Renutrition and management of severe anorexia nervosa in intensive care: Review and multidisciplinary approach

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Abstract: Anorexia nervosa is one of the most severe eating disorders among young adults and adolescents and thus represents a major public health problem. Its incidence has increased notably since the COVID-19 pandemic. The objective of this work is to expose somatic consequences of severe anorexia nervosa, especially in the case of refeeding syndrome. The authors also describe the medical care provided in their institution, with a particular focus on the needed multidisciplinary approach between intensive care unit and psychiatric teams.

Keywords: Severe anorexia nervosa, Intensive care unit, Medical complications, Renutrition, Refeeding syndrome, Multidisciplinary approach

Introduction

Anorexia nervosa (AN) is a mental disorder characterized by weight loss or lack of weight gain compared to the normal population [1]. Among other eating disorders, AN affects around 0.8-6.3% of women and 0.1-0.3% of men, and is quite similar to bulimia nervosa according to a recent study [2].

For more than 40 years, an inpatient eating disorder program for subjects with a severe form of AN [3-6] has been developed at our hospital in the department of adolescent and young adult psychiatry. This program is constantly updated with new findings and recommendations.

AN may adversely affect all organs as the weight falls; some can be life-threatening, but fortunately most of them resolves when nutritional status is restored. In the most severe cases, AN may require an intensive treatment.

There are few studies in the literature on the specific management of these patients in intensive care units, and to date there are no standardized recommendations or consensus among scientific societies. To our knowledge, there was only one study in France that assessed the prevalence and morbidity of AN in 11 intensive care units in 2010. In 68 patients, the main diagnoses on admission were metabolic problems, refeeding survey and voluntary drug intoxications and infections, with 10% developing refeeding syndrome. The mortality rate was 10%, mainly due to multi-visceral failure [7].

In addition to somatic complications, some of which...
may be life-threatening, patients suffering from AN may be in denial of their illness and be ambivalent to care. Thus, the medical management of severe forms of AN can be very challenging, and requires dual somatic and psychiatric care. In this context, the psychiatric inpatient team developed a collaboration with ICU department in our hospital [8].

The aim of this paper is first to review the medical complications of AN described in the literature, including the refeeding syndrome. The searches were completed in the subsequent databases: PubMed, Embase, Cochrane Library, Web of Science and CINAHL. The keywords used were: severe anorexia nervosa, intensive care unit, medical complications, renutrition, refeeding syndrome, treatment and multidisciplinary approach. Secondly, the management of patients suffering from this pathology in an intensive care unit in France is presented, highlighting the collaboration between the intensive care and psychiatry teams as the key point of treatment.

1. Definition, prevalence and outcome

1.1 Definition

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [9], three main criteria define AN: 1. an abnormally low body weight due to caloric restriction; 2. an intense fear of gaining weight; 3. a distorted perception of weight. These criteria are summarized in Table 1.

Two subtypes have been described, depending on whether or not there are episodes of binge eating and purging.

Table 1. DSM-5 Diagnostic criteria for AN and subtypes

<table>
<thead>
<tr>
<th>Disorder class: feeding and eating disorders</th>
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<tbody>
<tr>
<td>A. Restriction of energy intake relative to need, leading to a significantly low body weight in the context of age, gender, developmental trajectory, and physical health (less than minimally normal/expected).</td>
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<tr>
<td>B. Intense fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain.</td>
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<tr>
<td>C. Disturbed by one’s body weight or shape, self-worth influenced by body weight or shape, or persistent unawareness of the seriousness of low body weight.</td>
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<tr>
<td>Specified whether</td>
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<tr>
<td>Restricting type: has not regularly engaged in binge-eating or purging in the last three months.</td>
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<tr>
<td>Binge-eating/purging type: In the last three months, has regularly engaged in binge-eating or purging (ie self-induced vomiting, use of laxatives, diuretics or enemas).</td>
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The severity of the disorder is defined according to the impact of AN on the body mass index (BMI): mildly severe (BMI > 17 kg/m²), moderately severe (BMI 16-16.99 kg/m²), severe (BMI 15-16.99 kg/m²) or extremely severe (BMI < 15 kg/m²). Corresponding percentiles should be used for children and adolescents [9].

1.2 Prevalence

Classical estimates of prevalence in the general female population vary from 0.8 to 3.6 % for AN according to DSM-5 criteria. In men, the prevalence of AN is less than 0.1 % [10]. The initial onset of AN is highly concentrated in adolescence and young adulthood, on average around 18 years of age [11]. The overall incidence of the disease has been stable for fifty years, but is now increasing in children under the age of 15 [12]. The COVID-19 pandemic has accelerated this process. Several studies have pointed out a marked increase in new diagnoses and severity of preexisting cases of AN with higher rates of hospital admission during the first wave of the COVID-19 pandemic and lockdown [13-15].

1.3 Outcome

AN is a psychiatric disorder with one of the highest mortality rates. Mortality is about 5.2 times more common in individuals with lifelong AN [9, 16] and up to 16 times more common in extremely malnourished individuals with severe and chronic symptoms after 5 years compared to the same age general population [17]. The first two causes of death are suicide or cardiac death [18]. This mortality is even higher in adolescents who have been hospitalized in ICU during a psychiatric hospitalization [19].

2. Complications

Complications may be the reason for admission to the ICU or may arise during ICU stay, especially refeeding syndrome. The main complications are summarized in Table 2.

Table 2. Main and serious complications of AN

<table>
<thead>
<tr>
<th>Cardiac</th>
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<tr>
<td>Sudden death</td>
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<td>Bradycardia/sinus node dysfunction</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Left ventricular dysfunction</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Pericardial effusion</td>
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<td>Mitral valve prolapse</td>
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<th>Neuromuscular</th>
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<tr>
<td>Wernicke-Korsakoff encephalopathy</td>
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<tr>
<td>Coma/convulsions</td>
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<td>Cognitive impairment</td>
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<tr>
<th>Pulmonary complications</th>
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<tr>
<td>Pneumothorax</td>
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<td>Pneumomediastinum</td>
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</table>
2.1 Cardiovascular complications

Cardiac features are common in AN patients, reaching 80% or more in some studies [20, 21]. They may include myocardial dysfunction, arrhythmias, prolonged QT interval and even sudden death. Any part of the heart can be affected, myocardium, valves, pericardium as well as conduction system. Cardiac arrest secondary to cardiovascular complications accounts for nearly half the mortality in patients with AN. Cardiac complications may be life-threatening and therefore justifies admission of severe forms of AN to an ICU in order to prevent and detect them. Most of these abnormalities are related to weight loss and are reversible with refeeding. The few histological data available show atrophy of the heart with endocardial and interstitial fibrosis, a scarcity of myocytes which are smaller than expected [22].

2.1.1 Sinus bradycardia

It is the most common cardiac symptom present in nearly all cases. It is considered adaptive and is related to parasympathetic hyperactivity and low T3 level [23, 24]. It usually does not require drug treatment. Cardiac pacing should be avoided whenever possible because of the risk of major complications [25]. Sinus bradycardia resolves with weight recovery.

2.1.2 Sudden cardiac death

Until recently, a delay in repolarisation evidenced by an increase in QTc interval, was considered to be the main cause leading to sudden cardiac death. However, a recent large study conducted in Denmark showed no difference between the QTc interval of 430 AN women and 123 healthy controls. In contrast, the incidence of syncope, cardiac arrest or ventricular arrhythmias was significantly higher in AN participants compared to controls. Long-term cardiac monitoring was able to determine that the incidence of bradyarrhythias was more frequent than the incidence of ventricular arrhythmias and could therefore possibly explain part of the sudden deaths [26]. This difference may be explained by extrinsic factors such as hypokaliemia or medications that block ion channels, or by intrinsic factors such as changes in the histologic structure of the myocardium. A more recent study evaluating long-term cardiac monitoring determined that the incidence of bradyarrhythias was more frequent than those of ventricular arrhythmias [27]. This could therefore possibly explain the mechanism of sudden death in some cases.

2.1.3 Hypotension

In almost half of the cases, a blood pressure of less than 90 mmHg is observed, mainly related to chronic volume depletion and orthostatic changes [28], but also decreases in venous return induced by peripheral amyotrophy. Dysregulation of circadian rhythms may also contribute to arterial hypotension [29].

2.1.4 Myocardial impairment

Most ultrasound studies have revealed lower left ventricular end systolic and diastolic dimensions as well as left ventricular mass with a relatively preserved myocardial function as compared with normal weight participants [23, 30-33]. However, Hanachi and colleagues demonstrated a 15% incidence of subclinical left ventricular dysfunction associated with a diagnosis of AN/binge eating purging subtype and elevated liver enzymes [34]. As with previous symptoms, all of these ultrasound abnormalities are corrected with refeeding [23, 35].

2.1.5 Mitral valve prolapse

Mitral valve prolapse is found in up to 50% of cases [30]. It is more common than in the general population. The mechanism seems to be a consequence of the reduction in size of the left ventricular chamber due to myocardial atrophy [36]. It is usually not associated with significant regurgitation and disappears with renutrition.

2.1.6 Pericardial effusion

In some studies, a mild to moderate pericardial effusion was found in 30% to 60% of participants who underwent echographic evaluation. It is usually clinically unremarkable and occurs more likely with very low BMI and rapid weight loss [32]. Fortunately, cardiac tamponade is an extremely rare event, but it requires pericardiocentesis [37, 38]. Usually, the pericardial effusion resolves with weight recovery.

2.2 Neurologic complications

2.2.1 Wernicke-Korsakoff syndrome

The deficit in thiamine is about 10-15% of AN cases, depending on the series [39]. Deficiency-related
encephalopathy is usually described in alcohol abusers. However, this disorder can also occur in nonalcoholic malnourished patients; a recent meta-analysis found 12 cases of AN in the medical literature [40]. The clinical presentation includes confusion, ataxia, oculomotor abnormalities (nystagmus, diplopia) and memory impairment. Magnetic resonance imaging (MRI) shows high signal intensity on T2 and FLAIR sequences in the thalamus, mammillary bodies and periaqueductal areas [41]. Delayed treatment may affect the outcome of patients with Korsakoff syndrome, an irreversible residual syndrome with global amnesia, cognitive and behavioral impairment (especially confabulations) [42]. Treatment with parenteral administration of thiamine (300 mg daily) is urgently required. However, the most important thing is prevention by multivitamin therapy with thiamine as soon as possible after admission.

2.2.2 Coma and/or epilepsy

Loss of consciousness with or without convulsions may occur as a consequence of hypoglycemia or hyponatremia. Some non-specific resuscitation maneuvers (primarily airway control), rapid IV glucose or careful correction of hyponatremia to avoid central myelinolysis are mandatory. In addition to the neurological complications mentioned above, multiple studies have reported coexisting cognitive dysfunction with AN. These cognitive disorders are induced by undernutrition and affect mood, concentration, memory, analytical and reasoning skills. MRI scans have shown a reduction in grey and white matter. The areas most affected by starvation are the limbic structures (hippocampus, amygdala, cingulate cortex), the frontoparietal cortex and the thalamus [43]. They undoubtedly improve with refeeding, but it is uncertain that malnutrition is the only cause. These disorders usually occur in severely malnourished patients. The restoration of adequate nutritional status is a prerequisite for effective psychiatric treatment.

2.3 Pulmonary complications

Surprisingly, few respiratory complications have been reported in the medical literature, including some cases of spontaneous pneumothorax or pneumomediastinum. This is thought to be the result of weakness in the lung tissue. In the latter cases, esophageal perforation induced by vomiting or repeated tube feeding placement should be excluded by a computed tomography (CT) scan. Usually, spontaneous pneumomediastinum is benign and resolves spontaneously with conservative treatment as the nutritional status improves [44]. It is also assumed that the lungs are relatively spared from bacterial or viral infections. Nevertheless, a few cases of non-tuberculous infections have been associated with anorexia [45]. Aspiration pneumonia may also occur as a complication of self-induced vomiting or as a result of weakness of the swallowing muscles [46]. Finally, AN is not associated with more severe forms of COVID-19 infection than the general population [47].

2.4 Renal complications and electrolytes disturbances

2.4.1 Hypokalemia

Hypokalemia is a common metabolic disorder in AN patients [48] and may lead to life-threatening complications, primarily cardiac arrhythmias [49, 50] and acute kidney damage. Therefore, continuous ECG monitoring should be prompted for severe hypokaliemia. The mechanisms responsible for hypokalemia are various including binge-purge, abuse of laxatives and/or diuretics, and low potassium intake. Due to increased insulin needs, a refeeding phase may further decrease serum potassium levels. Hypokalemia correlates with hypophosphatemia, except in binge-purge behaviors [51]. Oral or enteral route should be preferred whenever possible to correct hypokalemia. If intravenous route is decided (vomiting, gastric aspiration), potassium should be replaced with extreme caution and serum potassium levels should be closely monitored. In fact, too fast correction may induce severe arrhythmia by rapid shift in the ratio of the intracellular to extracellular potassium. Concomitant hypomagnesemia and hypophosphatemia should also be corrected.

2.4.2 Hypophosphatemia

While uncommon on admission [52], hypophosphatemia is a well-known marker of refeeding syndrome (see below).

2.4.3 Hyponatremia

Although polydypsia is common, life-threatening hyponatremia due to water intoxication has occasionally been reported in AN patients; it manifests as coma and seizures. Treatment includes administration of IV hypertonic NaCl and water restriction [53]. Hyponatremia can also be caused by hypovolemia [54] or inappropriate secretion of vasopressin, leading to the syndrome of inappropriate antiureasis (SIAD) [55]. SIAD can also be caused by antidepressant medications taken by patients [56]. Otherwise, hyponatremia is uncommon.

2.4.4 Hypomagnesemia

Serum magnesium levels are normal on admission but decrease within the first 72 hours of refeeding in about 50% of patients, as does hypophosphatemia [57]. It may potentiate the proarrythmogenic effects of hypokalemia. Therefore, serum levels should be monitored and corrected.

2.4.5 Renal impairment

Renal damage is often overlooked by clinicians. In a retrospective case-control study, renal damage was found in nearly 400 participants on admission [58]. It is observed
more frequently in the binge/purging subtype than in the restrictive subtype of AN, because episodes of volume depletion are more common [59]. The exact mechanisms of renal damage in AN are not yet fully understood, but dehydration, hypotension, chronic hypokalemia, rhabdomyolysis or thyroid dysfunction may interact to cause renal damage.

Estimation of glomerular filtration rate is difficult in this cohort of patients; serum creatinine levels may overestimate renal function, 24-hour urine collection is unreliable, and the Cockroft is not suitable in children. Finally, serum cystatin levels seem a stronger marker of chronic renal dysfunction as they are not affected by muscle mass or diet [60].

- Acute renal failure may occur as a result of tubular necrosis caused by volume depletion and hypokalemia/hypophosphatemia induced rhabdomyolysis. Treatment does not differ from other causes of acute renal failure.
- Chronic kidney disease. In rare cases where renal histology is available, an aspect of chronic interstitial nephritis is shown [61]. In a long-term follow-up study, Zipfel and colleagues reported a end stage kidney disease in 5.2 % of long-term survivors [62].

2.5 Hepatic complications

2.5.1 Before renutrition

Liver damage is thought to be the result of macroautophagy and apoptosis induced by starvation [63]. Nevertheless, acute liver failure is unusual. It is reflected by an hypertransaminemia (alanin aminotransferase, ALT alanin aspartate transferase, AST) and correlates with weight loss. Liver dysfunction may be associated with hypophosphatemia and hypoglycemia.

When weight is restored, transaminase levels normalize quickly [64]. Radiological imaging on liver is rarely necessary. A liver biopsy is useless or even dangerous and does not contribute to treatment. It justifies the discontinuation of all potentially hepatotoxic drugs.

2.5.2 During renutrition

A rise in aminotransferases levels may occur during renutrition as part of an inappropriate refeeding syndrome; it regress after a reduction in nutrient intake. Sometimes hypertransaminemia is a manifestation of the deleterious effects of parenteral nutrition on the liver.

2.6 Gastrintestinal complications

Common symptoms in patients with AN are abdominal pain, diarrhea or constipation, loss of appetite; they improve significantly with refeeding. Further explorations are needed if these symptoms do not relapse with refeeding [65].

2.6.1 Acute gastric distension

Acute gastric distension is a rare but classical complication of AN. It is the result of reduced gastric motility. Binge/purge episodes are triggering factors. Symptoms are unremarkable and include nausea, vomiting, pain and abdominal distension. CT scan can reveal a dilated stomach and eliminate a complication [66]. Prompt nasogastric aspiration can prevent gastric ischemia and perforation with peritonitis.

2.6.2 Superior mesentric artery syndrome

Gastric distension may be associated with superior mesentric artery syndrome. The latter is a result of mesentric fat loss, which in turn compresses the third duodenum between the aorta and the vasculo-nervous axis of the superior mesentery. The clinical presentation is postprandial abdominal pain relieved by vomiting. The diagnosis is made by CT scan. Conservative treatment with a liquid diet is the first choice. Surgery is usually unnecessary [67].

2.7 Hematological complications

The hematologic consequence is pancytopenia as evidenced by gelatinous bone marrow transformation in bone marrow biopsies [68].

The extent of these abnormalities depends on the degree of weight loss and the duration of illness. Leukopenia and anemia are the most common with an incidence of about one-third of cases, and thrombopenia is less frequent (approximately 10 % of cases).

The refeeding period is characterized by a further and transient decrease of all three cell lines 5 to 10 days after admission [69].

2.8 Infectious complications, COVID-19

Despite leukopenia and a dysregulated immune system, anorexic patients do not have a higher risk of infection. This is especially the case for coronavirus infection, and we have seen above that AN is not associated with more severe forms of COVID-19 infection [47]. Two pathophysiological mechanisms can be put forward: either the immune disorders induced by anorexia are limited or, on the contrary, the inflammatory response (which is responsible for most symptoms of severe forms of COVID-19) is attenuated.

By contrast, several studies have pointed out a significant increase in new diagnoses and the severity of preexisting cases of AN with higher rates of hospital admission during the first wave of COVID-19 pandemic and lockdown [13,15].

3. Refeeding syndrome

Refeeding syndrome is a complex, life-threatening metabolic disease that occurs in early start of nutritional
support in severely malnourished patients. The consequences can be very serious and in the worst cases characterized by multi-organ failure. The major marker is a biologic one, namely hypophosphatemia. The importance of malnutrition correlates with the degree of hypophosphatemia and the occurrence of refeeding syndrome. Clinicians fear this dangerous complication as it is associated with increased short-term mortality [7]. Since there is no standard definition, the precise incidence is unknown. Using hypophosphatemia as the sole diagnostic criterion, Brown and her colleagues found an incidence of refeeding syndrome of almost 35% in AN [70]. The most vulnerable patients are those who have profound denutrition (weight < 70% of expected), rapid weight loss or have hypophosphatemia on admission.

3.1 Physiopathology

Phosphorus is the main marker as it plays a key role in the mechanism of the disease. The combination of hypophosphatemia and a decrease in total phosphorus accounts primarily for the occurrence of this syndrome [71].

However, other biochemical abnormalities may also contribute to the disorder, including low potassium and magnesium stores, fluid imbalance or thiamine deficiency [72,73].

Refeeding is a physiological response characterized by a switch from a catabolic state to an anabolic state with carbohydrates load in a patient depleted from main intracellular ions, i.e. phosphorus, potassium and magnesium [74]. In this situation, glucose metabolism suddenly increases the need for phosphorus and is accompanied by hyperinsulinism, which in turn induces an intracellular shift of electrolytes and retention of glucose, water and sodium [72]. In addition, thiamine deficiency leads to lactic acidosis due to anaerobic glycolysis. This leads to cellular damage in all vital organs and thus to multi-organ failure.

3.2 Clinical symptoms

The clinical symptoms are varied, non-specific and are summarized in the Table 3.

We would emphasize the importance of tachycardia as a common and early warning sign.

<table>
<thead>
<tr>
<th>Table 3. Refeeding syndrome criteria</th>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
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<td>Sudden death</td>
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<tr>
<td>Tachycardia</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td><strong>Neuromuscular</strong></td>
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<tr>
<td>Confusion</td>
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<td>Coma</td>
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The ASPEN (American Society for Parenteral and Enteral Nutrition) has recently published the refeeding syndrome criteria as follows [71]:

- « A decrease in any 1, 2, or 3 of serum phosphorus, potassium and/or magnesium levels by 10-20 % (mild refeeding syndrome), 20-30 % (moderate refeeding syndrome), or > 30 % and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamin deficiency (severe refeeding syndrome)
- And occurring within 5 days of reinitiating or substantially increasing energy provision ».

3.3 Prevention

In its most recent publication, ASPEN also provides recommendations for the prevention and treatment of refeeding syndrome [71]. Prevention based on systematic phosphorus supplementation is recommended by most authors (750 to 1500 mg elemental phosphorus daily). However, to date, there is no well-conducted prospective study to support this strategy. In a retrospective study, Leitner et al. demonstrated that prophylactic administration of phosphate was safe in 70 AN participants; mild asymptomatic hyperphosphatemia occurred in 15 % of participants and no refeeding syndrome was observed [75]. In that study, phosphatemia was monitored daily. In clinical practice, the benefits of systematic supplementation seem to outweigh the limited downsides.

A recent review from 2023 compared a low-calorie start to renutrition (in line with a conservative approach to renutrition in AN: "start slowly and proceed slowly") with a higher initial calorie intake (usually over 1400 kcal/day) and an associated rapid increase in this intake on the occurrence of refeeding syndrome or hypophosphatemia. There was no evidence of an increased risk of refeeding syndrome or ionic disorders in adolescent AN patients receiving high-calorie renutrition, even in patients with a low BMI, when they are under close medical monitoring with electrolyte correction [76].

3.4 Treatment

Treatment of refeeding syndrome should be accompanied by close monitoring [71]:

- A reduction or temporary cessation of carbohydrate intake, whether by the venous or enteral route.
• A correction of hypophosphatemia. Several protocols have been published, most of which are well tolerated [77]. In our institution, we proceed as follows: moderate (> 0.32 mmol/L) and uncomplicated hypophosphatemia: 0.08 mmol/kg for 6 hours; severe (< 0.32 mmol/L) and/or symptomatic hypophosphatemia: 0.5 mmol/kg within 4 to 6 hours.
• A correction of other electrolyte abnormalities (hypokaliemia, hypomagnesemia).
• Parenteral administration of vitamins (thiamine ++) and trace elements.

4. Management of severe AN patients at montsouris institute

4.1 ICU or intermediate care unit?

Because ICU resources are limited and a large number of patients only require close monitoring without life support, intermediate care units have been set up in many countries, such as in France. These units, of which are unfortunately still few in number, provide an intermediate level of care between ICUs and general care and are highly specialized in the care of patients suffering from severe malnutrition, both somatically (expertise in artificial nutrition) and psychiatrically, with an often multidisciplinary team (including psychiatrists or psychologists trained in ED) [48]. They are usually closed to an ICU to allow ICU transfer if the patient’s clinical course deteriorates [78].

4.2 Reason for ICU admission

In fact, in the context of AN, intensivists are rarely called for distress such as circulatory failure induced by severe arrhythmia associated with hypokaliemia in patients with purgative type of AN, respiratory failure or coma due to hypoglycemia or hyponatremia.

Patients with eating disorders may also be treated for organ failure associated with refeeding syndrome or voluntary drug intoxication. Such patients must be admitted to the ICU for active life support. The management on them do not differ from other ICU patients.

In almost all cases, the diagnosis of AN is already known before admission to the ICU. Actually, the vast majority of AN patients admitted to the critical care unit do not have organ failure per se, but there is a risk that they will develop it. Therefore, they should be admitted to an intermediate care unit in order to monitor their vital signs continuously.

Patients with AN are referred to the ICU by the psychiatric team based on the clinical evaluation. According to our experience, we have drawn up a list of criteria for possible admission to the ICU. A single sign in itself does not necessarily require admission for the critical care. Rather, it is their combination and progression that prompt us to transfer patients to the intensive care unit. A common reason for admission to the ICU is a state of severe malnutrition, which puts the patient at high risk of refeeding syndrome.

In our institution, criteria for admission are as follows (Table 4):
• A rapid and/or severe weight loss. A BMI of less than 12 kg/m² is almost always an indication for admission to critical care.
• Complete aphagia.
• Cardiovascular symptoms: hypotension, profound sinus bradycardia (< 40 b/min), ventricular or supraventricular arrhythmias, heart failure with a left ventricular ejection fraction lower than 50%.
• Hypertransaminasemia with liver failure due to starvation.
• Marked electrolytes disturbances: hypokaliemia (< 2.0 mmol/l), hyponatremia (< 125 mmol/L), hypernatremia (> 150 mmol/L), hypophosphatemia (< 0.5 mmol/L).
• Symptomatic hypoglycemia (< 2.5 mmol/L).
• Renal failure (creatininemia > 100 μmol/L, urea > 15 mmol/L).
• Refeeding syndrome with organ failure.
• Sepsis.

### Table 4. ICU admission criteria

<table>
<thead>
<tr>
<th>Severe denutrition</th>
<th>Aphagia</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
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<td>Hypotension</td>
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<td>Bradycardia &lt; 40/min</td>
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<td>Arrhythmias</td>
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<td>Renal failure</td>
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<td>Liver failure</td>
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<tr>
<td>Refeeding syndrome (or risk for)</td>
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<tr>
<td>Severe biochemical disturbances</td>
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<td>Hypoglycemia</td>
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<td>Hyponatremia</td>
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These admission criteria are largely taken from the French recommendations of the Haute Autorité de Santé on hospitalization criteria for pediatric patients suffering from AN [79], which are in line with other international recommendations [80-82].

The following assessment is performed on admission:
• 12 leads electrocardiogram, transthoracic echocardiography;
• Blood drawing for laboratory tests:
4.3 Aims of ICU admission

The purposes of ICU admission are as follows:

• Correction of somatic disorders; medical complications are usually associated with organ failure.
• Starting renutrition to achieve a BMI level that prevents a short-term recurrence of somatic disorders. In this regard, the prevention of refeeding syndrome is of major concern.
• Continuation of psychiatric support: for this purpose, close collaboration between intensivists and psychiatrists should be emphasized again.

4.4 Treatment implementation in practice

The patient is isolated in a room alone. Isolation is made necessary by the major difficulty in refeeding, which is challenging due to various processes without the knowledge of the caregivers. Indeed, some patients suffering from severe AN may show a strong ambivalence to care and have difficulty in accepting renutrition and weight regain, which leads them to adopt behaviours designed to avoid renutrition. For this reason, the room is empty without any item, especially those that are absorbent; sinks are covered with a plastic film and toilets are closed, particularly when artificial or oral nutrition is given. Access to the bathroom can be granted at the patient's request and will be supervised by the care team if necessary. During the ICU stay, we usually restrict family visits, but it is not the rule of all teams. It is not a question of human isolation, quite the contrary; the sustained presence of the healthcare team is necessary, whether it is the resuscitation team or psychiatric team.

4.4.1 Refeeding

Restoring a healthy weight is the primary therapeutic goal to avoid a short-term recurrence of somatic disorders; it is a prerequisite for the basic treatment of the disease. In our critical care unit, we aim to reach a BMI at 14kg/m² on discharge. Usually that will take about 10 to 15 days.

It should always be kept in mind that it is extremely difficult to assess the exact caloric intake received by patients, since purging maneuvers may continue during hospitalisation.

4.4.1.1 Parenteral nutrition

Parenteral nutrition is usually considered a contraindication. However, in some carefully selected cases, it may be an exception for refeeding even if it is sometimes used successfully; peripheral infusion should be preferred [83]. It can only be recommended for the correction of severe symptomatic metabolic disorders.

4.4.1.2 Enteral nutrition

In a recent systematic review, Rizzo and colleagues concluded that renutrition via a nasogastric tube is well tolerated and allows for a more significant weight gain than oral feeding alone [84].

In our ICU department, we start enteral feeding via a nasogastric tube as soon as possible after the correct positioning of the feeding tube has been checked by X-ray. In addition, we make an indelible mark on the tube to avoid any attempt of self-removal.

Until not too long ago, refeeding protocols started with a low calorie intake and were gradually increased in order to avoid the risk of refeeding syndrome, which can be life-threatening.

For patients at high risk of refeeding syndrome, the enteral nutrition should be started with 100-150 g dextrose or 10-20 kcal/kg for the first 24 hours, increasing the target by 33% every 1-2 days. The initiation or increase of calories should be delayed in patients with severely low phosphorus, potassium or magnesium levels, with a priority given to the correction of these levels [71].

More recently, several studies have challenged these practices by showing the effectiveness and safety of more aggressive refeeding protocols.

Most of these studies are retrospective with historical control groups and use wide calorie intakes ranging from 500 to 1600 kcal/d for the controls and 1000 kcal to 2000 kcal for the participants in study [85-87]. All these studies defend increased calorie intake, which appears to be more effective and safer with no side effects, especially refeeding syndrome (i.e. hypophosphatemia).

In a randomized clinical trial (RCT), Garber et al. compared the oral intake of a high calorie (started at 2000 kcal/d, increasing daily by 200 kcal) to a lower intake (starting at 1400 kcal, increasing by 200 kcal every other day) in 120 randomized moderately malnourished participants. They observed a significant weight gain and
a shorter hospital stay in the group with the high calorie intake [88].

O’Connor, in an RCT involving 36 adolescents (mean BMI = 13.5), found a greater weight gain without QTc prolongation or refeeding hypophosphatemia in participants who received an initial intake of 1500 kcal (versus 500) [89].

4.4.1.3 Oral nutrition

Oral feeding is offered as quickly as possible in addition to enteral feeding, in order to enable eating habits to be maintained. The meal tray distributed is the same as the one offered to other patients for a similar period of time. Support from a dietician trained in eating disorders can help the patient to gradually increase and diversify the oral intake of nutrition. Temporary withdrawal of oral food may happen if it generates a high level of anxiety.

4.4.2 Psychiatric care during ICU stay

4.4.2.1 Treatment implementation

The care contract for ICU must be drawn up by the medical team, the patient and parents in collaboration with the psychiatric team in order to set the target weight for discharge from the ICU. In our critical care unit, we aim to reach a BMI at 14kg/m² on discharge. The psychiatric team visits the patient at least once a day and as frequently as needed either by the patient or the ICU team.

The aims of the psychiatric team are:

• To support the patient and family by specifying the main benchmarks of the care in ICU and beyond.
• To enhance motivation for treatment.
• To treat psychiatric symptoms (anxiety, depression) with both supportive therapy and psychotropic medication if necessary.
• To help the ICU team to establish a framework for efficient care (explanation of AN symptoms, resistance to care).

4.4.2.2 Medicines

Today, no medication has been proven to be effective for AN, but recent developments in randomized controlled trials have provided new information for innovative therapies. Classically, antidepressants and/or anxiolytics may sometimes be useful, since depression and anxiety are common comorbidities in AN [90]. Among the antipsychotics, olanzapine is the most extensively studied. In a 2022 systematic review and meta-analysis, olanzapine showed efficacy in increasing BMI in adults, although this effect has not been demonstrated in adolescents [91]. Despite encouraging preliminary results, a study evaluating intranasal oxytocin treatment in AN patients found no improvement in anxiety symptoms or weight gain [92].

Hormonal approaches have been developed, focusing in particular on the peptides that regulate hunger and satiety, which are found to be disrupted in AN. Thus, a clinical study analyzing a ghrelin agonist administered to women with AN for 4 weeks found a significant reduction in gastric emptying time, with a tendency to weight regain [93]. Another team that demonstrated the association between relative androgen deficiency in AN and greater severity of depressive and anxiety symptoms, found no improvement in these symptoms after 24 weeks of treatment with low-dose testosterone [94].

Nutritional therapies were also tested. Among them, a tryptophan-depleted diet (with an expected impact on brain 5-HT) did not reduce anxiety symptoms or improve mood in AN patients who had returned to normal weight [95]. Similarly, a recent systematic review associated with a meta-analysis of five randomised controlled trials also showed no effect of omega-3 supplementation, combined with renutrition, on dietary and psychological symptoms in patients suffering from AN [96].

Over the past decade, the intestinal microbiota and the gut-brain axis have been at the center of efforts to understand the etiopathogenesis of AN. Several teams have identified alterations in the diversity and taxonomic composition of the intestinal microbiota of patients with AN [97]. Fecal transplantation in AN has so far only been conducted by two teams on single individuals, with encouraging results in terms of improving intestinal barrier function [98] and weight gain [99].

More recently, a study evaluated probiotic treatment in children with AN. It showed an effect on nutritional recovery after 6 months, but no improvement in constipation [100]. Research into these therapeutic options involving modulation of the intestinal microbiota, is currently in full swing and requires further investigation. Finally, in recent years, teams have been looking beyond the field of psychotherapy and cognitive-behavioral therapies, at neuromodulation, particularly through repetitive transcranial magnetic stimulation (rTMS) [101].

4.4.3 Treatment monitoring

Weight is measured daily at the same time and under the same conditions. The weight should not decrease or stagnate over 48 hours, which would indicate a failure of treatment. Complications are checked for daily in the same way. In our experience, the onset of tachycardia may indicate the occurrence of a complication, in particular a renutrition syndrome. Biological monitoring (glucose and electrolyte measurements, liver tests) is performed daily or every other day during the first week.

Patients discharged from the intensive care unit are transferred to psychiatric departments specializing in the treatment of eating disorders, in order to continue weight management and intensify psychotherapeutic work. When their health condition requires continued somatic care with close clinical and biological monitoring, transfer to endocrinology-nutrition departments is preferred. In the vast majority of cases, artificial nutrition initiated in intensive care is continued after discharge.
Conclusion

During the course of AN, the severity of malnutrition and its complications, the purgative behaviours and voluntary drug ingestion may require admission to the ICU for monitoring and renutrition. Insofar as adaptive mechanisms have been put in place gradually by the organism, care must be taken not to overtake them suddenly. Hastening slowly could sum up the spirit of somatic care.

Apart from a few exceptions, the digestive tract should be used as a priority for the implementation of renutrition. In all cases, it involves multidisciplinary care in collaboration with the psychiatric team; objectives and methods of care should be clearly explained to the patients and their family from the time of admission.

Authors' contributions

Maeva Duquesnoy and Christian Lamer drafted the initial manuscript. Laurent Tric, Mouna Hanachi and Nathalie Godart critically reviewed the manuscript. All authors have read and agreed to publish the manuscript.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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