ABSTRACT
Objective: Given the importance of weight restoration for recovery in patients with anorexia nervosa (AN), we examined approaches to refeeding in adolescents and adults across treatment settings.


Results: Of 948 screened abstracts, 27 met these inclusion criteria: participants had AN; reproducible refeeding approach; weight gain, hypophosphatemia or cognitive/behavioral outcomes. Twenty-six studies (96%) were observational/prospective or retrospective and performed in hospital. Twelve studies published since 2010 examined approaches starting with higher calories than currently recommended (≥1400 kcal/d). The evidence supports 8 conclusions: 1) In mildly and moderately malnourished patients, lower calorie refeeding is too conservative; 2) Both meal-based approaches or combined nasogastric+meals can administer higher calories; 3) Higher calorie refeeding has not been associated with increased risk for the refeeding syndrome under close medical monitoring with electrolyte correction; 4) In severely malnourished patients, there is insufficient evidence to change the current standard of care; 5) Parenteral nutrition is not recommended; 6) Nutrient compositions within recommended ranges are appropriate; 7) More research is needed in non-hospital settings; 8) The long-term impact of different approaches is unknown.

Discussion: Findings support higher caloric approaches to refeeding in mildly and moderately malnourished patients under close medical monitoring, however the safety, long-term outcomes, and feasibility outside of hospital have not been established. Further research is also needed on refeeding approaches in severely malnourished patients, methods of delivery, nutrient compositions and treatment settings.

Keywords: anorexia nervosa; refeeding; weight restoration; nutritional rehabilitation; refeeding syndrome; hypophosphatemia; medical complications; medical stability; length of stay

Resumen
Objetivo: Dada la importancia de la restauración del peso en la recuperación de pacientes con anorexia nervosa (AN), examinamos los abordajes para la realimentación de adolescentes y adultos a lo largo de los diferentes entornos de tratamiento.

Métodos: Se hizo una revisión sistemática de PubMed, PsycINFO, Scopus, y Bases de datos de ensayos...
A Systematic Review of Approaches to Refeeding Patients with Anorexia Nervosa

The primary goal of refeeding patients with anorexia nervosa (AN) is to reverse malnutrition and its complications. Weight gain during refeeding is crucial, as it sets the stage for long-term recovery. In hospitalized patients, faster weight gain and higher weight upon discharge predict weight recovery at 1 year. Weight recovery is typically defined as 95% of the median Body Mass Index (%mBMI) per CDC data and is associated with the reversal of long-term medical complications, including amenorrhea. In patients well enough to be managed in ambulatory settings, faster weight gain during the first 3–4 weeks (0.43–0.86 kg week⁻¹) of outpatient psychotherapy predicts full remission (both weight and cognitive recovery) at 12 months. However, the need for weight gain must be balanced against the potentially fatal complications of the refeeding syndrome, which can manifest in cardiac arrhythmia, cardiac failure or arrest, hemolytic anemia, delirium, seizures, coma, and sudden death. These clinical sequelae are thought to occur as a result of movements of glucose and electrolytes from the extracellular to the intracellular space in response to surges in insulin after nutrients are reintroduced following starvation and depleted hepatic glycogen stores.

The current standard of care for refeeding patients with AN is to commence at low caloric levels and advance slowly, with variable recommendations internationally. In the United States, recommendations are to start around 1,200 calories per day (kcal day⁻¹) and advance slowly by about 200 kcal every other day, whereas starting caloric prescriptions as low as 200–600 kcal day⁻¹ are recommended in Europe and the United Kingdom. The purpose of such “slow and go slow” approaches is to minimize the risk of refeeding syndrome. However, these lower calorie approaches have recently been linked to poor weight gain and prolonged hospitalization. Growing recognition of the so-called “underfeeding syndrome” has spurred renewed interest in more aggressive approaches to refeeding. These approaches are varied, but typically begin with higher calorie and/or more rapid advancement and may be delivered through meals alone or a combination of meals with supplemental nasogastric (NG) feeding.

Refeeding may occur in a variety of settings, including hospital, partial hospital and/or day treatment, residential programs, and outpatient settings. Patients who are physiologically or psychologically unstable are admitted to hospital for refeeding. Criteria for admission to hospital vary by country, region, age (adolescents vs. adults), and the type of treatment facility. However, published positions and guidelines for adolescent and adult care have suggested that hospital admission is warranted in the presence of vital sign abnormalities (bradycardia, hypotension, orthostatic heart rate and blood pressure, and hypothermia), failure to respond to lower levels of care, suicidality, or other severe psychiatric symptoms. Severe malnutrition alone, defined as BMI < 15 kg m⁻² in adults or <70% mBMI, may also warrant hospitalization.
The initial focus of refeeding is to restore physiological stability through weight gain. Bradycardia normalizes more quickly during refeeding than other signs, such as orthostatic changes, which may take weeks. In adolescents in the United States, normalization of vital signs is commonly used as a discharge criterion from medical inpatient units, which is why some studies of refeeding have used length of hospital stay as a proxy for the time required to achieve medical stability. In addition to physiological instability at presentation, patients are at risk of developing complications during the refeeding process itself. Refeeding hypophosphatemia (RH) is used to indicate risk for the development of the refeeding syndrome and is more likely to occur in severely malnourished patients. Studies of hospitalized patients show that the risk of developing refeeding syndrome is highest during the first week. However, there are no recommendations in place for electrolyte monitoring and correction with supplements, with wide variations in clinical practice. For these reasons, both the degree of malnutrition and electrolyte supplementation must be considered when evaluating studies of refeeding.

These findings underscore the need to identify approaches to refeeding that simultaneously maximize weight recovery and minimize the associated risks. In addition, they highlight the need to consider how relatively short-term approaches to inpatient refeeding may support the long-term goals of recovery, which include cognitive recovery and reduction of eating disorder psychopathology. The purpose of this review is to systematically examine published studies on approaches to refeeding in adolescents and adults with AN, with particular attention to the approach to refeeding (including caloric level, methods of delivery, and nutrient content) and characteristics of the study population (including age and degree of malnutrition). Pertinent medical outcomes are weight gain and rate of RH; cognitive outcomes include neurocognitive functioning and eating disorder thoughts and behaviors.

Method

Literature Search

We performed a comprehensive database search for abstracts published in English from 1960 to March 15, 2015, in Pubmed, PsycINFO, Scopus, and Clinical Trials databases. Search strategies combined controlled vocabulary terms (MeSH, Thesaurus) with keywords and phrases for the following concepts: refeeding, weight restoration, hypophosphatemia, and anorexia nervosa. Exclusion terms were: neoplasm(s) and cancer(s) and tumor(s). Studies were reviewed and cataloged for further bibliographic and referencing. In cases of uncertainty (e.g., the abstract was unavailable or contained insufficient detail to determine if inclusion criteria were met), the full-text of the paper was obtained and screened.

Procedure for Screening for Eligible Studies

Inclusion and exclusion criteria are described in Panel 1. Abstracts identified from the initial search were screened in a secondary review process, and full text papers were obtained of those meeting inclusion criteria. Abstracts of review papers and case studies were removed from this review but cataloged for further bibliographic and referencing. In cases of uncertainty (e.g., the abstract was unavailable or contained insufficient detail to determine if inclusion criteria were met), the full-text of the paper was obtained and screened.

Methods for Assessing Study Quality

The quality of the selected studies was independently assessed by three authors (AKG, SMS, and GR). We used the diagram for flow of information from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews as well as the organizational structure from the PRISMA checklist,
including a detailed description of the eligibility criteria (Panel 1) and the search and selection criteria for studies. The limited designs of the available studies did not allow for a formal quality assessment or statistical methods to evaluate the results (e.g., to compare or evaluate collective effect sizes). The majority of studies of refeeding in AN are retrospective and/or observational, and there is no empirically validated method to evaluate the quality of nutrient date resulting from such study designs. These study designs are known to be subject to several types of bias, which are described and discussed in the text where relevant.

### Results

#### Studies Selected for Inclusion in Systematic Review

A flow chart depicting the study selection process is shown in Figure 1. The initial search of electronic databases yielded 948 references. An additional 17 abstracts were identified from bibliographies of relevant review papers. After removing 47 duplicates, 918 abstracts were included for screening. Initial screening using the inclusion and exclusion criteria led to the exclusion of 846 abstracts. Studies were most often excluded because they were not a study of refeeding (e.g., a cross-sectional study comparing malnourished to refeeding patients with AN), did not include patients with AN, focused on pharmacotherapy, or utilized animal models. This process yielded 72 abstracts. The full texts of these abstracts were obtained and evaluated again according to the inclusion and exclusion criteria. Of these, 45 studies were excluded primarily because the refeeding protocol was not described in sufficient detail for it to be reproduced in other study or treatment settings. For example, several studies described refeeding protocols designed to achieve a desired rate of...
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<td>Study Design</td>
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<td>1 Krahn 1993&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>19–38</td>
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<td>1200; Target 3600 kcal/d after wk 2</td>
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<td>Increase 300 kcal/d during wk 2</td>
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<td>2 Solanto et al. 1994&lt;sup&gt;36&lt;/sup&gt;</td>
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<td>Meals; behavioral contracts distinguish groups</td>
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<td>5 Garber et al. 2012&lt;sup&gt;31&lt;/sup&gt;</td>
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<td>(250 q 2 days)</td>
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<td>7 Hart et al., 2011&lt;sup&gt;38&lt;/sup&gt;</td>
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<td>1500 kcal d&lt;sup&gt;−1&lt;/sup&gt;</td>
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<td>10 Golden et al. 2013&lt;sup&gt;42&lt;/sup&gt;</td>
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<td>14.7</td>
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<td>1500</td>
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<td>13 Redgrave et al. 2015&lt;sup&gt;15&lt;/sup&gt;</td>
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Combined approach with nasogastric feeding and oral intake

1 Bufano et al. 1990<sup>47</sup> | Retrospective Inpt 9 | NR | NR<sup>i</sup> |
|                       |                             |                  | Mean maximum of 2311 kcal/d |
|                       |                             |                  | Oral + NG at 25% of RE<sup>e</sup> |
|                       |                             |                  | 25% of target kcal on day 1, 50% on day 2, 75% on day 3 |
| 2 Robb et al. 2002<sup>48</sup> | Retrospective Inpt 52 NG+O<sup>s</sup> 48 O | 14.8 NG+ O 15.0 O | 15.5 (1.7) NG+ 16.0 (1.8) O |
|                       |                             |                  | Compare nocturnal NG+ oral to oral; mean maximum kcal; 3255 (NG+O), 2508 (O) |
|                       |                             |                  | Oral kcal NR |
|                       |                             |                  | 1.70 NG+ O 0.76 O |
| 3 Zuercher et al. 2003<sup>17</sup> | Retrospective Res 155 NG+O 226 O | 25.7 NG+ O 25.2 O | 14.2 (1.7) NG+ 15.7 (1.7) O |
|                       |                             |                  | Compare nocturnal NG+ oral to oral; |
|                       |                             |                  | 300 kcal every 3 days to goal |
|                       |                             |                  | 0.93 NG+ O 0.81 O |
| 4 Silber et al. 2004<sup>49</sup> | Retrospective Inpt 6 NG+O 8 O | 13.8 NG+ 17.4 (2.3) O | 14.2 (1.7) NG+ 15.7 (1.7) O |
|                       |                             |                  | Compare nocturnal |
|                       |                             |                  | 0.32 O 0.35 O |

<sup>a</sup>N: Number of participants; <sup>b</sup>N: Number of participants; <sup>c</sup>Age: Age of participants; <sup>d</sup>Admission BM: Admission body mass index; <sup>e</sup>Method of Delivery: Method of delivery; <sup>f</sup>Starting Kcal d<sup>−1</sup>: Starting calorie intake daily; <sup>g</sup>Nutrient Level: Nutrient level; <sup>h</sup>Caloric Advance (Kcal d<sup>−1</sup>): Caloric advance; <sup>i</sup>Rate of Weight Gain (kg wk<sup>−1</sup>): Rate of weight gain; <sup>j</sup>Rate of RH: Rate of recovery; <sup>k</sup>Study Design: Study design; <sup>l</sup>Study Setting: Study setting; <sup>m</sup>N: Number of participants; <sup>n</sup>N: Number of participants; <sup,o</sup>N: Number of participants; <sup>p</sup>N: Number of participants; <sup>q</sup>N: Number of participants; <sup>r</sup>N: Number of participants; <sup>s</sup>N: Number of participants; <sup>t</sup>N: Number of participants; <sup>u</sup>N: Number of participants; <sup>v</sup>N: Number of participants; <sup>w</sup>N: Number of participants; <sup>x</sup>N: Number of participants; <sup>y</sup>N: Number of participants; <sup>z</sup>N: Number of participants; <sup>AA</sup>N: Number of participants; <sup>BB</sup>N: Number of participants; <sup>CC</sup>N: Number of participants; <sup>DD</sup>N: Number of participants; <sup>EE</sup>N: Number of participants; <sup>FF</sup>N: Number of participants; <sup>GG</sup>N: Number of participants; <sup>HH</sup>N: Number of participants; <sup>II</sup>N: Number of participants; <sup JJ</sup>N: Number of participants; <sup>KK</sup>N: Number of participants; <sup>LL</sup>N: Number of participants; <sup>MM</sup>N: Number of participants; <sup>NN</sup>N: Number of participants; <sup>OO</sup>N: Number of participants; <sup>PP</sup>N: Number of participants; <sup>QQ</sup>N: Number of participants; <sup>RR</sup>N: Number of participants; <sup>SS</sup>N: Number of participants; <sup>TT</sup>N: Number of participants; <sup>UU</sup>N: Number of participants; <sup>VV</sup>N: Number of participants; <sup>WW</sup>N: Number of participants; <sup>XX</sup>N: Number of participants; <sup>YY</sup>N: Number of participants; <sup ZZ</sup>N: Number of participants;
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<th>BMI (SD/SE)</th>
<th>Method of Delivery</th>
<th>Starting Kcal d⁻¹ or Nutrient Level</th>
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<th>Rate of RH%</th>
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<td>RCT</td>
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<td>11.3 (0.7)</td>
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<td>Inpt</td>
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<td>31</td>
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<td>16.6 (2.2)</td>
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<td>Madden et al. 2015</td>
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<td>Diamanti et al. 2008</td>
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<td>Forbes et al. 1984</td>
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<th>Medical/Nutritional Outcomes</th>
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<td>Inpt psych</td>
<td>7 PUFA^{a,k}</td>
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<td>Inpt nutr</td>
<td>42 N^{l}</td>
<td>Ad lib</td>
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*Inpt = inpatient; med = medicine; psych = psychiatry; CRC = clinical research center; outpt = outpatient; res = residential; nutr = nutrition.*

*For studies that included comparison groups, we report Ns separately for low-weight-gain (L) and high-weight-gain (H) interventions.*

*Age is presented as mean.*

*BMI = body mass index (kg/m²).*

*Rates of caloric advancement are calculated for some programs, who may not advance calories every day.*

*In some cases these rates are calculated rather than derived directly from the published reports, and not all patients stayed at least a week in all studies.*

*RH = refeeding hypophosphatemia.*

*NR = not reported, mean (SD) weight at admission was 39.9 (4.3) kg.*

*A and B refer to differing behavioral contracts (all participants started on same range of calories).*

*Mean (SD) % average body weight at the end of the baseline period (before refeeding began) was 63.8 (1.4).*

*Mean (SD) % ideal body weight was 72.7% (7.1).*

*Mean (SD) percent of ideal body weight was 72.2% (5.4).*

*Mean (SD) % expected body weight was 78.4 (6.5).*

*Weight gain goal was 0.45–0.68 kg/wk.*

*REE = resting energy expenditure.*

*NG = nasogastric refeeding; O = oral refeeding.*

*"There were no cases of refeeding syndrome." (p 417)*

*REE = resting energy expenditure.*

*Patients with BMI < 12 received prophylactic phosphorous supplementation.*

*Most patients received prophylactic phosphorous supplementation.*

*Mean (SD) % ideal body weight was 79.1% (5.8).*

*Patients received prophylactic phosphorous supplementation.*

*All 6 patients with hypophosphatemia were in the oral-only group; however, 90.3% of patients in the enteral feeding group were on prophylactic phosphorous supplementation.*

*Mean (SD) % expected body weight = 78.4 (6.5).*

*Patients received prophylactic phosphorous supplementation.*

*PN = parenteral nutrition; O = oral.*

*H = high protein (20% of calories from protein); L = low protein (10% of calories from protein).*

*Mean (SD) % ideal body weight = 69.25 (8.3).*

*PUFA = n-3 polyunsaturated fatty acids; SFA = saturated fatty acids.*

*N = normal sodium diet; L = low sodium diet.*
weight gain, however no method to determine or estimate the study participants’ energy needs was provided. Such feeding protocols would be difficult to reproduce given the caloric requirements for weight gain vary markedly across age and sex and during stages of refeeding. In fewer cases, studies were excluded because they did not include the outcomes of interest (weight gain, rate of RH or cognitive/behavioral measures). Seven studies met eligibility based on initial screening, but details of the refeeding protocols were missing; these details were subsequently obtained via author communication. A total of 27 studies were included in the final systematic review and are summarized in Table 1.

Quality of Selected Studies

More than half of the studies meeting our selection criteria were published since 2010. Among all of the selected studies, 96% had retrospective or observational/prospective study designs. As expected with these designs, the most common types of bias were selection bias and bias due to differential loss to follow-up. Studies attempted to minimize these sources of error in different ways. For example, to avoid the potential effect of recent/multiple episodes of refeeding, two studies enrolled participants on their first hospital admission, while two others treated multiple admissions as statistically independent events. To limit the confounding effect of weight at presentation on the relationship between caloric level and rate of weight gain or occurrence of RH, two studies adjusted analyses for %mBMI at admission. Nevertheless, selection bias whereby high risk patients (with medical complications, severe malnutrition, and/or chronic illness) are disproportionately assigned to lower calorie refeeding groups could result in poor outcomes being overly attributed to the lower calorie refeeding approach. Selection bias could also result in disproportionate phosphate supplementation in patients perceived as high risk and must be considered when interpreting rates of RH as an outcome. Differential loss to follow-up can be a problem in long-term studies with open follow-up, whereby the characteristics of the remaining patient population become increasingly skewed as patients are lost to follow-up. Although this is a recognized problem in long-term outcome studies of AN, it is unlikely to have affected the one long-term study included here, since the authors report that “all” patients returned for follow-up. However, it is a possible source of bias in the two studies using length of stay as an outcome. In many short-term inpatient programs, especially those with standardized approaches to care, length of stay is a proxy for time to restore medical stability. However, medically complicated patients may remain in hospital longer for a variety of reasons, regardless of refeeding approach. Because of this potential bias, and the challenge of interpreting different lengths of stay across treatment settings and different countries, we did not include length of stay as a key outcome for the present review.

Meal-Based Refeeding

Thirteen studies described meal-based approaches to refeeding where the caloric level was divided into meals and snacks; any liquid supplements were taken orally and NG feeding was only used for acute food refusal.

Six studies in this group examined lower calorie diets, starting around 1,200 kcal day and advancing by about 100 kcal day. Weight gain was reported in five of these six studies and ranged from 0.62 to 1.30 kg week. Six studies in this group examined lower calorie diets, starting around 1,200 kcal day and advancing by about 100 kcal day. Solanto et al. (1994) and Garber et al. (2012) reported that adolescents who were refed starting at 1,000–1,200 kcal day and advancing by about 100 kcal day initially lost weight and then slowly gained at a rate of 0.68–0.88 kg week. Garber et al. (2012) further demonstrated an association between lower caloric prescription, poorer weight gain, and longer hospital stay in mildly malnourished adolescents (around 85% of mBMI). These findings may be partly explained by the excessive metabolic cost of weight gain in AN: both Krahn et al. and Obarzenak et al. demonstrated a large rise in Resting Energy Expenditure that was disproportionate to the amount of weight gained after 1 week of weight stabilization on lower calories and followed by 1 week of daily caloric increases to a specified weight or caloric goal. On the other hand, Gaudiani et al. (2012) demonstrated the utility of lower calorie refeeding in severely malnourished patients (<70% mBMI or BMI < 15 kg m). This study was notable for its comprehensive examination of medical complications. Seventy-seven percent of the cohort had abnormal liver function tests (LFTs), however, they peaked in the first 4 days and improved with refeeding.

A group of seven studies, starting with Whitelaw et al. (2010), examined higher calorie meal-based approaches to refeeding in hospitalized adolescents with AN. These approaches
started between 1,500 and 2,400 kcal day \(^{-1}\) and advanced by 67–250 kcal day \(^{-1}\). Rates of weight gain were reported in all studies except El Ghoch et al. (2014)\(^4^4\) and ranged from 0.62 to 1.98 kg week \(^{-1}\). Maximal caloric prescriptions achieved before discharge ranged from 2,800 to 4,350 kcal day \(^{-1}\). These studies established the feasibility of higher calorie meal-based refeeding to promote weight gain in hospitalized adolescents with AN. Only two studies compared lower versus higher meal-based refeeding protocols.\(^{4^1,4^2}\) In a prospective observational study of 56 adolescents, Garber et al. (2013)\(^{4^1}\) reported faster weight gain and a mean 5.7 days shorter hospital stay in higher meal-based refeeding protocols, and in a retrospective study of 310 adolescents, Golden et al. (2013)\(^{4^2}\) reported a mean stay of 3.6 fewer days.

Among the studies of lower\(^{1^8,2^5,3^7}\) and higher\(^{3^5,4^0–4^3}\) calorie meal-based approaches, a total of eight studies examined RH as an outcome. Ornstein et al. (2003)\(^{2^5}\) were the first to explore the rate of RH with caloric intake. This retrospective chart review found that 27.5% of mildly to moderately malnourished adolescents hospitalized with AN developed RH on a lower calorie refeeding approach starting at 1,200–1,400 kcal day \(^{-1}\) and increasing by 200 kcal every 24–48 h. In addition, low percent of ideal body weight upon admission was significantly associated with serum phosphorus nadir during refeeding. This study identified low admission BMI (or %mBMI) as a risk factor for the development of RH in mildly to moderately malnourished adolescents, an association confirmed by subsequent studies in this group, including Whitelaw et al. (2010),\(^{4^0}\) Golden et al. (2013),\(^{4^2}\) and Redgrave et al. (2015).\(^{3^5}\) On the other hand, in severely malnourished/critically ill patients, Gaudiani et al. (2012)\(^{3^7}\) did not find that admission BMI predicted RH. The elevated transaminases commonly occurring in this study population (as mentioned above) were also not predictive of RH; however they were associated with the occurrence of hypoglycemia. Variable approaches to electrolyte correction must be considered when interpreting these findings. For example, Garber et al. (2013)\(^{4^1}\) reported that 36% of adolescents received electrolyte correction, similar to Whitelaw et al. (2010).\(^{4^0}\) In contrast, Le Clerc et al. (2013) reported that only one of thirty patients required electrolyte replacement for low serum phosphorus.\(^{4^3}\) All of the studies in this group reported replacing phosphate as needed to treat low or declining levels, and none reported side effects of phosphate supplementation.

Four studies examined the association between caloric intake or rate of weight gain and RH and found no association. Golden et al. (2013)\(^{4^2}\) observed that 15.8% of adolescents developed RH, and that RH was associated with lower BMI on admission but not caloric intake. Consistent with this, Garber et al. (2013)\(^{4^1}\) did not find differences in electrolyte abnormalities between patients refed using higher and lower calorie protocols. RH occurred in 18.5% of a primarily adult cohort of patients in the study by Redgrave et al. (2015)\(^{3^5}\) and was associated with admission BMI rather than with rate of weight gain. Findings in severely malnourished patients were consistent: Gaudiani et al. (2012)\(^{3^7}\) found no association between caloric intake and RH in the first 2–6 days of refeeding.

Only two studies of higher calorie meal-based approaches have had sufficient sample sizes to examine a subsample of severely malnourished patients. In a study of 461 admissions for refeeding, Redgrave et al. (2015)\(^{3^5}\) analyzed 135 adolescents and adults with BMI < 15 kg m \(^{-2}\) refed with meals starting between 1,200 and 1,500 kcal, advancing rapidly by 500 kcal every 2–3 days, supported by continuous intravenous (IV) 5% dextrose at 75 mL h \(^{-1}\) and close medical monitoring until postprandial blood glucose normalized. Weight gain was comparable to the higher BMI participants, but rates of RH were higher (32.4% vs.18.5% in the whole sample). Similarly, using a higher calorie refeeding approach with careful medical supervision but without IV dextrose, Golden et al. (2013)\(^{4^2}\) compared a subsample of severely malnourished adolescents (%mBMI 65%) who were fed higher (\(N = 31\)) vs. lower (\(N = 18\)) calorie diets. Comparable weight gain was reported in both groups. The rate of RH was higher in the severely malnourished subsample than in the total sample but did not differ by caloric prescription.

Only one study\(^{4^4}\) of meal-based refeeding reported psychological outcomes, using a meals-only approach to refeeding. El Ghoch (2014) assessed 50 adults with chronic AN (mean length of illness of 8.7 ± 6.7 years) and severe malnutrition. The refeeding intervention took place over 20 weeks (13 weeks inpatient and 7 weeks partial hospitalization) and began with 1,500 kcal to 2,500 kcal day \(^{-1}\) for 3 weeks with subsequent dietary intake aimed at achieving a weight gain goal of 0.45–0.68 kg week \(^{-1}\). Participants also received intensive psychological treatment and cognitive behavioral therapy for eating disorders. At the mean maximal BMI achieved [19.6(0.8) kg m \(^{-2}\)], eating disorder thoughts and behaviors [measured by the Eating Disorder Examination\(^{5^6}\)] had improved significantly.
Combined Approach with Nasogastric Plus Oral Refeeding

Ten studies meeting inclusion criteria described approaches to refeeding using NG feeding in combination with oral feeding. Five of these studies began with a combination of supplemental NG feeding and oral intake upon admission \(^{46,48-51}\); three studies began with NG feeding only and then introduced meals \(^{33,34,52}\); and one study began with meals for 3 days, followed by 3 days of exclusive NG tube feeding, followed by transition back to meals only. \(^{45}\) NG feeding approaches were used to deliver both lower and higher calorie loads. Rate of weight gain was reported in all but one study \(^{33}\) and ranged from 0.63 kg week\(^{-1}\) in a study purposely designed to deliver lower caloric loads to severely malnourished/critically ill patients, to 2.79 kg week\(^{-1}\) in a study of adolescents who were, on average, moderately malnourished on average. \(^{34}\)

Four studies in this group reported using lower calorie approaches. Gentile et al. (2010, 2012) focused on severely underweight adolescents and adults with AN, with purposefully low weight gain goals (0.5–1 kg week\(^{-1}\)) to minimize potential complications in these higher risk patients. \(^{50,51}\) Similar to Gaudiani et al. (2012), \(^{37}\) biochemical and hematological parameters tended to improve during refeeding. This included LFTs, which were high in 43–48% of participants at onset and improved after 30 and 60 days of refeeding. \(^{50}\) Robb et al. (2002) and Silber et al. (2004) compared supplemental nocturnal NG feeding in hospitalized adolescents to historical controls fed with meals alone. \(^{46,48}\) The rate of NG feeding was set to bring the total starting kcal level (including meals) to 1,200 kcal day\(^{-1}\) and was then increased to support a consistent weight gain rate of 1–2 kg week\(^{-1}\). With this method, Robb et al. (2002) reported that the total mean calorie intake was greater and weight gain was faster in the supplemental NG Group (3,255 kcal day\(^{-1}\); 1.7 kg week\(^{-1}\)) compared to those fed meals alone (2,508 kcal day\(^{-1}\); 0.76 kg week\(^{-1}\)), with no difference in the length of stay among 100 females. \(^{46}\) Silber et al. (2004) confirmed this finding in 14 males. \(^{48}\)

Three studies reported higher calorie approaches. Hatch et al. (2010) and Madden et al. (2015) \(^{33,34}\) started with 24–72 h of continuous NG feeding in adolescents that began at 2,400 kcal day\(^{-1}\) and then transitioned to a combination of NG feeding and meals for a total of 2400–3,000 kcals day\(^{-1}\) to achieve a target rate of weight gain of 1 kg week\(^{-1}\) (author communication). \(^{33,34}\) This approach resulted in the largest weight gain (2.79 kg in week 1) \(^{34}\) reported among all of the studies included in the present review. Agostino et al. (2013) utilized a similar NG feeding approach, but began with a slightly lower caloric level of 1,500 or 1,800 kcal day\(^{-1}\) depending on age. Weight gain was greater in the group that received continuous NG feeding for 7 days and then transitioned to include meals, as compared to historical controls who received only meals. \(^{52}\)

The majority of studies in this group reported using prophylactic phosphate supplementation. \(^{33,34,46,49-52}\) One used supplementation for all participants with BMI < 12 kg m\(^{-2}\), \(^{49}\) and another supplemented all patients on NG but not mealsonly feeding. \(^{52}\) Among these studies reporting RH, rates ranged from 0 to 3.6%. \(^{34,49-52}\) By contrast, in a study where prophylactic phosphate was not used, RH occurred in one-third of participants. \(^{55}\)

The only study in this group to examine changes in cognition and eating disorder psychopathology was Hatch et al. (2010).\(^{33}\) At the end of the admission (12.7 weeks), participants showed significant improvements in cognitive processing speed in sensorimotor tasks and cognitive inhibition and less distractibility on memory tasks. The study did not report improvement in eating disorder cognitions measured by the Eating Disorder Inventory III or obsessionality as measured by the Maudsley Obsessive Compulsive scale following weight restoration, however there were significant improvements in depression, anxiety, and stress as measured by the Depression, Anxiety and Stress Scale.

Two studies in this group stand out due to differences in study setting and design. Zuercher et al. (2003) was the only study meeting criteria for the present review that was performed in a non-hospital setting. \(^{47}\) This study compared participants in a residential setting who elected to receive supplemental NG feeding to those who chose meals only and reported greater caloric intake and weight gain in the NG group however no differences in eating disorder psychopathology (per the Eating Disorder Inventory-2). Selection bias must be considered when interpreting this finding since NG feeding was voluntary and the group opting for NG refeeding had significantly lower BMI upon admission and stayed in the program longer. Indeed, rates of weight gain were similar between groups in statistical analyses adjusting for these variables.

A second study worth mentioning due to differing design was the only RCT comparing different approaches to refeeding. Rigaud et al. (2007) \(^{49}\) compared 70 days of NG feeding twice daily plus meals to meals alone in chronically ill young adults with a duration of illness of 3–4 years, at least one prior...
hospitalization, and BMI >11 kg m\(^{-2}\). The groups were separated in time, so that patients on the unit all received the same treatment; patients randomized to a treatment that was not active at the time of randomization waited up to 3 months for admission. Calorie levels in both groups were adjusted based on REE to produce a 1 kg week\(^{-1}\) weight gain. Patients were not restricted to bed, and there was little monitoring of activity levels during treatment. Consistent with the other studies described here, the NG group consumed more calories and gained more weight. Assessment of tolerance of the NG feeds indicated that any emotional distress occurred during the early phase of refeeding. Patients required an average of two tube changes over the 70-day course of treatment. No serious physical complications were reported. There was no difference in weight and eating disorder psychopathology at 1-year follow-up, however relapse was delayed by 7 weeks in the NG-fed group.

### Parenteral Refeeding

Only one study meeting our inclusion criteria examined total parenteral nutrition (TPN). Diamanti et al. (2008) reported that TPN in combination with oral feeding resulted in a greater rate of weight gain than oral feeding alone. The authors recommended that the rate of initial parenteral refeeding be limited to 600–800 kcal per day and the amount of protein be limited to 2 g kg\(^{-1}\) of body weight to avoid development of refeeding syndrome. Weekly weight gain rates were low in both groups (<1 kg week\(^{-1}\)), and TPN treated patients gained on average only 183 g week\(^{-1}\) faster than those fed orally. Various complications of TPN were reported, including elevated transaminases, lower extremity edema, and hypophosphatemia.

### Refeeding with Altered Nutrient Content

Three studies described refeeding protocols with a nutrient content that differed significantly from current dietary guidelines [such as the 2010 US Dietary Guidelines for Americans, the 2006 Nutrient Reference Values in Australia and New Zealand, and the United Kingdom Nutrient Reference Values]. First, Forbes et al. (1984) compared diets beginning at higher caloric levels but with lower and higher protein contents (10 vs. 20% of calories from protein) among 12 patients with AN admitted to a CRC for up to 4 weeks. They found no difference in rate of overall weight gain, lean mass, or REE and concluded that a high protein diet does not benefit body composition during refeeding. Second, Mauler et al. (2009) performed a controlled (but not randomized) feeding study in 25 participants with AN in an inpatient psychiatry unit comparing a diet higher in omega-3 polyunsaturated fatty acid (Ω-3) content to a diet with an equal proportion of calories from saturated fat. No differences in weight gain or serum leptin concentrations were observed, lending no support to the hypothesis that high Ω-3 diets may produce greater weight gain through attenuated leptin levels. The third and final study in this group was by Rigaud et al. (2010), who compared a low-sodium (1,600–2,000 mg) to a normal-sodium diet (4,000–4,800 mg) in a non-randomized study among severely malnourished adults with AN. Weight gain and peripheral edema were greater on the normal- compared to low-sodium diet, suggesting that reducing the sodium content of the refeeding diet may be useful in managing fluid shifts, especially in adults with a BMI <15 kg m\(^{-2}\).

We examined the studies included in the meal-based group (above) to determine if any conclusions could be drawn about the effect of nutrient content on refeeding outcomes. Six of the thirteen studies reported nutrient content of the refeeding diet; the nutrient information for an additional four studies was obtained by author communication. Within these 10 studies, the macronutrient distribution of the diets was consistent with currently recommended ranges (about 25–35% of calories from fat, 15–20% protein and 50–60% carbohydrate). As a result, no association between differing nutrient content and refeeding outcome could be determined. Some refeeding approaches reported using IV glucose due to concerns of post-prandial hypoglycemia and the risk of RH during the initial phase of refeeding. Gentile et al. (2012) described a protocol for refeeding severely malnourished adults (mean BMI 11.3 kg m\(^{-2}\)) that initially supplemented oral refeeding with 10% glucose intravenously. As mentioned earlier, Redgrave et al. (2015) used a similar approach, using 5% dextrose in severely malnourished patients.

### Discussion

For many years, a low calorie approach to refeeding hospitalized patients with AN has been recommended, beginning around 1,200 kcal day\(^{-1}\) or
lower and advancing slowly. The purpose of these conservative approaches was to minimize the risk of patients developing the refeeding syndrome. In this respect, it could be argued that these approaches have been successful, as only a few cases of the refeeding syndrome have been reported during the decades since lower calorie approaches became the standard of care for refeeding in AN. However, lower calorie refeeding has also been linked to poor weight gain and prolonged hospital stay. Increasing recognition that underfeeding leads to poor outcomes in AN is contributing to a growing interest in higher calorie refeeding in clinical practice and research, as reflected in the results of the present systematic review. Since 2010, ten studies have reported approaches to refeeding beginning with 1,400 kcal day or more through meals alone or from approaches that combine NG and oral feeding. Only two recent studies reported lower calorie approaches, both in higher-risk (severely malnourished) patients.

We found marked heterogeneity in approaches to higher calorie refeeding, with large variation in starting calorie levels, rates of advancement, and modes of delivery. The outcomes of interest were likely influenced by these differences, in addition to the effects of differences around length of stay, approaches to electrolyte correction, type of program (medical or psychiatric), and level and duration of psychotherapy provided. For example, the two available studies comparing groups on lower and higher meal-based refeeding come from comparable adolescent medical in-patient units. However, the feeding protocols differed by both initial calories and rate of energy advancement, which may explain why one study reported a faster rate of weight gain in the higher calorie group, and the other did not. For these reasons, we did not attempt to statistically quantify the relationship between calories and weight gain across studies.

Nevertheless, our systematic review supports the following evidence-based conclusions:

In Mild (%mBMI 80–90%) and Moderately Malnourished (% mBMI 70–79%) Patients, Lower Calorie Refeeding is Too Conservative

The large proportion of adolescents hospitalized in medical stabilization units across the United States, Canada, Australia, and the United Kingdom are mildly to moderately malnourished with relatively acute onset of AN. Studies have linked lower calorie refeeding to poor outcomes in this patient population, including poor weight gain and prolonged hospital stay. Subsequent studies of higher calorie refeeding in similar study populations, using either meals-only or NG feeding in combination with meals, report similarly good weight gain with wide variability in RH (see below for a discussion of safety).

Meal-Based Approaches and Combined Approaches Using NG Feeding with Meals Can Be Used to Administer Higher Calories to Hospitalized Patients with AN

There is insufficient evidence at this time to determine the superiority of meal-based to nasogastric plus meal-based refeeding approaches. This is largely due to limitations in study design: studies comparing supplemental enteral feeding to meal-only approaches were not designed to determine whether there was an independent effect of the method of delivery. Instead, these studies collectively demonstrate that supplemental NG feeding is useful for increasing the total caloric load. However, equally good weight gain has been reported using meal-only approaches. Tolerance and/or acceptability could tip the balance in favor of one approach over the other, however this has not been sufficiently examined. One study of higher calorie meal-based feeding reported that patients could complete the higher calorie meals to the same extent as those fed lower calorie meals, and none required NG feeding; other studies have reported that 8% and 15% of adolescents on higher calorie meal-based refeeding required supplemental NG feeding to meet caloric prescriptions. In a study of supplemental NG feeding, patients reported that it was acceptable when presented in the context of a standardized protocol that is uniformly applied within a specialty program for the treatment of AN. Acceptability of NG feeding is supported by a large study in a residential setting and with qualitative research examining attitudes among adolescents to an NG feeding protocol. Halse et al. reported that patients recognized the medical rationale for placement of the tube but also experienced some ambivalence towards the procedure, which may reflect a general resistance to weight gain (rather than tube feeding per se). Prospective trials comparing meal-based with NG plus meals are needed and should control for the number of calories prescribed and carefully assess tolerance.
Higher Calorie Refeeding Has Not Been Associated with Increased Risk for the Refeeding Syndrome under Close Medical Monitoring with Electrolyte Correction

No cases of refeeding syndrome were reported within the studies of higher calorie refeeding. Variable rates of RH, a sensitive marker of risk for the refeeding syndrome, were reported without incident. However, these aspects have not been compared within a controlled trial, and there are several limitations to the available evidence that preclude a comparison of safety across approaches to refeeding. First, sample sizes have been generally small; a very large, multicenter trial would be required to comprehensively examine the full range of clinical features associated with the refeeding syndrome using various refeeding approaches, since only a handful of cases of cardiac arrest and death have been reported in the AN literature. Second, while patients with severe malnutrition are at highest risk of RH they are not well represented in the available studies. Third, the incidence of RH may in fact be underrepresented by the current studies. This is due in part to the variety of approaches to electrolyte correction that are currently used in clinical practice. RH has been indicated by the lowest serum phosphorus level during hospitalization, and it is possible that this measure was obtained in participants who had already begun receiving supplements (meaning that a “true” nadir was never reached). Selection bias could also contribute to the underestimation of RH if more severely malnourished participants and/or those on higher calories were more likely to receive phosphate supplementation. Fourth, the relative safety of different methods of delivery has not been compared. The hypothesis that continuous NG feeding (as opposed to bolus feeds) ameliorates RH warrants examination. Finally, thresholds for low serum phosphate levels vary among clinical laboratories and therefore there are likely differences in dosing and timing of phosphate across studies. Difference in these variables are likely to occur even within clinical programs, related to differing interpretation of and comfort level with borderline laboratory values. These limitations, together with the gravity of the risk of the refeeding syndrome, underscore the need for close medical monitoring when higher calorie approaches are undertaken. Prospective studies using standardized protocols (for refeeding and electrolyte replacement as well as admission and discharge criteria) are needed.

In Severely Malnourished Inpatients with an (BMI < 15 kg m\(^{-2}\) in Adults or mBMI < 70% in Adolescents), There is Insufficient Evidence to Support Changing the Current Standard of Care for Refeeding

Greater caution continues to be used with more severely malnourished, chronically ill, and/or adult patients. A few recent studies have focused on this population and uniformly demonstrated improvements in the function of multiple organ systems using a lower calorie approach with slow advancement. These approaches involved rigorous medical monitoring, for example, two studies used NG feeding with prophylactic oral phosphate and potassium and intravenous glucose. It is not known whether such critically ill patients could tolerate higher caloric loads and what level of medical management this might require. Two studies of higher calorie refeeding found comparable weight gain and manageable RH in severely malnourished sub-samples within larger studies of primarily moderately malnourished patients. While low expected weight is a risk factor for RH in such populations, among critically ill adults with AN (average BMI around 13), Gaudiani et al. (2012) reported that admission BMI did not predict RH and neither did starting caloric prescription. On the other hand, elevated transaminases predicted the development of hypoglycemia. Future studies are needed to identify biochemical, behavioral, and anthropometric factors (such as rapidity/magnitude of weight loss) that must be considered when determining best approaches to refeeding.

TPN is Not Recommended Unless No Other Form of Refeeding is Possible

Given the extent of weight gain that can be achieved by other methods, the small incremental increase in weight gain reportedly attributable to supplemental TPN does not outweigh the potential risks. TPN is associated with high rates of significant complications and requires intensive medical monitoring, which adds to its expense. In a large nation-wide database study from Japan (which was beyond the scope of this review
because it included diagnoses other than AN, Michihata et al. (2014)\(^6^9\) compared TPN alone (\(N = 278\)) to NG feeding (\(N = 634\)). They found significantly higher rates of sepsis, disseminated intravascular coagulation, and death in the TPN group.\(^6^9\) Also beyond the scope of this systematic review are case reports of both successful weight restoration,\(^7^0\) as well as deaths from TPN refeeding in AN.\(^6^3\) Given the serious medical risks, further research is not indicated for TPN refeeding. The only indication for administering TPN in AN is when there are no alternatives for achieving weight restoration. This may be considered in cases where gastrointestinal complications preclude enteral refeeding (e.g., following gastroenterological surgery, or in the setting of severe recurrent vomiting when naso-jejunal feeding has also proven unsuccessful) or in the context of acute hepatitis or pancreatitis.

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**Meals and Liquid Formulas with Nutrient Compositions within Recommended Ranges Are Appropriate for Refeeding**

The macronutrient composition of the diets used in the studies included here fell within range of the standard recommendations for the general population (\(\sim 25\text{–}35\%\) of calories from fat, 15–20\% protein, and 50–60\% carbohydrate).\(^7^1\text{–}7^3\) In theory, lowering the glucose load of the diet or formula could attenuate risk for the refeeding syndrome.\(^6^8\) This may be accomplished by changing the nutrient content of the diet, such as lower carbohydrate or lower glycemic load meals or liquids. This has also been postulated as a benefit of NG feeding,\(^3^3,3^4,6^8\) since delivering a formula at a lower, continuous rate may avoid the wide glucose and insulin excursions associated with bolus-feeds. Another strategy employed to ameliorate the post-prandial hypoglycemia associated with risk for the refeeding syndrome is to continuously infuse intravenous glucose during the initial phase of refeeding.\(^3^5,5^0,5^1\)

The only study that focused on micronutrient content was Rigaud et al. (2010),\(^5^6\) which indicated that a lower sodium diet reduces fluid shifts during refeeding in severely malnourished patients. Beyond this review, Schebendach et al. reported that dietary variety and energy density may predict recovery outcomes in AN.\(^7^4,7^5\) Further study is needed to build on these lines of evidence and determine if there is an optimal nutrient profile for refeeding in AN.

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**Research is Needed on Approaches to Refeeding Outside of the Hospital**

Weight restoration can be successfully achieved in non-hospital treatment settings. A recent study has shown there is no evidence to support extended hospitalization as a strategy for weight restoration in adolescents who were discharged from hospital to Family Based Therapy (FBT), the ambulatory treatment that has the strongest evidence for effect in adolescents with AN. Madden et al. (2014) compared short-term medical stabilization to longer-term weight recovery in hospital, both followed by FBT, and found no difference in 12-month weight recovery despite about twenty additional days in hospital.\(^7^6\) Other treatment settings include day programs and residential programs.\(^7^7\text{–}7^9\) The only clinical trial in these settings is a large scale German RCT by Herpertz-Dahlmann et al. (2014),\(^8^0\) which reported that, after a 3-week admission to achieve medical stabilization, day treatment was not inferior to prolonged hospitalization (14.5 weeks) at achieving weight restoration at 12 months in adolescents presenting for their first admission for AN.\(^8^0\) An important feature of both of these RCTs\(^7^6,8^0\) is that patients were required to be physiologically stable prior to initiation of treatment. Therefore, these finding may suggest that non-inpatient settings are cost-effective for long-term nutritional rehabilitation.\(^7^6,8^0\) Short-term refeeding to restore medical stability is a critical requirement for many patients.

There is insufficient evidence to attribute the relative success of various treatment settings to a particular refeeding approach at this time. Only one study of refeeding in a non-hospital setting met criteria for inclusion in this systematic review,\(^4^6\) and it was biased by differing severity of illness between treatment groups. Most of the available studies did not meet our requirement that the refeeding protocol be described in sufficient detail that it could be reproduced in other settings. It is clear that FBT, an approach where parents temporarily take control of refeeding, produces superior remission rates (weight and cognitive recovery at 12 months) compared to adolescent-focused therapy in the outpatient setting.\(^7\) In both psychotherapeutic modalities, weight gain of 0.8–0.9 kg (1.7–1.9 lb) per week during the first 3–4 weeks predicted remission at the end of treatment. This importance of early weight gain early for long-term recovery has been demonstrated by other studies in both the outpatient\(^8^1\text{–}8^3\) and inpatient settings.\(^1\text{–}3\) These findings underscore the need to identifying approaches to refeeding that can safely optimize weight gain.
Successful components of refeeding approaches that may be implemented in other treatment settings have not been identified. While it is tempting to assume that higher calorie intake explains at least some of the success of FBT, the rate of weight gain predictive of remission is comparable to that in inpatient settings on lower calorie refeeding. On the other hand, rates ranging from 1.3 to 1.98 kg week\(^{-1}\) and as high as 2.79 kg week\(^{-1}\) have been reported in patients on higher calorie meals and combined NG feeding with meals in hospital, respectively. Thus, higher calorie intake alone does not account for the success of treatment modalities such as FBT. Researchers have elucidated some cognitive and behavioral factors that moderate the success of FBT, such as eating disorder psychopathology, however comprehensive diet and activity data have not been examined. Weight restoration strategies in FBT, such as parents limiting physical activity or serving higher energy density foods, have not been assessed. Identification of these components, in addition to actual caloric level and intake, nutrient quality, and eating behaviors could facilitate the dissemination of successful components of FBT by clinicians who currently lack guidance and across patient populations and settings, including those that lack parental involvement (such as young adults living independently or those in residential settings). Future studies of refeeding in all treatment settings should strive to collect both dietary and activity data.

### The Impact of Approaches to Refeeding on Long-Term Outcomes is Unknown

Studies associating better weight gain during refeeding with improved recovery support the hope that higher calorie refeeding could lead to better outcomes. Unfortunately, there is currently no evidence to support this. The only study comparing long-term outcomes of defined refeeding protocols was an RCT that compared a higher calorie combined enteral and meal feeding group to a lower calorie meals-only group and found no difference in 1-year weight recovery. However, this study did report earlier relapse in the meals-only group receiving lower calories. Limitations of this study include an open follow-up design (discussed earlier) and ‘wait-list’ randomization scheme, whereby one group of patients may have become sicker during the 3-month period while awaiting treatment. Nevertheless, the possibility that higher calorie refeeding may reduce relapse warrants further investigation since high relapse rates contribute to the recognition of AN as one of the most “common and costly” primary mental health diagnoses in pediatrics.

There is even less evidence to indicate how refeeding approach may impact long-term cognitive and behavioral recovery. Hatch et al. (2015) reported no reduction of eating disorder thoughts and behaviors in acutely malnourished adolescents after 12 weeks of higher calorie combined NG feeding plus meals. In contrast, El Ghoch et al. (2014) reported significant improvements in eating disorder and general psychopathology after 20 weeks of higher calorie refeeding in severely and chronically malnourished adults. These discrepant findings may be explained in part by differing lengths of follow-up (12 vs. 20 weeks) and variable types and intensity of psychotherapeutic interventions. Nevertheless, both of these studies demonstrate that refeeding in hospital impacts cognitive recovery. There is a pressing need to examine how refeeding that takes place over a relatively short period can support the long-term goals of recovery, since weight recovery in the absence of concomitant behavioral recovery does not bode well for complete or sustained recovery and renders patients vulnerable to relapse.

### Conclusion

This systematic review of approaches to refeeding reflects a growing body of evidence that supports higher initial calorie feeding and faster approaches to increasing calories in hospitalized patients with AN. Collectively, these studies demonstrate that higher calorie approaches than currently recommended are feasible for refeeding mildly and moderately malnourished patients with AN who are in hospital, where close medical monitoring is possible. In severely malnourished and more chronically ill patients, lower calorie approaches with slow advancement may still have a role. TPN is not indicated in these patients. The current evidence indicates that equally good weight gain can be achieved with meal-based approaches and approaches that combine meals and NG feeding to supplement oral intake. More evidence is needed to determine whether higher calorie refeeding is also feasible in non-hospital treatment settings, where rigorous medical monitoring may not be possible. This is particularly important because the safety of higher calorie refeeding has not been established. More studies are needed to determine best practices for electrolyte monitoring and correction. Another gap in the
evidence is nutrient content: the optimal refeeding diet and/or formula is not known. The available studies only indicate that higher calories can be delivered in standard macronutrient ranges that are consistent with the current dietary recommendations and that lower sodium diets may attenuate fluid shifts in severely malnourished patients. While reduced carbohydrate feeding has been suggested as a means to reduce the risk of RH, this hypothesis has not been tested. These research gaps highlight the need for prospective studies to directly compare different approaches to refeeding. Such studies should examine both short- and long-term outcomes, since the benefits of higher calorie refeeding in hospital, including faster weight gain or shorter hospital stay, could be easily outweighed by unintended consequences, such as higher rates of relapse.

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