**Review article: pathophysiology, differential diagnosis and
management of rumination syndrome**

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EDITOR'S COMMENTS TO AUTHOR:

Please consider the points raised by the reviewers.

REVIEWERS' COMMENTS TO AUTHOR:

Reviewer: 1

Comments for Transmission to the Authors

This review concerns the pathophysiology, differential diagnosis and treatment of a rather rare clinical problem which often remains undiagnosed (and untreated) due to poor understanding of the syndrome by the physicians.

The authors are well-known specialists on the field with an extensive experience on motility disorders of the upper GI and the use of manometry and impedance technology.

The article is well structured, didactic and highly informative including the new diagnostic modalities available for the diagnostic approach of the syndrome.

As minor comments:

1.I would omit the forth figure as the information provided is rather of minor importance.

We agree and have omitted figure number 4.

2. On page 12 line 8, the reference should be numbered as (40).

We agree. This has been corrected.

Reviewer: 2

Comments for Transmission to the Authors

This is a well illustrated and informative review of the diagnosis and management of rumination syndrome.

It is up to date and will be of interest to a wide GI readership.

My only comment is on the short section on epidemiology: it should be stated more clearly that there is no reliable data on prevalence of the disorder, but it is underdiagnosed because it is often not considered as a differential.

We agree. This has been clarified in the epidemiology section.

**Review article: pathophysiology, differential diagnosis and management of
rumination syndrome**

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Flanders. This work was supported by a Methusalem grant to Jan Tack, M.D., Ph.D.

Key words: rumination, high resolution manometry, esophageal impedance monitoring,
behavioral therapy, baclofen

ABSTRACT

Background: Rumination syndrome, characterized by the effortless, often repetitive, regurgitation of recently ingested food into the mouth, was originally described in children and in the developmentally disabled. It is now well-recognized that rumination syndrome occurs in patients of all ages and cognitive abilities. *Aim:* To provide a scholarly review on our current understanding of the rumination syndrome. *Methods:* The review was conducted on the basis of a medline search to identify relevant publications pertaining to the pathophysiology, clinical diagnosis and management of rumination syndrome. *Results:* The Rome III consensus established diagnostic criteria for rumination syndrome in adults, children and infants. A typical history can be highly suggestive but esophageal (high resolution) manometry/impedance with ingestion of a meal may help to distinguish rumination syndrome from other belching/regurgitation disorders. The pathophysiology is incompletely understood, but involves a rise in intra-gastric pressure, generated by a voluntary, but often unintentional, contraction of the abdominal wall musculature, at a time of low pressure in the lower esophageal sphincter, causing retrograde movement of gastric contents into the esophagus. To date, controlled trials in the treatment rumination syndrome are lacking. The mainstay of treatment for rumination syndrome is explanation and behavioral treatment which consists of habit reversal techniques that compete with the urge to regurgitate. Chewing gum, prokinetics, baclofen and even anti-reflux surgery have been proposed as adjunctive therapies, but high quality studies are generally lacking. *Conclusion:* The rumination is an under-recognized condition with incompletely understood pathophysiology. Behavioral therapy seems effective, but controlled treatment trials are lacking.

Introduction

Rumination is a phenomenon that occurs in animals such as sheep, cattle, and goats, with compartmentalized stomachs consisting of multiple chambers. (1) In these animals, food moves back into the mouth from the proximal two chambers of the stomach by retrograde peristalsis which is coordinated with a relaxation of the lower esophageal sphincter. The animals then re-chew and re-swallow the regurgitated food, and this aids in the digestion and absorption of food by reducing particle size and enhancing mechanical degradation (1).

Rumination syndrome in humans refers to a clinical entity which is characterized by the effortless, often repetitive, regurgitation of recently ingested food into the mouth (2,3). The regurgitated material can be chewed and swallowed again, or is spat out. Typically, the regurgitation in rumination is not preceded by nausea or retching. Rumination syndrome was originally described in children and in developmentally disabled (4-7), but it is now well-recognized that rumination syndrome occurs in patients of all ages and cognitive abilities, the majority of them female (2,3,8-13).

Clinically, rumination syndrome is probably under-diagnosed, and adults with rumination may be erroneously considered to have (refractory) vomiting secondary to gastroparesis or regurgitation due to gastroesophageal reflux disease. Lack of awareness amongst

physicians probably contribute to missed diagnoses of rumination syndrome, which should be considered in the differential diagnosis of all patients presenting with “regurgitation” and “vomiting”, especially when they occur postprandially and are associated with weight loss (14,15). Poor understanding of the syndrome by physicians may also reduce the effectiveness of therapeutic interventions in patients with this complex disorder.

Methods

To identify relevant studies, both computerized (Medline) and manual searches were performed, using the cited references of the retrieved articles. MeSH and free-text terms for rumination syndrome were used alone or combination with the terms pathogenesis, pathophysiology, pathogenesis, epidemiology, treatment and management for searches conducted for the period up to November 2010.

Epidemiology

The epidemiology of rumination syndrome in the adult general population remains to be carefully defined. Reliable data on the prevalence of the disorder are lacking, and data from clinical practice are probably inadequate for this underdiagnosed condition which is often not considered in the differential diagnosis of refractory vomiting or regurgitation. Based on the case numbers seen at referral centers, rumination syndrome is probably uncommon (10-15).

Diagnostic Criteria

According to the Rome I and II consensus, rumination syndrome in adults was defined as effortless regurgitation of recently ingested food into the mouth with subsequent remastication and reswallowing or spitting out, in the absence of structural disease. Furthermore, the Rome II definition stated that the regurgitation is effortless, not associated with abdominal discomfort, heartburn, or nausea, and can occurs in the postprandial period to cease when the food taste becomes acidic (16,17).

Rumination is well described in infants with the typical age of onset between three and six months. The Rome III committee based adult diagnostic criteria on the pediatric criteria and on the Rome II definitions. The definition was adapted to stress the absence of retching and nausea in most cases, as well as the time frame of 3 months for all functional disorders (14). The Rome III definition for rumination syndrome in adults is summarized in Table 1 (18). The definition for rumination in childhood and adolescence is closely related (19), but includes failure to respond to anti-reflux therapy. In infants an adapted definition has been proposed (20).

Clinical Evaluation and diagnostic approach

It is often stated that rumination syndrome can easily be diagnosed by history alone (15,17). Typical elements are the start of regurgitation during or immediately after the meal, the effortless nature, the absence of prodromal nausea and especially the ability to swallow the regurgitated material. In typical cases, repetitive regurgitation of gastric contents starts within minutes, often already during the meal, and usually persists for 1 up to 2 hours. To the subject, the regurgitated material is recognized as food, and often has a pleasant taste (12). The regurgitation is effortless or may be preceded by an immediately preceding sensation of belching. These features may help to distinguish rumination from vomiting, although history alone is not always accurate (21). In case of a sufficiently convincing history, a firm diagnosis of rumination can be made, the nature of the disorder can be explained to the patient (3,11,12,15,18), and treatment can promptly be initiated (see below). In some cases, there may still be diagnostic uncertainty, or the patient may be reluctant to accept this simple diagnosis (21).

In spite of the often typical presentation, a diagnosis of rumination is often delayed in clinical practice, and patients may initially be misdiagnosed as having gastro-esophageal reflux disease (GERD) or dyspepsia/gastroparesis with vomiting (11,22). Distinguishing rumination from regurgitation as a part of the typical GERD spectrum is sometimes difficult, especially if some heartburn is or was present and when the patient has already been treated with a proton pump inhibitor. Regurgitation, like rumination, occurs mainly postprandially, is effortless, may be swallowed again and is not preceded by nausea. Furthermore, endoscopy may reveal low-grade esophagitis, a consequence of caustic gastric contents that are brought up during rumination events, which may

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3 further complicate the diagnostic picture (11). Ambulatory esophageal pH/impedance
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5 monitoring may actually be suggestive of reflux disease in these patients, by showing a
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7 high number of reflux events and an elevated percentage of time with intra-esophageal
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9 pH below 4 (11,23). Upon detailed examination, the traces show a high number of
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11 repetitive events in the first postprandial hour, a busy erratic pattern of back- and forth-
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13 movement by regurgitation and re-swallowing, and absence of events at night (Figure
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15 1). Furthermore, when studied off acid suppression, there is often a discrepancy
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17 between the high number of reflux events and the relatively modest percentage of time
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19 that the esophageal pH is below 4, due to food buffering of gastric acidity during the
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21 postprandial period when repetitive regurgitation occurs (11).
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29 In the majority of patients, additional symptoms such as nausea, heartburn, abdominal
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31 discomfort, diarrhea and/or constipation are also present (1,11,18,22). Weight loss can
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33 also be a prominent feature of rumination syndrome, particularly in the adolescent
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35 population. (3,4,11,18,22). These features make distinguishing rumination from
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37 gastroparesis less obvious in certain cases, but in gastroparesis there is preceding
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39 nausea and often retching, and vomiting occurs typically late postprandially, and the
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41 food is no longer recognizable as such by taste. While vomiting may be intermittent, or
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43 dependent on the meal, rumination seems to occur invariably with every meal, and often
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45 also occurs after ingestion of only liquids. Occurrence of weight loss in young female
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47 adults may also lead to misdiagnosing as bulimia and/or anorexia nervosa. (24-26).
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In case of diagnostic uncertainty, and especially in case of poor patient's acceptance of a possible diagnosis of rumination, manometric evaluation may confirm the diagnosis. The manometric pattern associated with rumination has been described already a long time ago in the literature (12,27). More recently, the yield of adding stationary intraluminal impedance was evaluated. Performing stationary esophageal manometry and impedance with administration of a meal and monitoring of postprandial regurgitation events refined the diagnosis and was able to more accurately distinguish between rumination, regurgitation and belching (21). In the rumination events, a rise in intra-gastric pressure as assessed by manometry preceded or occurred simultaneously with retrograde intra-esophageal flow as detected by impedance (21) (Figure 2). More recently, the combined use of manometry, high resolution manometry and stationary esophageal impedance in the evaluation of rumination and regurgitation disorders was evaluated, and the combination of high resolution manometry with stationary impedance monitoring had the highest diagnostic accuracy and was able to detect some unusual patterns (Figure 3), including combinations of esophageal belching and rumination (28).

Pathophysiology

Rumination is characterized by a rise in intra-gastric pressure which precedes or coincides with retrograde movement of gastric contents into the esophagus (21,27). The rise in intra-gastric pressure is generated by a voluntary, but often not intentional, contraction of the abdominal wall musculature. In addition, it has been suggested that a

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3 forward extension of the head is used to open the upper esophageal sphincter at the
4 same moment (13, 29). The prerequisite for upward movement of gastric contents
5 during straining is a lower esophageal sphincter (LES) pressure which is lower than the
6 generated intragastric pressure. The reasons for this low LES pressure could be a
7 prolonged low LES pressure postprandially, or a temporary lowering during transient
8 LES relaxations (TLESRs) which are sensed by the subject.
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20 Indeed, it has been suggested that TLESRs at the time of belching are sensed by the
21 patients and used to strain and bring up gastric content (30). Alternatively, an
22 exaggerated response to gastric filling has been proposed to underlie transient drops in
23 LES pressure in rumination. Thumshirn et al demonstrated that patients of normal
24 intelligence with rumination syndrome required significantly lower fundic pressures to
25 induce LES relaxation and had increased sensitivity to gastric balloon distention
26 compared to healthy controls (31). The authors suggest that in these patients, the
27 pressure of food within the fundus results in reflex inhibition of lower esophageal
28 pressure leading to the induction of a modified belch reflex. A third hypothesis is a
29 learned, voluntary relaxation of the diaphragmatic crura that allows the normal
30 postprandial increase in intragastric pressure to overcome the resistance to retrograde
31 flow provided by the lower esophageal sphincter (32).
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50 The reason for the straining is unclear, and both psychological factors (see below) as
51 well as attempts to relieve dyspeptic symptoms with belching leading to a rumination
52 behavior have been suggested (11).
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Psychological Features

In some patients, stressful life events can be identified around the period of symptom onset (11). However, in most cases, rumination occurs in the absence of such identifiable eliciting factors. Associations between rumination and bulimia nervosa have also been described. Studies reported rumination in 20% of bulimics, and a history of bulimia in 17% of females with rumination (12,26). However, ruminators with bulimia tend to expel rather than to re-swallow their food, and they may also exhibit self-induced vomiting by digital stimulation of the hypopharynx. It has been suggested that rumination in this group is a learned behavior, aimed at controlling body weight without induction of frank vomiting, and therefore may be considered more a variant of an eating disorder. Because of the underlying aim of weight loss, treatment of rumination in bulimics has been reported to be less successful.

TREATMENT

To date, controlled trials in the treatment rumination syndrome are lacking, and the available evidence consists mainly of case series. Rumination is often misdiagnosed as GERD with regurgitation, and proton pump inhibitors (PPIs) are often started. In rumination syndrome, PPIs may provide some benefit by suppressing the symptom of

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3 heartburn and by better protect the esophageal mucosa. On the other hand, acid
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5 suppression may paradoxically prolong rumination behavior after a meal, which usually
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7 ceases when the food in the stomach becomes acidic. Hence, the therapeutic benefit of
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9 PPIs is limited and they are at best and adjuvant while more definitive therapy is
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13 instituted.

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17 The mainstay of treatment for rumination syndrome is explanation of the condition, the
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19 mechanism underlying the rumination events, and behavioral modification. Behavioral
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21 treatment consists of learning and using habit reversal techniques, usually
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23 diaphragmatic breathing, which compete with the urge to regurgitate (29,30,33-35). The
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25 application of diaphragmatic breathing during the postprandial period effectively
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27 eliminates rumination activity (29). Diaphragmatic breathing can easily be learned by
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29 putting a hand on the chest and on the abdomen during respiration, and instructing that
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31 only the hand on the abdomen may move with breathing (29). Case series report
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33 disappearance of rumination behavior in 30-66% and improvement in another 20-55%
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35 (11,34,36). Alternatively, chewing gum has been proposed as a treatment of rumination
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37 in the pediatric population. A number of case studies reported a positive effect of
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39 chewing gum, which led to a reduction of the number of rumination events in young
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41 children and adolescents (37,38).

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50 In theory, treatment aimed at restoring the barrier function of the LES should also be
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52 effective. In a small group of patients who did not respond to behavior therapy, a Nissen
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54 fundoplication was reported to be effective (39). However, clinical experience suggests
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that the outcome of surgery may be less favorable, potentially leading to persistent symptoms which may include retching, gas-bloat syndrome, and gastroparesis. Medical therapy aimed at improving LES pressure is another potential approach. One study used the prokinetic levosulpiride as adjuvant, but the focus of treatment was also on psychotherapy and education (40). The same authors also found that a higher LES pressure was associated with a better treatment outcome (40). However, prokinetic drugs are generally not very effective at improving LES pressure (41). On the other hand, baclofen was found to significantly enhance postprandial LES pressure and to suppress TLESRs, and this could potentially be beneficial in the treatment of rumination syndrome (42). In a preliminary series of 10 patients who underwent combined high resolution manometry with stationary impedance monitoring and administration of a 1000Kcal solid meal, we observed that baclofen 10 mg preprandially was able to decrease symptoms of regurgitation by approximately 50%. In addition we observed a 65% reduction in rumination episodes identified on the HRM-impedance recording (Blondeau et al., unpublished observations).

Future research

The exact epidemiology and the natural history of the rumination syndrome await detailed studies. The causes and onset of rumination syndrome also remain unclear. Future studies should establish whether this is indeed occurring as a consequence of dyspeptic symptoms, and whether having a low LES pressure or a certain psychological profile is a predisposing factor. Controlled trials are needed to assess the efficacy of

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3 drugs that enhance LES pressure, and whether these are equivalent or superior to
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5 behavioral therapy, or whether they are more suitable as an adjunctive measure.
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For Peer Review

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FIGURE LEGENDS

Figure 1. Rumination as observed during ambulatory pH/impedance monitoring. The trace is characterized by a busy erratic pattern of back- and forth- movement by rumination (left arrow) and re-swallowing (right arrow) on the impedance tracings (6 upper channels). There is no acid reflux (lower channel).

Figure 2. Rumination is observed as a rise in intra-gastric pressure on manometry (2 lower channels, block arrow), which precedes retrograde intra-esophageal flow on impedance (7 upper channels, line arrow).
LES: Lower Esophageal Sphincter, UES: Upper Esophageal Sphincter

Figure 3. Three consecutive rumination episodes on high resolution manometry/stationary impedance monitoring. Rumination is observed as a rise in intra-gastric pressure on the high resolution manometry colour plot (block arrow), which precedes retrograde intra-esophageal flow on impedance (line arrow).
LES: Lower Esophageal Sphincter, UES: Upper Esophageal Sphincter

TABLE

Rome III definitions of rumination syndrome in adults, adolescents and infants	
Rumination syndrome in adults:	
Must include both of the following:	
<ol style="list-style-type: none"> 1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or re-mastication and swallowing. 2. Regurgitation is not preceded by retching 	
Supportive criteria:	
<ol style="list-style-type: none"> 1. Regurgitation events are usually not preceded by nausea 2. Cessation of the process when the regurgitated material becomes acidic 3. Regurgitant contains recognizable food with a pleasant taste 	
Rumination syndrome in adolescents :	
Must include all of the following:	
<ol style="list-style-type: none"> 1. Repeated painless regurgitation and re-chewing or expulsion of food that <ol style="list-style-type: none"> a. begin soon after ingestion of a meal b. do not occur during sleep c. do not respond to standard treatment for gastroesophageal reflux 2. No retching 3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms 	
Rumination syndrome in infants :	
Must include all of the following for at least 3 months:	
<ol style="list-style-type: none"> 1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue 2. Regurgitation of gastric content into the mouth, which is either expectorated or re-chewed and re-swallowed 3. Three or more of the following: <ol style="list-style-type: none"> a. Onset between 3 and 8 months b. Does not respond to management for gastroesophageal reflux disease or to anticholinergic drugs, hand restraints, formula changes, and gavage or gastrostomy feedings c. Unaccompanied by signs of nausea or distress d. Does not occur during sleep and when the infant is interacting with 	

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individuals in the environment

For Peer Review

Figure 1

254x190mm (96 x 96 DPI)

Figure 2

254x190mm (96 x 96 DPI)

review

Figure 3

254x190mm (96 x 96 DPI)