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<th>Full Title of Guideline:</th>
<th>D15 Management of Gastroesophageal Reflux Disease on the Neonatal Unit</th>
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| Author (include email and role): | Dr. Elda Dermyshi (Clinical Fellow Neonatology)  
Chris Jarvis (Specialist Neonatal Dietitian)  
Dr. Phoebe Kigozi (Consultant Neonatologist)  
in consultation with Adriece Al Rifai (Neonatal Pharmacist) |
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This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.
**Key Points**

- Gastroesophageal (GOR) reflux is common in preterm and term infants and is often non-pathological.
- Symptoms and signs are non-specific particularly in the preterm population and could be attributed to other important clinical problems such as sepsis, developmental immaturity, cow’s milk protein allergy, and pyloric stenosis.
- When there is a strong clinical suspicion of GOR, non-pharmacological treatment approaches should be considered in the first instance including postural management, and altering feed frequency.
- Short and long-term safety and efficacy should be high priorities when pharmacological treatments are considered.
- Formal diagnostic testing should be considered in infants who are believed to have significant GOR.
In infants with suspected GOR:
Assess for other causes of symptoms e.g. sepsis

**GOR**

Assess evidence for GOR and severity e.g. by testing oropharyngeal secretions for acid, evaluate pattern and frequency of symptoms and impact on physiological stability.

**STEP 1***
- Parental education and reassurance
- Non-pharmacological treatment options:
  - Prone +/- 30 degree elevation or left side down (monitored baby)
  - Increase frequency of feeds

**STEP 2***
Discuss with Neonatal Consultant for consideration of;
- Use of feed thickener e.g. Gaviscon Infant
- Continuous feeding (gastric or transpyloric)

**STEP 3***
- Consider trial of pharmacotherapy
  - PPI e.g. Omeprazole
  - H2RA e.g. Ranitidine
- Consider formal diagnostic testing with MII-pH

**STEP 4***
- Consider trial of hydrolysed protein formula
- Consider sub-specialist referral e.g. for surgical intervention
- Consider and evaluate for other causes of symptoms

**Not GOR**
Workup for other causes: Sepsis (UTI); Drugs e.g. Caffeine

**Not significant GOR**
No intervention
Parental education and reassurance

**Improved or resolved**

**Unresolved significant GOR**

**Not GOR**
Parental education and reassurance

**No intervention**
No further intervention

**Review in 2-4 weeks**

**Not significant GOR**
No intervention

**Improved or resolved**

**Unresolved significant GOR**

**Improved or resolved**

**Unresolved significant GOR**

**Unresolved significant GOR**

**Continued**
Trial off treatment 1-3 months
1. Introduction:
Gastroesophageal reflux (GOR) is defined as the passage of gastric contents into the oesophagus. Episodes of GOR are common in both preterm and full-term infants. The majority of these infants however, do not exhibit clinical compromise from GOR. In preterm and full-term infants, transient lower oesophageal sphincter (LOS) relaxations have been shown to be the predominant mechanism of reflux.\(^1,2\)

Effects of GOR are poorly understood; cardio-respiratory symptoms are often attributed to GOR although studies have failed to consistently show this association or benefit from treatment.\(^3-6\)

Symptoms such as feed intolerance, apnoeas, desaturation, bradycardia, poor weight gain and irritability have been attributable to GOR, also known as GORD. Antacids containing alginate, Histamine-2 receptor antagonists (H2 RAs) and proton pump inhibitors (PPI) are among the most common interventions used with 60%, 53% and 23% of UK neonatal units using these products respectively,\(^7\) this is despite a lack of evidence for their safety or effectiveness in this population.\(^8,9\)

GORD and apnoea may be a manifestation of developmental immaturity, with natural resolution overtime.

Symptomatic GOR is reported to occur in a large proportion of infants following oesophageal atresia and tracheoesophageal fistula (OA/TOF) and congenital diaphragmatic hernia (CDH) repairs; it is also seen commonly in infants with neuro-disability and hypotonic syndromes. GOR in these patients presents as feed intolerance, recurrent non-bilious vomiting, dysphagia and respiratory symptoms if overflow into trachea occurs.

2. Diagnosis and Investigations

There is no truly reliable and widely available ‘gold standard’ diagnostic test for GORD in preterm infants. The standard for diagnosis in older infants is by detecting the number of acid reflux events by continuous intra-oesophageal pH monitoring over 24hr. A reflux index (% of time pH < 4) of > 10% is indicative of pathological GOR in term infants. There is little published data regarding normal reflux values in preterm infants.\(^10\) In addition, this technique is unable to detect non-acid reflux contents into oesophagus. Preterm infants receive frequent milk feeds which buffers the gastric acid and make the reflux contents weakly acidic or alkaline.\(^11\)

Multichannel intraluminal impedance-pH monitoring (MII-pH) is a technique that allows detection of both acid and non-acid reflux.\(^12\)
Clinical features of GORD include frequent vomiting, possets, effortless regurgitation of feeds, irritability, apnoea, and the more disputable features of bradycardia and desaturations.\textsuperscript{13-16}

Diagnosis may be aided by simple tests such as testing oropharyngeal secretions for acid.

2.1 In infants suspected of being symptomatic for GOR:

- A careful clinical assessment for other factors e.g. sepsis should be performed.
- Where sepsis and other physiological explanations are absent, careful assessment for evidence of GOR should be undertaken.
- Consider testing the pH of oropharyngeal secretions for acid (not reliable given the stomach and oesophageal pH is rarely < 4 with the frequent milk feeds)
- Consideration of MII-pH testing should be reserved for infants thought to be symptomatic from GOR who fail to respond to optimal management below.\textsuperscript{14}

3. Management recommendations

A step-wise therapeutic approach is advisable in the management of GORD in infants. (See flowchart above). Reassurance and parental education are the usual first-line management for uncomplicated reflux.\textsuperscript{17}

Conservative management of GORD should be considered the first-line treatment in symptomatic babies who are experiencing frequent vomiting and effortless regurgitations without significant clinical complications.

3.1 Reassurance and advice

The recommendation to offer reassurance and advice is based on expert opinion from the NICE guideline development group (GDG). Regurgitation is thought to resolve spontaneously in most infants (90%) before they are 1 year of age and reassurance may be all that is required. The GDG also stated that regurgitation that persists beyond one year may require further investigation.

Simple physiological reflux is associated with frequent regurgitation.

3.2 Non-pharmacological management approaches

3.2.1. Positioning and reflux

- As post-prandial GOR is increased in the right lateral (right side down) and supine positions, nursing infants left side down (left lateral) and prone may diminish transient lower oesophageal sphincter relaxations and reduce GOR.\textsuperscript{18,19}
3.2.1. Positioning and reflux

- Infants can also be nursed in a more upright sloping position on the assumption that the effect of gravity will move gastric contents away from the gastro-oesophageal junction; however this position has been less well studied.

The potential benefits of these positions for inpatients that are monitored must be balanced against the back to sleep message for SIDS prevention once monitoring is stopped.

3.2.2. Feed Manipulation

Apnoea that is resistant to standard treatment could in theory be exacerbated by GOR and though there is scant evidence of benefit, increased feed frequency and therefore reduced volume per feed may be of benefit. 13 Babies born prematurely in Nottingham are routinely started on two hourly feeds making the link between feeding and apnoea difficult to determine. As a short-term measure feed frequency can be increased to hourly bolus or possibly a trial of continuous NG feeding, though a Cochrane review found no trials to inform practice over use of continuous or bolus feeds as a means of reducing GORD. 20

There are numerous problems with continuous feeding such as waste of expressed breast milk (EBM) with pump tubing changes, the cream layer rising to surface and being discarded with tubing resulting in fat loss, and risks associated with hanging times, etc.

Intragastriac Tubes

Due to the inability of preterm infants to coordinate sucking, swallowing, and breathing, tube feeding is frequently used in NICUs. However, the presence of a tube through the gastroesophageal junction can exacerbate GOR through two different mechanisms: firstly, weakening the competence of LOS and subsequently enhancing the refluxing of gastric content into the oesophageal lumen; secondly by impairing oesophageal clearance.21,22 However, a recent retrospective study showed that preterm infants fed through an NG tube have fewer episodes of GOR compared to those fed without NG tube. 23

Non-nutritive sucking (NNS)

Non-nutritive sucking is sucking on a dummy (pacifier) before, during, or after feeding by tube; before or after a bottle/breast feed; or outside of feeding times. It has been proposed as a way to reduce gastro-oesophageal disease in preterm infants. However, a recent Cochrane review concluded that there was insufficient evidence to determine the effectiveness of NNS for GORD in preterm and low birth weight infants. 24
Hydrolysed Formulas

Extensively hydrolysed protein formulas (eHPFs) have been shown to improve GOR features in term infants and children symptomatic for GOR. A significant decrease in total acid GOR episodes and reflux index was observed in newborns fed with eHPF; however, the sample size was small, with low power to evaluate the clinical efficacy of the eHPF on GOR symptoms.

Breastfed infants

Feeding changes are not appropriate in breastfed infants as they often feed on demand. Breastfeeding should not be discontinued because of GOR. Kombol (2009) and Bonyata (2011) discuss in detail the non-pharmacological management of breastfeeding a baby with GOR. Whilst not able to claim it is evidence based, they do provide some practical advice based on physiology which may improve symptoms of GOR for breastfed babies.

Management advice includes: holding a baby in an upright position while breastfeeding, giving the baby short and frequent breastfeeds, and avoiding sudden movements after a feed.

3.2.3 Nasojejunal feeding and reflux

GOR should in theory be reduced by administering feed directly into the jejunum, bypassing the stomach where contents could be regurgitated through the gastro-oesophageal junction. A retrospective review of charts in a neonatal unit routinely using jejunal feeding in suspected reflux associated apnoea, found 41 infants who had been changed to transpyloric feeds but reviewed outcomes in the 15 babies who met their criteria for reflux associated apnoea. They reported significant improvement in 12 of the 15 with no adverse outcomes and suggest that continuous transpyloric feeding is a safe and useful diagnostic and therapeutic option in a select group of newborns with apnoea of prematurity, suspected to be due to gastroesophageal reflux. However a Cochrane review comparing gastric and transpyloric tube placement failed to find evidence of benefit, though GOR was not one of the outcomes in the included studies, but found some evidence of harm, including a higher risk of gastrointestinal disturbance resulting in stopping feeds and increased mortality. They expressed caution in the application of their findings due to the poor methodology of the included studies.

Jejunal tubes are notoriously difficult to pass and maintain in a position beyond the pylorus and require X-ray checking to confirm position. Jejunal feeds should be given as a continuous infusion due to by-passing the stomach which would normally allow gradual
transfer of milk into the jejunum, resulting in the same issues as mentioned in section 3.2.2 (see Nasojejunal feeding guideline G13)

Nasojejunal feeding should not routinely be used as first line management of GOR

**Summary of non-pharmacological recommendations**

- For infants that are monitored body positioning strategies described above can be used as the initial approach. The message about safe sleep practices should be emphasised to families and should be modelled in infants approaching discharge.

- Reduce the volume of feeds (only if this is excessive), then

- Offer a 1–2-week trial of smaller, more frequent feeds (ensuring that the total daily volume of feeds remains the same).

- In older, more mature neonates on 3 hourly feeds, a change to 2-hourly feeding may be beneficial but is not a long-term solution.

- If considered, jejunal feeds should be given as a continuous infusion

4. Pharmacological treatment approaches

GORD medications should only be used after non-pharmacological measures have been taken with incomplete success, as acid suppression may place immune-deficient infants and children at risk for the development of lower respiratory tract infections and nosocomial sepsis. ⁵⁰
4.1 Thickened feeds and reflux

The use of thickeners may slightly improve the occurrence of overt regurgitation /vomiting as symptoms of GOR in infants.\textsuperscript{31}

A recent systematic review and meta-analysis, found moderate-certainty evidence that feed thickeners should be considered if regurgitation symptoms persist in term bottle-fed infants. Due to the small number of studies available, the review provided insufficient information to conclude whether one type of feed thickener is superior to another. Although alginate can be used in breastfeeding infants, so far there is insufficient evidence to show its effectiveness and impact on breast feeding or preterm infants.\textsuperscript{32}

Theoretical adverse effects of some feed thickeners include diarrhoea, allergic reaction and the possibility that thickening agents may have an effect on the bioavailability of dietary nutrients. In vitro studies suggest bioavailability of calcium, iron, and zinc in infant formulas, may be decreased by thickening with non-digestible carbohydrates.\textsuperscript{33}

There are reports of preterm infants developing necrotising enterocolitis after treatment with thickened feeds using non-digestible thickeners.\textsuperscript{34, 35}

4.1.1 Recommendations

- Given the limited evidence of efficacy and the safety concerns, we only recommend for infants with severe persistent symptoms attributable to GOR, a 1–2-week trial of alginate therapy (Gaviscon\textsuperscript{®} Infant)

- If symptoms improve after a 1–2-week trial of alginate therapy (Gaviscon\textsuperscript{®} Infant) continue with this therapy

- Review treatment at regular intervals (for example every 2 weeks) in order to determine if symptoms have improved and if it is possible to stop treatment completely

- If symptoms remain troublesome despite a 1–2-week trial of alginate therapy, consider other diagnoses and pharmacological treatments (see section 4).

- Instant Carobel is another feed thickener that has occasionally been used in the Nottingham neonatal units. Similar to Gaviscon, the manufacturer does not recommend using it in preterm and low birth weight infants except under medical supervision, as there is no clinical data to support its use.
4.1.2 Considerations with Gaviscon® Infant

The manufacturer of Gaviscon Infant claims that its’ mode of action is physical through reacting with gastric acid and forming a gel.⁶⁶ Therefore, concurrent use with proton pump inhibitors such as Omeprazole or H2 receptor antagonists such as Ranitidine, would remove acidic pH required for its mode of action, making it less likely to form a viscous gel and limiting its effectiveness.

Gaviscon Infant should not be used in infants with known or suspected impairment of renal function and it should not be given with other preparations that contain thickening agents or if there is intestinal obstruction.

4.2 Antacid therapy: Proton pump Inhibitors (PPI) and H2 receptor antagonists (H2RA)

A recent systematic review concluded that there is limited evidence supporting the use of antacids in preterm infants.⁹ Further research is still needed into this topic and caution should be taken when administering antacids to preterm infants due to harm associated with their use. Reported harms include overgrowth of pathogenic bacteria in the GI tract, resulting from a rise in gastric pH, increasing length of antibiotic use, increased incidence of late-onset sepsis and NEC.₃⁷,₃⁸

There is no evidence for the use of Ranitidine or Omeprazole to treat possible gastritis in preterm babies or to treat small amounts of blood-stained NG secretions. In these situations, consider resumption of feedings if indicated rather than keeping nil enterally and starting antacid treatment.

Empiric trial of acid suppression should be started only after careful consideration of evidence for GORD causing significant symptoms and after discussion with Consultant.

Omeprazole is superior to Ranitidine in reducing oesophageal acid exposure in infants with pathological acid reflux. When required the smallest effective dose within the recommended dosage range should be used.¹³, ₃⁹

Long-term use is not advisable without a formal diagnosis. A 1-2-week trial is recommended.

In babies with surgical problems such as post-TOF, CDH repair and infants with neurodisability and hypotonic syndromes, consider treating routinely with omeprazole in addition to postural management after discussion with attending neonatal consultant and consultant surgeon.
4.3 Prokinetics: Domperidone, Erythromycin

There is no evidence for effectiveness of these medications, which both have potential side effects including cardiac arrhythmia and higher risk of pyloric stenosis (erythromycin), neurologic side effects (domperidone). They should therefore not be used in the routine management of reflux.

5. Cow’s Milk Protein Allergy (CMPA)

Some infants with cow’s milk protein allergy (CMPA) show symptoms that are difficult to distinguish from those of GOR – regurgitation, vomiting, and discomfort after feeding – so it is not surprising the link has been questioned. CMPA manifesting with such symptoms is likely to be a non IgE-mediated allergy. Although unlikely to be the only cause of GOR in infants, it is something that should be considered in those with significant and persistent symptoms.

NICE guidance where CMPA is suspected would be to take a detailed allergy focused clinical history, and family history which would be used alongside clinical signs to guide further management. 40

Exclusion of cow’s milk protein should not be used routinely in the management of GOR and must only be used after discussion with both the Attending Neonatal Consultant and Neonatal Dietitian.

5.1 Management of suspected cow’s milk protein allergy

5.1.1 Infants receiving maternal breast milk

Only about 1 in 200 exclusively breast-fed infants show clinical reactions to cow’s milk protein (CMP) and most of these are mild. This may be due to the level of CMP actually present in breast milk being ~100,000 times less than cow’s milk. 41 However, in very rare cases of severe CMPA the levels in breast milk may be sufficient to cause symptoms. Management would be to exclude CMP from the maternal diet and should only be considered following discussion with the consultant and involvement of the dietitian.
5.1.2 Infants receiving formula

1. An extensively hydrolysed protein formula would be first option such as Nutramigen 1 for infants born at term and possibly SMA PRO Gold Prem 1 or 2 for preterm infants depending whether a preterm or post-discharge formula is required. The latter is not so extensively hydrolysed.

2. If symptoms persist on the above, an amino acid-based formula such as Nutramigen AA or Neocate LCP could be tried, as they are totally free from cow’s milk protein. These are only likely to be necessary in severe CMPA and should be second line unless severe IgE-mediated allergy is suspected. There is no preterm equivalent.

Duration of trial

A trial of maternal exclusion of cow’s milk protein or an appropriate formula should last for 2-4 weeks. If symptoms improve in non IgE-mediated allergy a reintroduction of the appropriate cow’s milk-based formula should be undertaken to confirm the diagnosis. As most infants will grow out of their CMPA, challenging at a later date is advisable in order that a normal diet can be established as soon as possible. Infants should be challenged at about 6 months when diagnosis and treatment with CMP exclusion occurs in the first few weeks or at 1 year if much later or symptoms return on reintroduction. 42

6. Surgical intervention

Anti-reflux surgery should be reserved for infants with intractable symptoms and failure to gain weight despite optimising medications. Surgery is also considered for infants who are at risk of significant or life-threatening’ complications of GORD, such as recurrent aspiration pneumonias, and apparent life-threatening events. The antireflux surgery that is currently offered locally is Nissen’s fundoplication.

Audit Points:

- Number of Infants diagnosed with GOR(D)
- Number of Infants receiving pharmacotherapy for GOR(D)
- Outcomes of NEC, length of hospital stay, episodes of suspected or proven sepsis, time to full enteral feeds, other adverse events in infants receiving pharmacotherapy for GOR(D)
- Number of infants treated for CMPA


APPENDIX 1

Product name: Gaviscon Infant oral powder
Manufacturer: Reckitt Benckiser

What is it?

Gaviscon Infant contains two active ingredients – sodium alginate and magnesium alginate which act by thickening milk on contact with the acid found in the stomach.

Presentation

Gaviscon Infant is presented as 15 dual sachets = 30 doses/box. Each double sachet needs tearing along the serrated line to give 2 individual sachets.

Indications

Gaviscon Infant is used to manage mild symptoms of reflux and vomiting in infants by increasing the viscosity of the milk when it is in the stomach making it more difficult to regurgitate. It is usually tried if positioning or increased feed frequency hasn't helped.

If used on NICU

According to the manufacturer, 1 dose (i.e. one half of a dual sachet) of Gaviscon Infant should be added to 4oz milk (115ml). Infants on the neonatal unit rarely have this volume of milk - EBM is managed in units of 50ml due to addition of fortifier and liquid formulas come in various sizes —70, 90 and 125ml. It is not designed for use in small feed volumes as required for preterm infants so it is necessary to find a safe but practical way of mixing it.

Practical solutions include:

- Mix 1 dose (i.e. one half of a dual sachet) Gaviscon Infant with 5ml water and ensure it dissolves. Use 1ml of this to add to each 22ml milk and shake to mix (5ml + 110ml = 115ml)
  Mix the required amount of feed + Gaviscon Infant and feed to the baby - discarding remaining Gaviscon

- If the feed is too thick to go down the tube with gentle pressure then give as for breastfeeding infant after feed as below, however mixing is always better.

- When used in infants feeding at breast, Gaviscon Infant cannot be mixed with the feed so it should be mixed with a small amount of water and given by spoon or syringe part way through or after the feed. The amount of Gaviscon Infant given will depend on the volume of breast milk likely to be consumed. Example: A 1.5kg infant on 200ml/kg/day = 38ml every 3hrs for 8 feeds a day, should receive about 1.5ml of above with every feed.

- At discharge, mothers will be making up feed from powder and can make it up in units of 4floz and add 1 single sachet Gaviscon Infant to each 4floz.

NB – The maximum of 6 sachets daily stated on the box is advised by the company due to the sodium level, but in practice this is not an issue in preterm infants who require more sodium. We also only use part dose in each feed. To ascertain effectiveness, **it must be added to every feed.**