|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **C1 - Summary of methodological quality of included studies on basis of six items from QUADAS checklist for each diagnostic study** | | | | | | | | | | | | | | | |
| **QUADAS items** | **Salivary pepsin** | **pH-metry** | | | | | | | | **Endoscopy** | | | **GI scintiscan** | | **Upper GI series** |
|  | Farhath (2013) (1) | Boix-Ocha (1980) (2) | Arasu (1980) (3) | Da Dalt (1989) (4) | Kahn (1990)1 (5) | Cucchiara (1990) (6) | Cucchiara (1993) (7) | Ravelli (2006) (8) | Patra (2011)2 (9) | Cucchiara (1993) (7) | Ravelli (2006) (8) | Arasu (1980) (3) | Arasu (1980) (3) | Patra (2011) (9) | Arasu (1980) (3) |
| Was the spectrum of patients representative of the patients who will receive the test in practice? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Is the reference standard likely to correctly classify the target condition?  (yes if reference test was a clinical definition of GERD)2 | No\* | No | No | No\* | No | No | No\* | No | No | No\* | No | No | No | No | No |
| Was the execution of the index test described in sufficient detail? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Were the index test results interpreted without knowledge of the results of the reference test? | Unclear | No | Unclear | No | Yes | Yes | Unclear | Yes | Unclear | Histology: unclear  Macroscopy: yes | Histology: unclear  Macroscopy: yes | Unclear | Unclear | Unclear | Unclear |
| Were the reference test results interpreted without knowledge of the results of the index test? | Yes | No | Unclear | No | Yes | Yes | Unclear | Yes | Unclear | Histology: unclear  Macroscopy: yes | Histology: unclear  Macroscopy: yes | Unclear | Unclear | Unclear | Unclear |
| Were withdrawals from the study explained? | No | No | No | No | No | No | Yes | Yes | Yes | No | Yes | No | No | Yes | No |
| **Quality of evidence**  (Oxford Centre level of Evidence)4 | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C |

1. This study includes children with ALTE. This study was included because ALTE was regarded as a possible presentation of GERD.

2. This study includes children with recurrent or persistent wheezing (>3 attacks requiring hospital visit or almost daily wheezing for >4 weeks). Within this specific patient group, a division between children with and without a history suggestive or reflux is made. Therefore this study was included, but results should be interpreted in the light of the patient group (wheezers and not the general pediatric population) the study focuses on.

3. Since GERD signs and symptoms are not distinctive, and therefore, difficult to diagnose, it is not clear if the reference standard (signs and symptoms) used in the included studies was correctly classifying the target condition. Studies marked with an (\*) however did provide a clear definition/description of GERD.

4. All studies are case-control study, poor or non-independent reference standard and thus level 4 studies: grade of recommendation C.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **C2 - Summary of methodological quality of included studies on basis of the QUIPS tool for each prognostic study** | | | | | | |
| **Study, setting** | **Study Participation** | **Study attrition** | **Prognostic factor measurement** | **Outcome measurement** | **Study confounding** | **Statistical analysis and reporting** |
| **El-Serag (2004) (10)** | MODERATE | HIGH | HIGH | LOW | NA | LOW |
| **Orenstein (2006) (11)** | HIGH | HIGH | NA | LOW | NA | LOW |
| **Ruigomez (2015) (12)** | LOW | MODERATE | LOW | MODERATE | NA | MODERATE |
| **Shepherd (1987) (13)** | HIGH | HIGH | NA | MODERATE | NA | LOW |

NA = Not applicable

**References**

1. Farhath S, He Z, Saslow J, Soundar S, Amendolia B, Bhat V, et al. Detection of pepsin in mouth swab: correlation with clinical gastroesophageal reflux in preterm infants. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(8):819-24.

2. Boix-Ochoa J, Lafuenta JM, Gil-Vernet JM. Twenty-four hour exophageal pH monitoring in gastroesophageal reflux. Journal of pediatric surgery. 1980;15(1):74-8.

3. Arasu TS, Wyllie R, Fitzgerald JF, Franken EA, Siddiqui AR, Lehman GA, et al. Gastroesophageal reflux in infants and children comparative accuracy of diagnostic methods. The Journal of pediatrics. 1980;96(5):798-803.

4. Da Dalt L, Mazzoleni S, Montini G, Donzelli F, Zacchello F. Diagnostic accuracy of pH monitoring in gastro-oesophageal reflux. Archives of disease in childhood. 1989;64(10):1421-6.

5. Kahn A, Rebuffat E, Sottiaux M, Blum D, Yasik EA. Sleep apneas and acid esophageal reflux in control infants and in infants with an apparent life-threatening event. Biology of the neonate. 1990;57(3-4):144-9.

6. Cucchiara S, Staiano A, Gobio Casali L, Boccieri A, Paone FM. Value of the 24 hour intraoesophageal pH monitoring in children. Gut. 1990;31(2):129-33.

7. Cucchiara S, Bortolotti M, Minella R, Auricchio S. Fasting and postprandial mechanisms of gastroesophageal reflux in children with gastroesophageal reflux disease. Digestive diseases and sciences. 1993;38(1):86-92.

8. Ravelli AM, Villanacci V, Ruzzenenti N, Grigolato P, Tobanelli P, Klersy C, et al. Dilated intercellular spaces: a major morphological feature of esophagitis. Journal of pediatric gastroenterology and nutrition. 2006;42(5):510-5.

9. Patra S, Singh V, Chandra J, Kumar P, Tripathi M. Diagnostic modalities for Gastro-esophageal reflux in infantile wheezers. J Trop Pediatr. 2011;57(2):99-103.

10. El-Serag HB, Gilger M, Carter J, Genta RM, Rabeneck L. Childhood GERD is a risk factor for GERD in adolescents and young adults. Am J Gastroenterol. 2004;99(5):806-12.

11. Orenstein SR, Shalaby TM, Kelsey SF, Frankel E. Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. The American journal of gastroenterology. 2006;101(3):628-40.

12. Ruigomez A, Lundborg P, Johansson S, Wallander MA, Garcia Rodriguez LA. Follow-up of a cohort of children and adolescents with gastro-esophageal reflux disease who were free of reflux esophagitis at initial diagnosis. Scandinavian journal of gastroenterology. 2010;45(7-8):814-21.

13. Shepherd RW, Wren J, Evans S, Lander M, Ong TH. Gastroesophageal reflux in children. Clinical profile, course and outcome with active therapy in 126 cases. Clinical pediatrics. 1987;26(2):55-60.