Nutrition and Refeeding syndrome

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Overview

- Overview of Nutrition
- Malnutrition
- Macro and Micronutrients
- Physiologic and pathophysiologic factors affecting micronutrient requirements
- Hierarchy of feeding

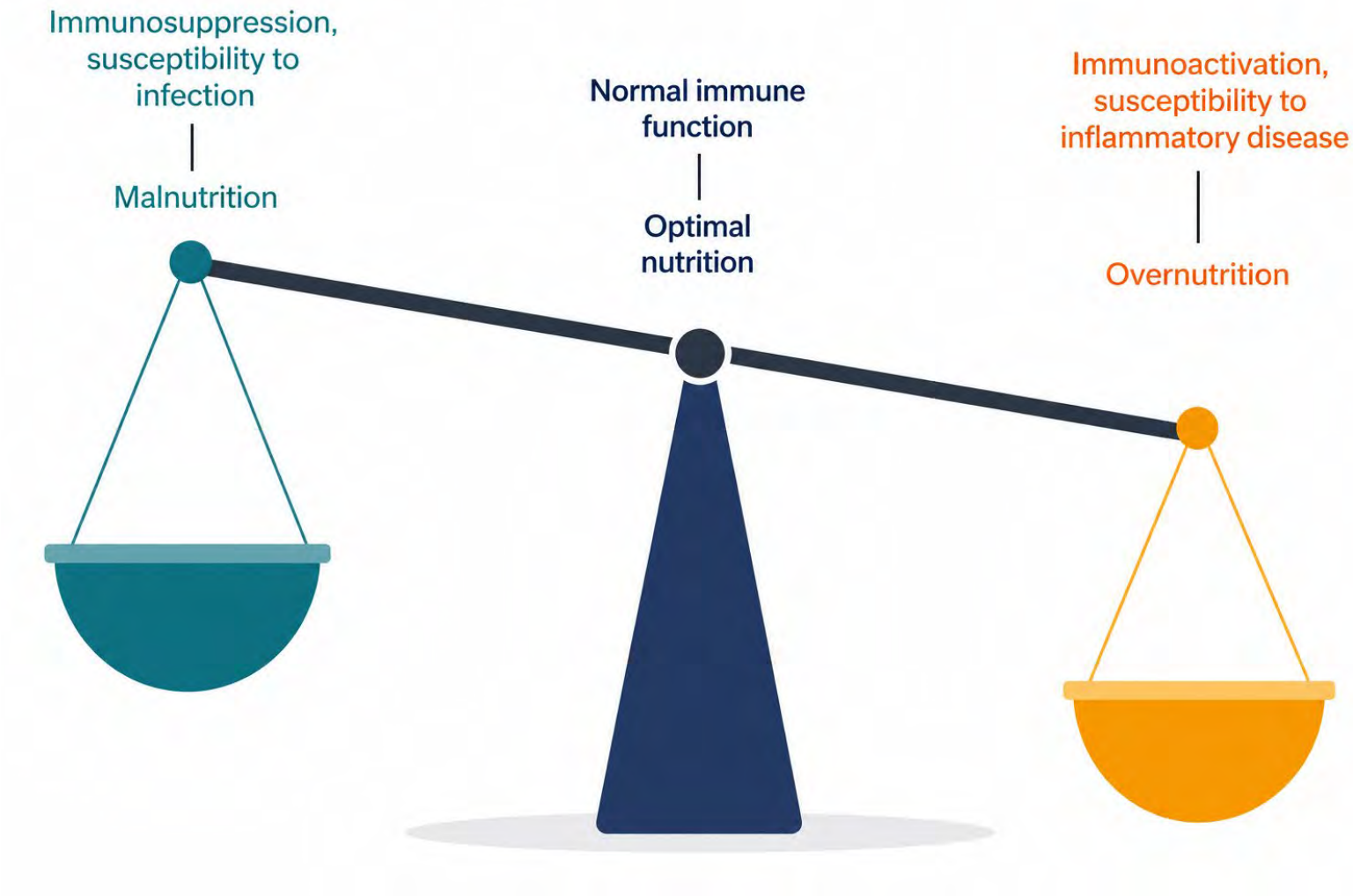
Refeeding syndrome:

- Definitions, Pathogenesis, Diagnosis, Classification and Management

G-ECHO

GI HEPATOLOGY ECHO
OF SUB-SAHARAN AFRICA
ESTABLISHED 2020

Optimal Nutrition?



Nutritional disorders

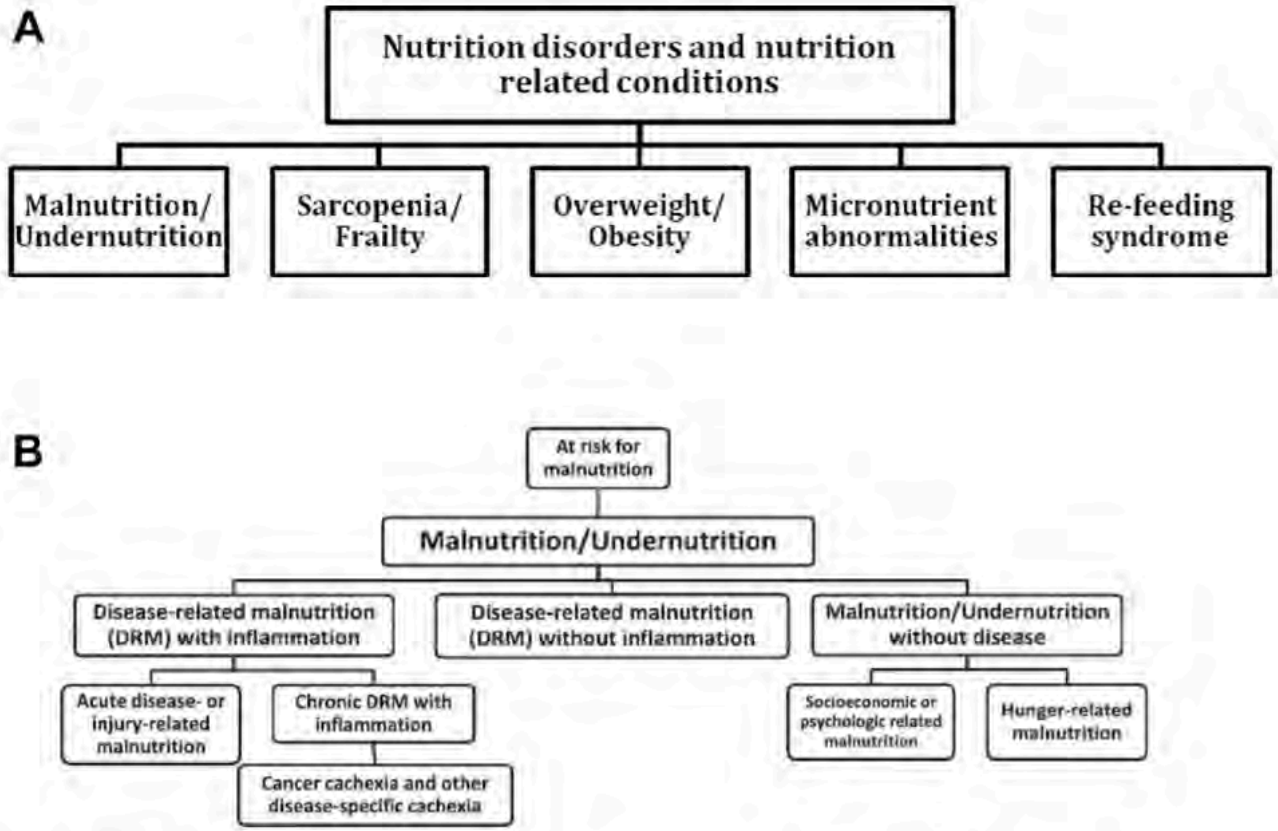


Fig. 1. A: Overview of nutrition disorders and nutrition-related conditions [13]. B: Diagnosis tree of malnutrition; from at risk for malnutrition, basic definition of malnutrition to etiology-based diagnoses.
From Cederholm et al. [20] with permission.

Source: Adapted from Singer P, Reintam Blaser A, Berger MM, et al. *ESPEN guideline on clinical nutrition in the intensive care unit*. Clin Nutr. 2019

ESPEN Definition Malnutrition

- Malnutrition can be defined as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired outcome from disease”
- Malnutrition can result from starvation, disease or advanced ageing (e.g. >80 years), alone or in combination

European Society for Clinical Nutrition and Metabolism. ESPEN guideline *Clin Nutr*. 2019

Malnutrition

- Leads to altered metabolism, organ dysfunction, and changes in body composition
- Usually refers to **protein-energy malnutrition (protein-calorie malnutrition)**
- May also include **excess states** (e.g., obesity, vitamin toxicity)

European Society for Clinical Nutrition and Metabolism. ESPEN guideline *Clin Nutr*. 2019

MALNUTRITION: A GLOBAL CHALLENGE

World Health Organization

Malnutrition, in all its forms, affects people of all ages and in every country.

Malnutrition, in all its forms, includes **undernutrition** (wasting, stunting, underweight), **inadequate vitamins** or **minerals**, **overweight**, **obesity**, and resulting **diet-related noncommunicable diseases**.

ADULTS (2022)

2.5 BILLION adults were **overweight**

including **890 MILLION** who were living with **obesity**

390 MILLION adults were **underweight**

CHILDREN UNDER 5 (2022)

Globally in 2022:

149 MILLION children were **stunted** (too short for age)

45 MILLION children were **wasted** (too thin for height)

37 MILLION children were **overweight** or living with **obesity**

DEATHS AMONG CHILDREN UNDER 5

NEARLY 1/2 of deaths among children under 5 years of age are linked to **undernutrition.**

These mostly occur in low- and middle-income countries.

THE IMPACT IS SERIOUS AND LASTING

The developmental, economic, social and medical impacts of the global burden of malnutrition are **serious and lasting,**

for **individuals** and their **families** for **communities** and for **countries.**

Addressing malnutrition in all its forms is essential for a healthier, more equitable and more prosperous world.

Source: World Health Organization (WHO) – Malnutrition Key Facts (2022) | www.who.int/nutrition

Who Should Receive Nutrition Therapy?

Recommendation

- All ICU patients expected to stay **>48 hours** should receive nutritional assessment and support.
- Every critically ill patient should be considered at risk of malnutrition.

Singer P et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019

Nutritional Assessment

- Main purpose of nutritional assessment- Identify **Protein energy malnutrition** and other nutritional deficits
- PEM may be present despite a normal appearance

Malnutrition ESPEN diagnostic criteria:

1. BMI < 18.5 kg/m2
2. Weight loss > 10% or > 5% in last 3 month

Challenges in assessing PEM

Stable/Chronic Patients

- Weight-for-height
- BMI
- Skinfold thickness
- Mid-arm circumference

Acutely ill Patients

- No gold standard exists.
- Weight and serum proteins are affected by illness and fluid shifts.
- Assessment is more difficult and less precise.

Biomarkers in Malnutrition

- **Albumin**
- **Prealbumin (Transthyretin) & Transferrin**
- **Markers of Muscle Mass & Protein Catabolism**
  - **Creatinine Height Index (CHI):** estimates muscle mass
  - **3-Methylhistidine (3-MH):** reflects muscle protein breakdown
  - **Nitrogen balance:** assesses protein catabolism and adequacy of protein intake (mainly in ICU)

Why Nutritional Assessment Matters

Malnutrition is associated with:

- Increased complications
- Higher morbidity
- Poorer clinical outcomes
- Longer hospital stays

Benefits of assessment:

- Identifies at-risk patients
- Predicts prognosis
- Guides nutritional intervention

Nutritional Assessment

Table 2. Nutritional Risk Screening (NRS-2002).

Impaired Nutritional Status		**Severity of Disease (Stress Metabolism)**	
Absent score 0	Normal nutritional status	Absent score 0	Normal nutritional requirements
Mild score 1	Weight loss 45% in 3 months or Food intake below 50–75% of normal requirement in preceding week	Mild score 1	Hip fracture; chronic patients, in particular with acute complications: cirrhosis; COPD; chronic hemodialysis, diabetes, oncology
Moderate score 2	Weight loss 45% in 2 months or BMI 18.5–20.5 + impaired general condition or Food intake 25–50% of normal requirement in preceding week	Moderate score 2	Major abdominal surgery; stroke; severe pneumonia, hematologic malignancy
Severe score 3	Weight loss >5% in 1 month >15% in 3 months or Body Mass Index of 18.5 + impaired general condition or Food intake 0–25% of normal requirement in preceding week	Severe score 3	Head injury; bone marrow transplantation; intensive care patients (APACHE 10)

Calculate the total score: 1. Find score (0–3) for impaired nutritional status (only one: choose the variable with highest score) and severity of disease (stress metabolism, i.e., increase in nutritional requirements); 2. Add the two scores (total score); 3. If age $\geq$ 70 years: add 1 to the total score to correct for frailty of elderly patients; 4. If age-corrected total =>3: start nutritional support.

Nutritional Assessment

Table 1: NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50 - <75	1
	≥75	2
APACHE II	<15	0
	15 - <20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6 - <10	1
	≥10	2
Number of Co-morbidities	0-1	0
	≥2	1
Days from hospital to ICU admission	0 - <1	0
	≥1	1
IL-6	0 - <400	0
	≥ 400	1

Heyland DK, Identifying critically ill patients who benefit the most from nutrition therapy. Critical Care. 2011

Table 2: NUTRIC Score scoring system: if IL-6 available

Sum of points	Category	Explanation
6-10	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-5	Low Score	➢ These patients have a low malnutrition risk.

Table 3. NUTRIC Score scoring system: If no IL-6 available*

Sum of points	Category	Explanation
5-9	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-4	Low Score	➢ These patients have a low malnutrition risk.

*It is acceptable to not include IL-6 data when it is not routinely available; it was shown to contribute very little to the overall prediction of the NUTRIC score.[2]

Nutritional Targets

- **Protein target 1.3 g protein/kg/day**
  - Based on **actual body weight** (or **adjusted body weight** in obesity)
  - Aim to preserve lean body mass and attenuate muscle catabolism
- **Carbohydrates (EN)** administered to ICU patients should not exceed 5 mg/kg/ min.
- **Intravenous lipid** (including non-nutritional lipid sources) should not exceed 1.5 g/kg/d

Singer P et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019

Measuring Energy Expenditure

Indirect Calorimetry (Gold Standard)

- Recommended method
- Measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) during respiration

If Indirect Calorimetry is Unavailable

- Weight based equations 20-25 kcal/kg/day

Singer P et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019

ENERGY TARGETS

Guiding calorie delivery to prevent underfeeding and overfeeding

DAYS 1–3 (ACUTE/EARLY PHASE)

- Start **hypocaloric** nutrition
- Provide **≤70%** of **measured energy expenditure (EE)**
- Avoid **overfeeding** during the early catabolic phase

AFTER DAY 3

- Progressively increase intake to **80–100% of measured EE**
- Use **indirect calorimetry** whenever available to determine energy requirements
- If indirect calorimetry is unavailable, use **20–25 kcal/kg/day** or estimate EE using **VCO_2** rather than predictive equations

KEY MESSAGE: *Advance calories gradually—avoid both underfeeding and overfeeding.*

Singer P et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019

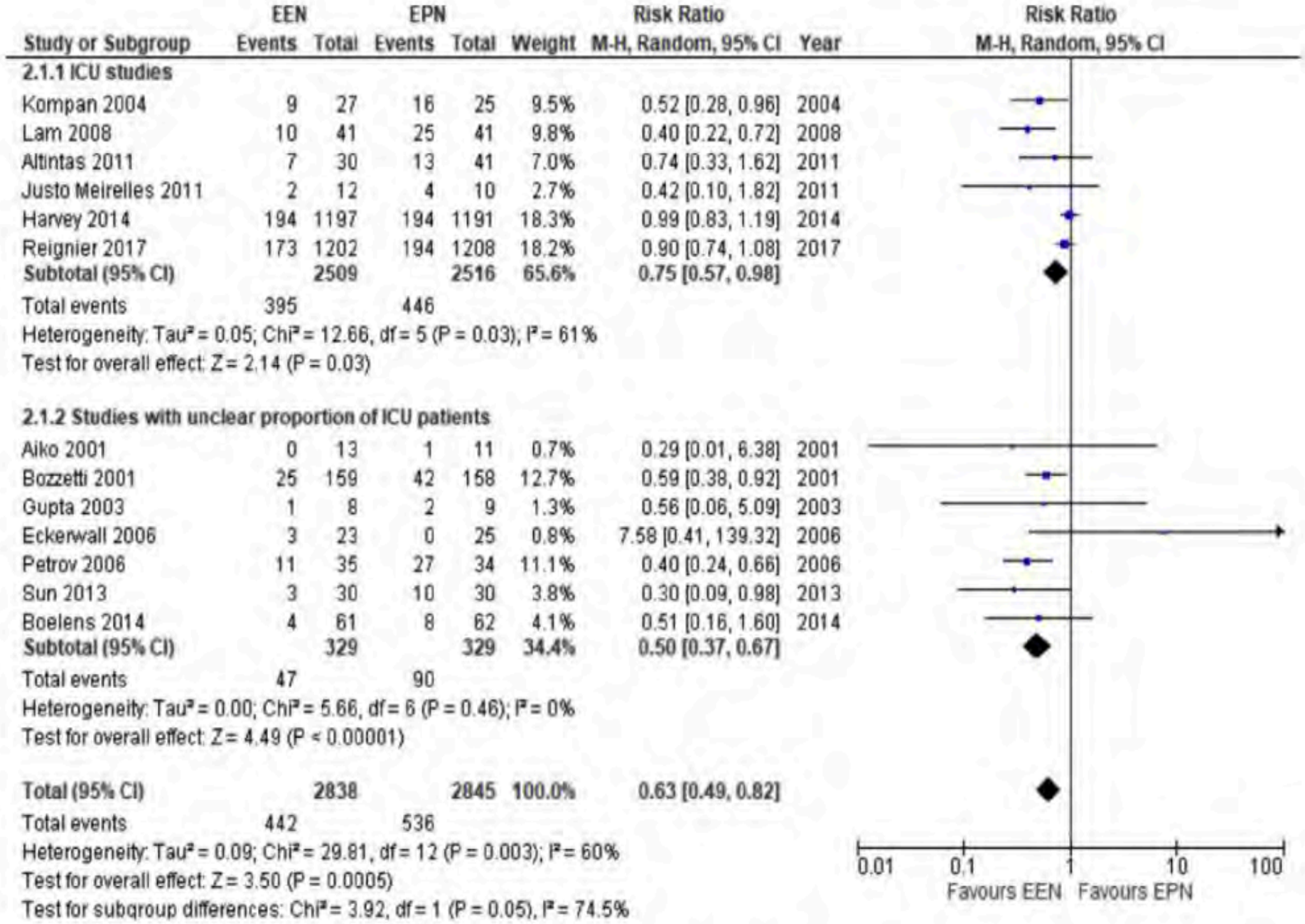


Fig. 3. Meta-analysis of studies comparing infection complications in patients receiving early enteral or parenteral nutrition (Meta-analysis II).

Micronutrient Recommendations

Recommendation

- **Provide micronutrients daily with parenteral nutrition (PN)**
- Daily **vitamins and trace elements** should accompany all PN.
- Commercial PN formulations **do not contain micronutrients** because of stability issues.
- Vitamins and trace elements **must be prescribed separately.**

ESPEN recommends replacing the full complement of:

- Water-soluble vitamins
- Fat-soluble vitamins
- Trace elements (including zinc, selenium, copper, chromium, manganese and others)

Singer P et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019

Preferred Route of Nutrition

Hierarchy of Feeding

1. **Oral diet** (if adequate intake possible)
2. **Enteral Nutrition (EN)** within 24–48 hours
3. **Parenteral Nutrition (PN)** if EN contraindicated or insufficient

Enteral Nutrition Preferred Because:

- Fewer infections
- Lower cost
- Maintains gut integrity
- Reduced ICU and hospital length of stay

Early Enteral Feed vs Early Parenteral Feed?

Benefits of Early Enteral Nutrition (within 24–72 hours)

Physiological Benefits

- Preserves gut barrier function
- Reduces gut permeability and bacterial translocation
- Decreases gut–lung inflammation
- Improves insulin sensitivity
- Supports normal gut microbiota
- Reduces the risk of malnutrition by providing early macro- and micronutrients

Haines KL et al. Early enteral nutrition is associated with improved outcomes in critically ill mechanically ventilated medical and surgical patients. Clin Nutr ESPEN. 2023

Compared with delayed enteral nutrition, early EN was associated with:

- **12% lower hospital mortality** (OR 0.88)
- **47% higher likelihood of discharge home** (OR 1.47)
- **Shorter duration of mechanical ventilation**
- **Shorter ICU length of stay**
- **Shorter hospital length of stay**
- **Reduced healthcare costs**

Haines KL, Ohnuma T, Grisel B, et al. Clin Nutr ESPEN. 2023

When to Start Feeding?

Early Enteral Nutrition

•Start within 48 hours of ICU admission if feasible.

Delay Enteral Nutrition if:

- Uncontrolled shock
- Severe hypoxemia/acidosis
- Bowel ischemia
- Bowel obstruction
- Active GI bleeding
- Abdominal compartment syndrome

Parenteral Nutrition

- Consider after **3–7 days** if EN impossible.
- PN: Stopped once EN provides 60% of nutritional needs

Introduction to Refeeding Syndrome

- Refeeding Syndrome (RS) was first described during World War II. Prisoners of war, concentration camp survivors, and victims of famine experienced unexpected morbidity and mortality during nutrition repletion.

Schnitker's Observations
Among malnourished Japanese prisoners of war:
•Many developed **high-output heart failure** (wet beriberi)
•Marked **peripheral oedema**
•**Neurological disorders** (peripheral neuropathy, weakness, paresthesia)
•When untreated, the condition was severe, and approximately **1 in 5 patients died within a few days**

Minnesota Starvation Study (Keys et al., 1944)

- Prospective study of **prolonged starvation and refeeding**
- **36 conscientious objectors** volunteered instead of military service
- Evaluated **physiological and psychological** effects of starvation
- Assessed **nutritional rehabilitation (refeeding)**
- Landmark study underpinning current understanding of **refeeding syndrome**

Definitions

- Refeeding Syndrome: Metabolic and electrolyte alterations occurring due to the reintroduction and/or increased provision of calories after a period of decreased or absent caloric intake.

- **Hallmark:** Hypo PO4 with onset within 2–5 days of resumed feeding, accompanied by hypokalemia and/or hypomagnesemia and thiamine deficiency

Aspen consensus definition

- A measurable reduction in levels of 1 or any combination of phosphorus, potassium, and/or magnesium, or the manifestation of thiamine deficiency, developing shortly (hours to days) after initiation of calorie provision to an individual who has been exposed to a substantial period of undernourishment.

ASPEN consensus recommendations for refeeding syndrome. **Nutr Clin Pract.** 2020

Incidence of RS

- Incidence of refeeding syndrome in hospitalized patients ranges from **0.43% to 18%**.
- **Incidence is about 34% in patients with hypophosphatemia** in a prospective ICU cohort after refeeding in critically ill patients
- Severe hypophosphataemia has a mortality of 18.2% compared to 4.6% in those without

Camp MA, Allon M. Severe hypophosphatemia in hospitalized patients. Miner Electrolyte Metab. 1990;16(6):365-8.

Refeeding syndrome and South Africa

- South African data on refeeding syndrome are **limited**, particularly in adults.
- Most published local evidence comes from **children with severe acute malnutrition**.

SA prospective ICU study

- 31% identified as high risk (NICE criteria)
- **1.5%** developed refeeding syndrome using **King's College criteria**
- **12.5%** developed refeeding syndrome using **ASPEN criteria**

Refeeding syndrome in surgical patients post initiation of artificial feeding: a prospective cohort study in a low-income country. *Clin Nutr ESPEN*. 2021

Refeeding Syndrome Pathogenesis

TABLE 4 Signs and symptoms of refeeding syndrome.

Hypophosphataemia	Hypokalaemia	Hypomagnesaemia	Thiamin deficiency	Sodium retention
Hypoxia	Neurological paralysis or weakness	Weakness	Encephalopathy (including Wernicke's syndrome and Korsakoff psychosis)	Fluid overload
Impaired cardiac function including hypotension	Cardiac arrhythmias and/or ECG changes	Muscle twitching	Lactic acidosis	Pulmonary oedema
Impaired diaphragm contractility	Respiratory failure	Tremor	Nystagmus	Cardiac decompensation
Respiratory failure	Nausea	Altered mental status	Neuropathy	
Paresthesias	Vomiting	Anorexia		
Weakness	Constipation	Nausea		
Lethargy	Muscle necrosis	Vomiting		
Somnolence		Diarrhoea		
Confusion		Refractory hypokalaemia and hypocalcaemia		
Disorientation/delirium		Cardiac arrhythmias and/or ECG changes		
Restlessness		Tetany		
Encephalopathy		Convulsions		
Areflexic paralysis		Seizures		
Seizures		Coma		
Shock				
Haemolysis				
Thromboyctopaenia				
Leukocyte dysfunction				
Coma				

Note: Adapted from Kraft et al.[102] and da Silva et al.[1]

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Note: Adapted from Kraft et al.[102] and da Silva et al.[1]

Who is at risk?

- Patients with anorexia nervosa
- Mental health disorders
- Critically ill
- Malignancy
- Alcohol and substance use disorders
- Malabsorption
- Bariatric surgery and bowel resection surgery
- Military recruits
- Athletes
- Renal failure and haemodialysis
- Starvation in protest, famine and migration

NB: Can occur in overweight individuals

Diagnosis of RS

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

Classification

- **Mild** - a decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10% to 20%
- **Moderate** - a decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 20% to 30%
- **Severe** - Decrease in any of PO_4^{3-} ,K^+, Mg^{2+} by >30% and/or organ dysfunction resulting from their low serum concentration, or due to thiamine deficiency

Occurring within 5 days of a reintroduction of calories

Clinical manifestations RFS

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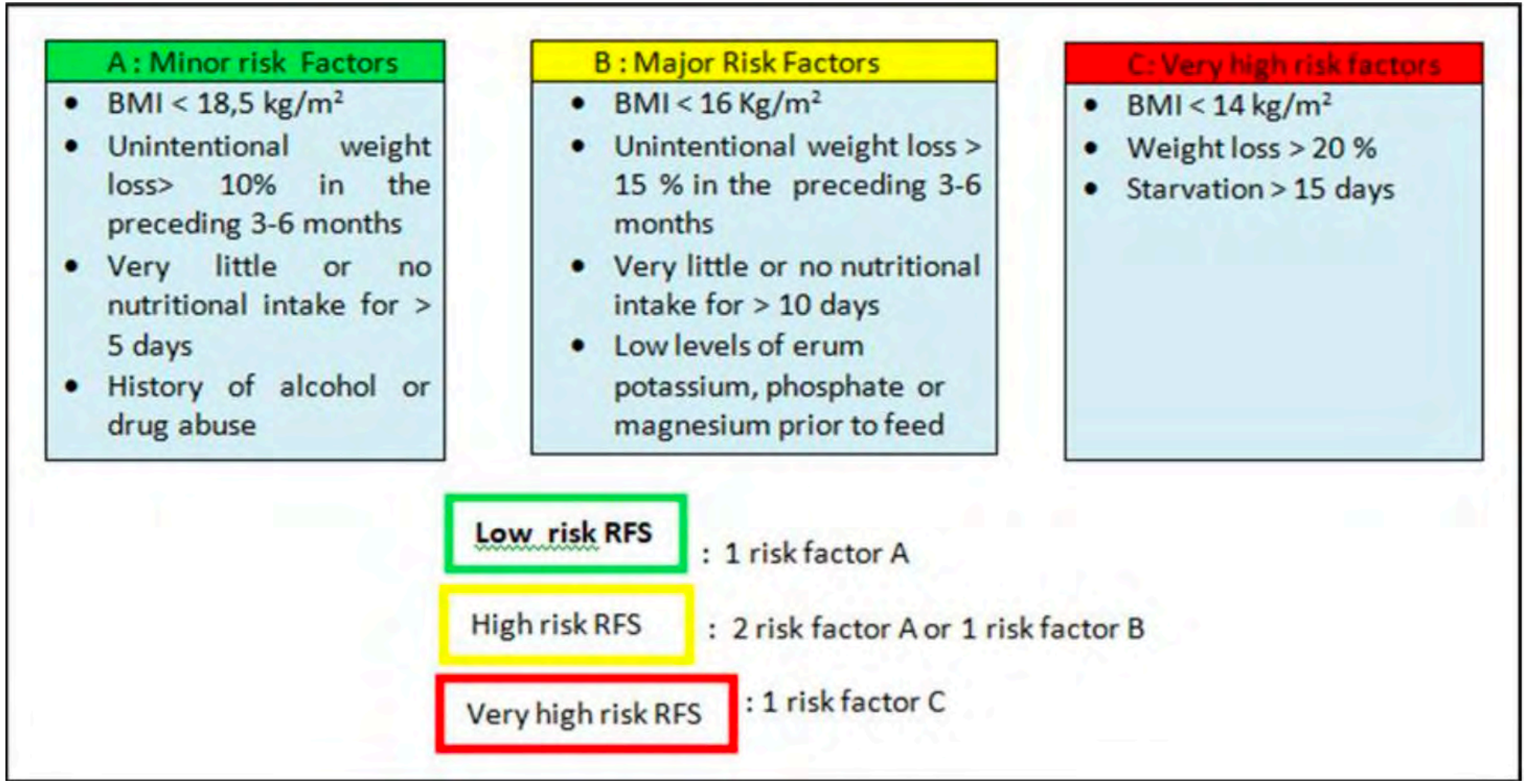
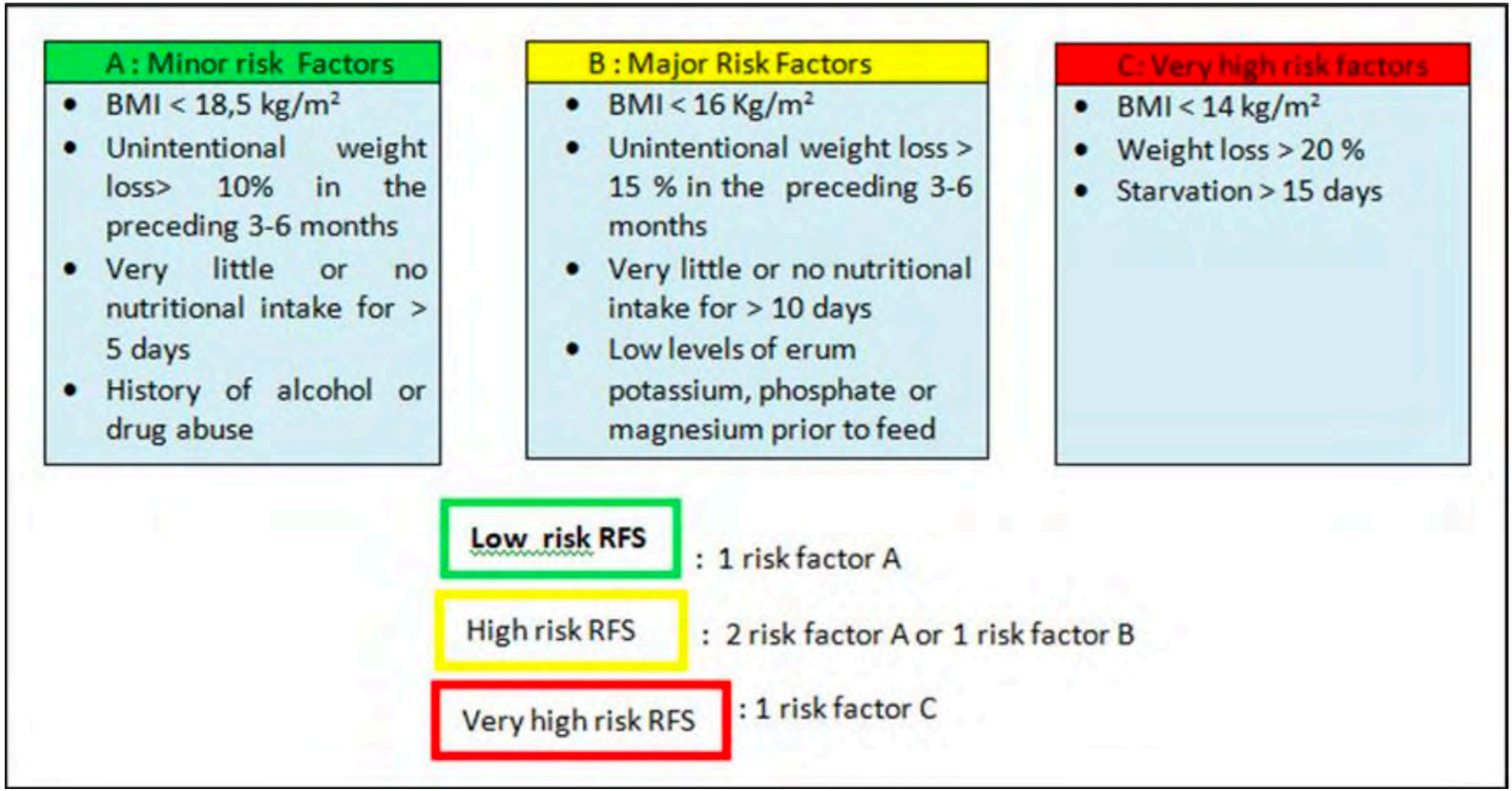
Management of RFS

Aspen criteria identifying adults at risk




A : Minor risk Factors
• BMI < 18,5 kg/m²
• Unintentional weight loss> 10% in the preceding 3-6 months
• Very little or no nutritional intake for > 5 days
• History of alcohol or drug abuse
B : Major Risk Factors
• BMI < 16 Kg/m²
• Unintentional weight loss > 15 % in the preceding 3-6 months
• Very little or no nutritional intake for > 10 days
• Low levels of erum potassium, phosphate or magnesium prior to feed
C: Very high risk factors
• BMI < 14 kg/m²
• Weight loss > 20 %
• Starvation > 15 days
Low risk RFS : 1 risk factor A
High risk RFS : 2 risk factor A or 1 risk factor B
Very high risk RFS : 1 risk factor C

Management

- Aspen consensus guidelines recommend extensive replacement of the required electrolytes and vitamins (in particular vitamin B1)
- A stepwise approach to refeeding with a reduced caloric intake

Initial caloric intake for RFS

- Initiate with 100–150 g of dextrose or 10–20 kcal/kg for the first 24 hours. Advance by 33% of goal every 1 to 2 days.
- Moderate-high risk RFS: Holding of initiation of feeds until electrolytes corrected
- Initiation of caloric intake should be delayed in patient with severely low PO4, K or Mg2 levels- until corrected
- Caution should be instituted when infusing IV dextrose constituted medications in cases moderate to severe risk for RS.
- No recommendations regarding fluid/sodium/protein restriction.

Electrolyte management in RFS

- Check serum potassium, magnesium, and phosphorus before initiation of nutrition.
- Monitor every 12 hours for the first 3 days in high-risk patients.
- Replete low electrolytes based on established standards of care.
- If electrolytes become difficult to correct or drop precipitously during the initiation of nutrition, decrease calories/grams of dextrose by 50% and advance the dextrose/calories by approximately 33% of goal every 1–2 days based on clinical presentation.
- Cessation of parental or enteral feeds may be considered when electrolyte levels are severely low or dropping precipitously

Electrolyte replacement Management

Table 1. Nutrition and fluid management in the refeeding syndrome.[11]

	Low risk for RFS	**High risk for RFS**	**Very high risk for RFS**
Nutritional support	• Days 1-3 : 15-25 kcal/kg/d • Day 4 : 30 kcal/kg/d • From day 5 : full requirement	• Days 1-3 : 10-15 kcal/kg/d • Days 4-5 : 15-25 kcal/kg/d • Day 6 : 25-30 kcal/kg/d • From day 7 : full requirement	• Day 1-3 : 5-10 kcal/kg/d • Day 4-6 : 10-20 kcal/kg/d • Day 6 : 25-30 kcal/kg/d • Day 7-9 : 20-30 kcal/kg/d • From day 10 : full requirement
Fluid management	30-35 ml/kg/d	• Day 1-3 : 25-30 ml/kg/d • From day 4 : 30-35 ml/kg/d	• Days 1-3 : 20-25 ml/kg/d • Days 4-56 : 25-30 ml/kg/d • From day 7 : 30-35 ml/kg/d
Sodium restriction	No sodium restriction	Days 1-7 : < 1 mmol/kg/d	Days 1-10 : < 1 mmol/kg/d
Thiamin	Days 1-3 : 200-300 mg	Days 1-3 : 200-300 mg	Days 1-5 : 200-300 mg
Multivitamin	Days 1-10	Days 1-10	Days 1-10

Importance of Thiamine

- Supplement thiamine 100 mg before feeding or before initiating dextrose-containing IV fluids in patients at risk.
- Supplement thiamine 100 mg/d for 5–7 days or longer in patients with severe starvation, chronic alcoholism, or other high risk for deficiency and/or signs of thiamine deficiency.

Nutrition and Fluid management

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Multivitamin	Days 1-10	Days 1-10	Days 1-10

Monitoring of RFS patient

1. **Vital signs every 4 hours**

Recommend vital signs every 4 hours for the first 24 hours after initiation of calories in patients at risk.

2. **Cardiorespiratory monitoring**

Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care.

3. **Daily weights**

Daily weights with monitored intake and output.

4. **Evaluate goals**

Evaluate short- and long-term goals for nutrition care daily during the first several days until the patient is deemed stabilized (e.g., no requirement for electrolyte supplementation for 2 days) and then based on institutional standards of care.

Goal: Ensure early detection of complications, monitor response to nutrition support, and adjust care based on patient status and established standards.

Wernickes-Korsakoff syndrome

- **Neuropsychiatric disorder caused by thiamine (Vitamin B1) deficiency**
- Occurs in conditions associated with **malnutrition or impaired thiamine absorption** (e.g., alcohol use disorder, prolonged vomiting, starvation, bariatric surgery)

Management of Wernicke-Korsakoff Syndrome

- Wernicke's preventative treatment (any patient in withdrawal): Thiamine 100-250 mg IM/IV x 1 dose.
- Wernicke's acute treatment: Thiamine 500 mg IV BID/TID x 72 h, then reassess.
- Korsakoff's: IV treatment as for Wernicke's followed by thiamine 100 mg PO TID x 3-12 months.

Conclusion

- Nutritional support is a treatment, not simply supportive care.
- The highest-risk period is the **first 72 hours after feeding begins**.
- Most cases of severe refeeding syndrome are **predictable and preventable**.
- **Identify risk → Replace thiamine → Correct electrolytes → Feed cautiously → Monitor closely.**