Advancements in Inpatient Medical Management of Malnutrition in Children and Adolescents with Restrictive Eating Disorders

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There is an urgent need to identify best practices for hospital treatment of youth with malnutrition secondary to restrictive eating disorders, including anorexia nervosa (AN) and avoidant/restrictive food intake disorder (ARFID). Certain physical health complications of malnutrition, such as bradycardia, hypotension, and hypothermia, often lead to hospitalization. These acute medical complications improve with refeeding or short-term nutritional rehabilitation and will resolve with ongoing recovery. Historically, refeeding was approached with extreme caution, with lower calorie protocols that advanced slowly and required weeks to restore medical stability.[1-3] Prolonged hospitalizations place eating disorders among the top 6 most common and costly pediatric mental health diagnoses.[4] This article reviews the current evidence on refeeding approaches for hospitalized youth with eating disorders. Recent findings suggest that high calorie refeeding (HCR) is a clinically safe method of inpatient management and, more importantly, improves clinical outcomes.

Restrictive Eating Disorders

Restrictive eating disorders include AN, atypical AN (AAN), and ARFID. AN is a serious psychiatric illness that includes three key diagnostic components: (1) intentional restriction of energy intake leading to an abnormally low weight or failure to gain expected weight; (2) intense fear of gaining weight or becoming fat; and (3) a disturbance in the self-perception of one's weight or shape.[5] It is important to note that there is no specific weight threshold required for the diagnosis of AN, and pediatric patients may begin to deviate dramatically from their prior growth trajectory simply with failure to gain over time with relatively little weight loss. There are 2 diagnostic subcategories of AN: the restricting type and the binge-eating/purging type. Those with the restricting type AN have not engaged in recurrent episodes of binge eating or purging behavior in the past 3 months, whereas those with the binge-eating/purging type AN have had ≥1 episode. Patients with AAN meet most of the criteria for AN, yet still have a weight that is in the normal range after significant weight loss. Although there is no diagnostic criterion for significant weight loss, loss of 10% body mass is often used clinically and aligns with the criteria for diagnosing malnutrition.[6] AAN is currently a diagnostic category under other specified feeding and eating disorder. Patients with AAN can experience psychological and physical impairments as significant as those with AN, yet the diagnosis may be delayed.[7] This delay may be due in part to being overweight or obese before the onset of AAN and therefore having a normal-appearing weight at presentation.[8] AN has a lifetime prevalence of 1.4% for females and 0.2% for males.[9] The lifetime prevalence of AAN is 2.1%-4.9% among females. Epidemiological studies of AAN among adolescent and young adult females reveal a prevalence of 2.8%-4.9%.[10] ARFID is characterized by avoidance of food intake that is severe enough to result in nutritional deficiencies or impact psychosocial development.[11] Epidemiological studies of ARFID reveal a wide range in prevalence from 0.3% to 15.5% in nonclinical populations of children and adolescents.[12-14] Although ARFID shares some similarities with AN, a key difference in presentation is that these patients do not exhibit the intense fear of gaining weight or disturbance in body image. Some individuals with ARFID have developed food intolerance after adverse food-related experiences, such as vomiting or choking, whereas others have extreme sensitives to food smells, tastes, textures, or even colors. Although weight loss is not part of the diagnostic criteria, ARFID may result in protein-calorie malnutrition as severe as AN. Given that eating disorders most commonly develop during adolescence, most practicing pediatricians will see patients with eating disorders regularly in their practices. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria for AN, AAN, and ARFID are outlined in **Table I**.

AAN	Atypical anorexia nervosa
AN	Anorexia nervosa
ARFID	Avoidant/restrictive food intake disorder
BMI	Body mass index
HCR	High calorie refeeding
LCR	Low calorie refeeding
mBMI	median body mass index
RS	Refeeding syndrome

Rationale for Medical Admission

The malnutrition associated with restrictive eating disorders can affect nearly every organ system (**Table II**). Although

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Table I. ***Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria for feeding and eating disorders**

Types of eating disorder	Diagnostic criteria
AN	A. Restriction of energy intake relative to requirements, leading to a significantly low weight, which is a weight that is less than that minimally expected in the context of age, sex, developmental trajectory, and physical health. B. An intense fear of weight gain or persistent behavior that interferes with weight gain, despite being at a significantly low weight. C. Disturbed perception in the experience of body weight or shape, self-evaluation that is disproportionately influenced by weight or shape, or persistent lack of acknowledgement of the severity of low body weight. Types: 1. Restricting type: Absence of recurrent binge eating or purging* behaviors in the preceding 3 months. 2. Binge-eating/purging type: Presence of recurrent binge eating or purging behaviors in the preceding 3 months.
AAN	Meets criteria for AN, except that weight is within normal or above normal range despite significant weight loss.
ARFID	A. A feeding or eating disturbance† resulting in failure to achieve appropriate nutritional and/or energy requirements associated with ≥1 of the following: 1. Failure to achieve expected weight gain or adequate growth. 2. Significant nutritional deficiency. 3. Enteral feed or oral nutritional supplementation dependance. 4. Significant interference with psychosocial functioning. B. The disturbance is not due to lack of access to food or by a culturally sanctioned practice. C. There is no disturbance in the perception of one's body weight or shape and the disturbance does not occur exclusively during a course of AN or bulimia nervosa. D. The disturbance is not due to a current medical condition or more appropriately explained by a different mental health disorder. When another condition or disorder does exist alongside the eating disturbance, the severity of the eating disturbance is disproportionate to that typically expected with the coexisting condition or disorder, warranting additional clinical attention.

*Purging is defined as self-induced vomiting or misuse of laxatives, diuretics, or enemas.
†Examples of feeding and eating disturbances include apparent lack of interest in eating or food, avoidance based on sensory characteristics of food, and concern about aversive consequences of eating.
Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[5]

Table II. Medical complications of eating disorders

Systems of involvement	Medical complication
General	Dehydration Hypokalemia Hypomagnesemia Hyponatremia Hypothermia Hypoglycemia Hypochloremic metabolic alkalosis Hyperchloremic metabolic acidosis Hyperuricemia Hypocalcemia Fluid retention
Ear, nose, and throat	Dental erosions
Cardiovascular	Prolonged corrected QT interval; increased QT dispersion Dysrhythmias (including supraventricular beats and ventricular tachycardia) Mitral valve prolapse Pericardial effusions Bradycardia Hypotension
Pulmonary	Aspiration pneumonia
Hematologic	Anemia, leukopenia, thrombocytopenia
Gastrointestinal	Delayed gastric emptying and impaired gastrointestinal tract motility Constipation Bloating, postprandial fullness Hypercholesterolemia Abnormal liver function tests Esophagitis, gastric rupture Mallory-Weiss tears Pancreatitis
Renal	Sterile pyuria Acute kidney injury
Reproductive	Amenorrhea and menstrual irregularities
Musculoskeletal	Low bone mineral density; osteoporosis
Endocrine	Sick euthyroid syndrome Growth delay
Psychiatric	Cognitive deficits, mood symptoms, obsessive/compulsive symptoms, suicidality and suicide
Neurological	Cortical atrophy

Adapted from Hornberger; American Academy of Pediatrics.[15]

there are no strict requirements for medical admissions related to these medical complications, frequently used criteria are summarized in **Table III**. The rationale for medical admission, as supported by the Society for Adolescent Health and Medicine and the American Academy of Pediatrics position statements, as well as the Academy for Eating Disorders' medical guidelines, usually involves electrolyte imbalance, cardiac arrhythmia such as bradycardia or prolonged QTc syndrome, or other acute medical consequences of disordered eating.[15,16] Our understanding of potential electrolyte disturbances seen with intensive refeeding has its origin in numerous case reports from the early twentieth century summarizing clinical effects of starvation and chronic malnutrition, mostly related to sieges or prisoners of war. After World War II, a case series describing the process of refeeding malnourished soldiers included 5 deaths among 24 subjects.[17] The individuals who died while attempting to restore weight developed weakness and worsening edema that the authors initially attributed to congestive heart failure or thiamine deficiency. However, autopsies were inconsistent with either diagnosis. Around the same time, a study known as the Minnesota Starvation Experiment, involving the deliberate starvation of civilians, also tracked the physiologic changes associated with refeeding. Study participants developed physical and cognitive decline, including anemia, edema, irritability, and fatigue.[18] Although unknown at the time, the symptoms described may have been caused by what is now understood as refeeding syndrome (RS). The first case reports refeeding hypophosphatemia associated with paresthesias, weakness, and seizures began to appear in the early 1970s in severely malnourished patients receiving parenteral nutrition.[19,20]

Table III. Clinical factors supporting hospitalization in an adolescent with an eating disorder

Factors
≤75% Median BMI for age and sex
Dehydration
Hypokalemia, hyponatremia, hypophosphatemia
EKG abnormality
Severe bradycardia (heart rate <50 beats/min daytime; <45 beats/min at night)
Hypotension (blood pressure <90/45 mm Hg)
Hypothermia (body temperature <96° F, <35° C)
Orthostatic sustained increase in pulse (>30 beats/min in adults >19 years or >40 beats/min in adolescents aged <19) or sustained decrease in blood pressure (>20 mm Hg systolic or >10 mm Hg diastolic)
Negative deviation or stagnation in growth trajectory
Lack of improvement with outpatient treatment
Acute food refusal
Uncontrollable bingeing and purging
Acute medical complications of malnutrition (eg, syncope, seizures, cardiac failure, pancreatitis)
Comorbid psychiatric or medical condition that prohibits or limits appropriate outpatient treatment (eg severe depression, suicidal ideation, obsessive compulsive disorder, type 1 diabetes mellitus)

EKG, electrocardiogram.
Adapted from the Society for Adolescent Health and Medicine.[6]

These collective findings are now recognized as RS, a potentially life-threatening complication of weight restoration that typically occurs in the first 72 hours after initiating treatment for severe malnutrition.[21] Although RS remains relatively understudied, the etiology involves the transition from a catabolic to an anabolic state. Within the first 28 hours of starvation, carbohydrate stored as glycogen in liver and muscle is depleted entirely. Tissues that are normally highly glucose dependent, such as the brain, can switch to the metabolism of ketones derived from fatty acids. This metabolic switch ameliorates lean tissue catabolism to provide glucose for cells (such as cardiac cells) that are obligate glucose metabolizers. It also decreases insulin production, which further enhances lipolysis.[22] Prolonged inadequate caloric intake and severe weight loss continue this process and initiate a cascade of homeostatic adaptations, including the need to maintain appropriate physiologic levels of serum phosphorus, potassium, and magnesium despite relative whole-body depletion. The initiation of refeeding makes glucose available for energy and insulin levels increase in response. Insulin then drives potassium into cells via direct effects on the sodium-potassium adenosine triphosphatase pump. Extracellular phosphorus is also depleted by cellular uptake and consumed in glucose metabolism to produce high-energy adenosine triphosphate.[23] Serum magnesium levels decline owing to insulin-stimulated cellular uptake and use as an essential cofactor in numerous metabolic pathways as well as DNA, RNA, and protein production in the anabolic phase.[24] The resulting serum electrolyte disturbances result in a spectrum of clinical features, including but not limited to metabolic acidosis, cardiac arrhythmia, congestive heart failure, respiratory failure, encephalopathy, hypotension, paresthesias, seizures, and sudden cardiac death.[25-27] There are no consistent diagnostic criteria for RS, yet hypophosphatemia, hypokalemia, and thiamine deficiency are considered early biochemical indicators for the risk of developing RS during initial refeeding.[24,28,29]

Managing RS Risk in AN

Studies have revealed several predictors of refeeding hypophosphatemia in patients with AN, including low admission weight (specifically a body mass index [BMI] of <70% of the median BMI (mBMI) or a BMI of <13 kg/m^2), low initial serum electrolyte levels, and magnitude of weight loss, specifically 20% body mass loss.[3,7,29-33] In an attempt to minimize the risk of RS, professional societies have previously recommended low calorie refeeding (LCR), that is, the initiation of a low caloric diet, 30-40 kcal/kg/day (approximately 1000-1200 kcal/day) and slow advancement, approximately 70-100 kcal/day, regardless of the severity of malnutrition.[34] However, within the context of more severe malnutrition, electrolyte derangements have been observed even with LCR.[35] O'Connor et al studied 2 different approaches to LCR in a randomized clinical trial of inpatient adolescents with AN or AAN with a BMI of <78% mBMI.[36] This clinical trial compared refeeding initiation at 500 kcal/day, advanced by 200 kcal/day, with initiation at 1200 kcal/day, advanced by 200 kcal/day, and found no significant differences in the frequency of refeeding hypophosphatemia and observed greater overall weight gain among the higher calorie group. This approach of low-calorie initiation and slow advancement can compromise clinical outcomes by delaying initial weight progress. In an observational study of adolescents initiated at 1000-2000 kcal/day and advanced by 200 kcal every 2-3 days, Solanto et al observed initial weight loss.[37] Similarly, a prospective observational study by Garber et al of adolescents initiated at approximately 1200 kcal/day and advanced by 200 kcal every other day revealed initial weight loss and stagnation in weight over the first 4-7 days of admission.[38]

With mounting evidence linking the start low and go slow approaches with poorer outcomes, several groups reported their findings starting with caloric levels approaching 1500 kcal/day and/or more rapid advancement. A retrospective chart review by Peebles et al of patients with a variety of eating disorders initiated an inpatient protocol at an average of 1466 kcal/day with rapid caloric advancement by 200 kcal/day, and prompt correction of low phosphorus, potassium, and magnesium levels. This study revealed zero cases of full threshold RS.[39] A retrospective chart review of a nutritional rehabilitation protocol by Leclerc et al also observed a 2-day delay in weight improvement from initiation at 1500 kcal/day and advancement by 250 kcal/day on days 2-3, followed by 250 kcal every other day for 7 days thereafter.[40]

Subsequently, refeeding with higher caloric levels have been investigated. This work includes a retrospective chart

review by Golden et al comparing adolescent patients initiated on meals providing 720-1320 kcal/day with those initiated at 1400-2800 kcal/day, with electrolyte surveillance at admission and every 24-48 hours for the first 7 days of admission.[3] This study revealed no significant difference in the rate of developing refeeding hypophosphatemia, hypokalemia, or hypomagnesemia, even in the context of severe malnutrition (admission BMI of <70% mBMI) in the 2 groups.[3] Maginot et al compared serum phosphorus, potassium, and magnesium of patients initiated at approximately 1185 kcal/day and advanced at 90 kcal/day with those initiated at approximately 1781 kcal/day and advanced at 100 kcal/day.[41] This group found no significant difference in the incidence of electrolyte disturbances between the 2 groups in the first 72 hours of management. In their subanalysis, Maginot et al found an admission BMI of <75% mBMI to be a predictor of refeeding hypophosphatemia, not initial kcal administered.[41] A prospective observational study by Garber et al comparing adolescents initiated on progressive oral feeds of 1065-1121 kcal/day to those initiated on 1704-1824 kcal/day found no significant increase in the incidence of refeeding hypophosphatemia and nearly twice the rate of weight gain with a significantly greater weight as early as day 4 of admission among the higher calorie group.[2] A retrospective study by Strandjord et al of pediatric and adolescent inpatients with moderate to severe malnutrition due to AN and ARFID initiated on 1750-2550 kcal/day and advanced at 250 kcal/day with prophylactic phosphorus supplementation found no cases of RS.[42]

High-quality evidence is now available from randomized clinical trials of refeeding. In a randomized clinical trial of inpatient adolescents and adults with AN and AAN with a BMI of > 60% mBMI, Garber et al compared the rate of RS-related electrolyte disturbances, including hypophosphatemia. Participants were randomized to meals providing LCR (initiation at 1400 kcal/day, advanced by 200 kcal every other day) or HCR (initiation at 2000 kcal/day, advanced by 200 kcal/day). Electrolytes were monitored daily for the first 7 days of admission, and any observed hypophosphatemia, hypokalemia, and hypomagnesemia were treated with electrolyte supplementation. Results revealed no significant difference in the incidence of electrolyte disturbances between the 2 groups and greater weight gain overall among the HRC group.[43] Work in the field also includes a pilot randomized controlled trial by Draffin et al of inpatient children and adolescents with AN comparing refeeding with 2000-2500 kcal/day comprised of <40% vs 50%-60% total energy from carbohydrates. Of note, these investigators administered a lower daily dose of nutrition (1500 kcal/day) to patients considered at high risk of RS, namely, those with minimal carbohydrate intake for 7-10 days before refeeding. Close electrolyte surveillance revealed no cases refeeding hypophosphatemia over the first 7 days of refeeding.[44]

Investigation of HCR through combination feeds, ie, a combination of oral feeds and nasogastric feeds have also yielded similar results. A retrospective chart review by Agostino et al comparing adolescent patients initiated on nasogastric tube feeds of 1500-1800 kcal/day and prophylactic phosphate supplementation, with caloric advancement of 200 kcal/day, with those initiated on progressive oral feeds of 1000-1200 kcal/day and advanced by 150 kcal/day revealed no cases of RS and demonstrated a significantly higher rate of weight gain over the first 2 weeks in the HCR group.[45] Similarly, a retrospective chart review by Parker et al that found no cases of RS upon examining inpatient HCR (initiation at an average of 2611.7 kcal/day), coupled with prophylactic phosphorus supplementation and daily electrolyte surveillance.[46] A randomized controlled trial by Madden et al in which adolescents were initiated on combination feeds of 2400 kcal/day and prophylactic phosphate supplementation of 500 mg (16 mmol) twice daily, with caloric advancement to achieve a rate of weight gain of 1 kg per week, demonstrated no occurrences of refeeding hypophosphatemia.[47]

Although studies have consistently found no significant relationship between caloric amount and the occurrence of RS, including refeeding hypophosphatemia, there are limitations. Many of the published studies comparing HCR with LCR have focused on moderately malnourished patients and excluded the most severely malnourished patients. A recent publication of a retrospective chart review including 121 patients ages 12-20 years old with AN and all with a BMI of <15 showed adequate weight gain without the development of RS with all patients being started at 2000 kcal/day.[48] Another major limitation is the lack of trials comparing meals with nasogastric tube feeding. To our knowledge, there has also been no empirical investigation of HCR and LCR using parenteral nutrition, which is contraindicated in patients with AN because the gastrointestinal system is functional (albeit slowed) and the risk of medical complications, including infection related to the central line, arterial injury, and cardiac arrhythmia related to central line placement, is high.[49,50]

Potential Benefits and Disadvantages of HCR

The primary goal of inpatient management of complications related to malnutrition is the restoration of physiologic stability. As such, a shorter duration of admission suggests a more optimal pace of physiologic stabilization and greater cost savings. Furthermore, in a noninferiority trial, stepdown from inpatient care to day treatment programs had similar outcomes to prolonged inpatient management for weight restoration and maintenance during the first year after admission.[47,51] Several of the aforementioned studies have revealed a decrease in length of admission by 3-6 days with HCR and subsequent cost savings per patient stay.[2,3,42,43,45] A potential concern with faster refeeding strategies and shorter hospitalizations is whether there will be a subsequent increase in rehospitalization rates or lower post-hospitalization success in eating disorder remission. The evidence so far from the randomized clinical trial comparing HCR and LCR with 1-year follow-up gives reassurance that

medical rehospitalizations and clinical remission were not different at 1 year.[52] Observational studies have demonstrated high variability in length of admission, yet similar outcomes in 1 year across a variety of clinical sites.[53-55] Another important area of concern is the tolerability of HCR both physically and psychologically. Data suggest that there is no increase in distress during mealtimes when comparing HCR with LCR.[56]

Current Best Practices

Mounting evidence in support of rapid refeeding has been summarized from a review of the current literature. Contrary to prior belief, HCR does not carry a significant risk of RS when close electrolyte surveillance and supplementation are implemented. Furthermore, LCR is associated with poor inpatient weight gain, a factor correlated with worse clinical outcomes and longer hospital admissions. Given the comparable safety, more optimal rate of weight gain, and cost savings, HCR is a valuable inpatient treatment strategy. As such, HCR is widely accepted by professional organizations to inform guidelines and is recommended by clinical references.[6,30,33,57-60] The evidence presented in our progress report supports an HCR strategy of initiating inpatient refeeding at 2000-2400 kcal/day divided into 3 meals and 2-3 snacks, and increasing by 200 kcal/day, in patients with an admission BMI of >60% mBMI. Baseline and daily electrolyte monitoring should occur for the first 7 days of refeeding and every other day thereafter for the duration of inpatient admission, with prompt supplementation to correct abnormal levels. Less frequent electrolyte surveillance may be considered for patients with moderate initial malnutrition with normal baseline electrolyte levels and prophylactic phosphorus supplementation. Although there is little evidence to determine indications for prophylactic supplemental phosphorus and thiamine, these strategies may be considered in patients with severely low weight. Individual caloric goals can be determined based on height, age, and treatment goal weight, using estimated energy requirement equations.[61] Given the increase in resting energy expenditure, daily caloric needs often exceed 3000 kcal/day in the initial weeks of refeeding, with eventual return to more normative energy needs once organ systems are more physiologically restored.[62,63] The inpatient medical stabilization of children, adolescents, and young adults with eating disorders can be managed safely and successfully with HCR as outlined in this review. Patients admitted at the onset of their diagnosis have a higher chance of being weight restored at 1 year and medical admission may serve as a wake-up call for patients and families to recognize the severity of the restrictive eating disorder and help to break the cycle of disordered behaviors.[53,64] ■

Declaration of Competing Interest

The authors declare no conflicts of interest.

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