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CLINICAL ALGORITHM

Refeeding in anorexia nervosa

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Abstract

Refeeding in anorexia nervosa is a collaborative enterprise involving multidisciplinary care plans, but clinicians currently lack guidance, as treatment guidelines are based largely on clinical confidence rather than more robust evidence. It seems crucial to identify reproducible approaches to refeeding that simultaneously maximize weight recovery and minimize the associated risks, in addition to improving long-term weight and cognitive and behavioral recovery and reducing relapse rates. We discuss here various approaches to refeeding, including, among others, where, by which route, how rapidly patients are best refed, and ways of choosing between them, taking into account the precautions or the potential effects of medication or of psychological care, to define better care plans for use in clinical practice.

Conclusion: The importance of early weight gain for long-term recovery has been demonstrated by several studies in both outpatient and inpatient setting. Recent studies have also provided evidence to support a switch in current care practices for refeeding from a conservative approach to higher calorie refeeding. Finally, the risks of undernutrition/"underfeeding syndrome" and a maintenance of weight suppression are now better identified. Greater caution should still be applied for more severely malnourished < 70% average body weight and/or chronically ill, adult patients.

What is Known:
- *Refeeding is a central part of the treatment in AN and should be a multidisciplinary and collaborative enterprise, together with nutritional rehabilitation and psychological support, but there are no clear guidelines on the management of refeeding in clinical practice.*
- *The risk of a refeeding syndrome is well known and well managed in severely malnourished patients ("conservative approaches").*

What is New:
- *There is evidence that early weight restoration has an impact on outcome, justifying an aggressive approach to refeeding in the early stages of the illness.*
- *The risks of "underfeeding syndrome" and of a maintenance of weight suppression are now better identified and there is sufficient evidence to support a switch in current care practices for refeeding from a conservative approach to higher calorie refeeding.*

Keywords Anorexia nervosa · Clinical practice · Guidelines · Underfeeding syndrome · Refeeding · Refeeding syndrome

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Abbreviations

AN	Anorexia nervosa
BMI	Body mass index
CDC	Centers for Disease Control
FBT	Family-based treatment
GH	Growth hormone
IGF-1	Insulin-like growth factor-1
MARSIPAN	MAnagement of Really SIck Patients with Anorexia Nervosa
NG	Nasogastric
PN	Parenteral nutrition
RFS	Refeeding syndrome
RH	Refeeding hypophosphatemia

Introduction

Anorexia nervosa (AN) is a life-threatening psychobiological condition, for which treatment, including refeeding, is complex. Patients with AN lose weight and keep their body weight low through a number of behaviors that are characteristically associated (e.g., dietary restriction, excessive exercise and purging behaviors) and typically have a strong ambivalence concerning weight gain. Clinicians currently lack guidance, as treatment guidelines are based largely on "best practice" or "clinical confidence" rather than more robust evidence [9]. One of the few points on which there is a general consensus is that refeeding and weight restoration in patients with AN is a "collaborative enterprise" [14], which must be set up so as to avoid, or at least minimize "unnecessary distress and further evasion of therapy" [14].

In the short term, the primary goal of refeeding is to restore physiological stability through weight gain and growth rate recovery in children, by correcting the biological and psychological disorders due to undernutrition [1, 13].

For many years, a low-calorie approach to the refeeding of hospitalized patients with AN was recommended ("conservative approaches"), but there is now evidence that early weight restoration has an impact on outcome, justifying an aggressive approach to refeeding in the early stages of the illness [34]. Indeed, partial weight restoration is associated with higher relapse rates after discharge and, in hospitalized patients, faster weight gain and higher weight upon discharge are predictive of weight recovery at 1 year [9]. However, in addition to physiological instability at presentation, patients are at risk of developing complications during the refeeding process itself. Indeed, the refeeding syndrome (RFS) describes the "clinical and metabolic derangements that can occur during refeeding (orally, enterally or parenterally) of a malnourished patient" [32]. It now appears to be a rare phenomenon, which corresponds to a severe fluid and electrolyte shift, and can result in serious harm and death [35].

However, budgetary constraints (such as the pressure to decrease the length of hospital stay in some countries) may make it difficult to hospitalize patients for long enough to restore weight and have been correlated with higher rates of rehospitalization [9]. Relapse rates are known to be high in AN, which is recognized as one of the most "common and costly" primary mental health diagnoses in pediatrics [9, 40].

All these elements highlight the need to identify reproducible approaches to refeeding that simultaneously maximize weight recovery and minimize the associated risks, in addition to improving long-term weight and cognitive and behavioral recovery and reducing relapse rates.

We discuss here various approaches to refeeding and psychological improvement and ways of choosing between them to define better care plans for use in clinical practice.

Aims of refeeding

- To decrease the risk of death due to undernutrition
- To improve nutritional status (weight gain)
- To normalize somatic disorders secondary to undernutrition (such as growth failure, and delayed or arrested puberty in prepubertal children and young adolescents, and low bone mineral density and functional digestive symptoms in adolescents and adults)
- To combat the acute somatic effects such as hypoglycemia, muscle weakness, bradyphrenia, severe hypotension, leucopenia and severe bradycardia
- To improve mental state (anxiety, depression)

How can patients best be refed?

Where: at what site and what level of care?

Refeeding may occur in various settings, including hospitals, during partial hospitalization, in outpatient settings, psychiatric units, or somatic services. The choice of setting depends on the severity of the disease, the management required, the availability of places, and local practice and recommendations [1, 3, 6, 17], as different healthcare policies may result in different admission strategies.

It appears preferable for patients to be treated as outpatients, where possible, and as soon as possible, to minimize the "side effects" of hospitalization (poor acceptability to the patients and their families, anxiety during admission and discharge, social isolation and absences from school, the coercive nature of the experience, patients choosing to leave hospital). As pointed out by Herpertz-Dahlman, in adolescents, "the need for inpatient treatment and the need for urgent weight restoration should be balanced alongside the educational and social needs of a young person" [8].

There is no international agreement on the admission criteria for in-patient care, and the thresholds specified in national guidelines differ between countries and with the age of the patient. However, in general, it may be considered that patients who are physiologically or psychologically instable are admitted to hospital for refeeding. Here, we focus on the reason to admit a patient to a medical stabilization unit, which can be [32]:

1. Less than or equal to 75% median BMI for age, sex, and height
2. Hypoglycemia
3. Electrolyte disturbance (hypokalemia, hyponatremia, hypophosphatemia, and/or metabolic acidosis or alkalosis)
4. ECG abnormalities (e.g., prolonged corrected QT (QTc) > 450, bradycardia, other arrhythmias)
5. Hemodynamic instability–bradycardia–hypotension–hypothermia
6. Orthostasis
7. Acute medical complications of malnutrition (e.g., syncope, seizures, cardiac failure, pancreatitis)
8. Comorbid psychiatric or medical condition that prohibits or limits appropriate outpatient treatment (e.g., severe depression, suicidal ideation, obsessive compulsive disorder, type 1 diabetes mellitus)
9. Uncertainty of the diagnosis of an ED

The criteria for discharge from medical inpatient units also depend on local practices and local recommendations. The normalization of vital signs may be used as a criterion for discharge from medical inpatients units, but many specialized units still require the patient to reach a target weight before discharge.

The results of recent follow-up studies have called into question the view that the inpatient setting is the setting of choice for the treatment of severely undernourished medically stable patients, and evidence is accumulating that less intensive treatment settings, such as day-patient or outpatient treatment approaches, can achieve outcomes similar to those for inpatient treatment, in medically stable adolescent patients [8]. In 2014, Herpertz-Dahlmann et al. showed that, after 3 weeks of treatment to achieve medical stabilization, day treatment was not inferior to prolonged hospitalization for achieving weight restoration at 12 months in adolescents presenting for a first admission for AN. Increasing numbers of studies are focusing on day-patient treatment and reporting possible advantages of day-patient treatment over inpatient treatment [15]:

- New skills acquired during treatment may be more easily transferred at home.
- Greater involvement of the family
- The patient continues to live with the family and remains integrated into social networks.
- More age-appropriate development of autonomy
- Significantly lower healthcare costs

Weight restoration can be successfully achieved in non-hospital treatment settings, but research and clinical guidance are lacking about how best to approach refeeding outside of the hospital [40].

Finally, for all settings, a multimodal approach, with an interdisciplinary team working in close collaboration, is the treatment of choice.

Which "route" (oral? enteral? parenteral?)?

All services generally begin with oral nutrition, but some switch to enteral (nasogastric) nutrition more quickly than others [3]. During oral refeeding ("meal-based refeeding"), the caloric level is divided into meals and snacks, and any liquid supplements are taken orally.

An intermediate step between offering normal meals and tube feeding should be replacing normal meals with liquid diet foods. It is often easier for a patient with AN to use liquid diet products than normal food products and, in this way, tube feeding can sometimes be prevented [27].

Nasogastric (NG) feeding is used in inpatient settings and is recommended over other enteral routes or parenteral nutrition in situations in which oral refeeding is not possible, but clinical practices for NG feeding vary considerably, particularly for children and adolescents, with some units using this method systematically and others only as a last resort or in cases of acute food refusal [13]. In all cases, recommendations stress that efforts must be made to avoid its explicit or implicit punitive application [13].

Approaches combining NG feeding with meals taken orally have been proposed as a method of administering larger numbers of calories to hospitalized patients with AN [3]. However, there is currently insufficient evidence to conclude that such an approach is superior to exclusively meal-based approaches; tolerance and/or acceptability could, therefore, tip the balance in favor of one approach or the other. It has been suggested [6] that "the lower threshold for use in young people is multifactorial and includes the fact that the impact of malnutrition in young people can be more acute and have lasting consequences on growth and development. The law also puts emphasis on adults being responsible for the care of young people up to the age of 18, taking into consideration increasing autonomy and capacity".

Parenteral nutrition (PN) is not recommended [9], as various complications have been reported (including sepsis, disseminated intravascular coagulation, high levels of transaminase activity, edema of the lower extremities and hypophosphatemia) and the slightly greater weight gain

reportedly attributable to supplemental PN does not outweigh these risks. The only indication for PN in AN is an absence of other alternatives to achieve weight restoration, in patients in which gastrointestinal complications preclude enteral feeding, or in a context of acute hepatitis or pancreatitis, for example.

The use of percutaneous feeding tubes has been reported in only one study [4].

How rapidly and with what frequency? Low- or high-calorie diet? Personalized or standard? Modification of nutritional content?

Weight gain during refeeding is crucial. The optimal refeeding diet and/or formula remains undefined [40], and personalized "nutritional therapy," with the formulation of a structured meal plan, including supervised meals, with the assistance of a dietitian, is recommended [15], as it is thought that "supervised and flexible individual food intake increases the patient's perception of control and allows him to accept weight gain" [13]. According to the Royal College of Psychiatrists, the calculation of energy intake during refeeding "must take into account the need to restore normal nutritional status as quickly as possible, but also the physiological limits imposed by the severity of undernutrition and the psychological capacity of the patient to tolerate weight gain" [6].

Until recently, standard care during the refeeding of patients with AN involved starting with low caloric levels, which were then slowly increased ("start low and go slow" approaches). Treatment guidelines [1] recommended mean weight gain rates for inpatients of between 0.5 and 1.4 kg/week to prevent refeeding syndrome. However, these lower calorie approaches have recently been linked to poor weight gain, weight loss until the second week of treatment, and prolonged hospitalization [8]. There is increasing recognition of the existence of a so-called underfeeding syndrome [36] and that underfeeding leads to poor outcomes in AN. These findings have stimulated interest in more aggressive, higher-calorie approaches to refeeding in clinical practice and research [14, 36]. Indeed, several studies performed since 2010 have described refeeding approaches beginning with higher caloric levels and/or with a more rapid increase in caloric intake, either exclusively through meals or through approaches combining NG and oral feeding and recent reports indicate that young patients may tolerate more rapid refeeding [8]. In these studies in hospitalized patients, faster weight gain and higher weight on discharge were predictive of weight recovery 1 year after discharge [9], and, in adolescents, weight gain early in treatment seems to be correlated with lower levels of eating disorder-associated psychological symptoms [2, 9, 12]. In patients well enough to be managed in ambulatory settings, faster weight gain during the first 3 to 4 weeks of treatment is predictive of full remission (weight and cognitive recovery) at 12 months [9, 21]. Moreover, maximizing rates of weight gain would result in more weight being gained during a stay of the same duration, decreasing costs per hospital stay [33].

In clinical practice, the choice between low- and high-calorie protocols [7] depends on the severity of the malnutrition, clinical habits, and target weight. There is now sufficient evidence to modify standard care, with a move towards the use of higher calorie meal-based approaches, starting at 1500 to 2400 kcal per day, with an increase of 67–250 kcal per day, with expected rates of weight gain of 0.5 to 2 kg per week. In severely malnourished patients, higher calorie refeeding (HCR) also seems to be well tolerated, provided that the patient is closely monitored highly controlled hospital setting with close medical monitoring and electrolyte replacement. No study of HCR to date has reported a case of the refeeding syndrome. [7, 26]

In terms of macronutrient content, the available studies suggest only that higher calorie intakes can be delivered in standard macronutrient ranges consistent with current dietary recommendations: about 25–35% of calories from fat, 15–20% from protein and 50–60% from carbohydrate [9], and that low-sodium diets may attenuate fluid shifts in severely malnourished patients.

No association between different nutrient contents (e.g., high-protein diet, diets with a higher omega-3 polyunsaturated fatty-acid content, low-sodium versus normal-sodium diets) and refeeding outcome has been identified.

What should the target weight be?

There is no international consensus concerning the most meaningful target weight for children, adolescents, and adults with AN, and no clear recommendations concerning weight goals for refeeding have been defined in good practice guidelines [22]. Some teams define the target weight as a minimum target weight, whereas others use a weight range, a BMI percentile, or a BMI percentile interval. Target weight may be set arbitrarily at an identical threshold for all patients (for example, between the 15th and 20th age-adjusted percentiles [17]), not taking into account the premorbid weight and/or BMI of the individual, thereby perpetuating "weight suppression," which is defined as the difference between premorbid and current weight, and that can be thought, for children and adolescents, as the difference between premorbid "couloir of BMI" and the current "couloir of BMI". Recent data suggest that the maintenance of this "weight suppression" during treatment is associated with a less favorable outcome in AN. In other words, patients have a less favorable outcome when the clinician calculated a too low target weight and/or let the patient stabilize on this weight. Thus, as previously reported, aiming for a target based on standards for sex, age, and stature may result in a target weight below the target weight that

would have been set taking into account individual premorbid weight and BMI [40].

In AN, weight recovery is typically defined as 95% of the median body mass index (% mBMI) for age according to CDC data and is associated with the reversal of long-term medical complications, including amenorrhea [9] and/or growth recovery, spontaneous puberty, and a normal pace of puberty, with spontaneous menarche and regular menstruation for girls prepubertal at the time of treatment. Indeed, in adolescent girls and women, one of the criteria for a minimum weight compatible with good health is the reappearance of menstruation. This criterion is not appropriate for use in young children with early-onset prepubertal AN, but, in this population, very specific growth failure [23] and pubertal delay or arrest can be considered a relevant clinical parameter, changes which can be used to assess the effectiveness of refeeding. Moreover, weight goals should be reviewed regularly during the refeeding of children and adolescents, to take into account their growth, given the limited time window available for potentially effective treatment [13]. One study showed that about one third of girls with severe early-onset AN are at risk of adult height deficit [38].

Based on all these findings, clinical practice has, in recent years, moved significantly towards the definition of personal goals concerning the minimum weight for good health. These personalized goals are determined from previous charts. For young children, this personalized target should be defined to determine the weight at which the child is likely to start growing again and at which puberty should occur [41].

Which precautions should be taken, and what kind of management should be applied?

Medical management during refeeding includes monitoring the effectiveness of refeeding and possible adverse effects. Indeed, in addition to physiological instability at presentation, patients are at risk of developing complications during the refeeding process itself.

Effectiveness: weight gain and physiological functioning According to international recommendations [1, 13, 14, 25, 36], the frequency of weighing should depend on the patient's clinical state. Depending on nutritional status, a twice-weekly weight check is recommended in most cases, with daily checks in cases of severe malnutrition and weekly checks once the patient's nutritional state has stabilized.

However, weight is only an approximate indicator when evaluating the extent to which an individual's nutritional heath has been restored [14] and indicators of normal physiological functioning, including normal blood glucose levels, reversal of hypotension and bradycardia, and normal blood cell counts with a reversal of bone marrow suppression [14], should also be taken into account, as biochemical and hematological parameters tend to improve during refeeding. Bradycardia seems to normalize more quickly than other signs, such as orthostatic changes, during refeeding [9].

At the start of refeeding, vital signs should be assessed twice daily, food and fluid intake and output should be monitored (if indicated), and the patient should be observed for signs of edema, rapid weight gain (primarily associated with fluid overload), congestive heart failure, and gastrointestinal symptoms once daily [41]. In severely malnourished children and adolescents, cardiac monitoring, especially at night, may be advisable.

There are no clear recommendations for electrolyte monitoring and correction with supplements (e.g., calcium, vitamin D). There are considerable differences between centers, and diverse approaches to electrolyte correction are currently used in clinical practice [9].

Serum electrolytes (sodium, potassium, phosphorous, magnesium…) and glucose should be checked prior to refeeding, and even if these may be normal prior to refeeding, blood tests for checking serum potassium, magnesium, and phosphorus levels should be performed at least once daily for the first 2 to 5 days, the timing of tests thereafter being adapted on a case by case basis according to clinical state [6], for patients with no risk factors, In those with risk factors for RFS (a high Hb, a low potassium, a low BMI and a low prealbumin level), recommendations are listed below [5].

Finally, it is especially important to recognize thiamine deficiency and patients with significant alcohol intake, as these patients are also at risk for the development of Wernicke's encephalopathy with refeeding (see below: prior to refeeding, these patients should receive thiamine and folate supplementation) [27].

Refeeding syndrome In patients with AN, the need for weight gain must be balanced against the potentially fatal complications of refeeding syndrome (RFS), a metabolic condition characterized by hypophosphatemia, hypomagnesemia, hypokalemia, and hypo or hyper glycemia.

RFS has been recognized in the literature for over 50 years and can result in serious harm and death. A key risk factor for the syndrome is starvation with early published reports being prisoners of war in the 1950s, who developed cardiac and neurological symptoms soon after the recommencement of feeding. In recent times, refeeding syndrome has been confirmed in hunger strikers, individuals with anorexia nervosa and chronic alcoholics. It also can occur in any individual but more commonly occurs in at-risk populations [35].

There is no internationally agreed definition of RFS, and its definition is imprecise and lacks definitive electrolyte threshold values to confidently diagnose the refeeding syndrome. As there is no strict definition, the incidence of RFS is unclear and robust epidemiological studies are lacking in part due to the absence of accepted diagnostic criteria or internationally

agreed guidelines for detecting RFS. Crude estimates of incidence, morbidity, and mortality are available for specific populations, but published data from prospective and retrospective case series do not reflect overall incidence [20].

In its most severe form, RFS is characterized by cardiac arrhythmia, cardiac failure or arrest, hemolytic anemia, delirium, seizures, respiratory failure through muscle weakness (especially caused by a low phosphate or potassium), coma, and sudden death. This syndrome is thought to result from the movement of glucose and electrolytes from the extracellular to the intracellular space in response to surges in insulin after the reintroduction of nutrients following starvation and the depletion of hepatic glycogen stores [41].

The patients most at risk of RFS are those with a very low BMI, little or no nutritional intake over a period of more than a few days, rapid weight loss, or abnormal electrolyte levels before refeeding [36].

Severe RFS may occur when severely malnourished patients (weighing < 70% of their healthy body weight) are refed too rapidly. It occurs particularly in a context of enteral or parenteral feeding but may also occur in patients treated by vigorous oral refeeding [1]. Studies of hospitalized patients have shown the risk of developing RFS to be highest during the first week [9].

Refeeding hypophosphatemia (RH) is known to be a sensitive marker of the risk of RFS [5, 31]. In recent studies [33], the only statistically significant predictor of RH was BMI centile on admission. Risk factors for developing hypophosphatemia are published by Brown et al. in [5]. They are a higher hemoglobin level (adjusted odds ratio [aOR], 1.56; 95% confidence interval [CI], 1.12–2.18), lower prealbumin level, and the lower potassium together with the already mentioned lower BMI. Statistically significant protective factors against the development of hypophosphatemia were observed with higher body mass index, higher serum potassium, and higher serum prealbumin.

RFS can be both prevented and treated by slowing the rate of refeeding (with increments of 5–10 kcal/kg/day [36], for example) and monitoring serum phosphate, potassium, and magnesium concentrations. Junior MAnagement of Really SIck Patients with Anorexia Nervosa (MARSIPAN) [25] recommends daily blood tests during the first 2 to 5 days and, because of the risk of late RFS, to repeat testing after 7–10 days of refeeding in those with risk factors for RFS (a high Hb, a low potassium, a low BMI and a low prealbumin level). Phosphorus may be normal prior to refeeding, and will reach its lowest point 3–7 days after initiation of refeeding/nutritional rehabilitation [32].

In severely malnourished patients, most clinicians monitor electrolytes the first 2 weeks if refeeding.

It remains unclear whether patients with AN should receive prophylactic phosphate supplementation when refeeding is initiated or be treated with phosphate only if RH is confirmed by laboratory tests ("wait and see" approach) [24, 31]. In one study in which phosphate was not administered prophylactically, RH occurred in one third of participants [9, 24]. It has been suggested that continuous NG feeding (as opposed to bolus feeds) improves RH [9].

All electrolyte deficiencies should be aggressively replete; oral repletion is preferable, but IV supplementation may be necessary. It is not necessary to correct fluid and electrolyte imbalance before initiating feeding; with careful monitoring, this can be safely achieved simultaneously [27].

Refeeding protocols should then be individualized to minimize both the risk of refeeding syndrome and complications due to underfeeding, and clinicians should refer to existing national guidelines or to MARSIPAN/junior MARSIPAN.

Other frequent complications Before the initiation of refeeding, about 50% of patients present an abnormal increase in transaminase levels [37] and about 25% following the initiation of refeeding [13, 41]. These abnormalities seem to be of hepatic origin (after the elimination of other potential causes, including the use of hepatotoxic drugs) and, for the first ones, to be due to starvation-induced autophagy, which can lead to hepatocyte injury and death. They are usually moderate (less than 10 times the upper limit of the normal range) and gradually improve, generally with a return to normal levels with the continuation of refeeding and weight gain (median of 20 days) [13]. Further, ALAT tends to be elevated disproportionately more than ASAT in AN, similar to non-alcoholic liver disease and in contrast to other common forms of liver disease such as that due to alcohol. As BMI falls to values near 12 kg/m2 or less, the risk of marked elevations of aminotransferases increases [37]. High levels of transaminases seem to be predictive of the development of hypoglycemia.

Routine laboratory testing for secondary causes of liver dysfunction in patients with AN and elevated aminotransferase levels are not recommended, unless there remains a high clinical suspicion for another underlying cause of the liver disease or the aminotransferase levels are severe and not improving with purposeful weight restoration [37].

In cases of hypokalemia, the correction should be progressive, particularly if no signs of hypokalemia are evident on ECG.

Prolongation of the QTc interval are also described: in one study, patients with anorexia nervosa had normal average QTc intervals, but in patients with anorexia nervosa binge purging subtype, they had longer QTc intervals (433.9 ms, $p < .001$) [28].

Neurological complications may occur during refeeding, due to vitamin B1 deficiency, hypo- or hyperglycemia, or ionic disorders, and any acute neurological complication should be treated by urgent vitamin B1 injection, without waiting for the results of blood tests for this molecule [41].

Finally, AN is accompanied by multiple neuroendocrine dysfunctions involving the growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis, thyroid function,

hypercortisolemia, hypogonadotropic hypogonadism, and the levels of several adipokines and gut peptides, such as ghrelin and peptide YY [23], but the clinical relevance of monitoring this parameters is lacking; these laboratory tests are expansive.

It is on the other hand very contributive to measure bone density with a DEXA scan, which has clinical importance and could lead to advice concerning for instance sport activities and follow up bone densitometry after weight restoration [29, 39].

Prealbumin is a good marker of the state of malnutrition [11] and should be monitored closely during refeeding. It has previously been demonstrated in patients with AN, to be a more sensitive marker of malnutrition than albumin [11, 30], leading to the message that clinician has to be aware of not be lulled into complacency by a normal admission serum albumin level in AN [30].

Potential effects of medication on weight gain during refeeding

No drug has yet been shown to improve weight gain during refeeding in AN, and there is limited evidence supporting benefits of medications in this condition [19]. At present, pharmacotherapy with antipsychotics is not recommended according to treatment guidelines and psychotherapeutic treatment approaches appear to be more promising. However, the number of prescriptions of second-generation antipsychotic drugs to anorectic patients has substantially increased over the last years. These medications, particularly olanzapine, appear to demonstrate some benefit for weight gain in anorexia nervosa, although are not advised as a stand-alone treatment.

A recent meta-analysis of antipsychotic drugs in AN patients revealed that olanzapine was associated with greater weight gain than risperidone, quetiapine, or placebo. In clinical practice, it is frequently administered to inpatients gaining insufficient weight in the first few weeks of admission. Himmerich et al. [19] pointed out that "in addition to its action on the salience network […], the antihistaminergic effect of olanzapine at the hypothalamic histamine H1 receptor3 should be highlighted as a further important cause of weight gain".

Transdermal administration of hormonal agents is also being explored for improving bone health in anorexia nervosa.

Keeping in mind the warnings on drugs which are contra indicated because of the possible prolongation of the QTc interval, some drugs may be useful for controlling anxiety during refeeding (depending on clinical practice in the institution concerned) or for abdominal pain. Indeed, patients with AN may develop non-specific gastrointestinal symptoms, both in the course of the illness itself and during refeeding and many patients even carry a diagnosis of irritable bowel syndrome. In most cases, the gastrointestinal symptoms are functional in nature and resolve spontaneously with nutritional rehabilitation and weight restoration in most patients.

Constipation, which can be due to intestinal hypomotility of underweight [10], is "nearly universal in AN," and there seems to be no medical reason to use stimulant laxatives, which should be replaced by clinically effective doses of osmotic laxatives (sometimes as much as 34 g, or a double dose, of polyethylene glycol three times a day). Maintenance of normal electrolyte levels and hydration status is also contributive in these cases.

Pharmacotherapy trials of drugs designed to increase appetite have yielded inconsistent results [4].

Finally, a recent pilot study showed that GH treatment in young adolescents with AN and severe growth failure was associated with significant improvements in linear growth [23]. These improvements in linear growth may, in turn, have a major impact on weight restoration and refeeding. A randomized placebo-controlled study is now required to determine whether GH therapy is an appropriate option for the management of these patients.

Psychological care

As indicated above, AN treatment is a collaborative enterprise, requiring a multidisciplinary team (doctors, dieticians, psychologists, etc.) and multidisciplinary care plans. Refeeding is necessary, but not sufficient on its own. Psychotherapy alone is never sufficient for the treatment of severe AN [13], and a combination of psychotherapy and refeeding is recommended [1, 6, 13, 25]. During the acute refeeding and weight gain stages, it has been suggested that individual psychotherapeutic management, including empathy, explanations, praise for positive efforts, coaching, support, encouragement, and other positive behavioral support, is clinically relevant [1]. Psychotherapy techniques based on motivational enhancement should be used for patients who initially lack motivation. A written or verbal therapeutic contract may be used to deal with eating behavior and associated manifestations (e.g., hyperactivity) [13].

In children and young people with AN, family therapy has been shown to be more effective than other interventions [13, 25], during all phases of treatment, and consultations with the patients' families also seem to help [1]. Family-based interventions (e.g., family-based therapy, FBT, such as the Maudsley approach) are outpatient treatments focusing on the role of the parents [16, 40]. In FBT for AN, weight gain is essential and mediates psychological recovery. At the start of treatment, the parents are temporarily left in control of refeeding and provided with support to help them take charge of meal routines, help their adolescent to adopt more normal eating behavior, and to initiate weight gain [40]. Weight restoration strategies in FBT also involve the parents in limiting physical activity or serving foods with a higher energy density. FBT seems to result in better remission rates (weight restoration and cognitive recovery at 12 months) than treatments

focusing on the adolescent, in outpatient settings. Moreover, in both types of psychotherapy, a weight gain of 0.8–0.9 kg per week during the first 3 to 4 weeks was predictive of remission at the end of treatment [9, 21], suggesting that rapid weight gain during the initial phase is associated with a favorable long-term outcome in terms of the normalization and maintenance of weight and recovery from eating disorder-associated mental conditions. In family-based interventions of this kind, the parents are seen as a resource for recovery [1]. Unfortunately, patients with little or no parental involvement, such as young adults living independently, cannot benefit from such approaches.

Discussion and conclusion

Refeeding is a collaborative enterprise involving multidisciplinary care plans, together with nutritional rehabilitation and psychological support.

The importance of early weight gain for long-term recovery has been demonstrated by several studies in both outpatient and inpatient setting. Recent studies have also provided evidence that refeeding in AN can be undertaken safely and effectively with rapid rates of weight gain, in both adults and minors. Finally, the risks of undernutrition/"underfeeding syndrome" and a maintenance of weight suppression are now better identified. There is also now sufficient evidence to support a switch in current care practices for refeeding from a conservative approach to higher calorie refeeding. Greater caution should still be applied for more severely malnourished < 70% average body weight [36], and/or chronically ill, adult patients, and the refeeding of these patients should only be done in a medical stabilization unit/hospital.

Nevertheless, the impact of approaches to refeeding on long-term outcomes is unknown, and there is currently no evidence of an association between higher calorie refeeding and better long-term outcome. The possibility that higher calorie refeeding may reduce the risk of relapse warrants further investigation, because the benefits of higher calorie refeeding in hospital, including faster weight gain or a shorter hospital stay, might easily be outweighed by unforeseen consequences, such as higher rates of relapse.

All these findings highlight the need to identify approaches to refeeding that can safely optimize weight gain, long-term outcome, and recovery. In all cases, clinicians should bear in mind that "weight recovery in the absence of concomitant behavioral recovery does not bode well for complete or sustained recovery and renders patients vulnerable to relapse" [9].

Prospective trials are also required, for direct comparisons of standardized protocols for refeeding, electrolyte monitoring and replacement, admission and discharge criteria, and for a comparison of exclusively meal-based with NG feeding plus meals approaches. More research is also needed in non-hospital settings [9], to evaluate the safety, long-term outcomes and feasibility of refeeding outside of hospital environments. Finally, pharmacotherapy trials are required to assess the suitability of certain drugs (e.g., olanzapine, GH) for use in the management of this life-threatening condition.

In conclusion, as pointed out by Herpertz-Dahlmann et al. [18] in their promising study on the microbiome, there is currently no empirical agreement about how best to refeed patients with AN. We therefore need to consider how interactions between the gut and brain affect treatment, in terms of determining the appropriate target weight, rapidity of weight gain, refeeding methods, and diet composition, all of which may have an effect on long-term outcome.

Algorithm

Cf algorithm.

Authors' contributions AB and JC did review the literature, AB wrote the first draft, and AP and JL made substantial corrections and corrected the first draft. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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