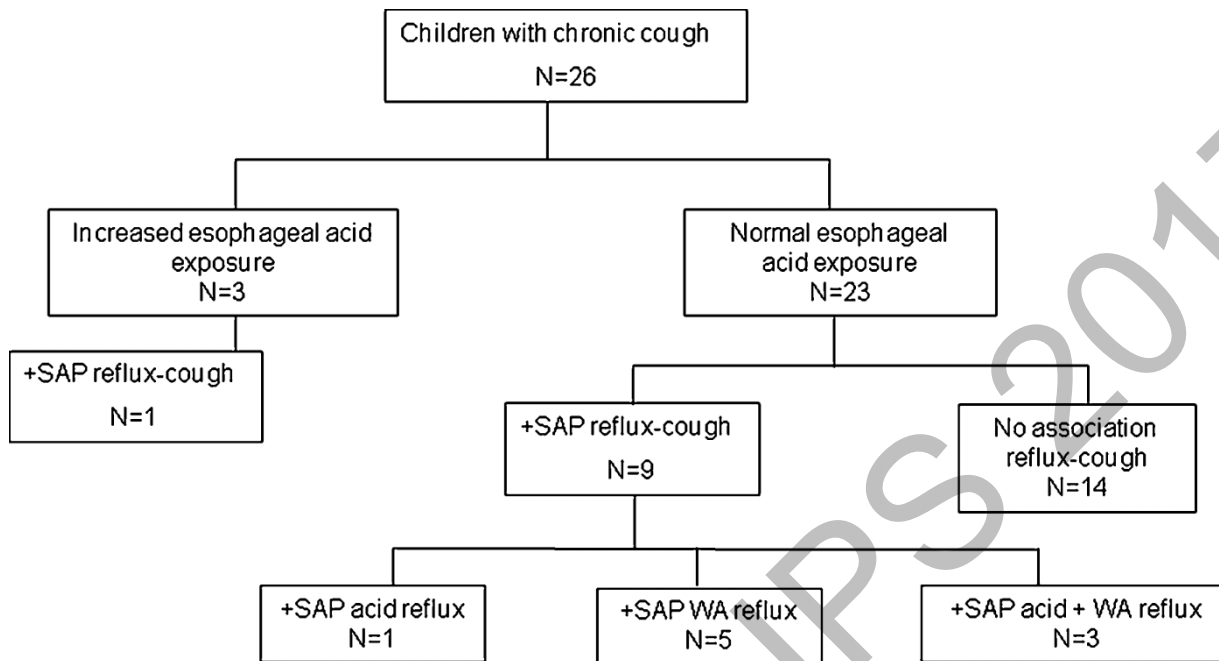
Salvatore S. *JPGN* 2013;57:506-13.

Baseline = age dependent



The relationship between GER and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings.

Blondeau K. Pediatr Pulmonol. 2011;46:286–294



Both acid and WA GER may precede cough in children with unexplained cough, but cough does not induce GER.

Objective cough recording improves symptom association analysis

Esophageal impedance in children: symptom-based results

S. Salvatore *J Pediatr* 2013

No treatment !!!!

Reflux episodes in relation with the 3 age groups and the 3 predominant symptoms.

ITEM	CRYING			COUGH			VOMITING		
	1-6mo	6-12mo	>12mo	1-6mo	6-12mo	>12mo	1-6mo	6-12mo	>12mo
No. patients	37	30	21	31	34	37	22	15	11
No. events	456	279	137	338	311	326	115	53	61
Median	11	6	5	9	7	4	4	2	1
GER related (%)	44	44	50	56	58	43	90	87	75
AR associated (%)	36	57	43	29	60	57	20	52	76
WAR associated (%)	62	42	54	69	39	34	69	46	22
AlkR associated (%)	2	1	3	2	2	9	11	2	2

AR & WAR = age dependent

Gastroesophageal reflux disease and childhood asthma.

Blake K. Curr Opin Pulm Med. 2013;19:24-9

Clinical studies show that GERD is highly prevalent in children with asthma, with estimates as high as 80%, but nearly half of the children are asymptomatic. However, there is no conclusive evidence per se that asymptomatic GERD informs asthma control, and treatment of GERD in the few controlled trials available for review does not substantively improve asthma outcomes. In a recent large controlled clinical trial, treatment with a PPI was not only ineffective, but adverse effects were common, including an increased prevalence of symptomatic respiratory infections.

Current evidence does not support the routine use of anti-GERD medication in the treatment of poorly controlled asthma of childhood.

<u>Techniques</u>	<u>Indication</u>
1. Questionnaires	1 st to do, but.... limitations
2. Radiology	anatomy
3. Scintigraphy	respiratory symptoms ?
4. Ultrasound	??
5. Endoscopy (+ biopsy)	Esophagitis
6. Manometry	Pressure, motility
7. pH metry	⇒ acid GER
8. Impedance-metry	⇒ acid & non-acid GER
9. Therapeutic trial	no data in children



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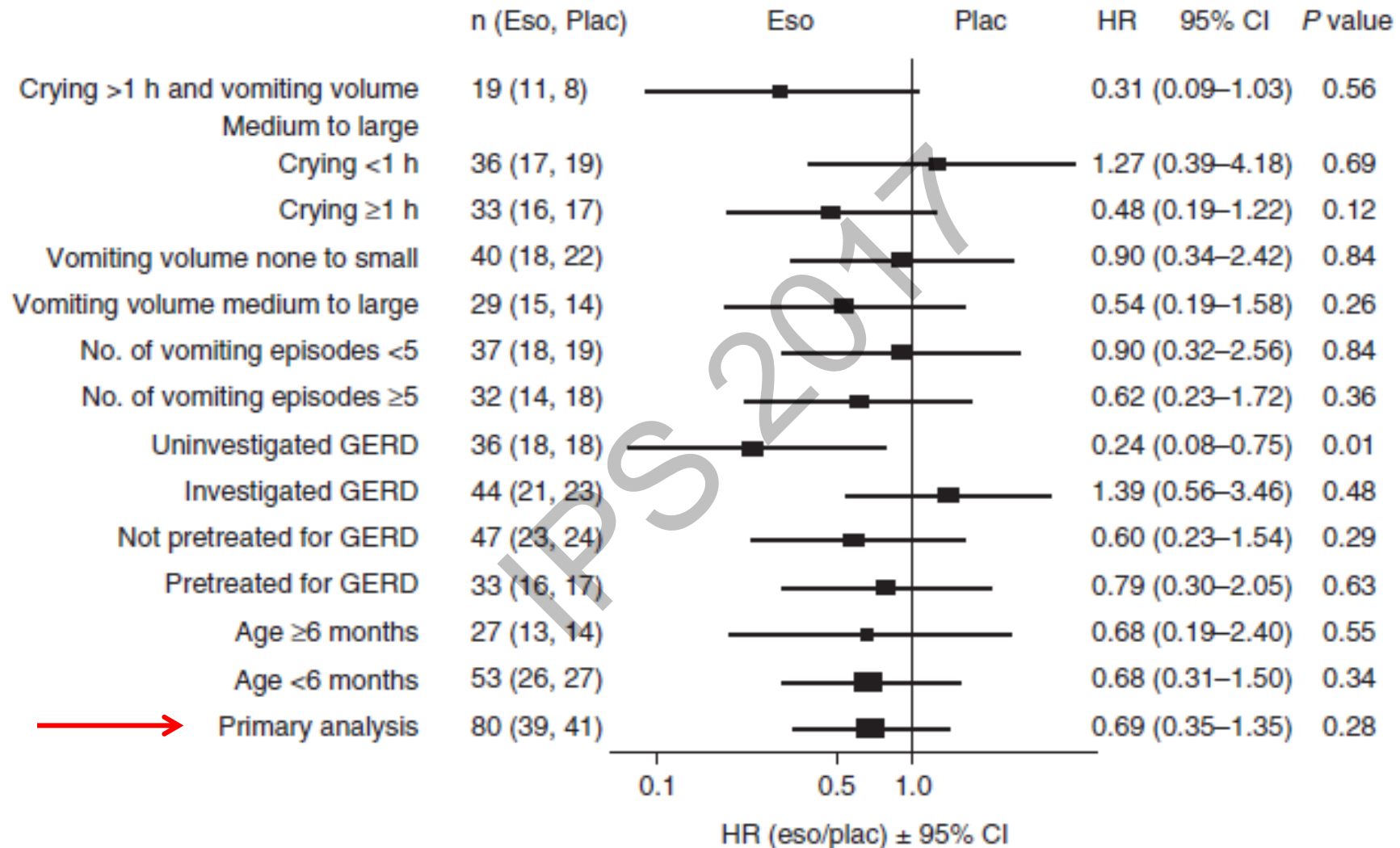
Changes in prescription patterns of acid-suppressant medications by Belgian pediatricians: analysis of the national database [1997-2009].

De Bruyne P. J Pediatr Gastroenterol Nutr. 2014;58:222-7

- increased 7-fold from 20,782 daily defined doses (DDDs) in January 1997 to 142,912 DDDs in June 2009.
- During this study period, reimbursed volume of H2-RAs increased from 2575 to 38,996 DDDs and of PPIs from 3472 to 103,926 DDDs per month.

Esomeprazole for the treatment of GERD in infants ages 1-11 months.

Winter H. *J Pediatr Gastroenterol Nutr.* 2012;55:14-20



Clinical predictors of pathological GER in infants with persistent distress

Heine RG. *J Paediatr Child Health*. 2006;42:134-9

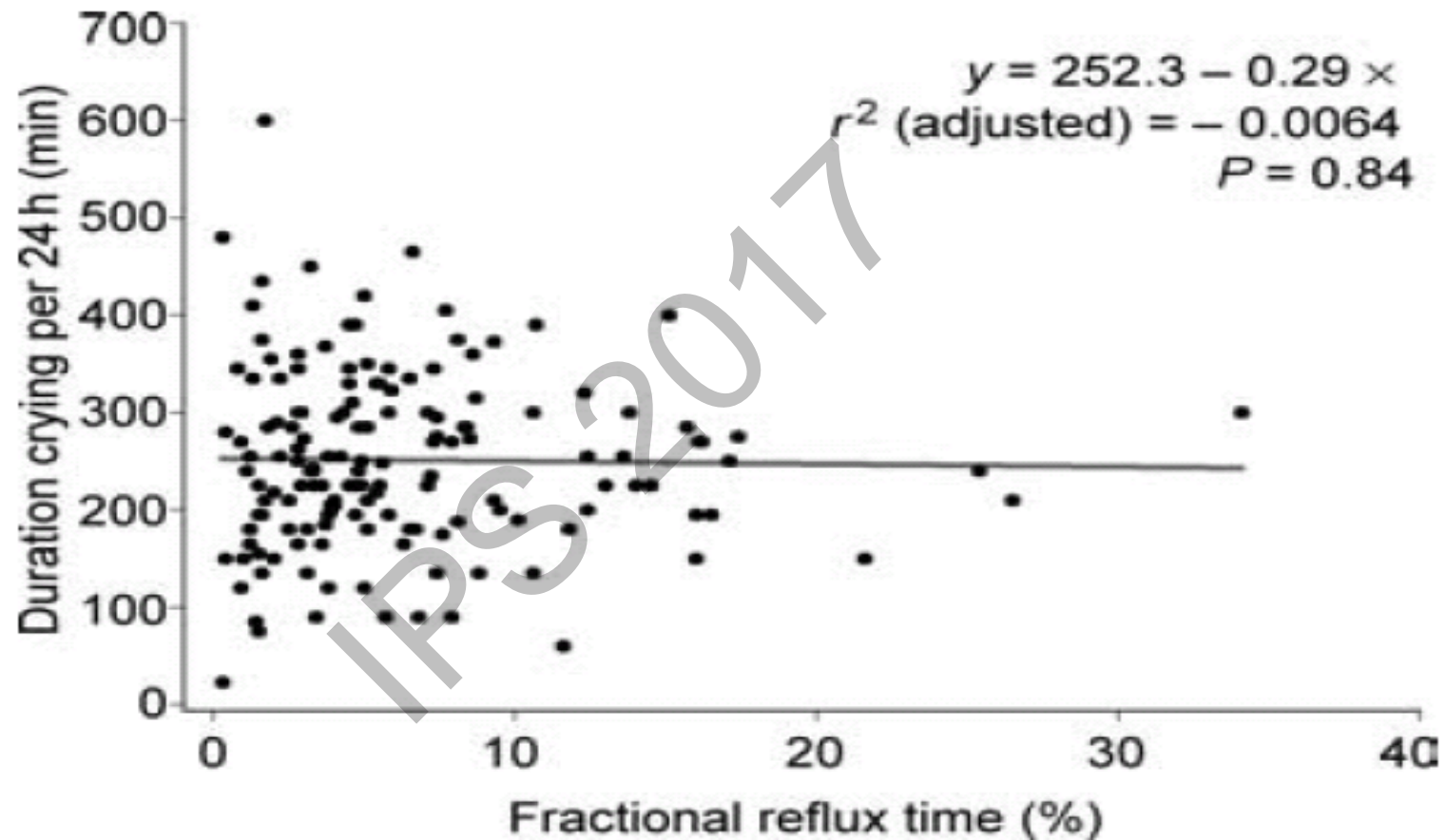


Fig. 1 Linear regression analysis of fractional reflux time in relation to duration of crying per 24 h.

PPI: side effects

- bacterial overgrowth (dysbiosis, ↓ diversity)
- community-acquired pneumonia (children, adults)
- gastroenteritis (children)
- clostridium difficile infection
- Vit B12 deficiency
- candidemia (preterms)
- necrotizing enterocolitis (preterms)
- ↑ GI bleeding
- parietal cell hyperplasia / benign gastric polyps
- case reports: acute interstitial nephritis, acute hepatitis
- osteopenia, hip fractures
- ? Allergy
- ? Magnesium
- ? Coeliac disease

*No effect of proton pump inhibitors on crying and irritability in infants:
systematic review of randomized controlled trials.*

*Gieruszczak-Białek D, Konarska Z, Skórka A, Vandenplas Y, Szajewska H.
J Pediatr (2014;in press)*

Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns.

Terrin G, Pediatrics. 2012 ;129:e40-5.

- ❑ infections OR 5.5, 95% CI 2.9-10.4, P < .001
- ❑ NEC OR 6.6, 95% CI 1.7-25.0, P = .003
- ❑ Mortality rate : 9.9% vs 1.6%, P = .003)

Prenatal exposure to acid-suppressive drugs and the risk of allergic diseases in the offspring: a cohort study.

Mulder B. Clin Exp Allergy. 2014;44:261-9

Prenatal exposure to PPIs and/or H2As

- Atopic dermatitis 1.32 (95% CI 1.06-1.64)
- Astma 1.57 (95% CI 1.20-2.05)
- Allergic rhinitis 2.40 (95% CI 1.42-4.04)

The adjusted Hazard Ratios (aHR) for the development of two or more (aHR 2.13 95% CI: 1.43-3.19) and three allergic diseases (aHR 5.18 95% CI: 2.16-12.42) were even more elevated after prenatal exposure to PPIs or H2As.

Development of food allergies in patients with GERD treated with gastric acid suppressive medications.

Trikha A. Pediatr Allergy Immunol. 2013;24:582-8

Table 4 Hazard ratio of developing food allergy in cohort 1 (patients with history of GERD on GAS medications) compared to cohort 2 (patients with GERD with no history of prescribed GAS medications) as a reference

Treatment	Unadjusted model			Adjusted model		
	Hazard ratio	95 (%) Confidence interval	p Value	Hazard ratio	95 (%) Confidence interval	p Value
Dx of reflux with GAS medication	1.69	1.16 2.48	0.007	1.68	1.15 2.46	0.007
Dx of reflux with no GAS medication	Reference			Reference		

Children with GERD who were treated with GAS were more likely to be diagnosed with a food allergy (Hazard ratio (HR): 3.67, 95% CI 2.15-6.27), as were children with GERD diagnosis but who were not treated with GAS medications (HR: 2.15, 95% CI: 1.21-3.81).

A direct comparison of the two GERD cohorts showed that children with GERD who were treated with GAS had a greater risk of food allergy than those with GERD who were untreated (HR, 1.68, 95%CI, 1.15-2.46).

***Prenatal exposure** to acid-suppressive drugs
and the risk of allergic diseases in the offspring: a cohort study.
Mulder B. Clin Exp Allergy. 2014;44:261-9*

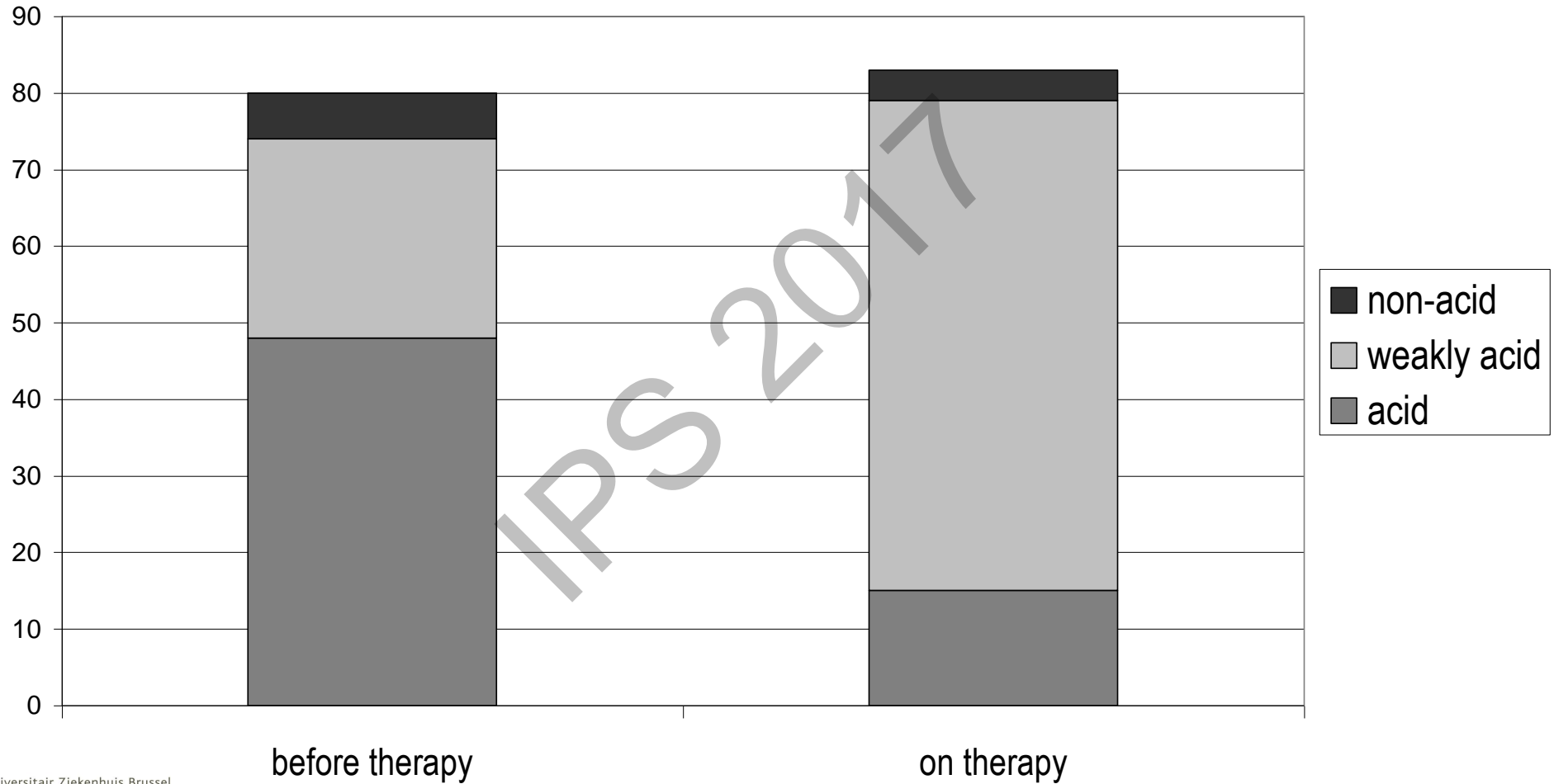
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Effect of proton pump inhibition on acid, weakly acid and weakly alkaline GER in children.

Turk H. *World J Pediatr.* 2013;9:36-41



Efficacy and safety of Histamine-2 Receptor Antagonists.

van der Pol R. JAMA Pediatr 2014,68:947-54

8 studies with a total of 276 children (0-15 years of age)
Compared with placebo, H2RAs were more effective
in the reduction of symptoms in terms of histologic healing
increasing gastric pH
larger overall treatment effect.

In infants, H2RAs were only more effective in terms of histologic healing.
Comparing H2RAs with antacids, H2RAs were more effective in symptom reduction
in only 1 study.

H2RAs compared with proton pump inhibitors were not significantly different in any of the
outcome measures.

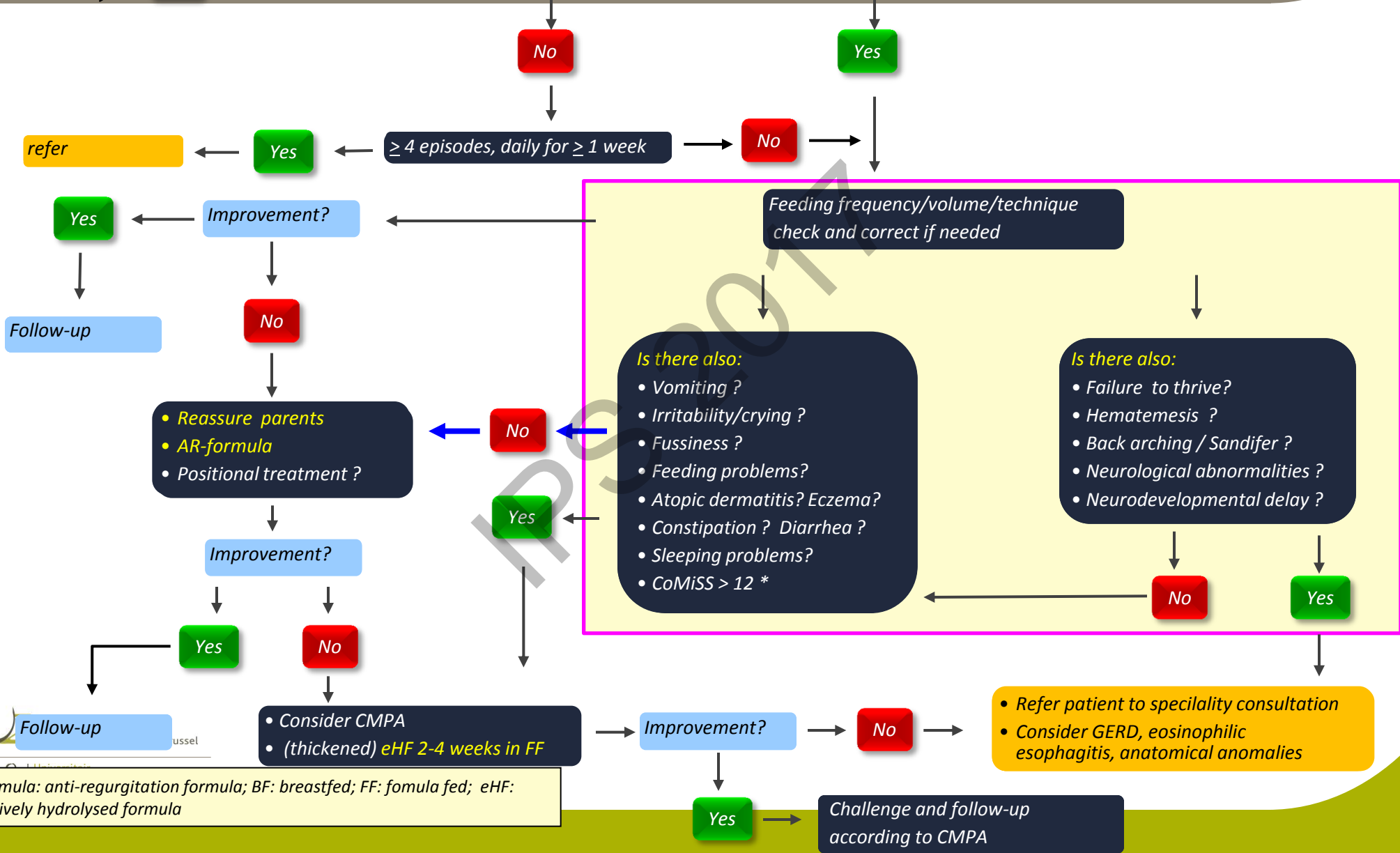
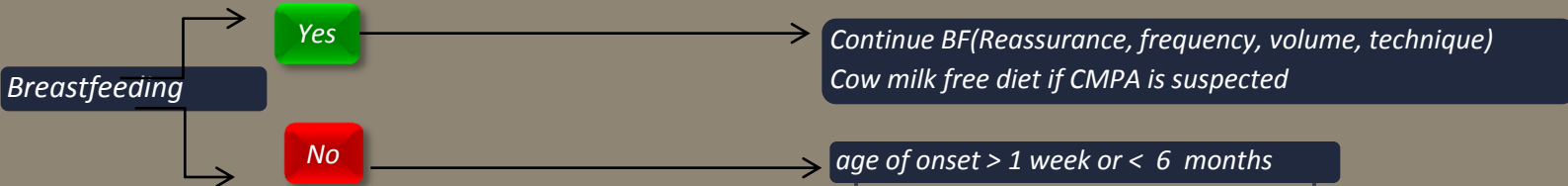
Evidence to support the efficacy and safety of H2RAs
in infants and children is limited and of poor quality.

Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies.

Vandenplas Y. Acta Paediatr. 2016;105:244-52

Stat		Consensus	Mean
2	Diagnostic investigations are not indicated for the diagnosis and management of “troublesome regurgitation”.	Yes (20/22) Agree: 91%	7.36
3	Anti-Regurgitation formula may be considered in infants with physiologic regurgitation.	Yes (20/22) Agree: 91%	7.41
4A	Drug treatment is not indicated in the management of physiologic regurgitation.	Yes (22/22) Agree 100%	8.68
4B	Drug treatment is not indicated in the management of physiologic and troublesome regurgitation.	Yes (17/22) Agree 77%	7.18

Regurgitation



AR-formula: anti-regurgitation formula; BF: breastfed; FF: formula fed; eHF: extensively hydrolysed formula



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*The older the child,
the more the therapeutic approach
is equal to the approach in adults*

- Once-daily morning dose, fasting, followed by a meal (activation proton pumps in the pre- and postprandial periods)
- No liquid formulations available
- Capsules, granules and tablets should not be crushed, chewed or dissolved
- Intact capsules with enteric-coated granules and enteric-coated tablets
- Granules suspended in acidic medium: applesauce, fruit juice, yoghurt
- Powder dissolved in 8.4 % sodium bicarbonate solution (SOS)

(Chun 2002, Ferron 2003, Gottrand 2004, Gunasekaran 1993, Haizlip 2005, Hassall 1997, Lasky 1998, Litalie 2005, Mohiuddin 1997, Phillips 1996-1998-2001, Quercia 1997, Sharma 2000, Wayne 1997, Woods 1993, Zimmerman 1997-2001)

Pharmacokinetics of two formulations of omeprazole administered through a gastrostomy tube in patients with severe neurodevelopmental problems

Boussery K, Br J Clin Pharmacol. 2011;72:990-6.

Omeprazole is often administered through a gastrostomy tube as either (i) a Multiple Unit Pellet System (MUPS®) tablet disintegrated in water (MUPS® formulation), or (ii) a suspension in 8.4% sodium bicarbonate (suspension formulation). This bioavailability study evaluates this practice in tube-fed patients with severe neurodevelopmental problems.

METHODS

Nonblinded, two-phase cross-over trial.

RESULTS

In seven of 10 patients, bioavailability was higher for the suspension formulation than for the MUPS® formulation. Median (90% confidence interval) area under the plasma concentration–time curve ratio (MUPS® over suspension) was 0.5 (0.06–2.37).

CONCLUSIONS

In this population, omeprazole MUPS® formulation has no apparent advantage over the more easily administered suspension formulation.



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Children who are at higher risk for developing severe chronic GERD

Infants and children with:

- History of neurological impairment (fluctuation of symptoms)
- Oesophageal and anatomical disorders (trachea-oesophageal fistulas, hiatus hernias, ...)
- Chronic respiratory disorders including lung transplantation
- History of prematurity
- Obesity
- Certain genetic disorders (Down's syndrome, Cornelia de Lange syndrome..)



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Lightdale JR. Pediatrics. 2013;131:e1684-95

Lifestyle changes are emphasized as first-line therapy
in both GER and GERD,
whereas medications are explicitly indicated
only for patients with GERD

Infant ≠ young child ≠ older child ≠ adult

***Pediatric Gastroesophageal Reflux Clinical Practice Guidelines:
Joint Recommendations of NASPGHAN and ESPGHAN***

Vandenplas Y and Rudolph CD

J Pediatr Gastroenterol Nutr 2009;49:498-547

At present,

*no single diagnostic test can prove or exclude
extraesophageal presentations of GERD
in pediatrics.*

***Pediatric Gastroesophageal Reflux Clinical Practice Guidelines:
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*In many cases the clinician must
make management decisions
based on inconclusive diagnostic studies
with no certainty regarding outcome.*

Infant with suspicion of GERD

History and physical exam

Presence of alarm features

- Tailor testing for differential diagnosis of GERD
- Refer to specialty consultation

Continue

Not better

No

- Reassure & anticipatory guidance
 - Avoid overfeeding
 - Continue breastfeeding
- Thicken(ed) feeds in formula fed infants or in women who already pump (no thickening in preterm)

Better

Abnormality identified?

Treat accordingly

No

Not better

GER

- **If CMPA suspected**
- Formula fed: consider 2-4 weeks eHF or AAF
- Breast fed: consider 2-4 weeks CM free diet mother

Not better

Yes

Symptoms and signs of GERD?

No

Not better

Refer to Pediatric GI if available (preferred option)
or
Therapeutic acid suppression up to 8 weeks

Better

Not better

- Reassurance and anticipatory guidance
 - No testing
 - Avoid overfeeding
 - Continue breastfeeding
- Thicken(ed) feeds in formula fed or in women who already pump (no thickening in preterm)

Not better

Not better

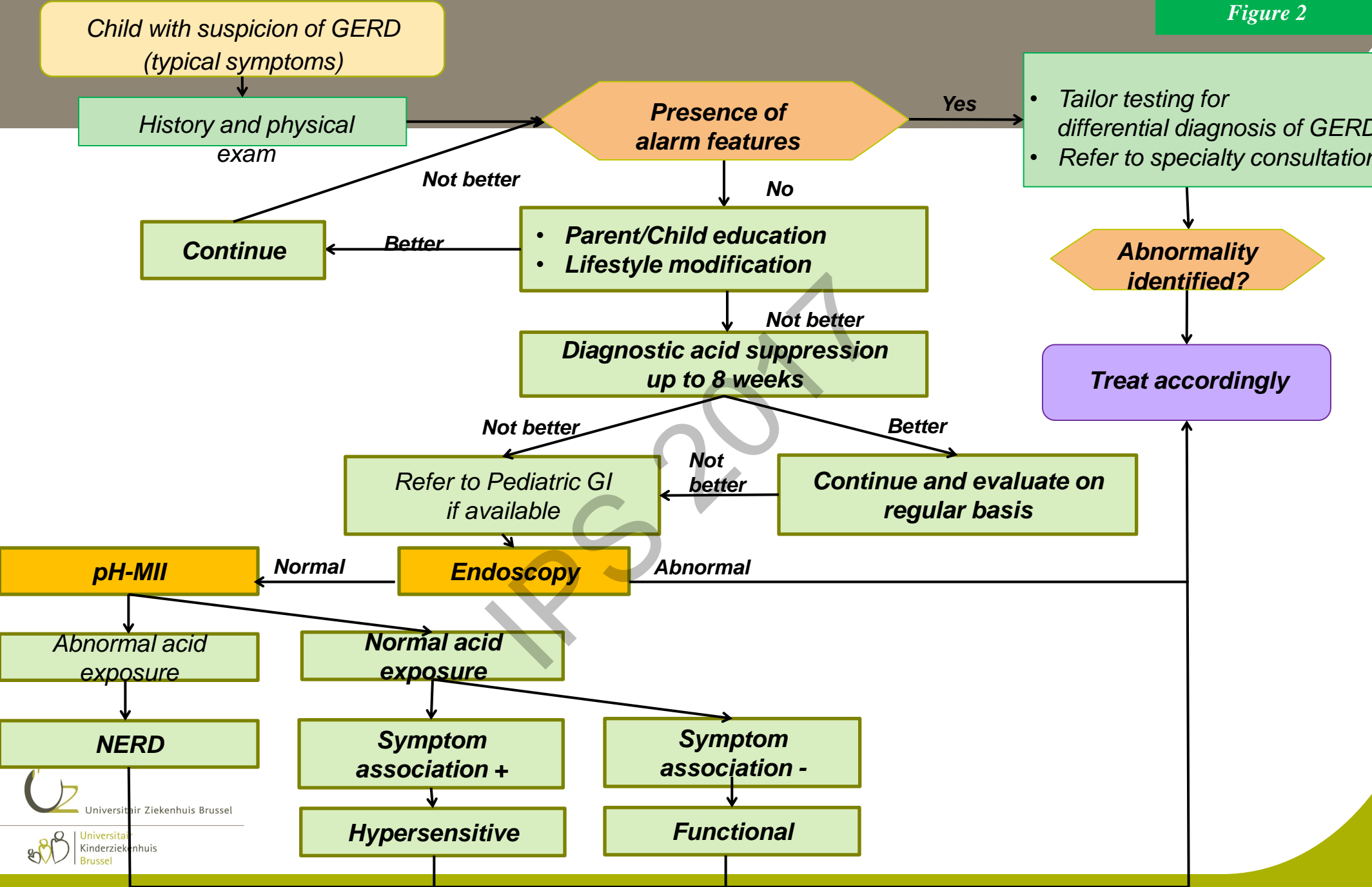
Continue and evaluate on regular basis

Evaluate further

Not better

Consider other treatment

Figure 2



IPS 2017