Review Article

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

Disorder class: feeding and eating disorders
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).
B. Intense fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain.
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.
Specified whether
Restricting type: has not regularly engaged in binge-eating or purging in the last three months.
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).

The severity of the disorder is defined according to the impact of AN on the body mass index (BMI): mildly severe (BMI > 17 kg/m^2), moderately severe (BMI of 16-16.99 kg/m^2), severe (BMI 15-15.99 kg/m^2) or extremely severe (BMI < 15 kg/m^2). 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

Cardiac
Sudden death
Bradycardia/sinus node dysfunction
Hypotension
Left ventricular dysfunction
Arrythmias
Pericardial effusion
Mitral valve prolapse
Neuromuscular
Wernicke-Korsakoff encephalopthy
Coma/convulsions
Cognitive impairement
Pulmonary complications
Pneumothorax
Pneumomediastinum

Aspiration pneumonia
Renal and electrolytes
Hypokalemia
Hypophosphatemia (refeeding)
Hyponatremia
Hypomagnesemia
Renal failure
Hepatic
Hypertransaminemia
Liver failure
Gastrointestinal
Gastroparesis
Superior mesenteric artery syndrome
Esophageal rupture
Hematological
Anemia
Leucocytopenia
Thrombocytopenia
Refeeding (see Table 3)

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 adaptative 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 arythmias was significantly higher in AN participants compared to controls. Long-term cardiac monitoring was able to determine that the incidence of bradycardic arrhmias 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 bradyarrhythmias 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 symtoms, 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, mamillary 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 confibulations) [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 eletrolytes 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 hypokaliema. 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 antidiuresis (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 impairement

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 hypokaliemia/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 macro-autophagy 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 regresses after a reduction in nutrient intake. Sometimes hypetransaminemia 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 mesenteric artery syndrome

Gastric distension may be associated with superior mesenteric artery syndrome. The latter is a result of mesenteric 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 3. Refeeding syndrome criteria

Cardiovascular
Sudden death
Tachycardia
Heart failure
Arrythmias
Neuromuscular
Confusion
Coma
Seizures
Rhabdomyolysis
Pulmonary complications
Respiratory failure
Main laboratory findings
Hypophosphatemia
Hypokalemia
Hypomagnesemia
Hepatic cytolysis

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 occuring 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

Severe denutrition
BMI < 12
Aphagia
Cardiovascular
Hypotension
Bradycardia < 40/min
Heart failure
Arrhythmias
Renal failure
Liver failure
Refeeding syndrome (or risk for)
Severe biochemical disturbances
Hypoglycemia
Hypophosphatemia
Hypokalemia
Hyponatremia
Hypernatremia

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:

- Glucose
- Electrolytes (sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus)
- Kidney tests (blood urea nitrogen, creatinine)
- Complete blood count and white blood cell differential
- Blood proteins: total proteins, albumin, transthyretin.
- C Reactive Protein
- Liver tests (bilirubin, ALT, AST)
- 25 hydroxyvitamin D3 level
- Thyroid function tests (Thyroide Stimulating Hormone, free T3)

It is important to specify that the decision of ICU admission should be made in agreement with the referring psychiatric team. In addition, the objectives and conditions of ICU stay should be clearly explained to the patients (if possible) and their relatives. Indeed, multidisciplinary care together with the psychiatric team is crucial and determines the course of the ICU stay.

Finally, the principle "primum non nocere" must be kept in mind throughout ICU stay, as many of the abnormalities observed have occurred gradually and should therefore be carefully restored, except in case of emergency.

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/m^2 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 caloric 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 $14kg/m^2$ 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.

References

[1] Mitchell JE, Peterson CB. Anorexia Nervosa. *The New England Journal of Medicine*. 2020; 382(14):1343-51. doi: 10.1056/NEJMcp1803175.

[2] Silén Y, Keski-Rahkonen A. Worldwide prevalence of DSM-5 eating disorders among young people. *Current Opinion in Psychiatry*. 2022; 35(6):362-71. doi: 10.1097/YCO.0000000000000818.

[3] Jeammet P, Brechon G, Payan C, Gorge A, Fermanian J. [The outcome of anorexia nervosa: a prospective study of 129 patients evaluated at least 4 years after their first admission]. *Psychiatr Enfant*. 1991; 34(2):381-442.

[4] Godart N, Wallier J, Hubert T, Curt F, Galès O, Perdereau F, et al. Detemining factors for target weights in an anorexia nervosa inpatient program for adolescents and young adults: Study on the links between theory-based hypotheses and the realities of clinical practice. *Eating and Weight Disorders*. 2009; 14(4):e176-83. doi: 10.1007/BF03325114.

[5] Godart N, Atger F, Perdereau F, Agman G, Rein Z, Corcos M, et al. Treatment of adolescent patients with eating disorders: Description of a psychodynamic approach in clinical practice. *Eating and Weight Disorders*. 2004; 9(3):224-7. doi: 10.1007/BF03325071.

[6] Strik Lievers L, Curt F, Wallier J, Perdereau F, Rein Z, Jeammet P, et al. Predictive factors of length of inpatient treatment in anorexia nervosa. *Eur Child Adolesc Psychiatry*. 2009; 18(2):75-84. doi: 10.1007/s00787-008-0706-8.

[7] Vignaud M, Constantin JM, Ruivard M, Villemeyre-Plane M, Futier E, Bazin JE, et al. Refeeding syndrome influences outcome of anorexia nervosa patients in intensive care unit: an observational study. *Critical Care*. 2010;14(5): R172. doi: 10.1186/cc9274.

[8] Tric L, Agman G, Tran D, Godart N, Benmansour EL, Lamer C. Prise en charge de l'anorexie mentale en réanimation (Management of anorexia nervosa in Intensive Care Unit). *Réanimation*. 2004; 13(6-7):407-16. doi: 10.1016/j.reaurg.2004.06.004.

[9] American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc. doi:10.1176/appi.books.9780890425596.

[10] Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. *Current Opinion in Psychiatry*. 2016; 29(6): 340-5. doi: 10.1097/YCO.0000000000000278.

[11] Hudson JI, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry*. 2007; 61(3):348-58. doi: 10.1016/j.biopsych.2006.03.040.

[12] Van Eeden AE, Van Hoeken D, Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Current Opinion in Psychiatry*. 2021; 34(6):515-24. doi: 10.1097/YCO.0000000000000739.

[13] Chauvet-Gelinier JC, Roussot A, Vergès B, Petit JM, Jollant F, Quantin C. Hospitalizations for Anorexia Nervosa during the COVID-19 Pandemic in France: A Nationwide Population-Based Study. *Journal of Clinical Medicine*. 2022; 11(16):4787. doi: 10.3390/jcm11164787.

[14] Milliren CE, Richmond TK, Hudgins JD. Emergency Department Visits and Hospitalizations for Eating Disorders During the COVID-19 Pandemic. *Pediatrics*. 2023; 151(1): e2022058198. doi: 10.1542/peds.2022-058198.

[15] Agostino H, Burstein B, Moubayed D, Taddeo D, Grady R, Vyver E, et al. Trends in the Incidence of New-Onset Anorexia Nervosa and Atypical Anorexia Nervosa Among Youth During the COVID-19 Pandemic in Canada. *JAMA Network Open*. 2021; 4(12): e2137395. doi: 10.1001/jamanetworkopen.2021.37395.

[16] Keshaviah A, Edkins K, Hastings ER, Krishna M, Franko DL, Herzog DB, et al. Re-examining premature mortality in anorexia nervosa: A meta-analysis redux. *Comprehensive Psychiatry*. 2014; 55(8):1773-84. doi: 10.1016/j.comppsych.2014.07.017.

[17] Guinhut M, Godart N, Benadjaoud M, Melchior J, Hanachi M. Five-year mortality of severely malnourished patients with chronic anorexia nervosa admitted to a medical unit. *Acta Psychiatrica Scandinavica*. 2021; 143(2):130-40. doi: 10.1111/acps.13261.

[18] Cost J, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa. *Cleveland Clinic Journal of Medicine*. 2020; 87(6):361-6. doi:10.3949/ccjm.87a.19084.

[19] Stheneur C, Ali A, Tric L, Curt F, Hubert T, Godart N. Impact of somatic severity on long-term mortality in anorexia nervosa. *Eating and Weight Disorders*. 2017; 22(2):285-9. doi: 10.1007/s40519-016-0346-9.

[20] Mehler PS, Anderson K, Bauschka M, Cost J, Farooq A. Emergency room presentations of people with anorexia nervosa. *Journal of Eating Disorders*. 2023; 11(1): 16. doi: 10.1186/s40337-023-00742-x.

[21] Friars D, Walsh O, McNicholas F. Assessment and management of cardiovascular complications in eating disorders. *Journal of Eating Disorders*. 2023; 11(1): 13. doi: 10.1186/s40337-022-00724-5.

[22] Lamzabi I, Syed S, Reddy VB, Jain R, Harbhajanka A, Arunkumar P. Myocardial Changes in a Patient With Anorexia Nervosa. *American Journal of Clinical Pathology*. 2015; 143(5): 734-7. doi: 10.1309/AJCP4PLFF1TTKENT.

[23] Paysal J, Thireau J, Terral D, Rochette E, Obert P, Merlin E, et al. Cardiac Remodeling and Its Determinants in Anorexia Nervosa Adolescents: Impact of Weight Recovery. *Children*. 2022; 9(4): 458. doi: 10.3390/children9040458.

[24] Sachs KV, Harnke B, Mehler PS, Krantz MJ. Cardiovascular complications of anorexia nervosa: A systematic review. *The International Journal of Eating Disorders*. 2016; 49(3): 238-48. doi: 10.1002/eat.22481.

[25] Cotter R, Lyden J, Mehler PS, Miceli J, Schuller J, Krantz MJ. A case series of profound bradycardia in patients with severe anorexia nervosa: Thou shall not pace? *HeartRhythm Case Reports*. 2019; 5(10): 511-5. doi: 10.1016/j.hrcr.2019.07.011.

[26] Frederiksen TC, Krogh Christiansen M, Charmoth Østergaard P, Hove Thomsen P, Graff C, Clausen L, et al. QTc Interval and Risk of Cardiac Events in Adults With Anorexia Nervosa: A Long-Term Follow-Up Study. *Circ: Arrhythmia and Electrophysiology*. 2018; 11(8): e005995. doi: 10.1161/CIRCEP.117.005995.

[27] Farasat M, Watters A, Bendelow T, Schuller J, Mehler PS, Krantz MJ. Long-term cardiac arrhythmia and chronotropic evaluation in patients with severe anorexia nervosa (LACE-AN): A pilot study. *Journal of Cardiovascular electrophysiology*. 2020; 31(2): 432-9. doi: 10.1111/jce.14338.

[28] Warren MP, Vande Wiele RL. Clinical and metabolic features of anorexia nervosa. *American Journal of Obstetrics and Gynecology*. 1973; 117(3): 435-49. doi: 10.1016/0002-9378(73)90053-7.

[29] Spaulding-Barclay MA, Stern J, Mehler PS. Cardiac changes in anorexia nervosa. *Cardiology in the Young*. 2016; 26(4): 623-8. doi: 10.1017/S104795111500267X.

[30] Spina G, Clemente A, Roversi M, Marchili MR, Silvestri P, Mascolo C, et al. Early echocardiographic evaluation of children admitted to the emergency department for anorexia nervosa during the COVID-19 pandemic. *Eating and Weight Disorders*. 2022; 27(8): 3409-17. doi: 10.1007/s40519-022-01474-8.

[31] Choi SY, Lee KJ, Kim SC, Lee EH, Lee YM, Kim YB, et al. Cardiac Complications Associated with Eating Disorders in Children: A Multicenter Retrospective Study. *Pediatric Gastroenterology, Hepatology & Nutrition*. 2022; 25(5): 432-440. doi: 10.5223/pghn.2022.25.5.432.

[32] Kastner S, Salbach-Andrae H, Renneberg B, Pfeiffer E, Lehmkuhl U, Schmitz L. Echocardiographic findings in adolescents with anorexia nervosa at beginning of treatment and after weight recovery. *European Child & Adolescent Psychiatry*. 2012; 21(1): 15-21. doi: 10.1007/s00787-011-0227-8.

[33] Paysal J, Merlin E, Terral D, Chalard A, Rochette E, Obert P, et al. Corrigendum: Left Ventricular Strains and Myocardial Work in Adolescents With Anorexia Nervosa. *Frontiers in Cardiovascular Medicine*. 2022; 9: 895870. doi: 10.3389/fcvm.2022.895870.

[34] Hanachi M, Pleple A, Barry C, Dicembre M, Latour E, Duquesnoy M, et al. Echocardiographic abnormalities in 124 severely malnourished adult anorexia nervosa patients: frequency and relationship with body composition and biological features. *Journal of Eating Disorders*. 2020; 8(1): 66. doi: 10.1186/s40337-020-00343-y.

[35] Flamarique I, Vidal B, Plana MT, Andrés-Perpiñá S, Gárriz M, Sánchez P, et al. Long-term cardiac assessment in a sample of adolescent-onset anorexia nervosa. *Journal of Eating Disorders*. 2022; 10(1): 12. doi: 10.1186/s40337-022-00533-w.

[36] Meyers DG. Mitral Valve Prolapse in Anorexia Nervosa. *Annals of Internal Medicine*. 1986; 105(3): 384-6. doi: 10.7326/0003-4819-105-3-384.

[37] Kircher JN, Park MH, Cheezum MK, Hulten EA, Kunz JS, Haigney M, et al. Cardiac tamponade in association with anorexia nervosa: A case report and review of the literature. *Cardiology Journal*. 2012; 19(6): 635-8. doi: 10.5603/cj.2012.0117.

[38] Shapiro M, Davis AA, Nguyen ML. Severe Anorexia

Nervosa in a 20-Year-Old Male with Pericardial Effusion and Cortical Atrophy. *International Journal of Psychiatry in Medicine*. 2014; 48(2): 95-102. doi: 10.2190/PM.48.2.b.

[39] Hanachi M, Dicembre M, Rives-Lange C, Ropers J, Bemer P, Zazzo JF, et al. Micronutrients Deficiencies in 374 Severely Malnourished Anorexia Nervosa Inpatients. *Nutrients*. 2019; 11(4): 792. doi: 10.3390/nu11040792.

[40] Oudman E, Wijnia JW, Oey MJ, Van Dam M, Postma A. Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports. *Journal of the Neurological Sciences*. 2021; 426: 117482. doi: 10.1016/j.jns.2021.117482.

[41] Sparacia G, Anastasi A, Speciale C, Agnello F, Banco A. Magnetic resonance imaging in the assessment of brain involvement in alcoholic and nonalcoholic Wernicke's encephalopathy. *World Journal of Radiology*. 2017; 9(2): 72-78. doi: 10.4329/wjr.v9.i2.72.

[42] Arts N, Walvoort S, Kessels R. Korsakoff's syndrome: a critical review. *Neuropsychiatric Disease and Treatment*. 2017; 13: 2875-90. doi: 10.2147/NDT.S130078.

[43] Kappou K, Ntougia M, Kourtesi A, Panagouli E, Vlachopapadopoulou E, Michalacos S, et al. Neuroimaging Findings in Adolescents and Young Adults with Anorexia Nervosa: A Systematic Review. *Children*. 2021; 8(2): 137. doi: 10.3390/children8020137.

[44] Kuroiwa M, Kita K, Wakakuri A, Sekijima A, Takibayashi M, Watanabe F, et al. Spontaneous pneumomediastinum in young women: Comparison between anorexia nervosa and nonanorexic patients. *Journal of General and Family Medicine*. 2017; 18(5): 268-70. doi: 10.1002/jgf2.43.

[45] Grayeb DE, Chan ED, Swanson LM, Gibson DG, Mehler PS. Nontuberculous mycobacterial lung infections in patients with eating disorders: plausible mechanistic links in a case series. *AME Case Reports*. 2021; 5: 9-9. doi: 10.21037/acr-20-101.

[46] Holmes SRM, Sabel AL, Gaudiani JL, Gudridge T, Brinton JT, Mehler PS. Prevalence and management of oropharyngeal dysphagia in patients with severe anorexia nervosa: A large retrospective review. *The International Journal of Eating Disorders*. 2016; 49(2): 159-66. doi: 10.1002/eat.22441.

[47] Winston AP, Taylor MJ, Himmerich H, Ibrahim MAA, Okereke U, Wilson R. Medical morbidity and risk of general hospital admission associated with concurrent anorexia nervosa and COVID -19: An observational study. *The International Journal of Eating Disorders*. 2023; 56(1): 282-7. doi: 10.1002/eat.23851.

[48] Guinhut M, Melchior JC, Godart N, Hanachi M. Extremely severe anorexia nervosa: Hospital course of 354 adult patients in a clinical nutrition-eating disorders-unit. *Clinical Nutrition*. 2021; 40(4): 1954-65. doi: 10.1016/j.clnu.2020.09.011.

[49] Tse G, Li KHC, Cheung CKY, Letsas KP, Bhardwaj A, Sawant AC, et al. Arrhythmogenic Mechanisms in Hypokalaemia: Insights From Pre-clinical Models. *Frontiers in Cardiovascular Medicine*. 2021; 8: 620539. doi: 10.3389/fcvm.2021.620539.

[50] Tazmini K, Frisk M, Lewalle A, Laasmaa M, Morotti S, Lipsett DB, et al. Hypokalemia Promotes Arrhythmia by Distinct Mechanisms in Atrial and Ventricular Myocytes. *Circulation Research*. 2020; 126(7): 889-906. doi: 10.1161/CIRCRESAHA.119.315641.

[51] Funayama M, Mimura Y, Takata T, Koreki A, Ogino S, Kurose S, et al. Hypokalemia in patients with anorexia nervosa during refeeding is associated with binge–purge behavior, lower body mass index, and hypoalbuminemia. *Journal of Eating Disorders*. 2021; 9(1): 95. doi: 10.1186/s40337-021-00452-2.

[52] Funayama M, Mimura Y, Takata T, Koreki A, Ogino S, Kurose S. Body mass index and blood urea nitrogen to creatinine ratio predicts refeeding hypophosphatemia of anorexia nervosa patients with severe malnutrition. *Journal of Eating Disorders*. 2021; 9(1):1. doi: 10.1186/s40337-020-00356-7.

[53] Krogulska A, Nowicka D, Nowicki Z, Parzęcka M, Sakson-Słomińska A, Kuczyńska R. A loss of consciousness in a teenage girl with anorexia nervosa, due to polydipsia: case report and a minireview. *Eating and Weight Disorders*. 2019; 24(5): 969-74. doi: 10.1007/s40519-018-00636-x.

[54] Caregaro L, Di Pascoli L, Favaro A, Nardi M, Santonastaso P. Sodium depletion and hemoconcentration: Overlooked complications in patients with anorexia nervosa? *Nutrition*. 2005; 21(4):438-45. doi: 10.1016/j.nut.2004.08.022.

[55] Gold PW, Kaye W, Robertson GL, Ebert M. Abnormalities in Plasma and Cerebrospinal-Fluid Arginine Vasopressin in Patients with Anorexia Nervosa. *The New England Journal of Medicine*. 1983; 308(19):1117-23. doi: 10.1056/NEJM198305123081902.

[56] Leth-Møller KB, Hansen AH, Torstensson M, Andersen SE, Ødum L, Gislasson G, et al. Antidepressants and the risk of hyponatremia: a Danish register-based population study. *BMJ Open*. 2016; 6(5): e011200. doi: 10.1136/bmjopen-2016-011200.

[57] Maginot TR, Kumar MM, Shiels J, Kaye W, Rhee KE. Outcomes of an inpatient refeeding protocol in youth with anorexia nervosa: Rady Children's Hospital San Diego/University of California, San Diego. *Journal of Eating Disorders*. 2017; 5(1):1. doi: 10.1186/s40337-016-0132-0.

[58] Gurevich E, Steiling S, Landau D. Incidence of Impaired Kidney Function Among Adolescent Patients Hospitalized With Anorexia Nervosa. *JAMA*

Network Open. 2021; 4(11): e2134908. doi: 10.1001/jamanetworkopen.2021.34908.

[59] Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. Anorexia Nervosa and the Kidney. *American Journal of Kidney Diseases*. 2012; 60(2): 299-307. doi: 10.1053/j.ajkd.2012.03.019.

[60] Delanaye P, Cavalier E, Radermecker RP, Paquot N, Depas G, Chapelle JP, et al. Estimation of GFR by different creatinine- and cystatin-C-based equations in anorexia nervosa. *Clinical Nephrology*. 2009; 71(05): 482-91. doi: 10.5414/cnp71482.

[61] Marumoto H, Sasaki T, Tsuboi N, Ito T, Ishikawa M, Ogura M, et al. Kidney Disease Associated With Anorexia Nervosa: A Case Series With Kidney Biopsies. *Kidney Medicine*. 2020; 2(4): 418-24. doi: 10.1016/j.xkme.2020.03.007.

[62] Zipfel S, Löwe B, Reas DL, Deter HC, Herzog W. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. *The Lancet*. 2000; 355(9205): 721-2. doi: 10.1016/S0140-6736(99)05363-5.

[63] Hanachi M, Melchior JC, Crenn P. Hypertransaminasemia in severely malnourished adult anorexia nervosa patients: risk factors and evolution under enteral nutrition. *Clinical Nutrition*. 2013; 32(3): 391-5. doi: 10.1016/j.clnu.2012.08.020.

[64] Cuntz U, Voderholzer U. Liver Damage Is Related to the Degree of Being Underweight in Anorexia Nervosa and Improves Rapidly with Weight Gain. *Nutrients*. 2022; 14(12): 2378. doi: 10.3390/nu14122378.

[65] Gibson D, Workman C, Mehler PS. Medical Complications of Anorexia Nervosa and Bulimia Nervosa. *Psychiatric Clinics of North America*. 2019; 42(2): 263-74. doi: 10.1016/j.psc.2019.01.009.

[66] Pitre T, Mah J, Vertes J, Tugwell B. Acute gastric dilatation in a patient with severe anorexia nervosa: a case report. *Journal of Medical Case Reports*. 2021; 15(1): 61. doi: 10.1186/s13256-020-02575-7.

[67] Rao SJ, Lakra P, Paudel K, Haas CJ. A case of superior mesenteric artery syndrome. *Radiology Case Reports*. 2022; 17(6): 2235-7. doi: 10.1016/j.radcr.2022.03.090.

[68] Hariz A, Hamdi MS, Boukhris I, Boujelbène N, Azzabi S, Khalfallah N. Gelatinous Transformation of Bone Marrow in a Patient with Anorexia Nervosa: An Uncommon but Reversible Etiology. *American Journal of Case Reports*. 2018; 19: 1449-52. doi: 10.12659/AJCR.911287.

[69] Funayama M, Koreki A, Mimura Y, Takata T, Ogino S, Kurose S, et al. Restrictive type and infectious complications might predict nadir hematological values among individuals with anorexia nervosa during the refeeding period: a retrospective study. *Journal of Eating Disorders*. 2022; 10(1): 64. doi: 10.1186/s40337-022-00586-x.

[70] Brown CA, Sabel AL, Gaudiani JL, Mehler PS. Predictors of hypophosphatemia during refeeding of patients with severe anorexia nervosa. *The International Journal of Eating Disorders*. 2015; 48(7): 898-904. doi: 10.1002/eat.22406.

[71] da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutrition in Clinical Practice*. 2020; 35(2): 178-95. doi: 10.1002/ncp.10474.

[72] Krutkyte G, Wenk L, Odermatt J, Schuetz P, Stanga Z, Friedli N. Refeeding Syndrome: A Critical Reality in Patients with Chronic Disease. *Nutrients*. 2022; 14(14): 2859. doi: 10.3390/nu14142859.

[73] Brown K, Everwine M, Nieves J. A Case of Wernicke Encephalopathy Secondary to Anorexia Nervosa Complicated by Refeeding Syndrome and Takotsubo Cardiomyopathy. *American Journal of Case Reports*. 2021; 22: e929891-1-e929891-7. doi: 10.12659/AJCR.929891.

[74] Cahill GF. Fuel Metabolism in Starvation. *Annual Reviews of Nutrition*. 2006; 26(1): 1-22. doi: 10.1146/annurev.nutr.26.061505.111258.

[75] Leitner M, Burstein B, Agostino H. Prophylactic Phosphate Supplementation for the Inpatient Treatment of Restrictive Eating Disorders. *Journal of Adolescent Health*. 2016; 58(6): 616-20. doi: 10.1016/j.jadohealth.2015.12.001.

[76] Mosuka EM, Murugan A, Thakral A, Ngomo MC, Budhiraja S, St Victor R. Clinical Outcomes of Refeeding Syndrome: A Systematic Review of High vs. Low-Calorie Diets for the Treatment of Anorexia Nervosa and Related Eating Disorders in Children and Adolescents. *Cureus*. 2023; 15(5): e39313. doi: 10.7759/cureus.39313.

[77] Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. *Critical Care*. 2010; 14(4): R147. doi: 10.1186/cc9215.

[78] Simpson CE, Sahetya SK, Bradsher RW, Scholten EL, Bain W, Siddique SM, et al. Outcomes of Emergency Medical Patients Admitted to an Intermediate Care Unit With Detailed Admission Guidelines. *American Journal of Critical Care*. 2017; 26(1): e1-10. doi: 10.4037/ajcc2017253.

[79] Haute Autorité de Santé. Anorexie mentale : prise en charge. 30 septembre 2010. Available at :https://www.has-sante.fr/jcms/c_985715/fr/anorexie-mentale-prise-en-charge. [Accessed 20th June 2024].

[80] Hay P, Chinn D, Forbes D, Madden S, Newton R, Sugenor L, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *The Australian and New Zealand Journal of Psychiatry*. 2014; 48(11): 977-1008. doi: 10.1177/0004867414555814.

[81] Lock J, La Via MC, American Academy of Child and Adolescent Psychiatry (AACAP) Committee

on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with eating disorders. *Journal of American Academy of Child and Adolescent Psychiatry*. 2015; 54(5): 412-25. doi: 10.1016/j.jaac.2015.01.018.

[82] National Guideline Alliance (UK). Eating Disorders: Recognition and Treatment [Internet]. London: National Institute for Health and Care Excellence (NICE); 2017 [cited 2024 May 12]. (National Institute for Health and Care Excellence: Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK436876/

[83] Ko JK, Lee YK, Na JC, Kim DY, Kim YR. A Retrospective Analysis Evaluating the Outcome of Parenteral Nutrition in the Treatment of Anorexia Nervosa in Korea. *Journal of Clinical Medicine*. 2020; 9(11): 3711. doi: 10.3390/jcm9113711.

[84] Rizzo SM, Douglas JW, Lawrence JC. Enteral Nutrition via Nasogastric Tube for Refeeding Patients With Anorexia Nervosa: A Systematic Review. *Nutrition in Clinical Practice*. 2019; 34(3): 359-70. doi: 10.1002/ncp.10187.

[85] Garber AK, Mauldin K, Michihata N, Buckelew SM, Shafer MA, Moscicki AB. Higher Calorie Diets Increase Rate of Weight Gain and Shorten Hospital Stay in Hospitalized Adolescents With Anorexia Nervosa. *Journal of Adolescent Health*. 2013; 53(5): 579-84. doi: 10.1016/j.jadohealth.2013.07.014.

[86] Dalenbrook S, Naab S, Garber A, Correll C, Voderholzer U, Haas V. Outcomes of a Standardized, High-Caloric, Inpatient Re-Alimentation Treatment Protocol in 120 Severely Malnourished Adolescents with Anorexia Nervosa. *Journal of Clinical Medicine*. 2022; 11(9): 2585. doi: 10.3390/jcm11092585.

[87] Staab R, Campagna J, Ma J, Sengar A. Rapid refeeding in anorexia nervosa: A dialectic balance. *The International Journal of Eating Disorders*. 2022; 55(5): 653-63. doi: 10.1002/eat.23698.

[88] Garber AK, Cheng J, Accurso EC, Adams SH, Buckelew SM, Kapphahn CJ, et al. Short-term Outcomes of the Study of Refeeding to Optimize Inpatient Gains for Patients With Anorexia Nervosa: A Multicenter Randomized Clinical Trial. *JAMA Pediatrics*. 2021; 175(1): 19-27. doi: 10.1001/jamapediatrics.2020.3359.

[89] O'Connor G, Nicholls D, Hudson L, Singhal A. Refeeding Low Weight Hospitalized Adolescents With Anorexia Nervosa: A Multicenter Randomized Controlled Trial. *Nutrition in Clinical Practice*. 2016; 31(5): 681-9. doi: 10.1177/0884533615627267.

[90] Blanchet C, Guillaume S, Bat-Pitault F, Carles ME, Clarke J, Dodin V, et al. Medication in AN: A Multidisciplinary Overview of Meta-Analyses and Systematic Reviews. *Journal of Clinical Medicine*. 2019; 8(2): 278. doi: 10.3390/jcm8020278.

[91] Han R, Bian Q, Chen H. Effectiveness of olanzapine in the treatment of anorexia nervosa: A systematic review and meta-analysis. *Brain and Behavior*. 2022; 12(2): e2498. doi: 10.1002/brb3.2498.

[92] Maguire S, Kesby A, Brownlow R, Hunt GE, Kim M, McAulay C, et al. A phase II randomised controlled trial of intranasal oxytocin in anorexia nervosa. *Psychoneuroendocrinology*. 2024; 164: 107032. doi: 10.1016/j.psyneuen.2024.107032.

[93] Fazeli PK, Lawson EA, Faje AT, Eddy KT, Lee H, Fiedorek FT, et al. Treatment With a Ghrelin Agonist in Outpatient Women With Anorexia Nervosa: A Randomized Clinical Trial. *The Journal of Clinical Psychiatry*. 2018; 79(1): 17m11585. doi: 10.4088/JCP.17m11585.

[94] Kimball A, Schorr M, Meenaghan E, Bachmann KN, Eddy KT, Misra M, et al. A Randomized Placebo-Controlled Trial of Low-Dose Testosterone Therapy in Women With Anorexia Nervosa. *The Journal of Clinical Endocrinology & Metabolism*. 2019; 104(10): 4347-55. doi: 10.1210/jc.2019-00828.

[95] Weinert T, Bernardoni F, King J, Steding J, Boehm I, Mannigel M, et al. No effects of acute tryptophan depletion on anxiety or mood in weight-recovered female patients with anorexia nervosa. *European Archives of Psychiatry and Clinical Neuroscience*. 2023; 273(1): 209-17. doi: 10.1007/s00406-022-01414-8.

[96] Candido ACR, Ferraz SD, Uggioni MLR, Zanevan IR, Colonetti L, Grande AJ, et al. Omega-3 as an adjuvant in the treatment eating and psychological symptoms in patients with anorexia nervosa: a systematic review and meta-analyses. *Journal of Human Nutrition and Dietetics*. 2023; 36(5): 1970-81. doi: 10.1111/jhn.13187.

[97] Nikolova VL, Smith MRB, Hall LJ, Cleare AJ, Stone JM, Young AH. Perturbations in Gut Microbiota Composition in Psychiatric Disorders: A Review and Meta-analysis. *JAMA Psychiatry*. 2021; 78(12): 1343-1354. doi: 10.1001/jamapsychiatry.2021.2573.

[98] Prochazkova P, Roubalova R, Dvorak J, Tlaskalova-Hogenova H, Cermakova M, Tomasova P, et al. Microbiota, Microbial Metabolites, and Barrier Function in A Patient with Anorexia Nervosa after Fecal Microbiota Transplantation. *Microorganisms*. 2019; 7(9): 338. doi: 10.3390/microorganisms7090338.

[99] de Clercq NC, Frissen MN, Davids M, Groen AK, Nieuwdorp M. Weight Gain after Fecal Microbiota Transplantation in a Patient with Recurrent Underweight following Clinical Recovery from Anorexia Nervosa. *Psychotherapy and Psychosomatics*. 2019; 88(1): 58-60. doi: 10.1159/000495044.

[100] Žaja O, Fiolić M, Ćuk MC, Tiljak MK. "The role of L. reuteri DSM17938 in nutritional recovery and treatment of constipation in children and adolescents with anorexia nervosa - a randomized, double blind, placebo controlled study". *Clinical*

Nutrition ESPEN. 2021; 46: 47-53. doi: 10.1016/ j.clnesp.2021.08.016.

[101] Muratore AF, Attia E. Current Therapeutic Approaches to Anorexia Nervosa: State of the Art. *Clinical Therapeutics*. 2021; 43(1): 85-94. doi: 10.1016/j.clinthera.2020.11.006.