NICU CLINICAL GUIDELINE

☒ Medication included ☐ No medication included

Title:	Clinically Significant Gastroesophageal Reflux (GER) in Infants Born Prematurely
This document is attached to:	1. Provide consensus-based diagnostic criteria for clinically significant GER in infants born prematurely 2. Provide a consensus-based treatment algorithm for clinically significant GER in infants born prematurely

1. PURPOSE

Gastroesophageal reflux (GER) occurs in > 90% of infants born prematurely. The majority of premature infants will not require treatment for this natural phenomenon. However, there is a subset of infants born prematurely who have clinically significant GER that impairs their age-appropriate function and development. There is no evidence-based investigation to distinguish this subset of infants nor is there evidence-based treatments that consistently improve GER. There is also emerging evidence that pharmacologic agents to treat GER can result in harm. Therefore, the following consensus-based definition and treatment algorithm were designed to target the subset of infants with impaired function or development as a result of GER and treat them in a step-wise approach from least aggressive to more aggressive therapies.

2. GUIDELINE APPICABLE IN THE FOLLOWING SETTING:

The following patients are included in this guideline:

- Infants born < 34 weeks' gestation and admitted to the MUHC NICU

The following patients are excluded from this guideline:

- Infants with a gastrointestinal congenital malformation (e.g. TEF/EA, gastroschisis)

OR

- Infants with an ostomy

OR

- Infants with an anatomical or functional short gut

3. GUIDELINE HAS BEEN APPROVED BY: TBD (Ongoing as of June 8, 2021)

4. ELEMENTS OF CLINICAL ACTIVITY

Diagnosis of Clinically Significant GER in Infants Born Prematurely

Good **VIBEs** only for reflux!

The infant must have at least 2 of the following[1]:

V – **VOMITING** on average > 2 times in 24 hours for at least 1 week

I – **IRRITABILITY** that prevents age-appropriate activities for at least 1 week

B – Poor **BOTTLE/BREAST** feeding progression at 37 weeks corrected gestational age or later[2]

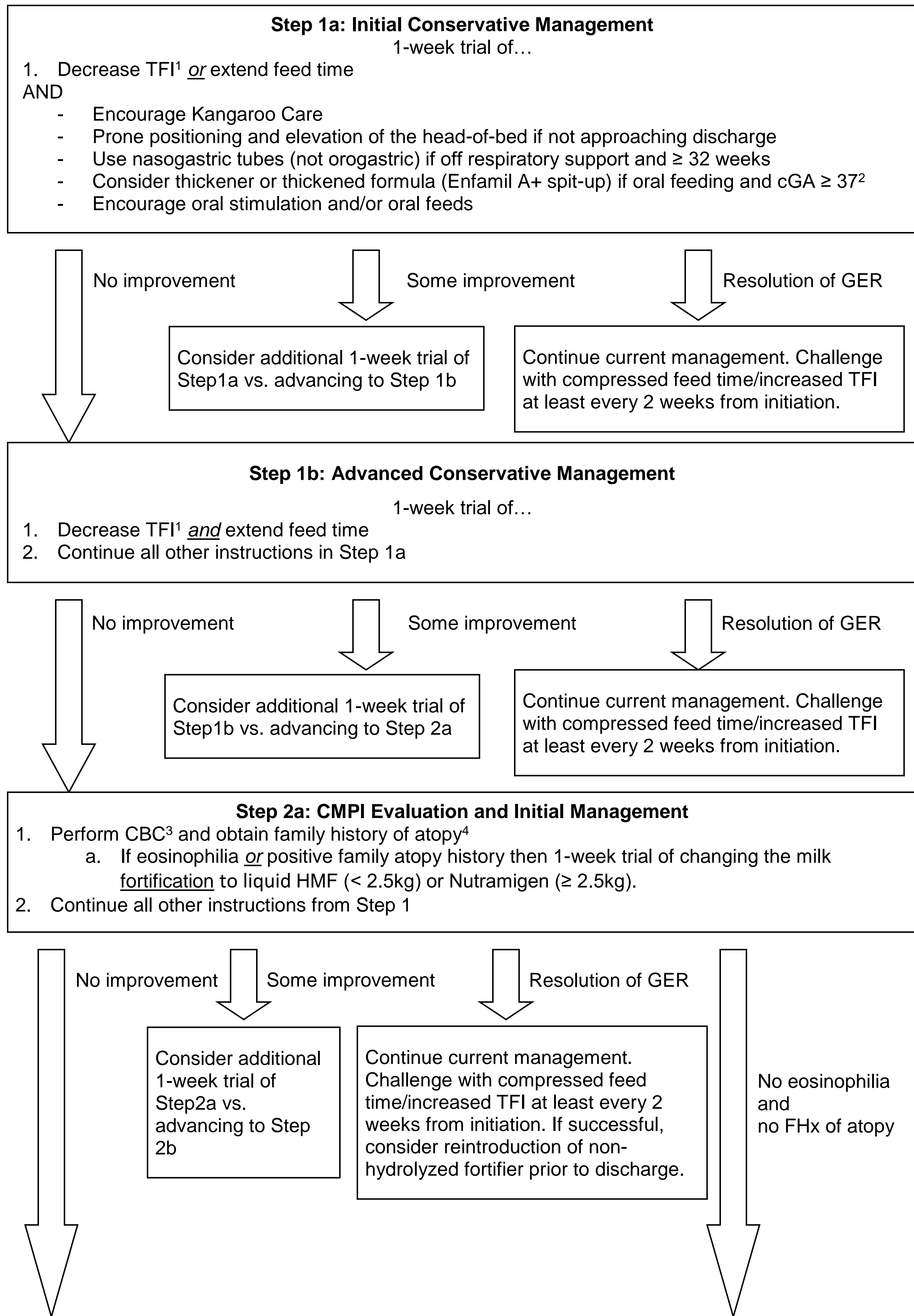
E – Requires **EXTENDED** gavage feed time for age-appropriate physiology (i.e. inability to compress feeds)

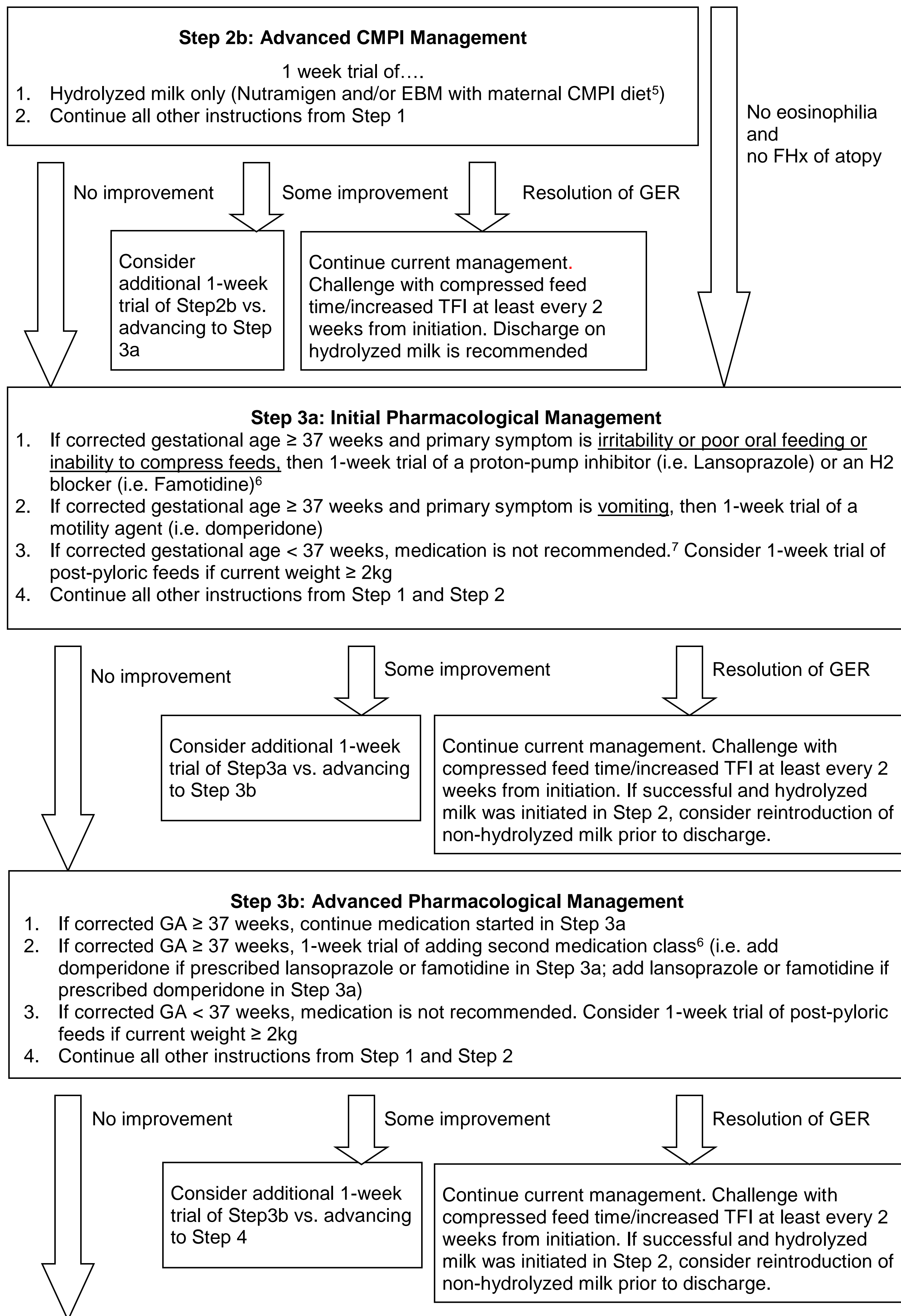
Footnotes

[1]Clinically significant GER is a multi-disciplinary diagnosis requiring patient care continuity and should not be diagnosed during a night, weekend or holiday shift.

[2]Occupational therapy needs to be consulted to fulfill this criterion. Failure to remove CPAP by 37 weeks corrected gestational age does not automatically fulfill criterion.

Treatment Algorithm for Clinically Significant GER in Infants Born Prematurely




Step 2b: Advanced CMPI Management
1 week trial of….
1. Hydrolyzed milk only (Nutramigen and/or EBM with maternal CMPI diet[5])
2. Continue all other instructions from Step 1
No eosinophilia and no FHx of atopy
No improvement
Some improvement
Resolution of GER
Consider additional 1-week trial of Step2b vs. advancing to Step 3a
Continue current management. Challenge with compressed feed time/increased TFI at least every 2 weeks from initiation. Discharge on hydrolyzed milk is recommended
Step 3a: Initial Pharmacological Management
1. If corrected gestational age ≥ 37 weeks and primary symptom is irritability or poor oral feeding or inability to compress feeds, then 1-week trial of a proton-pump inhibitor (i.e. Lansoprazole) or an H2 blocker (i.e. Famotidine)[6]
2. If corrected gestational age ≥ 37 weeks and primary symptom is vomiting, then 1-week trial of a motility agent (i.e. domperidone)
3. If corrected gestational age < 37 weeks, medication is not recommended.[7] Consider 1-week trial of post-pyloric feeds if current weight ≥ 2kg
4. Continue all other instructions from Step 1 and Step 2
No improvement
Some improvement
Resolution of GER
Consider additional 1-week trial of Step3a vs. advancing to Step 3b
Continue current management. Challenge with compressed feed time/increased TFI at least every 2 weeks from initiation. If successful and hydrolyzed milk was initiated in Step 2, consider reintroduction of non-hydrolyzed milk prior to discharge.
Step 3b: Advanced Pharmacological Management
1. If corrected GA ≥ 37 weeks, continue medication started in Step 3a
2. If corrected GA ≥ 37 weeks, 1-week trial of adding second medication class[6] (i.e. add domperidone if prescribed lansoprazole or famotidine in Step 3a; add lansoprazole or famotidine if prescribed domperidone in Step 3a)
3. If corrected GA < 37 weeks, medication is not recommended. Consider 1-week trial of post-pyloric feeds if current weight ≥ 2kg
4. Continue all other instructions from Step 1 and Step 2
No improvement
Some improvement
Resolution of GER
Consider additional 1-week trial of Step3b vs. advancing to Step 4
Continue current management. Challenge with compressed feed time/increased TFI at least every 2 weeks from initiation. If successful and hydrolyzed milk was initiated in Step 2, consider reintroduction of non-hydrolyzed milk prior to discharge.

Step 4: Refractory Gastroesophageal Reflux

1. Consult Pediatric Gastroenterology (GI) for further investigations and management.
2. Consult Neonatal Follow-Up (i.e. Bridge Team) to facilitate long-term management plans
3. Continue lansoprazole/famotidine and domperidone pending GI consult
4. Consider trial of post-pyloric feeds if > 2kg pending GI consult
5. Continue all other instructions from Step 1 and Step 2

Footnotes:

[1]Consult with nutritionist to ensure adequate caloric intake

[2]Discuss thickening options with occupational therapist and nutritionist

[3]Eosinophilia definition: mild: 0.70-0.99 x 10^9/L; moderate 1.00-2.99 x 10^9/L; severe ≥3.00 x 10^9/L

[4]Questions to ask for family atopy history:

- Sibling with CMPI?
- Siblings with allergies/asthma/eczema?
- Parents with allergies/asthma/eczema?

[5]Consult nutritionist and lactation consultant for details of maternal CMPI diet.

[6]Dosing as per Lexicomp guidelines and clinician discretion.

5. *MAIN AUTHOR:*

Jessica Duby – Neonatologist, Montreal Children's Hospital, MUHC

6. CONSULTANTS (listed in alphabetical order):

Amanda Camacho – Lactation Consultant, Montreal Children's Hospital, MUHC
Alexandra Breton-Piette – NICU Nurse, Montreal Children's Hospital, MUHC
Daphney Ducharme-Roy – NICU Nurse, Montreal Children's Hospital, MUHC
May Khairy – Neonatal Follow-Up Pediatrician, Montreal Children's Hospital, MUHC
Christine Labelle – Occupational Therapist, Montreal Children's Hospital, MUHC
Shani Lugasi – Nutritionist, Montreal Children's Hospital, MUHC
Stephanie Mardakis – NICU Nurse Educator, Montreal Children's Hospital, MUHC
Katryn Paquette- Neonatologist, Montreal Children's Hospital, MUHC
Dariane Racine – Pharmacist, Montreal Children's Hospital, MUHC
Elissa Remmer – NICU Nurse Educator, Montreal Children's Hospital, MUHC
Ana Sant'Anna – Gastroenterologist, Montreal Children's Hospital, MUHC
Megan Smith-Morin – Occupational Therapist, Montreal Children's Hospital, MUHC
Emilie St. Germain – Neonatal Nurse Practitioner, Montreal Children's Hospital, MUHC
Sharon Taylor-Ducharme – NICU Nurse Manager, Montreal Children's Hospital
Rebecca Thorne – NICU Nurse, Montreal Children's Hospital, MUHC

7. SPECIAL CONSIDERATIONS

None

8. APPROVAL PROCESS

Institutional and professional approval

Committees	Date [yyyy-mm-dd]
☐ NICU Multidisciplinary GER Committee	2021-05-04
☐ Pediatric Clinical Practice Review Committee (CPRC) (if applicable)	
☐ Pediatric Pharmacy and Therapeutics (Peds P&T) (if applicable)	

9. REVIEW DATE

To be updated in maximum of 4 years or sooner if presence of new evidence or need for practice change.

10. REFERENCES

1. Angelidou A, Bell K, Gupta M, Tropea Leeman K, Hansen A. Implementation of a Guideline to Decrease Use of Acid-Suppressing Medications in the NICU. Pediatrics. 2017;140(6).
2. Bines JE, Quinlan JE, Treves S, Kleinman RE, Winter HS. Efficacy of domperidone in infants and children with gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 1992;14(4):400-5.
3. Borrelli O, Mancini V, Thapar N, Giorgio V, Elawad M, Hill S, et al. Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease. J Pediatr. 2012;161(3):476-81 e1.
4. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006;117(5):e817-20.
5. Corvaglia L, Mariani E, Aceti A, Galletti S, Faldella G. Extensively hydrolyzed protein formula reduces acid gastro-esophageal reflux in symptomatic preterm infants. Early Hum Dev. 2013;89(7):453-5.
6. Cresi F, Marinaccio C, Russo MC, Miniero R, Silvestro L. Short-term effect of domperidone on gastroesophageal reflux in newborns assessed by combined intraluminal impedance and pH monitoring. J Perinatol. 2008;28(11):766-70.
7. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163(3):692-8 e1-2.
8. Djeddi D, Kongolo G, Lefaix C, Mounard J, Leke A. Effect of domperidone on QT interval in neonates. J Pediatr. 2008;153(5):663-6.
9. Eichenwald EC, Committee On F, Newborn. Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants. Pediatrics. 2018;142(1).
10. Guillet R, Stoll BJ, Cotten CM, Gantz M, McDonald S, Poole WK, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics. 2006;117(2):e137-42.
11. Gunlemez A, Babaoglu A, Arisoy AE, Turker G, Gokalp AS. Effect of domperidone on the QTc interval in premature infants. J Perinatol. 2010;30(1):50-3.
12. Malchodi L, Wagner K, Susi A, Gorman G, Hisle-Gorman E. Early Acid Suppression Therapy Exposure and Fracture in Young Children. Pediatrics. 2019;144(1).
13. Mitchell DJ, McClure BG, Tubman TR. Simultaneous monitoring of gastric and oesophageal pH reveals limitations of conventional oesophageal pH monitoring in milk fed infants. Arch Dis Child. 2001;84(3):273-6.
14. Omari TI, Barnett C, Snel A, Goldsworthy W, Haslam R, Davidson G, et al. Mechanisms of gastroesophageal reflux in healthy premature infants. J Pediatr. 1998;133(5):650-4.
15. Omari TI, Barnett CP, Benninga MA, Lontis R, Goodchild L, Haslam RR, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut. 2002;51(4):475-9.
16. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. J Pediatr. 2009;154(4):514-20 e4.
17. Premji SS, Chessell L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. The Cochrane database of systematic reviews. 2011(11):CD001819.
18. Richards R, Foster JP, Psaila K. Continuous versus bolus intragastric tube feeding for preterm and low birth weight infants with gastro-oesophageal reflux disease. The Cochrane database of systematic reviews. 2014(7):CD009719.
19. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. 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. J Pediatr Gastroenterol Nutr. 2018;66(3):516-54.
20. Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? Pediatrics. 2002;110(5):972-84.
21. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Neonatal Histamine-2 Receptor Antagonist and Proton Pump Inhibitor Treatment at United States Children's Hospitals. J Pediatr. 2016;174:63-70 e3.
22. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics. 2012;129(1):e40-5.
23. Vieira MC, Miyague NI, Van Steen K, Salvatore S, Vandenplas Y. Effects of domperidone on QTc interval in infants. Acta Paediatr. 2012;101(5):494-6.
24. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. J Pediatr. 2009;155(4):516-21.
25. Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the Treatment of GERD in Infants Ages 1-11 Months. J Pediatr Gastroenterol Nutr. 2015;60 Suppl 1:S9-15.

Version History

(for Administrative use only)

Version	Description	Author/responsable	Date
1	GER Guideline	Jessica Duby	2022-02-07