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Pharmacological management of gastroesophageal reflux disease in infants: current opinions

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Gastroesophageal reflux disease (GERD) constitutes a troublesome symptom complex resulting from retrograde passage of gastric contents into the esophagus or extra-esophageal regions. Premature-born, high-risk infants and those with neuro-aero-digestive pathologies are at increased risk. Critical review over the last 3 years was conducted, and current opinions on pharmacological targets include agents aimed at prevention of transient lower esophageal sphincter relaxation, modification of the physico-chemical composition of gastric contents, modification of gut motility, or altering sensory thresholds to ameliorate the troublesome symptoms. As data from well-designed studies is limited in the infant population, information from adult studies has been cited where potential application may be helpful.

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Introduction

Definition of GERD

As per NASPGHAN and ESPGHAN societies, gastroesophageal reflux disease (GERD) constitutes a troublesome symptom complex resulting from retrograde passage of gastric contents into the esophagus or extra-esophageal regions [1]. Premature and high-risk infants and those with neuro-aero-digestive pathologies are at increased risk of GERD [1,2].

Pathophysiology and symptomatology of infant-GERD

The physiological form, gastroesophageal reflux (GER), occurs daily in up to 65% of infants of 3–4 months of age, and these infants eat and thrive well amidst non-specific symptoms [3]. A decline in aerodigestive symptom variability and troublesome events occurs with infant maturation. The lower esophageal sphincter (LES) remains a strong anatomical and functional barrier to retrograde transit. In infants, LES maintains a normal resting tone 5–20 mmHg and relaxes briefly during peristaltic waves. In infants and adults, transient lower esophageal sphincter relaxation (TLESR) is the most frequent cause of GER due to pressure gradient between the stomach and the esophagus. The opening of the LES is dependent on its relaxation, inhibition of the diaphragmatic sling, shortening of the esophagus, and on the pressure gradient between the stomach and the gastroesophageal junction. The pathophysiology of GERD in infants is likely to be a multidimensional aero-digestive disorder resulting from foregut-airway interactions and communications [4••]. The pathological sequence of events leading to GERD manifestations include: firstly failure of the anti-reflux barrier, secondly loss of esophageal mucosal integrity due to exposure to gastric contents that alter esophageal defense and clearance mechanisms, thirdly activation of the esophageal mucosa nociceptor, identified as transient receptor potential vanilloid receptor1 (TRPV1), by natural irritants (acid) or mechano-distension [5], or finally triggering of afferent signaling pathways caused by visceral hypersensitivity leading to pain perception or other symptoms [6].

Infants' developmental anatomy and maturational physiology heighten the vulnerability for GER and may result from firstly a short esophagus that allows rapid retrograde spread, secondly cephalad positioning of the LES, thirdly delayed gastric emptying, fourthly frequent liquid feedings and smaller stomach size, thus predisposing to distension induced LES relaxation, and finally decreased gastrointestinal motility [7]. These mechanisms may accentuate GER in conditions such as prematurity, chronic lung disease, and neurologic illness. Common reflux-type of troublesome symptoms are summarized in Table 1, and contribute to increased morbidity, parental anxiety, recurring clinic/hospital visits, prolonged hospital stay, and increased costs [8,9•]. Symptoms can be reflexive in nature or generated by the presence of refluxate in the esophagus or extra-esophageal regions. Refluxate characteristics vary widely in chemical

Table 1

Troublesome GERD-type symptoms in infants

Neurosensory	Respiratory
Oral aversion	Apnea
Gag	Desaturation
Failure to thrive	Apparent life threatening Events
Arching	Brief resolved unexplained events
Irritability	Wheezing
Sleep disturbances	Stridor
	Bronchospasm
	Cough
	Sneeze
	Aspiration
	Dependence on respiratory support

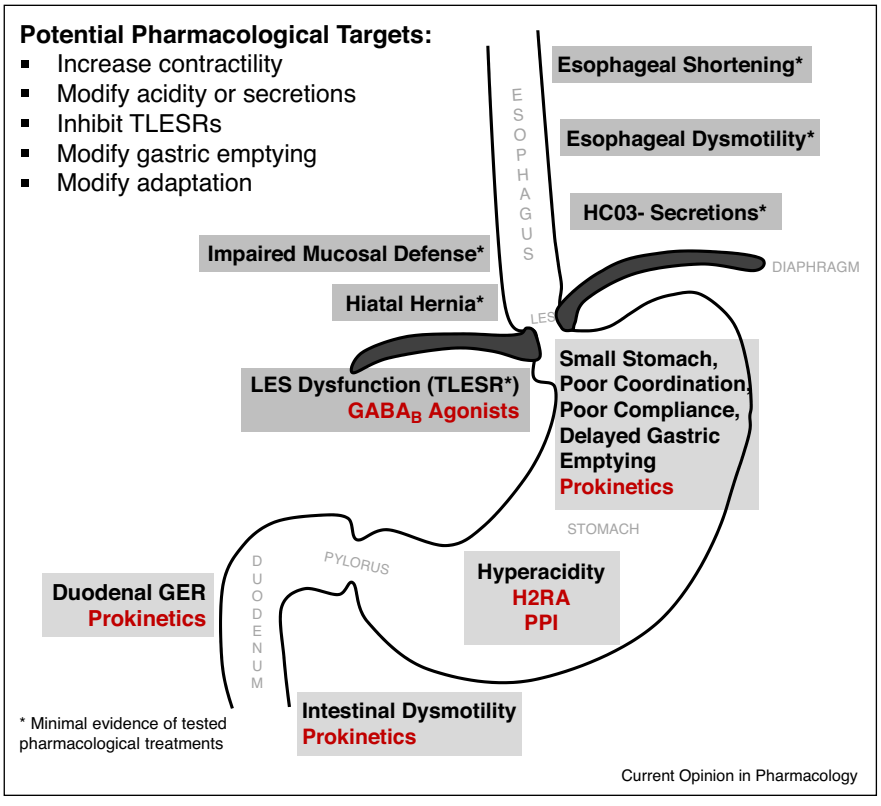
Cardiac	Gastrointestinal
Bradycardia	Vomiting
	Regurgitation
	Feeding Difficulty
	Poor oral intake

composition, physical composition, height, and duration of exposure [10,11••]. Potential mechanisms and pharmacological targets of GERD are summarized in Figure 1.

Management of GERD

Distinction between physiological GER and pathological GERD is important to identify proper management strategies, risks, and benefits. Empirical treatment of GERD in infants is frequent, despite a low yield in improvement of GERD type symptoms [8,9•,12••]. Maximal extent of acid reflux events on symptoms generated in dysphagic neonates was characterized to define true acid GERD in neonates. The most proximal ascent into middle or proximal esophagus likely activates protective aerodigestive reflexes or vigilant states to facilitate bolus and chemical clearance. Heightened esophageal sensitivity, acid neutralization delay, or delays in clearance mechanisms accentuate multi-systemic troublesome symptoms [11••].

Figure 1



Potential gastroesophageal reflux disease (GERD) mechanisms and pharmacological targets in infants and those with aerodigestive reflex problems (presented in grey boxes and in red font, respectively). These have been tested in adults and children, although the potential mechanisms (denoted with *) have not been thoroughly tested as pharmacological targets in premature infants; others have been tested with varying results. The most frequent GERD mechanism is the transient lower esophageal sphincter relaxation (TLESR), the target for $GABA_B$ agonist's effects. Potential pharmacological targets are: **(1)** increasing esophageal contractility, **(2)** modifying acidity or secretions, **(3)** inhibiting TLESRs, **(4)** modifying gastric emptying, and **(5)** modifying adaptation of the lower esophageal sphincter (LES)-$GABA_B$: Gamma-amino-butyric acid B receptor; H2RA: H2 receptor antagonist; PPI: proton pump inhibitor.