SYNTHESIS AND REVIEW (CE ACTIVITY)

Gastrointestinal Complications Associated with Anorexia Nervosa: A Systematic Review

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ABSTRACT
Objective: A systematic review identifying gastrointestinal (GI) complications attributable to anorexia nervosa (AN) was completed.

Method: Studies of any design exploring the pathogenesis of complications and treatment strategies were included. The review was completed in accordance with PRISMA standards.

Results: A total of 123 articles were retained, including one randomized control trial. The majority of included studies were case reports and case series. Controlled studies demonstrated that patients with AN were more likely to have delays in gastric motility, gastric emptying and intestinal transit than comparator groups although results were not uniform across all studies. Published reports suggest that complications can occur at any segment of the GI tract. These issues may derive as a consequence of severe malnourishment, from eating disorder related symptoms such as self-induced purging or from the refeeding process itself. Multiple studies noted that patients with AN report high rates of GI symptoms although in the few cases where medical testing was undertaken, correlations between self-reported symptoms and measurable pathology were not demonstrated.

Discussion: GI complications may occur throughout the entire GI tract in patients with AN. It is recommended that clinicians use careful judgment when pursuing targeted investigation or introducing symptom specific treatments in response to GI complaints. Evidence suggests that most GI complications resolve with refeeding and cessation of ED symptoms.

Keywords: systematic; review; gastrointestinal; anorexia nervosa; gastric emptying; gastric motility; constipation; transit; gastric dilatation; superior mesenteric artery syndrome

Resumen
Objetivo: Se completó una revisión sistemática para identificar complicaciones gastrointestinal (GI) atribuibles a la anorexia nervosa (AN).

Método: Se incluyeron estudios de cualquier diseño, que exploraran la patogénesis de las complicaciones y las estrategias de tratamiento. La revisión fue completada de acuerdo a los estándares PRISMA.

Resultados: un total de 123 artículos fueron revisados incluyendo un estudio aleatorio controlado. La mayoría de los estudios incluidos fueron reportes de casos y series de casos. Los estudios controlados demostraron que los pacientes con AN fueron más propensos a tener motilidad gástrica, vaciamiento gástrico y tránsito intestinal retardados en comparación con el grupo control, aunque los resultados no fueron uniformes en los diferentes estudios. Los reportes publicados sugieren que las complicaciones pueden ocurrir en cualquier segmento del tracto GI. Estos problemas pueden ser consecuencia de la severa desnutrición, de síntomas relacionados con el trastorno alimentario tales como conductas purgativas o del proceso de realimentación por sí mismo. Múltiples estudios reportaron que los pacientes con AN presentan altos índices de síntomas GI, aunque en los pocos casos donde se practicaron estudios médicos, no se demostró correlación entre síntomas auto-reportados y patología medible.

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Introduction

Anorexia nervosa (AN) is a psychiatric disturbance that can result in serious and potentially deadly medical complications. The gastrointestinal tract is susceptible to complications that are directly and indirectly attributed to weight loss and purging behaviours. Scientific study as well as clinical practice suggests that eating disorder patients commonly report symptoms related to the GI tract, although it can sometimes be challenging to differentiate complaints that represent functional issues as opposed to recognizable pathology. To date there has not been a systematic review on the topic which has utilized internationally recognized and accepted search criteria such as that outlined by PRISMA guidelines.

This systematic review addresses the following objectives:

To identify gastrointestinal complications attributable to anorexia nervosa
To review studies exploring the pathogenesis of these complications
To describe treatment strategies intended to address GI complications related to AN.

In accordance with PRISMA guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 24 March 2015 (registration number CRD42015017854).

Search Strategy

The following databases were searched focusing on gastrointestinal disease and AN: MEDLINE including In-Process & Other Non-Indexed Citations (1946 to Mar 5 2015) and Embase (1980 to 2015 Week 09). All were searched using the Ovid interface. The MEDLINE search strategy was developed by a librarian experienced in systematic review searches (MS). No language or study design limits were applied. The search strategies are presented in the Appendix.

Non-English articles were included assuming they could be translated sufficiently, using Google Translate, for evaluation. Bibliographies of relevant manuscripts were also searched to ensure any potentially relevant articles were included in the initial screen.

Eligibility Criteria

Studies were selected according to the criteria outlined below:

Studies
Studies of any design, including published case reports, were included.

Participants
Studies were included that involved pediatric and adult patients with AN. In cases where studies included both adults and children, or cohorts with AN and bulimia nervosa (BN), data was aggregated separately where possible.

Intervention or Exposure
Publications were targeted that examined the prevalence of GI complications and that reported on interventions implemented in patients with AN.

Outcomes
Primary endpoints were publications that increased knowledge and influence clinical practice. Pertinent endpoints addressed the myriad of GI complications including but not limited to: esophageal complications such as gastro-oesophageal reflux (GER); gastric complications such as dilatation, perforation; hepatic and pancreatic complications; intestinal complications such as ileus, obstruction, constipation; anorectal issues including prolapse. Outcomes have been presented where feasible in tabular format.
Setting

Studies conducted in hospital or outpatient clinical settings were included.

Abstract and Article Selection

Titles and (where available) abstracts of studies obtained using the search strategy were reviewed independently by two researchers using the outlined inclusion criteria. In cases where agreement was not reached, a third reviewer helped determine suitability. The full text of potentially eligible studies was retrieved and assessed for eligibility by two review team members, with input from a third reviewer as required. We recorded and tracked reasons for excluding trials (Fig. 1). Reviewers were not blinded to study authors or institutions during the review. Articles were excluded if they could not be obtained during the search time frame (March 15-April 30th, 2015).

Results

Database searching identified 717 records, with 631 retained for screening after duplicates were removed. Reference lists identified 40 additional reports that were assessed for eligibility. A total of 123 articles met criteria for the review and were
retained (Fig. 1). Figure 2 illustrates a breakdown of study designs of the 123 included papers. In an attempt to provide as concise a review as possible, the authors have chosen to only present complications primarily observed in AN, as opposed to those more frequently observed in bulimia nervosa (BN) but also co-occurring in AN.

Gastro-Esophageal Complications

Tables 1 and 2 summarize reports that focused on gastric findings and complications. Studies that focused on sialadenosis, which is characterized by noninflammatory salivary gland enlargement,

and esophageal perforation,

and rumination syndrome,

will not be discussed as part of the results given these complications are more frequently observed in BN (although pertinent references have been made available).

Esophageal Motility and Achalasia/Dysphagia. Two studies using esophageal manometry to investigate motility in patients diagnosed with AN reported a high frequency of esophageal-related symptoms in AN patients but almost all (23/24) had normal esophageal manometry. Stacher identified a high rate of primary esophageal motility disorders in 50% of the study sample (15/30), including seven who were subsequently diagnosed with achalasia. In this case series of 30 women (age range of 14–43 years old) with a presumed diagnosis of AN, 10 of 15 patients with esophageal motility disorders required medical interventions (mechanical dilation for achalasia; fundoplication for patient with severe GERD and esophagitis; nifedipine to treat abnormal esophageal contractions and spasms) to address the esophageal abnormalities, highlighting the importance of the medical history and work-up of patients with AN. There is potential for selection bias in Stacher’s group given all study AN patients were selected from individuals who were referred to a tertiary care site for esophageal disorders.

There is scant research exploring achalasia and dysphagia in AN; we identified two studies which are described here. Of note, a large number of cases were identified in which patients had improperly been diagnosed with AN, and were later found after undergoing more intensive medical investigation to have achalasia. Given the reality that dysphagia impacts a patient’s ability to be successfully refeed, it is imperative that the initial clinical assessment include questions pertaining to swallowing and that appropriate investigations be undertaken in cases where difficulties are identified. Oro-pharyngeal dysphagia symptoms were the presenting symptoms described in a case series of three female patients ages 24–33 years with severe AN [body mass index (BMI) range 9.6–12.7 kg/m²].

During bedside swallowing tests (video-fluoroscopic swallowing study scales), all the three patients were found to have dysphagia (mild to moderate in two patients; severe in one patient), abnormal oro-pharyngeal swallowing function, and signs of aspiration. Authors described significant improvements in the dysphagia symptoms and swallowing function score tests for all three patients following dysphagia therapy using 6–9 sessions of neuromuscular electrical stimulation (NMES) and swallowing therapy (including strengthening exercises). Additionally, patients displayed no further signs of aspiration, tolerated oral diets, and gained weight (0.4–3 kg). Authors speculate that patients with AN may suffer from dysphagia because of the weakening of smooth and skeletal musculature secondary to starvation mediated atrophy, as well as damage caused by potentially long-standing GERD and recurrent vomiting. In a case-control prospective study that aimed to evaluate the frequency of esophageal motility abnormalities and related symptoms in a small group of female patients with AN (11 patients with AN-R, mean age 19.9 years, mean body mass index (BMI) 13.2 kg/m²; 12 patients with AN-binge/purge (AN-BP), mean age 25.4, mean BMI 15.5 kg/m²), Benini et al. found a relatively low rate of dysphagia with no difference between AN subtypes (3/11 patients with ANR, 1/12 patients with AN-BP); of note the rate of dysphagia in AN was higher than the rate seen in the matched control group. Patients in the latter study had relatively higher BMIs than those described in the former case series. The small sample sizes in both studies described make it difficult to speculate an overall rate and nature of dysphagia in
### TABLE 1. Gastric complications in patients with AN

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender (F/M)</th>
<th>Age (years)</th>
<th>BMI, If Noted (kg/m²)</th>
<th>Imaging (If Completed)</th>
<th>Complication Described</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russell5 (1966)</td>
<td>F</td>
<td>16</td>
<td>NR</td>
<td>Physical exam</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Evans6 (1968)</td>
<td>F</td>
<td>20</td>
<td>NR</td>
<td></td>
<td>Gastric dilatation, necrosis and perforation</td>
<td>Gastrectomy and pyloroplast</td>
</tr>
<tr>
<td>Jennings7 (1974)</td>
<td>F</td>
<td>14, 25</td>
<td>NR</td>
<td>xray</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Bessingham8 (1977)</td>
<td>F</td>
<td>16, 19</td>
<td>NR</td>
<td>xray</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Browning9 (1977)</td>
<td>F</td>
<td>17</td>
<td>NR</td>
<td>laparotomy</td>
<td>Gastric dilatation, Necrosis/gangrene; esophagogastric fistula with subphrenic abscess</td>
<td>Surgical (subtotal gastrectomy, esophagogastrostomy, feeding jejunostomy)</td>
</tr>
<tr>
<td>Jennings7 (1974)</td>
<td>2 cases (F)</td>
<td>14, 25</td>
<td>NR</td>
<td>xray</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Bessingham8 (1977)</td>
<td>F</td>
<td>16, 19</td>
<td>NR</td>
<td>xray</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Browning9 (1977)</td>
<td>F</td>
<td>17</td>
<td>NR</td>
<td>laparotomy</td>
<td>Gastric dilatation, Necrosis/gangrene; esophagogastric fistula with subphrenic abscess</td>
<td>Surgical (subtotal gastrectomy, esophagogastrostomy, feeding jejunostomy)</td>
</tr>
<tr>
<td>Keane11 (1978)</td>
<td>F</td>
<td>16</td>
<td>NR</td>
<td>xray, exploratory</td>
<td>Gastric perforation</td>
<td>Conservative*, then surgical for duodenal ileus (duodenojejunal anastomosis)</td>
</tr>
<tr>
<td>Lebriquir12 (1978)</td>
<td>F</td>
<td>23</td>
<td>11</td>
<td></td>
<td>Gastric dilatation, necrosis and perforation</td>
<td>Death</td>
</tr>
<tr>
<td>Kline13 (1979)</td>
<td>F</td>
<td>20</td>
<td>11.5</td>
<td></td>
<td>Gastric perforation</td>
<td>Death</td>
</tr>
<tr>
<td>Saul14 (1981)</td>
<td>F</td>
<td>22</td>
<td>NR</td>
<td></td>
<td>Gastric dilatation, necrosis and perforation</td>
<td>Total gastrectomy, then developed small bowel and large intestine infarctions</td>
</tr>
<tr>
<td>Backett15 (1985)</td>
<td>F</td>
<td>17</td>
<td>NR</td>
<td>xray</td>
<td>Gastric dilatation and acute pancreatitis, Gastric dilatation, Necrosis, stricture</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Abdri16 (1987)</td>
<td>2 cases (F)</td>
<td>14</td>
<td>NR</td>
<td>laparotomy</td>
<td>Gastric dilatation, Necrosis, stricture</td>
<td>Surgery</td>
</tr>
<tr>
<td>Coste17 (1992)</td>
<td>F</td>
<td>19</td>
<td>13.1</td>
<td>xray</td>
<td>Gastric dilatation, Necrosis, limb ischemia</td>
<td>Surgery, DEATH</td>
</tr>
<tr>
<td>Van Dijk18 (1994)</td>
<td>F</td>
<td>31</td>
<td>13.5</td>
<td></td>
<td>Gastric dilatation, Gastric dilatation</td>
<td>Surgical (total gastrectomy)</td>
</tr>
<tr>
<td>De Caprio19 (2000)</td>
<td>M</td>
<td>16</td>
<td>13.7</td>
<td>xray, CT scan, endoscopy</td>
<td>Gastric dilatation, Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Nakao20 (2000)</td>
<td>F</td>
<td>17</td>
<td>16.6</td>
<td></td>
<td>Gastric dilatation, Necrosis and perforation</td>
<td>Gastric resection and reconstruction</td>
</tr>
<tr>
<td>Lo21 (2004)</td>
<td>F</td>
<td>26</td>
<td>NR</td>
<td>CT scan, enteroscope</td>
<td>Gastric dilatation, Necrosis and perforation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Mathevon22 (2004)</td>
<td>F</td>
<td>25</td>
<td>15.4</td>
<td>xray, CT scan</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Simicina23 (2005)</td>
<td>F</td>
<td>19</td>
<td>17.9</td>
<td></td>
<td>Gastric dilatation</td>
<td>Death</td>
</tr>
<tr>
<td>Barad24 (2006)</td>
<td>F</td>
<td>24</td>
<td>NR</td>
<td>CT scan</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Birmingham25 (2007)</td>
<td>F</td>
<td>19</td>
<td>NR</td>
<td></td>
<td>Gastric dilatation</td>
<td>Unremarkable; No further gastric complications</td>
</tr>
<tr>
<td>Arie26 (2008)</td>
<td>F</td>
<td>16</td>
<td>11.3</td>
<td></td>
<td>Gastric necrosis and perforation</td>
<td>Total gastrectomy</td>
</tr>
<tr>
<td>Watanabe27 (2008)</td>
<td>F</td>
<td>31</td>
<td>16.2</td>
<td>Autopsy</td>
<td>Gastric dilatation</td>
<td>Death</td>
</tr>
<tr>
<td>Choirat28 (2010)</td>
<td>F</td>
<td>19</td>
<td>NR</td>
<td>CT scan</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Morse29 (2010)</td>
<td>F</td>
<td>18</td>
<td>NR</td>
<td></td>
<td>Gastric dilatation, Necrosis and perforation</td>
<td>Complete gastrectomy, right hemicolectomy, repair of the ruptured diaphragm, and placement of an esophageal drain and colostomy; subsequent distal ileum resection</td>
</tr>
</tbody>
</table>

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patients with AN but suggest that targeted therapy helps alleviate symptoms.

**Gastric Complications**

**Gastroesophageal Reflux (GER) and Related Complaints.** Symptoms of GER or re-gurgitation and heartburn occur in patients in AN, although perhaps more commonly in those with BN. In a case control trial, Winstead et al. found that patients with eating disorders (including 34 patients with AN) self-reported significantly higher rates of GER symptoms per week as compared with controls. Unfortunately, authors did not inquire about purging in the study sample and did not specify the type of AN patients were diagnosed with (i.e., AN-R vs AN-BP). Benini et al. found a high rate of esophageal complaints including re-gurgitation and heartburn as compared to controls. Interestingly, at the end of a 22 week rehabilitation program, there was significant improvement in gastric and colonic symptoms but no improvement seen in esophageal related complaints. Symptoms of regurgitation and heartburn did not improve with weight gain, nor did they correlate with improvements in patients' psychopathologic scores. Similarly Waldholtz et al. prospectively identified no statistical improvement in heartburn complaints following a hospital-based program of refeeding and psychiatric care. This was despite finding significant improvement, compared to non-age matched controls, in the number and severity of GI complaints overall. In contrast, Santolicola et al. did not find elevated rates of epigastric pain or burning in a sample of 20 patients with AN compared with constitutionally thin women, obese women, or healthy controls using standardized questionnaires.

**Gastric Dilatation and Perforation.** Acute gastric dilatation was first described in 1833 and has been well documented in the literature since then. In addition to eating disorders, gastric dilatation has been reported to result from superior mesenteric artery syndrome, volvulus of hiatal hernias, trauma resuscitation, medications, and other conditions. Although symptoms of gastric dilatation can be vague, patients often present with emesis and gradual abdominal distention with pain. Patients with AN are at an increased risk of acute gastric dilatation after an episode of severe bingeing/overeating because of decreased gastric motility, increased gastric capacity, and decreased gastric emptying. A total of 30 cases (Table 1) describing acute gastric dilatation in patients with AN were included in this review. Patients were managed conservatively in approximately one-third of the cases, while others underwent surgical intervention as a result of compromised clinical status. Three cases were managed medically initially, but then required surgical intervention for complications. Eight cases of gastric dilatation led to perforation. Gastric necrosis was commonly noted in the cases of dilatation. Less commonly, gastric dilatation was associated with: duodenal ulcer, acute pancreatitis, acute cardiac output impairment, superior mesenteric artery syndrome, acute renal failure, and leg ischemia.

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender (F/M)</th>
<th>Age (years)</th>
<th>BMI, If Noted (kg/m²)</th>
<th>Imaging (If Completed)</th>
<th>Complication Described</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tweed-Kent</td>
<td>F</td>
<td>26</td>
<td>18.75</td>
<td>AXR, CT scan, laparotomy</td>
<td>Gastric dilatation</td>
<td>Surgical (gastrotomy, surgical decompression)</td>
</tr>
<tr>
<td>Hausler</td>
<td>F</td>
<td>21</td>
<td>14.1</td>
<td>CT scan, gastroscopy</td>
<td>Gastric dilatation</td>
<td>Conservative* for dilatation, but surgical for other complications (intubation, chest tube, cholecystectomy)</td>
</tr>
<tr>
<td>Darji</td>
<td>M</td>
<td>11</td>
<td>NR</td>
<td>CT scan</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Repesse</td>
<td>F</td>
<td>18</td>
<td>11.4</td>
<td>CT scan</td>
<td>Gastric dilatation</td>
<td>Conservative*</td>
</tr>
<tr>
<td>Van Eetvelde</td>
<td>F</td>
<td>19</td>
<td>NR</td>
<td>CT scan, gastroscopy</td>
<td>Gastric dilatation</td>
<td>Surgical x 2 (decompression, sleeve gastrectomy)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI - Body Mass Index; NR - Not Reported; CXR - Chest X-ray; CT - Computerized Tomography; AXR - Abdominal X-ray.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Age in Years (Mean, Range)</th>
<th>Gender</th>
<th>Sample Size</th>
<th>Pts with AN</th>
<th>Mean %HBW or BMI (kg/m²)</th>
<th>GI Complication</th>
<th>Measures/Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubois35 (1981)</td>
<td>Case control</td>
<td>20 (15-22)</td>
<td>All female</td>
<td>15</td>
<td>5</td>
<td>Not reported</td>
<td>Gastric motility</td>
<td>Dye dilution technique</td>
<td>Gastric emptying: sig delayed in patients vs controls before treatment, no diff after treatment</td>
</tr>
<tr>
<td>Bethanechol chloride 0.06mg/kg sc</td>
<td>Bethanechol increases gastric output, but to a lesser degree prior to treatment for AN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holt36 (1981)</td>
<td>Case control</td>
<td>Mean not reported (17–32)</td>
<td>All female</td>
<td>22</td>
<td>10</td>
<td>Not reported</td>
<td>Gastric motility</td>
<td>Scintigraphy post-liquid and post-solid meal</td>
<td>Gastric emptying: sig slower for both liquid and solid meals in patients vs controls</td>
</tr>
<tr>
<td>Russell37 (1983)</td>
<td>Case report</td>
<td>27</td>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>82% HBW</td>
<td>Gastric motility</td>
<td>Scintigraphy post-meal</td>
<td>Effect of Domperidone 10 mg TID for 14 d</td>
</tr>
<tr>
<td>McCallum38 (1985)</td>
<td>Case control</td>
<td>20 (14–40)</td>
<td>All female</td>
<td>32</td>
<td>16</td>
<td>75% HBW</td>
<td>Gastric motility</td>
<td>Scintigraphy post-meal measured over 2 hrs-</td>
<td>Effect of metoclopramide 10mg IM</td>
</tr>
<tr>
<td>Stacher39 (1986)</td>
<td>Case Control-Dark-blind cross-over for Domperidone</td>
<td>23.1 (14–43)</td>
<td>All female</td>
<td>40</td>
<td>16</td>
<td>63.8% HBW</td>
<td>Gastric motility</td>
<td>Gamma camera q5min for 50 min after meal</td>
<td>Effect of Domperidone 10 mg IV vs placebo (n=8 patients)</td>
</tr>
<tr>
<td>Rigaud40 (1988)</td>
<td>Case Control</td>
<td>26.7 (18–61)</td>
<td>13F 1M</td>
<td>28</td>
<td>14</td>
<td>64.5% HBW</td>
<td>Gastric motility</td>
<td>Scintigraphy post-meal</td>
<td>Gastric emptying of both solid and liquid meal components sig delayed at baseline</td>
</tr>
<tr>
<td>Effect of refeeding on gastric emptying rate</td>
<td>Refeeding led to improvement in gastric emptying of both solid and liquid meal components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson41 (1988)</td>
<td>Case series</td>
<td>28.7 (26–32)</td>
<td>All female</td>
<td>22</td>
<td>22</td>
<td>BMI = 16.5</td>
<td>Gastric motility</td>
<td>Scintigraphy post-meal, saline, and glucose solution</td>
<td>Patients with AN who were actively restricting had significant slower gastric emptying than those in refeeding program: post-meal and glucose solution</td>
</tr>
<tr>
<td>Effect of active restriction vs refeeding treatment on gastric emptying rate</td>
<td>No difference in gastric emptying between patients actively restricting and in refeeding program after saline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson42 (1989)</td>
<td>Case control</td>
<td>29.1 (18–40)</td>
<td>21 F 1M</td>
<td>42</td>
<td>22</td>
<td>BMI = 15.4</td>
<td>Gastric motility and satiety/hunger</td>
<td>Gamma camera q5min for 2 hrs after meal-Garfinkel Questionnaire</td>
<td>Significant lower correlations between gastric contents and hunger, no difference in correlations with fullness</td>
</tr>
<tr>
<td>Hutson43 (1990)</td>
<td>Case control</td>
<td>29 (18–39)</td>
<td>9 F 1 M</td>
<td>10</td>
<td>10</td>
<td>76 (65 – 88)</td>
<td>Gastric emptying</td>
<td>Dual radioisotope technique, mixed liquid and solid meal</td>
<td>Patients with AN had overall delayed emptying, although 6 of 10 had normal results</td>
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<tr>
<td>Gastric emptying of liquids longer in AN, but not significant</td>
<td></td>
<td></td>
<td></td>
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<td>Age in Years (Mean, Range)</td>
<td>Gender</td>
<td>Sample Size</td>
<td>Pts with AN</td>
<td>Mean %HBW or BMI (kg/m²)</td>
<td>GI Complication</td>
<td>Measures/Intervention</td>
<td>Outcome</td>
</tr>
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<td>All female</td>
<td>22</td>
<td>22</td>
<td>BMI 14.7</td>
<td>Gastric motility</td>
<td>Gastric scintigraphy q2 min for 90 min, measured at baseline, 1 mo, and 2-3 mo post-meal</td>
<td>Delayed gastric emptying improved rapidly (within 3 mo) of refeeding process</td>
</tr>
<tr>
<td>Stacher45 (1992)</td>
<td>Case control</td>
<td>22.5 (14-36)</td>
<td>All female</td>
<td>67</td>
<td>53</td>
<td>63.9% HBW</td>
<td>Gastric motility</td>
<td>Gamma camera over 50 min post-meal</td>
<td>Gastric emptying significantly delayed and aniinal motor activity significantly lower in patients vs controls</td>
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<tr>
<td>Ravelli46 (1993)</td>
<td>Case Control</td>
<td>13.6 (11-15)</td>
<td>5F 1M</td>
<td>14</td>
<td>6</td>
<td>Not recorded</td>
<td>Gastric antral activity</td>
<td>Effect of cisapride 8 mg 30 min pre-meal EGG pre and post-meal</td>
<td>No consistent abnormality of gastric antral activity or gastric emptying</td>
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<tr>
<td>Stacher47 (1993)</td>
<td>RCT</td>
<td>22.5 (19-34)</td>
<td>All female</td>
<td>12</td>
<td>N/A</td>
<td>62.4%</td>
<td>Gastric motility</td>
<td>Effect of cisapride 10 mg TID vs placebo for 6 weeks in 1/2 patients, then all patients received cisapride for another 6 weeks &amp; gastric emptying after meal</td>
<td>Cisapride for 6 and 12 weeks significantly accelerated gastric emptying in patients vs placebo and over time</td>
</tr>
<tr>
<td>Benini48 (2004)</td>
<td>Case control</td>
<td>22.6 (19-32)</td>
<td>All females</td>
<td>47</td>
<td>23</td>
<td>Not reported</td>
<td>Gastric motility</td>
<td>Ultrasound measure of gastric emptying post-meal</td>
<td>Antral distension greater for AN-B/P than AN-R or controls at baseline and 30 min post-meal</td>
</tr>
<tr>
<td>Ogawa49 (2004)</td>
<td>Case Control</td>
<td>Mean not reported (16-30)</td>
<td>All female</td>
<td>38</td>
<td>15</td>
<td>Not reported</td>
<td>Gastric motility</td>
<td>Electro-gastrography (EGG) before and after 250ml water</td>
<td>Gastric emptying improves with refeeding over 22 weeks no significant correlation between rate of gastric emptying and feelings of hunger and satiety</td>
</tr>
<tr>
<td>Perez50 (2013)</td>
<td>Case Control</td>
<td>15.5 (10-22)</td>
<td>All female</td>
<td>38</td>
<td>16</td>
<td>BMI = 17.3</td>
<td>Gastric motility</td>
<td>Ultrasound gastric residual volume and post-meal antral diameter at baseline and after 12-16 wks refeeding</td>
<td>Degree of EGG abnormality positively correlated with duration of illness No difference by subtype of AN Patients sig had improved gastric accommodation at baseline compared to control Gastric accommodation improved sig with refeeding</td>
</tr>
</tbody>
</table>

Abbreviations: AN-R = anorexia nervosa, restricting subtype AN-B/P = anorexia nervosa, binge-purge subtype; HBW = healthy body weight; BMI = body mass index.
There are a total of 13 reported cases of gastric perforation.\textsuperscript{3} In these cases, intra-gastric pressure is hypothesized to have exceeded gastric venous pressure producing ischemia, necrosis and ultimately perforation of the gastric wall.\textsuperscript{6,14,16,20} Of the patients that presented with gastric rupture, four (31\%) occurred in the context of over-eating/bingeing,\textsuperscript{14,18,29} seven (54\%) presented with severe abdominal pain,\textsuperscript{14,16,18,20,26,29} and/or abdominal distention,\textsuperscript{6,10,12,16,18,26} and six (46\%) showed signs of shock at initial presentation.\textsuperscript{5,14,18,20,29,32} Diagnosis of gastric rupture was confirmed by abdominal X-ray,\textsuperscript{6,12,14,16,20,26} CT of the abdomen,\textsuperscript{20,26} and/or during emergency laparotomy.\textsuperscript{5,14,18,20,29,32} In two cases, the diagnosis of gastric perforation was confirmed on post mortem examinations.\textsuperscript{13,23} The mortality rate associated with gastric perforation is reportedly as high as 80\%.\textsuperscript{7} In this current review, gastric perforation was fatal in 8 of 13 patients with AN (62\% death rate). Table 2 summarizes the reported cases.

**Gastric Motor Function, Gastric Motility, and Gastric Emptying.** Few studies investigated gastric electrical activity and antral phase pressure activity in patients with AN. Abell et al\textsuperscript{87} completed a case control prospective study and found that all patients with AN had increased episodes of gastric dysrhythmia as well as impaired antral contractility as compared with matched controls.\textsuperscript{87} This is clinically significant as the antrum is the part of the stomach most involved with grinding and processing of solid meals.\textsuperscript{88} Dysrhythmias were noted pre and post meals and were postulated to be interfering with antral contractility. Five of eight patients (63\%) underwent retesting after at least 4 months of treatment and continued to exhibit gastric dysrhythmias and impaired antral contractility. It should be noted that 4/5 of these patients continued to have extremely low levels of body fat at the time of retesting and 2/5 patients had gained 3 kg or less in the 4 months since initiating treatment. Similarly, Benini et al.\textsuperscript{48} found AN patients had more antral distension than controls using an ultrasonographic gastric emptying test during a test meal and that maximal dilatation was reached much more quickly.\textsuperscript{48}

Evidence from case control,\textsuperscript{35,36,38–40,42,43,45,48,49,87} case series,\textsuperscript{41,44} and case report\textsuperscript{37} studies would suggest that gastric emptying is significantly delayed in patients with AN (Table 2). There is a paucity of data that examines the threshold for weight loss in which gastroparesis is likely to occur, as well as how long it is likely to persist after nutritional rehabilitation and weight gain begins. Illness factors identified as being associated with gastric emptying abnormality include longer duration of illness\textsuperscript{44,48} and severity of malnutrition.\textsuperscript{44,48}

Delayed gastric emptying is present at baseline in the fasting state, as well as after ingestion of 250 mL of water\textsuperscript{49} or test meal.\textsuperscript{35–41,43–45,47,48,50,87} Abell et al.\textsuperscript{87} noted that the delay was occurring as a result of slowing of the “emptying phase” as the lag time between meal ingestion and onset of emptying was normal in patients.\textsuperscript{87} Mixed results have been noted when examining solid versus liquid test meals. Significantly delayed emptying occurred with both liquid and solid meal components in three studies.\textsuperscript{36,41,87} In other studies, a significant delay in gastric emptying was noted after a solid meal but no difference between patients with AN and controls after ingestion of a liquid meal.\textsuperscript{36,38,41,43}

It is unclear whether rate of gastric emptying differs among AN subtypes. Results from studies that have examined correlates of body weight and gastric emptying are inconsistent.\textsuperscript{46,43} There was no significant difference found in gastric emptying rate based between subtypes of AN in 3 studies.\textsuperscript{44,45,49} Benini et al.\textsuperscript{48} concluded that only patients with AN-R had significantly delayed gastric emptying compared to controls and that the antral region of the stomach was more hypotonic in patients with AN-binge/purge subtype\textsuperscript{48} but other researchers could not replicate this finding.\textsuperscript{45}

Individuals with early onset AN (mean age = 13.6 years)\textsuperscript{46} or who are early in the course of their illness (mean age 15.5 years)\textsuperscript{50} have not been shown to demonstrate delayed gastric emptying although the pathophysiology remains unexplained in these cases. A short duration of illness may confer some protection but further research is warranted.

Measured gastric emptying delay was mapped to feelings of hunger and satiety in two studies and gastric symptoms in another.\textsuperscript{32,43,48} Robinson et al.\textsuperscript{42} found no difference in feelings of hunger (measured with the Garfinkel Questionnaire\textsuperscript{89}) between patients and controls, and that patients with AN were significantly more likely to report feeling bloated and having a full stomach immediately after eating than controls and display significantly lower correlations between gastric content and urge to eat. Also of note, patients were more likely to report nausea, urge to be sick, sadness, fatness, and tension, with some scores continuing to rise at the 100 minute post meal mark. Benini et al.\textsuperscript{48} found no significant correlation between rate of gastric emptying and feelings of hunger and
Patients’ gastric emptying parameters improved through refeeding and weight restoration in several studies. Benini et al.48 showed that 4 weeks into refeeding, the time for full gastric emptying measured by ultrasound decreased significantly by 33.4 minutes, and by 22 weeks gastric emptying decreased by another 41.2 minutes (p < 0.03). Similarly, Dubois et al.35 and Rigaud40 demonstrated normalization of the delayed gastric emptying of liquid and solid meal components on admission when re-measured after 10 weeks of refeeding or after return to being fully re-nourished, respectively. One cross-sectional study40 found that patients who are low weight and actively restricting their intake have a slower gastric emptying than those who were similarly underweight but consuming sufficiently to achieve weight restoration. Using a case series design, Szmuckler et al.44 confirmed that whereas many patients are found to have delayed gastric emptying upon admission to hospital, four achieved normal gastric emptying within 2–3 months of having initiated refeeding (mean half-emptying time 64 ± 10 minutes).

Five studies tested the effect of pro-kinetic medication in improving gastric emptying. Dubois et al.35 observed gastric emptying before and after injections of bethanechol chloride 0.06 mg/kg. They found a three-fold increase in gastric emptying rate 60 minutes after bethanechol injection. Stacher and Bergmann43 provided either cisapride 8 mg or placebo to 22 patients with known delayed gastric emptying and noted a significant improvement in the rate of gastric emptying (p < 0.001) in the experimental group. Using a randomized control design Stacher et al.47 prescribed cisapride 10 mg or placebo three times daily for 6 weeks, followed by both groups receiving cisapride for an additional 6 weeks. In the first phase after six weeks those receiving cisapride substantially reduced their median gastric emptying time (195.6 minutes to 76 minutes) compared to placebo (173.8 minutes to 150.2 minutes). During the second phase (weeks 7 – 12) when all patients received cisapride the entire group manifested a significant decrease in their median gastric emptying time from baseline to 12 weeks (184.0 minutes to 93.3 minutes) (p < 0.001). Russell et al.37 described a case report of a patient with AN whose gastric emptying rate, measured as half-emptying time, decreased from 119 minutes to 75 minutes after 14 days of Domperidone 10 mg three times daily before meals. Similarly Stacher39 identified that Domperidone 10 mg intravenous significantly shortened half-emptying time compared to placebo in patients with AN and known delay in gastric emptying. In the most recent clinical guidelines by the American College of Gastroenterology,91 metoclopramide is suggested as the first line prokinetic therapy that should be considered for the treatment of gastroparesis symptoms, in addition to dietary therapy. Caution should be used with its administration due to the risk of side effects, including tardive dyskinesia and prolongation of the corrected QT (QTc) interval.91 Recent studies have also examined the dual use of erythromycin and metochlopramide,92 although clinicians should again be aware of the potential for QTc prolongation, especially in patients with AN.

Liver Abnormalities

Multiple studies have demonstrated the presence of elevated transaminases, hypoglycemia, and impaired coagulation in AN in the absence of other liver pathology (Table 3). More severe descriptions of serious hepatic complications such as severe hypoglycemia, encephalopathy,97,111,117 and death from liver failure have been reported in patients severely malnourished as a result of AN.103,111,113

While many of the studies looking at liver dysfunction in AN examined low weight hospitalized patients, others have identified that between 6.7 and 52% of patients presenting for outpatient assessment or treatment, and who have no confounding liver pathologies, also demonstrate elevated transaminases.95,108 In the outpatient setting, the state of malnutrition (as measured by BMI) predicts the likelihood of having elevated transaminases that indicate liver involvement. No difference was noted between patients with AN-R and AN-B/P subtypes.108

In the inpatient setting, where patients are often more severely medically compromised, estimates of the percentage of patients with elevated transaminases range from 26% to 45%.94,104,113,120 Risk factors associated with the likelihood of liver injury in hospitalized patients with AN include: younger age, lower BMI, lower % body fat, AN-R, male sex, and aggressive refeeding.104,113,120
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Mean Age in Yrs (Range)</th>
<th>Gender</th>
<th>Sample Size</th>
<th>Treatment Setting</th>
<th>Mean %HBW or BMI (kg/m²)</th>
<th>Hepatic Complication</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
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<td>All female</td>
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<td>Transaminitis</td>
<td>Transaminits can occur in patients with AN</td>
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<tr>
<td>Milner</td>
<td>Retrospective cohort</td>
<td>14</td>
<td>47 F 4 M</td>
<td>51</td>
<td>Hospital</td>
<td>NR</td>
<td>Transaminitis</td>
<td>- 43% of AN patients experienced elevated transaminases</td>
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<tr>
<td>Mickley</td>
<td>Retrospective cohort</td>
<td>22.5 (11–57)</td>
<td>278 F 4 M</td>
<td>282</td>
<td>Outpt clinic</td>
<td>NR</td>
<td>Transaminitis</td>
<td>- 6.7% of AN patients experienced elevated transaminases</td>
</tr>
<tr>
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<td>Case report</td>
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<td>Female</td>
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<td>Hospital</td>
<td>12.6</td>
<td>Transaminitis</td>
<td>Hepatic failure</td>
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<td>Hypoglycemia Encephalopathy</td>
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<td>Transaminitis</td>
<td>All inpts had elevated transaminases</td>
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<tr>
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<td>Resolved with refeeding</td>
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<td>Hepatic failure</td>
<td>ALT and GGT levels inversely correlated with %body fat</td>
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<tr>
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<td>20 F 2 M</td>
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<td>11.3</td>
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<td>Coagulopathy</td>
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<td>Resolved with refeeding</td>
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<td>Giordano</td>
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<td>Female</td>
<td>1</td>
<td>Hospital</td>
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<td>Hepatic failure</td>
<td>Severe hepatic failure can occur in patients with AN</td>
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<td>10.9</td>
<td>Transaminitis</td>
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</tr>
<tr>
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<td>1</td>
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<td>12.3</td>
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<td>Transaminits can occur in patients with AN</td>
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<tr>
<td>Yoshiuchi</td>
<td>Case report</td>
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<td>Female</td>
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<td>Hospital</td>
<td>13.7</td>
<td>Hepatic failure</td>
<td>Transaminits can occur in patients with AN</td>
</tr>
<tr>
<td>Hanachi</td>
<td>Retrospective cohort</td>
<td>30</td>
<td>117 F 9M</td>
<td>126</td>
<td>Hospital</td>
<td>12</td>
<td>Transaminitis</td>
<td>Coagulopathy</td>
</tr>
</tbody>
</table>
In the vast majority of patients with AN and elevated transaminases, the only treatment necessary is gradual refeeding and hydration, which leads to complete normalization of liver enzymes over time.\textsuperscript{100,101,105,106,110,113,114} The time course to peak transaminase levels during refeeding appears to be 2 to 5 days after which transaminase level then start to recede and normalize between Day 20 and Day 40 of the refeeding process\textsuperscript{99,106,110}.

Published studies have not presented a consistent pattern with regards to the elevation of liver enzymes. Several studies reported elevations in alanine transaminase (ALT) greater than aspartate transaminase (AST)\textsuperscript{101–103,113,117–119} and others have shown the reverse.\textsuperscript{94,96,97,100,101,104,106,109,111,114–116} Similarly a number of studies noted elevated alkaline phosphatase (ALP)\textsuperscript{94,96,101,109,114,116} and bilirubin\textsuperscript{94,96,97,102,111} while others have not. Several studies noted the patients developed severe hypoglycemia,\textsuperscript{97,102,111,114} all of which then required transfer to the ICU at some point during their treatment, suggesting that significant hypoglycemia may be a marker for imminent severe liver failure. This pattern may differ from what is most often observed clinically, and it should be noted that most studies did not consistently report on all liver function parameters, making it difficult to draw meaningful conclusions. The noted discrepancies could also reflect the fact that most of the available studies are either case reports or case series designs, which focus on reporting abnormal results, or very severe cases.

Several studies have observed impaired coagulation secondary to impaired liver function as evidenced by elevated INR in patients with AN.\textsuperscript{93,105,106,112} Similar to elevated transaminases, abnormalities in coagulation appear to resolve with refeeding and improvement in overall liver function.

Hypotheses regarding the mechanism of liver damage during the course of AN include autophagy based on the presence of autophagosomes identified on liver biopsy,\textsuperscript{106,114,116} acute hypoperfusion,\textsuperscript{101,109,116} or possibly oxidative stress secondary to iron deposits in the liver.\textsuperscript{121}

Three studies have described fatal outcomes during treatment in patients initially presenting with elevated transaminases.\textsuperscript{103,113,117} These deaths were attributed to the sequelae of severe liver failure. In an attempt to try and better understand if there were any factors that may have contributed to these deaths, or provide insight into factors that differentiate poorer outcomes associated with liver

### TABLE 3. (Continued)

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Mean Age in Yrs (Range)</th>
<th>Gender</th>
<th>Sample Size</th>
<th>Treatment Setting</th>
<th>Mean %HBW or BMI (kg/m²)</th>
<th>Hepatic Complication</th>
<th>Hepatic Failure</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
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<td>Bridet\textsuperscript{114} (2014)</td>
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<td>35</td>
<td>Female</td>
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<td>Hospital</td>
<td>10.5</td>
<td>Hepatic failure</td>
<td>Resolved with refeeding</td>
<td>Possible mechanism is hypoperfusion and autophagy</td>
</tr>
<tr>
<td>Ohno\textsuperscript{115} (2014)</td>
<td>Case report</td>
<td>66</td>
<td>Female</td>
<td>1</td>
<td>Hospital</td>
<td>11.1</td>
<td>Hepatic failure</td>
<td>Resolved with refeeding</td>
<td>Possible hepatic failure can occur in patients with AN</td>
</tr>
<tr>
<td>Ramsoekh\textsuperscript{116} (2014)</td>
<td>Case report</td>
<td>43</td>
<td>Female</td>
<td>1</td>
<td>Hospital</td>
<td>12.4</td>
<td>Hepatic failure</td>
<td>Resolved with refeeding</td>
<td>Autophagy and hypoperfusion may be related to hepatic failure</td>
</tr>
<tr>
<td>Saito\textsuperscript{117} (2014)</td>
<td>Case series</td>
<td>22.4 (16-32)</td>
<td>All female</td>
<td>9</td>
<td>Hospital</td>
<td>10.5</td>
<td>Hepatic failure</td>
<td>Hypoglycemia</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Nagata\textsuperscript{118} (2015)</td>
<td>Retrospective cohort</td>
<td>16.1</td>
<td>Female</td>
<td>317</td>
<td>F 39M</td>
<td>15.9</td>
<td>Transaminis</td>
<td>Transaminis associated with BMI, male sex, and rate of refeeding</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NR – not reported; F – female; M – male; ICU – intensive care unit; AN – anorexia nervosa; AN-R – anorexia nervosa-restricting; BMI – body mass index; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase.
dysfunction, we offer a brief summary of the information provided regarding the three deaths. Hanachi provided details on two patients that experienced severe liver-related complications, both of which were eventually transferred to the intensive care unit, one of which died.\textsuperscript{113} It was noted by authors that both patients had initiated refeeding in a psychiatric unit and had not received early phosphate, vitamins, or trace elements. Upon transfer to the medical team, they were noted to have severe hypophosphatemia and hypoglycemia. It was also felt that refeeding had proceeded too quickly given their very severe state of malnutrition (the noted BMI for one of the two patients was 9.2 kg/m\textsuperscript{2}). In Sakada’s case report, their patient was noted to be very severely malnourished with a BMI on admission of 7.3 kg/m\textsuperscript{2} although other pertinent medical case details were not reported.\textsuperscript{103} Saito also reported 1 death (BMI on admission 9.9 kg/m\textsuperscript{2}) related to hepatic failure in a case series of 9 patients.\textsuperscript{117} This patient was also managed on a psychiatric floor and although no mention was given of phosphate/vitamins supplementation, authors did note that the patient failed to receive adequate fluid resuscitation and refused all but oral nutrition, thus limiting their ability to refeed cautiously. As noted above, the literature relevant to liver dysfunction in AN derives primarily from case reports and retrospective chart reviews. The largest of these studies included 356 patients,\textsuperscript{118} but most included only relatively small numbers of patients.\textsuperscript{54,56,58} While important, these limited data preclude any clear conclusions and further study is warranted.

\textbf{Pancreas Complications}

Whereas an elevated amylase is often associated with pancreatic injury, in asymptomatic patients, usually with BN, the elevated total amylase, when associated with a normal lipase or pancreatic isoamylase, derives from the salivary glands rather than the pancreas.\textsuperscript{54,56,58} This section summarizes literature that describes pancreatic injury associated with AN.

A review of the endocrine function of the pancreas, including insulin and gastrointestinal hormones, in AN is outside the scope of this paper. The nature of pancreatic insult in the context of AN ranges in severity from asymptomatic to life-threatening. Two case reports describe low grade abdominal pain which one to three months later, at the time of admission, was diagnosed as pancreatitis.\textsuperscript{122,123} In a consecutive series of 10 patients with ANR,\textsuperscript{124} 40% had abdominal symptoms without biochemical or ultrasound confirmation of pancreatitis. Sixty percent, including two who were asymptomatic had either an elevation of serum amylase or amylase creatinine clearance ratio abnormalities; three of the ten had ultrasound abnormalities. This is consistent with the non-inflammatory fibrotic pancreatic abnormalities that are associated with protein calorie malnutrition and marked by acinar cell atrophy and stellate cell activation (reviewed in Morris\textsuperscript{125}). Low grade chronic injury is thought to explain the pseudocyst formation reported in two case reports\textsuperscript{126,127} and the elevation of elastase-1.\textsuperscript{96,128} A study that examined pancreatic function based on fecal elastase measurements in nine severely malnourished patients with AN (7 restrictors; 3 binge-purge), at the time of admission and then when weight restored, could find no evidence of pancreatic dysfunction through measurement of fecal elastase and digestion of \textsuperscript{13}C-labelled triglycerides.\textsuperscript{129} These studies report conflicting evidence as to the prevalence of baseline pancreatic dysfunction in the context of severe wasting because of AN, which might predispose the compromised pancreas to more severe injury if challenged by other factors. Such decompensated patients present as severely ill with profound cachexia, hemodynamic instability and possibly a surgical abdomen. Several pathogenetic mechanisms, perhaps mediated by trypsin activation\textsuperscript{125} have been hypothesized: hypoperfusion causing multiple organ damage including the pancreas\textsuperscript{100}; pancreatic atrophy resulting in a reduced capacity to defend against oxidants generated in severe anorexia\textsuperscript{127,135}; and reflux into the pancreatic duct caused by SMA syndrome associated with marked proximal dilatation of the duodenum and stomach.\textsuperscript{11,15,131} Such dilatation may be augmented by overzealous refeeding. While limited in scope, this literature recommends the following: a normal lipase or pancreatic isoamylase rules out pancreatitis and suggests purging as the source of high amylase; the pancreas must be assessed in the context of persistent abdominal pain in a severely malnourished patient; over aggressive refeeding should be avoided in patients who are severely malnourished.\textsuperscript{131}

A case report on a 15 year old adolescent with AN-purging and a BMI of 13 identified whose elevated sweat chloride and impaired exocrine function (based on measurements of para-amino benzoic acid excretion) at the time of admission resolved with renourishment.\textsuperscript{132} Pancreatic enzymes and amino acid supplementation were used in treatment. Whereas this report cautioned against over diagnosis of cystic fibrosis, based on
sweat electrolytes, in the face of severe malnutrition, it also questioned the potential role of pancreatic enzymes in the context of severe cachexia.\textsuperscript{132}

**Intestinal Complications**

Relatively few studies of AN patients have investigated or reported on complications associated with the small and large intestine. We have included superior mesenteric artery (SMA) syndrome in this section, a rare complication of AN that occurs when the duodenum is compressed between the SMA anteriorly and the aorta and vertebral column posteriorly. This occurs because of the loss of the retroperitoneal fat pad that separates the transverse portion of the duodenum and the SMA.\textsuperscript{133} This compression leads to complete or partial duodenal obstruction. Case reports of SMA syndrome are described in Table 4; all other case reports of intestinal complications can be found in Table 5. We have omitted any discussion on colonic pneumatosis intestinalis, as our search identified just two cases.\textsuperscript{155,156}

**Superior Mesenteric Artery (SMA) Syndrome.** We report 15 cases which involved AN and SMA syndrome, ranging from 11 – 47 years old (Table 4).\textsuperscript{86,134–147} All but two\textsuperscript{139,142} of the cases were diagnosed with radiological imaging. Both upper GI (UGI) series and CT scanning are useful for diagnosis. CT scan is used to assess the angle between the aorta and the SMA, which is narrow in those with SMA syndrome. CT scanning can also assess duodenal distension, as well as intra-abdominal and retroperitoneal fat. UGI series with contrast can diagnose the partial or complete duodenal obstruction that is seen in SMA syndrome by showing dilatation of the proximal duodenum and an abrupt narrowing with failure of contrast passage beyond the third portion of the duodenum.\textsuperscript{157,158} Most cases of SMA syndrome can be treated conservatively with gastric decompression, electrolyte correction and nutritional support, with surgery reserved only as an absolute last resort in those that fail conservative management given the lack of data to support such measures. A recent case series suggested that a minimally invasive surgical approach offers advantages to an open procedure in those that fail supportive measurements although case descriptions of patients that underwent the procedure were not provided.\textsuperscript{159} Of the cases we describe, 11 (73%) were treated conservatively, and 4 (29%) underwent surgical intervention reinforcing the importance of conservative management whenever possible.

**Intestinal Absorption and Permeability.** The small intestine has the capacity for active and passive absorption. It has been hypothesized that starvation may compromise the integrity of the intestinal mucosa thereby permitting increased absorption of nutrients at a time of need.\textsuperscript{160} Such compromise of the anatomo-functional barrier would theoretically also potentially increase the risk that noxious agents, including pathogenic bacteria, could gain access into the bloodstream. Controlled studies in patients with AN however have demonstrated otherwise. In a study of 14 patients with AN (10 restrictors; 4 binge/purge) having a mean BMI of 16.97, investigators found through measurement of lactulose and mannitol absorption, that intestinal permeability was decreased.\textsuperscript{160} The maintained efficacy of intestinal mucosal absorption was demonstrated by measurement of xylose absorption in anorexics at low weight and then again at recovery. This finding supports the clinical observation that sepsis is in fact an uncommon occurrence in patients with AN. This contrast between starvation because of AN, compared with other etiologies, suggests the presence of, as yet unidentified factors.\textsuperscript{129}

Whereas impaired functionality has not been demonstrated, a controlled study (21 ANR; 15 AN-BP; 20 controls) found that diamine oxidase, a marker for intestinal villi integrity and maturity, was significantly reduced in patients with ANR. Whereas this reflects the importance of food exposure to the health of the intestinal villi, the lack of functional measures precluded correlations of diamine oxidase levels with intestinal permeability as had been suggested in other animal and human studies.\textsuperscript{161}

**Intestinal transit times/constipation.** In a descriptive study of radiologic findings in 50 patients with AN, Haller et al.\textsuperscript{162} noted transient non-obstructive mild jejunal dilatation in one-third of the cases and that small bowel transit ranged from normal to occasionally delayed although no case-specific information was included. Only four controlled studies were identified that measured intestinal transit times or focused on measures of constipation as a primary outcome\textsuperscript{163–166} Hirakawa et al.\textsuperscript{165} compared gastro-cesal transit times using a lactulose hydrogen breath test in 10 patients with AN and 11 healthy controls. Each of the patients (who ranged in age between 13 and 28 with a mean of 19 years) was considerably malnourished (18%–52% (mean 32% ± 9 SD) below their target body weight) and complained of numerous GI symptoms. Investigators found that the small bowel transit time as well as the overall transit time was significantly prolonged in patients with AN compared with controls (117 minutes ± 31 so vs. 81 minute ± 33 SD,
In a study that investigated the same primary outcomes, Kamal et al. compared whole gut and mouth to cecum transit times of ten patients with AN and 18 in-patients with BN to 10 healthy controls. All patients with AN (90% female; mean age 26 years, mean BMI 15.1 ± 2.2 kg/m²) complained of constipation. Whole gut transit was significantly delayed in all AN patients. Although mouth to cecum transit times were also longer in the AN group, no significant differences were observed between groups (although the authors noted they failed to control for conditions known to influence test results). Chun et al. prospectively studied colonic transit times (CTTs) in 13 female patients with AN admitted to an inpatient treatment unit and compared them to 20 matched controls. They showed that four of six patients tested within 3 weeks of admission had slow CTT but that all patients had normal transit times after three weeks of treatment. Chiarioni et al. tested CTTs in twelve women (19–29 years, BMI 13.1 kg/m² ± 1.6) that complained of chronic constipation and found significantly slowed CTT in 8/12 (67%) patients whereas all control patient’s results were normal. In the later study, CTT normalized after a 4 week refeeding program. We were unable to identify any controlled study that investigated the use or looked at outcomes associated with prescribed laxatives in the early course of refeeding.

**Ano-Rectal Complications**

**Anorectal Manometry.** In an attempt to better understand factors that may impact constipation in patients with AN, two studies were completed which compared results of anorectal manometry in patients with AN to those of matched controls. Anorectal manometry measures pressures of the anal sphincter muscles, the sensation in the rectum, and neural reflexes required for normal bowel movements. In both studies, patients were low weight and reported constipation. Rectal sensation, internal anal sphincter relaxation threshold, rectal compliance, sphincter pressures, and

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Sex (F/M)</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Imaging (if completed/noted)</th>
<th>Diagnosis Modality</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentlow134 (1981)</td>
<td>F</td>
<td>21</td>
<td>NR</td>
<td>AXR, barium study</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>Sours135 (1981)</td>
<td>F</td>
<td>17</td>
<td>NR</td>
<td>AXR, gastroscopy, abdominal ultrasound</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>Kalouche136 (1991)</td>
<td>F</td>
<td>20</td>
<td>16.7</td>
<td>Barium study</td>
<td>Imaging</td>
<td>Surgical -</td>
</tr>
<tr>
<td>Elbadaway137 (1992)</td>
<td>F</td>
<td>18</td>
<td>12.4</td>
<td>Barium study</td>
<td>Imaging</td>
<td>*Conservative x 2 months, then surgery – gastrojejunostomy</td>
</tr>
<tr>
<td>Stheneur138 (1995)</td>
<td>F</td>
<td>14</td>
<td>14.3</td>
<td>AXR, Imaging</td>
<td>Barium study, CT scan abdomen</td>
<td>*Conservative</td>
</tr>
<tr>
<td>Adson139 (1996)</td>
<td>F</td>
<td>35</td>
<td>NR</td>
<td>Barium study</td>
<td>CT</td>
<td>Laparotomy (due to concern for appendicitis)</td>
</tr>
<tr>
<td>De Silva140 (1998)</td>
<td>F</td>
<td>28</td>
<td>NR</td>
<td>Barium study</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>Schmidt-Troschke141 (1998)</td>
<td>F</td>
<td>11</td>
<td>14.5</td>
<td>Barium study</td>
<td>Imaging</td>
<td>Surgical -</td>
</tr>
<tr>
<td>Jordan142 (2000)</td>
<td>F</td>
<td>13</td>
<td>NR</td>
<td>Barium study</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>duodenoejunostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gwee143 (2010)</td>
<td>F</td>
<td>17</td>
<td>16.4</td>
<td>AXR, barium study, CT scan abdomen</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>Listernick144 (2010)</td>
<td>M</td>
<td>15</td>
<td>14.8</td>
<td>Barium study</td>
<td>Imaging</td>
<td>Surgical -</td>
</tr>
<tr>
<td>Fernandez145 (2011)</td>
<td>F</td>
<td>31</td>
<td>16.7</td>
<td>Barium study and arteriography</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
<tr>
<td>duodenoejunostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehman146 (2011)</td>
<td>F</td>
<td>15</td>
<td>NR</td>
<td>Barium study, CT scan abdomen, gastroscopy</td>
<td>Imaging</td>
<td>*Conservative treatment failed, required surgery</td>
</tr>
<tr>
<td>Mearelli147 (2014)</td>
<td>M</td>
<td>47</td>
<td>NR</td>
<td>Esophagogastroduodenoscopy, CT scan abdomen</td>
<td>Imaging</td>
<td>*Conservative, required surgical mobilization of ligament of Treitz</td>
</tr>
<tr>
<td>Mascolo86 (2015)</td>
<td>F</td>
<td>47</td>
<td>10.6</td>
<td>AXR, CT scan abdomen</td>
<td>Imaging</td>
<td>*Conservative</td>
</tr>
</tbody>
</table>

*NG tube insertion +/− gastric decompression, fluid hydration +/− total parental nutrition.

Abbreviations: BMI - Body Mass Index; NR - Not Recorded; CT - Computerized Tomography; AXR - Abdominal X-ray.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Age Yrs (range)</th>
<th>Sample Size</th>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>Complication</th>
<th>Investigation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaye</td>
<td>Case Report</td>
<td>17</td>
<td>1</td>
<td>F</td>
<td>NR</td>
<td>Necrotizing colitis</td>
<td>Abdominal X-ray</td>
<td>Faecal Peritonitis Recto-sigmoid junction to distal 1/3 of ileum affected by necrotizing colitis thought to be due to faecal impaction Died due to sepsis and DIC</td>
</tr>
<tr>
<td>Miller</td>
<td>Case Report</td>
<td>30</td>
<td>1</td>
<td>F</td>
<td>12.1</td>
<td>Mesenteric volvulus and bowel necrosis</td>
<td>Abdominal X-ray, Abdominal CT scan</td>
<td>Laparotomy Died in OR prior to surgery, autopsy showed gangrene of small bowel Megaduodenum</td>
</tr>
<tr>
<td>Buchman</td>
<td>Case Report</td>
<td>21</td>
<td>1</td>
<td>F</td>
<td>14.3</td>
<td>Intestinal motility</td>
<td>Gastroduodenal manometry, Barium swallow and follow through</td>
<td>Resolved in 4 wks with wt restoration ≥85% HBW</td>
</tr>
<tr>
<td>Sakka</td>
<td>Case Report</td>
<td>20</td>
<td>1</td>
<td>F</td>
<td>NR</td>
<td>Necrotizing colitis</td>
<td>Abdominal X-ray</td>
<td>Laparotomy</td>
</tr>
</tbody>
</table>
| Inui         | Case Report  | 32              | 1           | F      | NR          | Intussusception                | Abdominal X-ray | Laparotomy Died after second laparotomy 
-Imagination and strangulation in jejunum | Gangrenous portion of bowel resected Recovered well post-op AXR showed intestinal pneumatosis and the presence of portal venous gas in absence of free abdominal air. Pt treated with gastric decompression, antibiotics, and TPN. Patient eventually recovered. |
| Diamant      | Case Report  | 17              | 1           | F      | 10          | Necrotizing colitis            | Abdominal X-ray | Extensive portal vein gas and bowel wall pneumonitis | Laparotomy Necrosis of entire small bowel and right hemi-colon Died in immediate post-op period |
| Neychev      | Case Report  | 30              | 1           | F      | 11          | Bowel ischemia and necrosis   | Abdominal X-ray | Extensive portal vein gas and bowel wall pneumonitis | Laparotomy Necrosis of entire small bowel and right hemi-colon Died in immediate post-op period |

Abbreviations: BMI - Body Mass Index; NR - Not Recorded; CT - Computerized Tomography.
expulsion pattern were measured and normal in the 13 patients with AN in Chun et al.’s study.\textsuperscript{164} Chiarioni et al.’s study demonstrated conflicting results as patients with AN were significantly more likely to have anorectal dysfunction similar to that described in severe chronic idiopathic constipation, and the blunted rectal sensation did not improve with refeeding.\textsuperscript{163} Rectal Prolapse. Rectal prolapse, the full thickness protrusion of the rectal wall through the anal canal, can be a rare complication of AN. Five cases of rectal prolapse and AN are described in the literature, from ages 16–40 years.\textsuperscript{167–169} Four of the five cases required surgical correction, although one patient refused the recommendation. Conservative management with fiber supplementation, polyethylene glycol (PEG) 3350, and pelvic floor strengthening exercises was successful in the remaining case.\textsuperscript{170} Functional Complaints Digestive symptoms and functional GI disorders (FGIDs) are frequently reported by patients with AN.\textsuperscript{170} Although some studies identified the frequency of GI complaints by AN patients, few investigated such complaints (and instead were limited to self-report), making it difficult to conclude what proportion of patient complaints are functional as compared to those that occurred as a result of measurable GI dysfunction or disease. Salvio\textsubscript{170} administered digestive symptom questionnaires that were completed at baseline, discharge, at 1 and 6 months’ followup in 48 consecutive with EDs (81% of the sample had AN). The authors demonstrated that pooled esophageal and GI symptoms significantly decreased at 6 months’ follow-up and that GI symptoms significantly correlated with hypochondriasis, a finding which has been demonstrated in non-ED patients with functional GI disorders.\textsuperscript{171} The authors did not offer any indication as to what percentage, if any of patients underwent clinical testing to investigate the GI symptoms. Boyd et al. studied FGID symptoms in 108 consecutive ED patients at admission and 12 month follow up\textsuperscript{172}. They noted 97% prevalence of at least one FGID at admission and that 77% continued with symptoms at 1-year follow-up. Few FGIDs decreased over time and significant patient variation was noted in the disappearance, persistence, and appearance of individual FGIDs and FGID regional categories. Of note, 34% of patients met criteria for at least one new FGID regional category at follow-up. There was no relationship between changes in BMI, symptoms such as self-induced vomiting, or laxative use, or co-morbid mental health diagnoses. They concluded that FGID symptoms are prevalent in patients for prolonged periods, and that there were no relationships between FGIDs and weight or ED behaviors.

Discussion

Many patients with AN struggle with various digestive symptoms, which is important given the critical role of feeding and requirement for weight gain in treatment. As patients with AN generally require high caloric feeds for extended periods; it is important that clinicians understand the medical complications that patients may experience as a consequence of weight loss and of the refeeding process. While case reports have demonstrated objective evidence of dysfunction affecting every element of the GI system and at all points on the treatment spectrum, many patients report GI related symptoms and distress despite the absence of measurable medical pathology. It is important to investigate medical symptoms that persist or fail to remit with weight restoration. As demonstrated in this review, the possibility of underlying, possibly comorbid, medical illness must at times be considered.

This review raises several other issues. First, this systematic review is limited by the likelihood that despite the comprehensiveness of the focused search supplemented by reference list review there may be some reports and studies that were not captured. Studies published in languages for which translation was unavailable were excluded. Furthermore 27 identified articles could not be located.

Combined with the small sample size and the merging in some studies of different AN subtypes (AN-R, AN-B/P), the bias inherent to case control, case series, and case report designs, caution must be exercised in drawing strong conclusions.

The majority of articles that were retrieved were case reports or case series (74%) with few controlled experimental studies identified. Of the prospective studies that were completed, the majority investigated issues related to gastric motility, gastric emptying and intestinal transit.

It should be noted that only one controlled study was identified that medically investigated esophageal related complaints.\textsuperscript{39} In this single study, Benini and colleagues showed that despite the fact that esophageal symptoms were frequent and severe in patients with AN, they could not be explained by manometric abnormalities.

Findings from esophageal, gastric, and intestinal transit studies suggest that the majority of patients
with AN experience delays in gastric emptying and intestinal transit. Results however were not always consistent, and delays in gastric emptying did not uniformly relate to subjective feelings of hunger and satiety. Based upon the results in Robinson's study, the authors concluded that AN patients over- estimate gastric contents in an analogous way to the overestimation of body image.42

Although pro-kinetic medications were shown to improve gastric emptying, studies have also clearly demonstrated that weight rehabilitation and refeeding alone have demonstrated normalization of gastric emptying in a majority of patients. This is relevant when considering the utility of targeted pharmacological treatment. Pro-kinetics were the only class of medications investigated in any trial, and medications such as cisapride and domperidone have documented cardiac side effects that synergistically with severe malnutrition may endanger the ED patient through prolongation of the QTc.154 Because of such risks cisapride can no longer be prescribed in Canada or the United States and health advisories have been issued by Health Canada regarding domperidone.154,173 Prescribers must balance the need for medication for symptoms such as bloating, fullness and satiety with a careful risk-benefit analysis. Depending on case specifics, confirmation and demonstration of gastroparesis by nuclear gastric emptying scan may be considered prior to the administration of a pro-kinetic agent.

Evidence of liver complication and dysfunction was largely limited to case reports and descriptive case series. Despite these limitations, studies suggest that increased liver transaminases in low weight patients with AN is common and not provoked exclusively by rapid refeeding.95,108 While most patients with AN and elevated transaminases recover with appropriate nutrition and supportive therapy alone, it is important that severely malnourished patients be monitored carefully to ensure early identification and effective management, with the appropriate level of medical support, for metabolic abnormalities that evolve negatively. Refeeding syndrome (RFS), (which was recognized in at least one of the three cases of noted liver-related mortality) can result in mortality if not anticipated, recognized early and managed carefully.

Although limited in sample size and number, intestinal transit studies demonstrate that the majority of low weight patients that underwent testing showed evidence of slowed CTT, which would predispose to constipation. Of note, all patients studied complained of severe constipation but not all patients had prolonged CTT, even at low BMIs, again suggesting the discrepancy between subjective feelings of fullness, bloating, and constipation and objective findings. Evidence suggests that CTTs normalize within weeks of starting targeted nutritional treatment programs. No reports or studies were found that looked at the potentially controversial role of prescribed laxatives in patients with AN, despite its potential to alleviate constipation noted in most patients during the early refeeding phase.

Outside of the evidence presented above, almost all remaining case reports and case series were limited to individual descriptions of GI related findings and complications. Indeed, complications, such as gastric dilatation and perforation, pancreatitis, superior mesenteric artery syndrome and rectal prolapse have been noted by multiple authors. Each of these respective complications occurs generally as a result of severe malnutrition (a proportion of which can be a complication of RFS) and ED-related symptoms (such as self-induced vomiting). Given the nature of reporting, it is difficult to establish incidence rates for any of these complications. Larger databases with common measurable variables could however shed better light into the prevalence of some more commonly reported complications (gastric dilatation for example).

In conclusion, there is an intricate interplay between organic pathology, subjective symptomatology and cognitive resistance to eating, and weight gain associated with AN—an illness wherein the integrity of the GI tract is compromised by malnutrition and any effort to reverse this malnutrition is opposed by ED cognitions. The greater the degree of malnutrition, the more intense the cognitions. This poses a complex challenge to the provider whose job it becomes to discern between those complications that have been referred to as functional and those that may be life-threatening. Adequately powered prospective research is lacking that might help with this task. A thorough understanding of the pathophysiology of the various morbidities, careful consideration of the many dimensions of GI symptomatology in AN, a solid understanding of refeeding syndrome and judicious use of investigation and medication is essential to optimizing outcome.

Appendix

Search Strategies

Medline
1. exp Gastrointestinal diseases
2. Anorexia nervosa
3. 1 and 2.
The authors would like to acknowledge the assistance of Mrs. Patricia Graziano for her help in article retrieval. MN is the guarantor and led the development of the protocol. MN, MH, LI, AR and SF executed the review of proposed studies, and drafted the manuscript. MN, MH, LI, AR and MS helped develop the selection criteria, the risk of bias assessment strategy and data extraction criteria. MS developed the search strategy. All authors read, provided feedback, and approved the final manuscript.

There are no disclosures.

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GASTROINTESTINAL COMPLICATIONS IN ANOREXIA NERVOSA


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