Gastro-esophageal reflux in children : a burning problem



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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 Gastroentoerol Nutr 2009;49:498-547

A Global, Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Pediatric Population

P. Sherman, E. Hassall, U. Fagundes-Neto, B. Gold, S. Kato, S. Koletzko, S.Orenstein, C. Rudolph, N. Vakil, Y. Vandenplas Am J Gastroenterol 2009;104:1278-95

Extraesophageal symptoms of gastroesophageal reflux disease (GERD) in children: a systematic review

V. Tolia, Y. Vandenplas Aliment Pharmacol Ther 2009;29:258-72





Introduction Symptoms Prevalence Diagnosis Treatment Conclusions

GER is not associated with dental erosion in children. *Wild YK. Gastroenterology* 2011;141:1605-11

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59 children (9-17 y) with symptoms of GER
cross-sectional study
                        20 asymptomatic children (controls)
Controlling for age
                dietary intake
                oral hygiene,
        there was no association between GER symptoms
        and dental erosion by tooth location or affected surface.
Salivary flow did not correlate with GER symptoms or erosion.
Location-specific dental erosion is not associated with GER,
salivary flow, or bacterial load.
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Kinderziekenhuis Brussel The "typical reflux syndrome..."

- A. Does not exist in children
- B. Cannot be diagnosed before the age of 8 years
- c. Unconsolable crying in infants is the "infant manifestation" of the typical reflux syndrome



The "typical reflux syndrome..."

- A. Does not exist in children
- B. Cannot be diagnosed before the age of 8 years
- C. Unconsolable crying in infants is the "infant manifestation" of the typical reflux syndrome





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

Yvan Vandenplas and Colin D. Rudolph 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



The natural course of gastro-oesophageal reflux.

Salvatore S. Acta Paediatr. 2004;93:1063-9

Symptoms/signs	Infants	Children	Adults
Vomiting	++	++	+
Regurgitation	++++	+	+
Heartburn	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Excessive crying/irritability	+++	+	_
Anaemia/melaena/haematemesis	+	+	+
Food refusal/feeding disturbancies/anorexia	++	+	+
Failure to thrive	++	+	_
Abnormal posturing/Sandifer's syndrome	++	+	_
Persisting hiccups	++	+	+
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Persistant cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	_
Chronic asthma/sinusitis	-	++	+
Laryngostenosis/vocal nodules problems	-	+	+
ALTE/SIDS/apnoea/desaturation	+	_	_
Bradycardia	+	?	?
Sleeping disturbancies	+	+	+
Impaired quality of life	++	++	++
Esophagitis	+	+	++
Stenosis	-	(+)	+
Barrett's/oesophageal adenocarcinoma	-	(+)	+

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Kinderziekenhuis Brussel GERD in children and adolescents in primary care (1) *Ruigómez A. Scand J Gastroenterol.* 2010;45:139-46.

GERD cases during 2000-05 The Health Improvement Network (THIN) UK primary care database via a computer search for diagnostic codes for GERD, followed by manual review of the patient records.

1700 children with a first diagnosis of GERD during 2000-05

Incidence GERD 0.84 / 1000 person-years

Incidence ↓ with age from 1.48/1000 person-years among 1-year-old children until the age of 12 years, whereupon it increased to a maximum at 16-17 years of 2.26/1000 person-years for girls 1.75/1000 person-years for boys.

Kinderziekenhuis Brussel In addition to typical GERD symptoms (epigastric pain, heartburn, reflux, regurgitation), 21.2% of children reported nausea or vomiting.

Children with neurological disorders were at increased risk of a GERD diagnosis.

Hiatus hernia and congenital esophageal disorders were also associated with a diagnosis of GERD.

Children and adolescents using antiepileptics, oral/inhaled steroids, betaagonists and paracetamol had an increased risk of a GERD diagnosis.



. . .

Follow-up of a cohort of children and adolescents with GERD who were free of reflux esophagitis at initial diagnosis. *Ruigómez A. Scand J Gastroenterol* 2010;45:814-21.

The Health Improvement Network UK primary care database (which includes data on more than 2 million patients) to identify individuals aged 1-17 years with a first diagnosis of GER or heartburn in the period 2000-2005, via a computerized search followed by a manual review of the patient records.

⇒ 1242 individuals with an incident diagnosis of GERD but no record of esophagitis. This cohort was followed-up to detect new diagnoses of esophageal complications and extra-esophageal conditions.

 \Rightarrow During a mean follow-up period of almost 4 years,

40 children and adolescents had a confirmed new diagnosis of reflux esophagitis (incidence: 10.9/1000 person-years).

No cases of Barrett's esophagus, esophageal stricture or esophageal ulcer



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GER Amsterdam

Individuals with GERD had double the risk of an extra-esophageal condition such as asthma, pneumonia, cough or chest pain compared with children and adolescents with no diagnosis of GERD. Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy (1) *Nelson SP. J Med Eco 2009;12:348-55*.

> Cohorts of GERD/ARC children (age 0-18 years) were identified from a large US administrative claims database covering 1999-2005 using ICD-9 codes.

Comparison between various age and patient groups for incidence healthcare utilization (HCU) costs therapy discontinuation switching rates



Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy (2) *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



Pediatric GERD and acid-related conditions (ARC): trends in incidence of diagnosis and acid suppression therapy (3)

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

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Limitations:

- the use of an exploratory definition for GERD/ARC
- administrative claims data
- potential coding errors

 ⇒ The diagnosis of GERD/ARC incidence increased for children of all ages between 2000 and 2005.
 Primare Care Physicians made the majority of diagnoses.
 PPI initiations have surpassed H²RA initiations.



Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(1) *Martigne L. Eur J Pediatr 2012 Aug 18*.

Nationwide prevalence GERD in French children and adolescents 404 GP & 180 paediatricians (P): register of all children and adolescents (n = 10,394, 0-17 yrs, mean 3.8 ± 5.6 years; 5143 by GP and 5251 by P) who presented over two 3-day periods (14-16 and 26-28 May 2008).

For all children who, in the physician's opinion, showed symptoms of GOR, a 24-item questionnaire covering the history and management of GOR was completed.

Children with symptoms that impaired their daily lives were defined as having GERD, the remainder as having physiological GER.



Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(2) *Martigne L. Eur J Pediatr 2012 Aug 18*.

15.1 % showed GER symptoms.

Extrapolation to French population: prevalence GER 10.3 % -- GERD 6.2 %

There was a significantly (p < 0.05) greater use of volume reduction or milk thickeners and dorsal positioning among infants with GERD versus physiological GER.

Significantly (p < 0.05) more infants and children with GERD received pharmacological therapy. PPI increased with age and was significantly (p < 0.05) higher among those with GERD.

Bruss

Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(3) *Martigne L. Eur J Pediatr 2012 Aug 18*.

	Prevalence of GER in France according to age								
		0-23 month	2-11 year	12-17 year	Total				
	Extrapolation to French 24.4%		7.2%	10.7%	10.3%				
		GER	symptoms						
			0-23 month	2-11 year	12-17 year				
T	Mean duration (mo	nth)	4.4	20.9	21.8				
ľ	Typical symptom	IS							
	Regurgitation	IS	85% ^{BC}	36%	33%				
	Vomiting		26% ^C	32% ^C	13%				
	Crying		45% ^{BC}	-	-				
	Heartburn		-	37% ^a	86% AB				
	Atypical sympton	าร							
	Feeding difficulties,	anorexia	42% ^{BC}	-	-				
	Failure to thriv	ve	6% ^{BC}	-	-				
	Postural defec	ts	8% ^{BC}	-	-				
	Stridor		10% ^{BC}	4% ^c	<1%				
	Chronic coug	h	6% ^{BC}	68% ^{AC}	33% ^A				
Un ve	rsitair Ziekenhuis Brussel Laryngitis, otil	tis	-	35% ^{AC}	12% ^A				
Univ m Kind m	sitair ziekenhuis Asthma		-	24% ^{AC}	15% ^A				
Brus -	Sinusitis		-	2% ^{AC}	6% ^A				

SER Amsterdam. The superscript letter signifies that the column value is significantly different (P<0.05) to the value of the presented column.

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Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study.(4) *Martigne L. Eur J Pediatr 2012 Aug 18*.



4/9/2013







4/9/2013



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

> > antimony4.0 +/- 0.8%ISFET5.7 +/- 1.1%glass pH electrodes9.0 +/- 1.7%







Impedance Scale





High Conductivity = Low impedance



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Kinderziekenhuis

- 1. Questionnaires
 - $\Rightarrow 1^{st}$ to do, but.... limitations
- 2. Radiology
 - \Rightarrow anatomy
- 3. Scintigraphy
- 4. Ultrasound
- 5. Endoscopy (+ biopsy)
 - \Rightarrow ? Esophagitis
- 6. Manometry
- 7. pH metry
- ⇒ ? acid GER-D in extra-esophageal symptoms
 8. Impedance-metry
 ⇒ ? acid & non-acid GER-disease
 9. Therapeutic trial
 ⇒ no data

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.

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

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Detection of GER in children using combined MII and pH measurement: data from the German Pediatric Impedance Group. *Pilic D. J Pediatr. 2011;158:650-654.e1*

Table I. Number of patients in the different subgroups with abnormal measurement data based on different pathological findings

	Patients with GI symptoms (n = 325)	Patients with pulmonary symptoms (n = 329)	Patients with neurologic symptoms (n = 46)	All patients (n = 700)
Abnormal measurements, n	114 (48 female, 66 male)	133 (57 female, 76 male)	23 (11 female, 12 male)	270 (116 female, 154 male)
Age, years, median (range)	6.5 (1 month-16 years)	2 (1 month-16 years)	0.5 (3 weeks-15 years)	2.8 (6 weeks-16 years)
Only pathological pH	26 (23%)	21 (16%)	2 (9%)	49 (18%)
Pathological MII and pH	55 (48%)	35 (26%)	11 (48%)	101 (37%)
Pathological MII	33 (29%)	77 (58%)	10 (43%)	120 (45%)



Cough and GER...

- A. There is evidence that chronic cough is caused by GER
- B. There is evidence that reflux may induce cough
- C. There is evidence that PPI decrease cough
- D. In patients with CF, mainly acid reflux is increased



Cough and GER...

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inderziekenhuis

Esophageal impedance in children: symptom-based results *S. Salvatore J Pediatr 2010;157:949-54*

Symptoms with associated reflux events

Symptoms	Pts No.	Symp No.(me	toms edian)	GER related	AR related	WAF relate	۲ ed	AlkF relate	R ed
				No.(%)	No.(%)	No.	(%)	No.	(%)
Crying	88	872	(8)	395 (45)	174 (44)	215	(54)	6	(2)
Vomiting	48	229	(3)	196 (86)	80 (41)	103	(52)	13	(7)
Cough	102	975	(7)	510 (52)	243 (48)	247	(48)	20	(4)
Others	13	64	(3)	29 (45)	16 (55)	13	(45)	0	
All	126	2172	(6)	1136 (52)	516 (45)	581	(51)	39	(3)



Esophageal impedance in children: symptom-based results *S. Salvatore J Pediatr 2010;157:949-54*

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

	CRYING			COUGH			VOMITING		
ITEM	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 Median	456 11	279 6	137 5	338 9	311 7	326 4	115 4	53 2	61 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



4/9/2013

Cow's milk challenge increases weakly acidic reflux in children with CMA and GERD.

Borrelli O. J Pediatr 2012;161:476-481

Table II. Reflux characteristics during AAF and CM administration

74	AAF period	CM period
Total number of reflux episodes [median (25 th to 75 th)]	65 (39-87.5)	105 (58-127.5)*
[median (25 th -75 th)]		
Acid episodes	31 (9.5-44)	34 (14-41)
Weakly acidic episodes	19 (13-26.5)	53 (38.5-60.5)*
Weakly alkaline episodes	5 (3.5-10)	10 (2.5-15)
pH-only reflux episodes	9 (7-16)	11 (5.5-15)
Reflux composition		10100303-5 00005
Liquid	71%	78%
Mixed	27%	21%
Gas	2%	1%
Esophageal acid exposure time (mean \pm SD)	3.4 ± 2.6	$\textbf{3.6} \pm \textbf{2.7}$
Number of long-lasting episodes (>5 min) [median (25 th -75 th)]	3 (1-3)	2 (1.5-2.5)



Figure 2. Proportion of the type of reflux episodes during the 2 recording periods. Note the significant decrease in proportion of acid and pH-only reflux episodes, and the significant increase in the proportion of the weakly acidic reflux episodes. Data are expressed as percentage of the total number of reflux episodes.

*P < .001 by Wilcoxon signed rank test.

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Related to allergy ? Or faster gastric emptying AAF?

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 Characteristics of GER and potential risk of gastric content aspiration in children with cystic fibrosis.

Blondeau K. J Pediatr Gastroenterol Nutr. 2010;50:161-6

Although WA-GER is uncommon, acid GER is prevalent in children with CF. It is a primary phenomenon and is not secondary to cough.

One third of the children with CF have bile acids (BA) in saliva, which may indicate an increased risk for aspiration. However, the impact of salivary BA and potential aspiration on CF pulmonary disease needs further investigation.



than in CRR and CUR

45 children with chronic cough: 24-hour MII-pH 20 children with erosive reflux disease (ERD): controls. 24 children had cough-related reflux (CRR) in 24/45(19 no GI symptoms) cough-unrelated reflux (CUR) in 21/45 CRR + ERD: $\hat{\parallel}$ AR, WAc, WAlk reflux ↑ eso acid exposure & acid clearance time ERD:



g/g/2013

Role of GER in children with unexplained chronic cough (2) Borrelli O. J Pediatr Gastroenterol Nutr 2011;53:287-92

CRR group 158 cough episodes related to reflux episodes 66% AR // 18% WAc // 16% Walk

17 children had positive SAP

7 for AR 5 for AR & WAc 4 for WAc & Walk 1 for WAlk.

But still. No RCT !!! In children with unexplained chronic cough, asymptomatic acid and nonacid GER is a potential etiologic factor. The increased acid exposure time and delayed acid clearance characteristic of ERD are absent in cough-related GER.



GER Amsterdam
Nocturnal reflux in children and adolescents with persistent asthma and gastroesophageal reflux (1) *Molle LD. J Asthma 2009;46:347-50*

38 patients 10 years (range 5 - 15) with persistent asthma for at least 2 years GI symptoms: regurgitation, heartburn, and abdominal pain

GER: considered positive RI > 5%

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV(1)), forced mid-expiratory flow rate (FEF(25-75%)), and FEV(1)/FVC ratio

GER prevalence was 47.3%.
RI supine 8.7% (3.2 to 23.6); upright 10.5% (5.2 to 15.0)
FEF(25-75%) was below the predicted value: 54.5% (39.4 to 96.9).
RI was not significantly correlated with FVC, FEV(1) and FEF(25-75%).



Nocturnal reflux in children and adolescents with persistent asthma and gastroesophageal reflux. *Molle LD. J Asthma 2009;46:347-50*

A high prevalence of GER was found in children and adolescents with persistent asthma, equally distributed in the supine (nocturnal) and upright positions.

There was no correlation with pulmonary function test.







Kinderziekenhuis

4/9/2013

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

Yvan Vandenplas and Colin D. Rudolph J Pediatr Gastroenterol Nutr 2009;49:498-547

The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy

What is the evidence in infants?



Multicenter, DB, R, PC trial assessing the efficacy and safety of PPI lansoprazole in infants with symptoms of GER disease. *Orenstein SR. J Pediatr. 2009;154:514-520.e4*.

Symptoms were tracked through daily diaries and weekly visits Efficacy: \geq 50% reduction of feeding-related crying

216 infants screened, 162 randomized lansoprazole placebo responder 44/81 (54%) 44/81 (54 %)

No difference in any secondary measures or analyses of efficacy

> 1 AEs 62% 46% (P=.058) Serious AEs lower RTI (n) 10 2 (P=.032).



Proton pump inhibitor use in pediatric patients less than 12 months of age *Chen IL. JPGN 2012;54:8-14.*





Results: Of the 98 patients enrolled, 81 (82.7%) experienced symptom improvement determined by physician global assessment (PGA) during open-label esomeprazole treatment; 80 entered the double-blind phase. During this phase, discontinuation rates owing to symptom worsening were 48.8% (20/41) for placebo-treated versus 38.5% (15/39) for esomeprazole-treated patients (hazard ratio 0.69; P = 0.28). Posthoc analysis of infants with symptomatic GERD (ie, no diagnostic procedure performed) revealed that time to discontinuation was significantly longer with esomeprazole than placebo (hazard ratio 0.24; P = 0.01); the complementary subgroup difference was not significant (hazard ratio 1.39; P = 0.48). Esomeprazole was well tolerated.



PPI: side effects

bacterial overgrowth

- community-acquired pneumonia (children, adults)
- gastroenteritis (children)
- candidemia (preterms)
- necrotizing enterocolitis (preterms)
- parietal cell hyperpalsia / benign gastric polyps
- case reports: acute interstitial nephritis, acute hepatitis
- osteopenia, hip fractures
- ? Allergy
- ? Magnesium



4/9/2013

Trends of outpatient prescription drug utilization in US children, 2002-2010. *Chai G. Pediatrics 2012;130:23-31*

ABLE 3	Тор	Drug Molecules	Dispensed to	the	Pediatric	Population	From	US	Retail	Pharmacies	According	to Pa	tient	Age i	n 20	10
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0-23 Months (N = 31.6 million prescriptions)		2-11 Years (N = 134.2 million presc	riptions)	12–17 Years ($N = 96.6$ million prescriptions)		
Drug Molecule Share, %		Drug Molecule	Share, %	Drug Molecule	Share, %	
Amoxicillin	17.3	Amoxicillin	11.3	Methylphenidate	4.5	
Azithromycin	6.1	Azithromycin	5.8	Albuterol	3.7	
Nystatin	5.9	Albuterol	5.6	Azithromycin	3.5	
Albuterol	5.8	Montelukast	4.5	Amoxicillin	3.5	
Cefdinir	4.9	Methylphenidate	3.9	Amphetamine/dextroamphetamine	3.1	
Prednisolone	4.2	Fluticasone	2.9	Montelukast	2.2	
Amoxicillin/clavulanate	3.4	Prednisolone	2.7	Norgestimate ethinyl estradiol	2.2	
Dextromethorphan/phenylephrine/ chlorpheniramine	2.4	Cefdinir	2.6	Lisdexamfetamine	2.2	
Ranitidine	2.2	Cephalexin	2.3	Fluticasone	1.9	
Hydrocortisone	2.0	Amoxicillin/clavulanate	2.2	Hydrocodone bitartrate/apap	1.9	
Ibuprofen	1.8	Amphetamine/dextroamphetamine	2.0	Ibuprofen	1.7	
Multivitamins with fluoride	1.7	Multivitamins with fluoride	1.7	Amoxicillin/clavulanate	1.5	
Budesonide	1.6	Lisdexamfetamine	1.6	Sulfamethoxazole/trimethoprim	1.5	
Lansoprazolea	1.6	Sodium fluoride	1.5	Doxycycline hyclate	1.5	
Cephalexin	1.5	Ibuprofen	1.4	Cephalexin	1.5	
Mupirocin	1.4	Mometasone	1.4	Sertraline	1.4	
Sulfamethoxazole/trimethoprim	1.3	Dexmethylphenidate	1.4	Fluoxetine	1.4	
Polymyxin b sulfate/tmp	1.0	Sulfamethoxazole/trimethoprim	1.2	Minocycline	1.1	
Triamcinolone	1.0	Clonidine	1.1	Prednisone	1.1	
Montelukast	0.9	Budesonide	1.1	Clindamycin phosphate/benzoyl peroxide	1.1	
All others	32.0	All others	41.8	All others	57.5	

Data include all formulations (eg, oral tablet, oral syrups, topical cream). Source: VONA, 2002 through 2010; extracted March 2011.

- * A total of 515 000 lansoprazole prescriptions (358 000 prescriptions in patients aged 0 to <1 year and 157 000 prescriptions in patients aged 1 to <2 years).</p>

Brussel

TOP 5 medications infants 0 - 1 year

Medication group (ATC 3)	DDD	% DDD (<u>**</u>)	N° patients	RIZIV (in 10 ⁶ €)
Astma, inhalation (R03B)	4.242.010	45%	78.545	2,9
Sympathicomimetics inhalation (R03A)	983.727	11% 56.729		0,5
Betalactam-antibiotics, penicilline (J01C)	758.308	8%	94.809	0,8
PPI (A02B)	652.901	7%	14.484	0,3
Antimicrobials (S01A)	550.638	5%	27.292	0,1



2007: 120 663 births

2007: 14 484 infants treated with PPI/H2RA = 12 %

Pediatric use of H2RA and PPI in Belgium (Inami/Riziv) Daily Defined Dosis



Prevalence and management of GERD in children and adolescents: a nationwide cross-sectional observational study. *Martigne L. Eur J Pediatr 2012 Aug 18.*



4/9/2013

Omeprazole and asthma outcome in children with asthma and GER-disease: a randomised control trial.

Stordal K. Arch Dis Child 2005;90:956-60

38 children (7-16 years): asthma and symptoms suggesting GERD and 24 hr pH metry RI > 5 %

 Table 3
 Outcome measures in children with asthma and GORD treated with omeprazole and placebo

	Omeprazole (n = 18)	Placebo (n = 18)	p value
Symptom score	-1.28 (-2.65 to 0.1)	-1.28 (-3.27 to 0.72)	1.00
PAQLQ	-0.62 (-0.29 to -0.95)	-0.50 (-0.29 to -0.70)	0.51
FEV1% (mean, median)	-1.38 (0.33)	-2.01 (-0.50)	0.77
FEF ₂₅₋₇₅ (mean, median)	-0.07 (-0.05)	0.04 (0.05)	0.12
Rescue medication (mean, median)	-1.9 (0.0)	-1.9 (0.5)	0.89
ECP baseline	25.9 (14.3. 37.5)	20.2 (12.7 to 27.7)	
ECP change	1.27 (-5.5 to 8.1)	1.39 (-4.3 to 7.1)	0.98

Values expressed as changes from baseline (week 0) to end of treatment (week 12) with 95% confidence intervals for mean (\pm 1.96 SEM) unless otherwise stated.

NO effect



Lansoprazole for children with poorly controlled asthma: a RCT (1) Writing Committee for the American Lung Association Asthma Clinical Research Centers. JAMA.2012;307:373-81

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Lansoprazole (n:149) 15 mg/d if weighing less than 30 kg
30 mg/d if weighing 30 kg or more
Placebo (n = 157).
Mean age was 11 years (SD, 3 years)
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- Mean difference in change (lansoprazole minus placebo) in the Asthma Control Questionnaire score: 0.2 units (95% CI, 0.0-0.3 units).
- No statistically significant difference in the mean difference in change for the secondary outcomes of
 - forced expiratory volume in the first second (0.0 L; 95% CI, -0.1 to 0.1 L)
 - asthma-related quality of life (-0.1; 95% CI, -0.3 to 0.1)
 - rate of episodes of poor asthma control (RR 1.2; 95% CI, 0.9-1.5)



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Lansoprazole for children with poorly controlled asthma: a RCT (2) Writing Committee for the American Lung Association Asthma Clinical Research Centers. JAMA.2012;307:373-81

115 children with pH metries: prevalence of GER was 43%In the subgroup with a positive pH study,no treatment effect for lansoprazole vs placebowas observed for any asthma outcome.

Children treated with lansoprazole reported more respiratory infections (relative risk, 1.3 [95% CI, 1.1-1.6]).

Children with poorly controlled asthma without symptoms of GER who were using inhaled corticosteroids, the addition of lansoprazole, compared with placebo, improved neither symptoms nor lung function but was associated with increased adverse events.

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

J Pediatr Gastroentoerol Nutr 2009;49:498-547

Patients with asthma and heartburn should be treated for the heartburn.

Despite a high frequency of abnormal reflux studies in asthmatic patients, only a select group with nocturnal asthma symptoms, or with steroid dependent, difficult to control asthma may benefit from long term medical or surgical anti-reflux therapy.



4/9/2013

Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study. (1) *Andersen AB. Aliment Pharmacol Ther. 2012;35:*

In this cohort study, 197,060 singletons born between 1996 and 2008 in northern Denmark were followed until the end of 2009. Data were obtained through Danish medical registries.

Asthma in offspring was defined as at least two prescriptions of both a β -agonist and an inhaled glucocorticoid and/or a hospital diagnosis of asthma during the follow-up.



Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study (2) *Andersen AB. Aliment Pharmacol Ther. 2012;35:*

2238 (1.1%) children were prenatally exposed to PPIs and 24,506 (12.4%) children developed asthma during follow-up (median follow-up = 6.8 years).

The adjusted IRR of asthma associated with prenatal exposure to PPIs was 1.41 (95% CI: 1.27-1.56), compared with those unexposed.

The association did not vary by trimester of exposure *Prenatal exposure to H2RAs was associated with similar increase in risk.* The aIRR for maternal PPI and H2RA use in the year after, but not during pregnancy was 1.32 (95% CI: 1.20-1.46) and 1.13 (0.93-1.36), respectively, compared with non-use during and in the year after pregnancy.

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http://www.youtube.com/watch?v=5VzEMr4Nh gE&feature=player_detailpage



http://<u>www.youtube.com/watch?v=PvxTf</u> <u>gBszc8&feature=player_detailpage</u>





Gaviscon® vs. omeprazole in symptomatic treatment of moderate GER, a direct comparative randomised trial. *Pouchain D. BMC Gastroenterol.2012 ;12:18.*

A 14-day multicentre randomised double-blind double-dummy non-inferiority trial compared Gaviscon® (4×10 mL/day) and omeprazole (20 mg/day) in patients with 2-6 day heartburn episodes weekly without alarm signals.

The primary outcome was the mean time to onset of the first 24-h heartburn-free period after initial dosing.

Secondary outcomes were the proportion of patients without heartburn by D7, pain relief by D7, and reduction in pain intensity by D7 and D14.

RESULTS:

278 patients were recruited; 120 were included in the Gaviscon® group and 121 i **CONCLUSION:**

Gaviscon® was non-inferior to omeprazole in achieving a 24-h heartburn-free per

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<u>Chin J Integr Med.</u> 2010 Aug;16(4):298-303. Epub 2010 Aug 10. <u>Clinical study on the treatment of gastroesophageal reflux by acupuncture.</u> <u>Zhang CX</u>,

Sixty patients with confirmed diagnosis of GER were randomly assigned to **RESULTS:**

Compared with those detected at T0, 24-h intraesophageal pH and bile reflux **CONCLUSION:**

Acupuncture can effectively inhibit the intraesophageal acid and bile reflux



Crit Care. 2009;13(5):R164. Epub 2009 Oct 19.

Gastroesophageal reflux in mechanically ventilated pediatric patients and <u>Abdel-Gawad TA</u>,

The study is a prospective cohort study of mechanically ventilated pediatric **RESULTS:**

All VAP patients had GER (50% alkaline reflux, 12.5% acidic reflux and 3 **CONCLUSIONS:**

GER is a constant incident in mechanically ventilated pediatric patients, wi



Nucl Med Commun. 2009 Oct;30(10):802-6.

Does gastroesophageal reflux scintigraphy correlate with clinical findings in <u>Bingol Boz A</u>

A total of 72 children older than 7 years with chronic cough of unknown et **RESULTS:**

Of 72 children, 65 children with a mean age of 10.3+/-2.3 (7-19) years had **CONCLUSION:**

Scintigraphy should be used for the detection of GER in children who prese



Pol Merkur Lekarski. 2008 Sep;25(147):217-20.

[The clinical manifestation of duodeno-gastroesophageal reflux (DGER) in [Article in Polish] <u>Sidor K</u>

59 patients (37 girls, 22 boys) aged 7-17 years (mean 14.7) with the symptom **RESULTS:**

The most common complain--in 16 (88.89%) patients was recurrent and/or conclusions:

The clinical manifestation of duodenal reflux was very much alike as in acid



<u>Zhongguo Zhen Jiu.</u> 2012 Jun;32(6):491-8. [Clinical efficacy of electroacupuncture combined with dalitong granule for [Article in Chinese] <u>Zhang CX</u>,

Five hundred cases diagnosed as gastroesophageal reflux disease were random **RESULTS:**

Compared with those before treatment, esophageal acid reflux, bile reflux, er **CONCLUSION:**

Electroacupuncture and Dalitong granule can both inhibit esophageal acid ref



Pediatrics. 2012 Jul;130(1):23-31. Epub 2012 Jun 18.

Trends of outpatient prescription drug utilization in US children, 2002-20 <u>Chai G</u>,

Large prescription databases (the IMS Vector One: National and Total Patient **RESULTS:**

In 2010, a total of 263.6 million prescriptions were dispensed to the US pedia 7% lower than in 2002, while prescriptions dispensed to the adult population 22% during the same time.

Analysis of pediatric drug utilization trends for the top 12 therapeutic areas in compared with 2002 showed decreases in systemic antibiotics (-14%), allergin (-14%), depression (-5%), and cough/cold without expectorant (-42%) p whereas asthma (14%), attention-deficit/hyperactivity disorder (46%),

and contraceptive (93%) prescriptions increased. In 2010, amoxicillin was th **CONCLUSIONS:**

GER Amsterdam

J Otolaryngol Head Neck Surg. 2011 Dec;40(6):499-503.

Role of nasopharyngeal reflux **in the etiology of otitis media with effusion.** <u>Aydın E</u>,

The study was performed in 20 children with OME and adenoid hypertroph **RESULTS:**

In the study group, 25% (5 of 20) of the patients were found to have nasoph **CONCLUSIONS:**

We detected higher nasopharyngeal and esophageal reflux rates in the OME



<u>J Allergy Clin Immunol.</u> 2011 Nov;128(5):964-9. Epub 2011 Aug 6. **The association of** obesity **and asthma severity and control in children.** <u>Quinto KB</u>,

Even after adjusting for demographics, parental education level, asthma **CONCLUSIONS:**

Our findings suggest that childhood obesity is associated with an increa



Laryngoscope. 2012 Jun;122(6):1397-400. doi: 10.1002/lary.23250. Epub 2012 M Impedance and extraesophageal manifestations of reflux in pediatrics. <u>Greifer M</u>,

We retrospectively reviewed charts from patients who underwent MII-pH. Inclu **RESULTS:**

A total of 119 MII-pH studies were performed. Of those, 63 studies met inclusio **CONCLUSIONS:**

No association was demonstrated between the extraesophageal signs and sympt



<u>Pediatr Radiol.</u> 2012 May;42(5):515-24. Epub 2012 Mar 9. US in the diagnosis of gastroesophageal reflux in children. <u>Savino A</u>,

Several techniques have been used to diagnose gastroesophageal reflux (GEF



Pediatr Radiol. 2012 May;42(5):515-24. Epub 2012 Mar 9. US in the diagnosis of gastroesophageal reflux in children. Savino A,

Author and year	Intraabdominal esophageal length (mm)	Esophageal wall thickness (mm)	Esophageal diameter (mm)	His angle		
De Meester et al. 1979 [45]	20-25					
Gomes et al. 1993 [3]	25-30 including gastric folds					
Halkiewicz et al. 2000 [42]	17.6±5.2	-	-	70-100°, normal,		
				100-130°, obtuse		
				130-180°, completely obtuse		
Esposito et al. 2001 [10]	From 18 in newborns to 34 in children>6 years old	2.4-5.7				
Koumanidou et al. 2004 [2]	From 22.2 in neonates to 27.2 in infants 6-12 months old	-	<u> 200</u>			
Fallahi et al. 2007 [28]	21.53±9	3.9 ± 1.2	10.1 ± 2.0	-		
Hashemi et al. 2009 [43]	22.2±10.0	4.0 ± 1.3	10.1 ± 2.4	-		
Dehdashti et al. 2010 [44]	22.0±1.8			-		
Karabulut et al. 2010 [46]		2.1±0.2	Proximal, 4.5±0.4 Distal, 8.5±0.6	107.4±5.9 in male and 106.2±5.2 in female infants		

Table 1 Reported sonographic features of the normal gastroesophageal region



Otolaryngol Head Neck Surg. 2012 Mar;146(3):345-52. Epub 2011 Dec 9. Association between otitis media and gastroesophageal reflux: a systematic reflux Miura MS,

- Studies with planned data collection, in children with chronic otitis media wit **RESULTS:**
- Of 242 initial studies, 15 met inclusion criteria. The authors found a mean pre **CONCLUSION:**
- The prevalence of gastroesophageal reflux disease in children with chronic otitis media with effusion/recurrent acute otitis media may be higher than the overall prevalence for children.

Presence of pepsin/pepsinogen in the middle ear could be related to physiologic reflux.

Universitair Construction of the ser and the ser and

J Pediatr Gastroenterol Nutr. 2012 May;54(5):664-71.

PedsQL gastrointestinal symptoms module item development: qualitative r Varni JW,

The objective of the present qualitative study was to develop the items and support **METHODS**:

The iterative process included multiphase qualitative methods. A literature review **RESULTS:**

Eleven domains were derived from the qualitative methods involving patient and **CONCLUSIONS**:

Qualitative methods involving pediatric patients and their parents in the item gen



J Gastroenterol Hepatol. 2012 Jan;27(1):21-7. doi: 10.1111/j.1440-1746.2011.069 Oral manifestations of gastroesophageal reflux disease. <u>Ranjitkar S</u>,

Numerous case-control and other studies involving confirmation of gastroesople



<u>J Gastrointest Surg.</u> 2011 Oct;15(10):1872-8. Epub 2011 Jul 29. **The effects and efficacy of antireflux surgery in children with** gastroesophag <u>Mauritz FA</u>,

In total, 17 eligible studies were identified, reporting on a total of 1,280 ch **CONCLUSION:** ARS in children shows a good overall success rate (median 86%) in terms


Dev Med Child Neurol. 2011 Oct;53(10):938-43. doi: 10.1111/j.1469-8749.201 Influence of percutaneous endoscopic gastrostomy on gastro-oesophageal re Toporowska-Kowalska E

Fifteen children with neurological impairments (cerebral palsy, n=10; cerebral palsy, n=

At baseline, GOR was detected in 6 of the 15 participants, and the secon **INTERPRETATION:**

Identification of GOR based on MII/pH in children with neurological in



Reflux associated with symptoms according to age

Age group	Patients No.	Symptoms No.	Refluz related No.	x- 1 %	AR relate No.	d %	WAR related No.	1 %	AlkR related No.	d %
1-6 mo	40	938	505	54	152	30	335	66	18	4
6-12 mo	36	649	354	54	204	58	145	41	5	1
> 12 mo	50	575	276	48	160	58	100	36	16	6





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Delayed gastric emptying rates and impaired antral motility in children fulfilling Rome III criteria for functional abdominal pain. *Devanarayana NM. Neurogastroenterol Motil 2012;24:420-5*

102 children (4-14 years)fulfilling Rome III criteria for FAP Age and sex compatible group of healthy children (n = 20)

	patients	control	S
Average Gastr Empt Rate	42.1%	66.2%	< 0.01
Amplitude antral contractions	56.5%	89%	< 0.01
Frequency contractions / 3 min	8.5	9.3	< 0.01
Antral motility index	4.9	8.3	< 0.01
Fasting antral area	1.4	0.6	< 0.0001

Gastric Emptying Rate negatively correlated with the scores obtained for severity of abdominal pain (r = -0.29, P = 0.004).



<u>Pediatr Pulmonol.</u> 2012 Jun;47(6):582-7. doi: 10.1002/ppul.21598. Epub 2011 D **The impact of reflux burden on Pseudomonas positivity in children with cys** <u>Palm K</u>

We reviewed the multichannel intraluminal impedance (pH-MII) tracings of **RESULTS:**

The mean age was 13.5 ± 5.8 years. Twenty-seven patients (76%) were Pa p **CONCLUSIONS:**

Increased reflux burden may predispose patients to Pa infection and worse lu



<u>J Pediatr.</u> 2012 Mar;160(3):441-446.e1. Epub 2011 Sep 15. **Interobserver and intraobserver variability in pH-impedance analysis betw** <u>Loots CM</u>,

Ten pediatric 24-hour pH-impedance tracings were analyzed by 10 obser **RESULTS:**

Overall, 1242 liquid and mixed GER events were detected, 490 (42%) we **CONCLUSION:**

Interobserver agreement in combined pH-multichannel intraluminal impe



<u>J Pediatr.</u> 2011 Apr;158(4):650-654.e1. Epub 2010 Oct 29. **Detection of gastroesophageal reflux in children using combined multichar** <u>Pilic D</u>

The patients were divided into 3 symptom groups based on the main indi **RESULTS:**

Overall, 270 measurements were abnormal: 101 (37%) showed abnormal **CONCLUSIONS:**

From this large systematically standardized data collection of MII-pH me



Esomeprazole for the treatment of GERD in infants ages 1-11 months. *Winter H. J Pediatr Gastroenterol Nutr.* 2012;55:14-20





TABLE 2. Parent/guardian-reported symptom severity score^{*} at screening and final week of open-label study phase and change from baseline during the double-blind study phase

	Mean (SD) s during open	symptom score n-label phase	Mean (SD) change from baseline in symptom score during double-blind phase		
Symptom	Screening, n = 84	Final week, n=79	Esomeprazole, $n = 37$	Placebo, $n = 40$	
Vomiting/regurgitation	1.42 (0.76)	1.00 (0.72)	0.04 (0.56)	0.09 (0.61)	
Irritability (crying/fussiness)	1.50 (0.67)	1.02 (0.74)	0.06 (0.58)	0.19 (0.59)	
Feeding difficulties	$1.16(0.76)^{\dagger}$	$0.83 (0.76)^{\ddagger}$	0.09 (0.48)	0.10 (0.61)	
Supraesophageal/respiratory disturbances (coughing, wheezing, labored breathing)	0.54 (0.69)	0.44 (0.69)	0.12 (0.48)	0.03 (0.58)	

SD=standard deviation.

* Symptom severity: 0 = none; 1 = mild; 2 = moderate; 3 = severe. † n = 83. ‡ n = 78.



Cow's milk challenge increases weakly acidic reflux in children with CMA and GERD.

Borrelli O. J Pediatr 2012;161:476-481

	CM period	AAF period	
Total reflux episodes			
Proximal	50 (24.5-61.5)	72 (47-94.5)*	
Intermediate	6 (5-10)	10 (6.5-16)‡	
Distal	3 (0-3.5)	4 (3-6) [‡]	
Acid reflux episodes		000000000	
Proximal	25 (6-38)	25 (10-34)	
Intermediate	4 (3-7)	5 (2-7.5)	
Distal	0 (0-2)	1 (0-2.5)	
Weakly acidic reflux episodes			
Proximal	16 (12-20.5)	43 (33-51.5)	
Intermediate	2 (0.5-2)	3 (2-5.5)+	
Distal	0 (0-2)	1 (0-3)‡	
Weakly alkaline reflux episodes	Contraction of the second second	COLLARSON CO.	
Proximal	5 (0-10)	5 (0-10)	
Intermediate	0 (0-1)	0 (0-5)	
Distal	0 (0-0)	0 (0-2)	

Values given as median (25th-75th).

*P < .001 by Wilcoxon signed rank test.

†P < .01 by Wilcoxon signed rank test.

P < .05 by Wilcoxon signed rank test.



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Introduction Symptoms Prevalence Diagnosis Treatment Conclusions

Cow's milk challenge increases weakly acidic reflux in children with CMA and GERD. *Borrelli O. J Pediatr 2012;161:476-481*

> 17 (median age: 14 months) proven CMA + ? GERD
> 48-hour MII-pH monitoring first 24 hours: amino acid-based formula
> 2nd 24 hours: CM-based fromula

```
Reflux episodes
```

AAF (25-75th)CM (25-75th)Total65 (39-87.5)105 (58-127.5)<0.01</td>weakly acid19 (13-26.5)53 (38.5-60.5)<.001</td>

No differences in acid or weakly alkaline episodes

