Refeeding Syndrome Tenets

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Disclosures

- Fresenius Kabi-Consultant, Speaker
- Baxter-Speaker

Learning Objectives

- Discuss Refeeding Syndrome and what patients are at risk
- Describe common signs and symptoms associated with Refeeding Syndrome
- Explain how to address the nutrition in patients at risk for Refeeding Syndrome

Refeeding Syndrome

- Constellation of electrolyte abnormalities and symptoms associated with rapid re-introduction of nutrition (especially carbohydrates) after prolonged starvation
- The Minnesota Experiment: 36 conscientious objectors of war
- Prisoners of War (WWII)
- Hallmark Sign: hypophosphatemia
- Other S/Sx:
  - Hypokalemia, hypomagnesemia
  - Thiamine deficiency, fluid/sodium intolerance, possibly hyperglycemia
- Can lead to severe sequelae: paresthesias, mental status changes, seizures, coma, and death

Keys A, et al. The Biology of Human Starvation, vols I-II. University of Minnesota Press, Minneapolis, MN, 1950. Kalm LM, et al. J Nutr 2005; 135:1347-52; Schnitker MA, et al. Ann Intern Med 1951; 35:69-96; Kraft MD, et. al. Nutr Clin Pract 2005; Stanga Z, et. al. Eur J Clin Nutr 2008; Skipper A. Nutr Clin Pract 2012

Refeeding Syndrome - Pathophysiology

Prolonged Starvation / Severe Malnutrition

Nutrient depletion → glycogen, gluconeogenesis/ protein catabolism, fatty acid catabolism→ ketone production

Electrolyte, vitamin depletion; salt/water intolerance

↓ metabolic rate, ↓ insulin secretion

Re-introduction of CHO → ↑ metabolic rate, ↑ insulin secretion, ↑ glycolysis, anabolism

↑ Glucose uptake, ↑ demand for ATP and O_2, ↑ uptake of Phos, K+, Mg++, ↑ utilization of thiamine

Hypophosphatemia

Hypokalemia

Hypomagnesemia

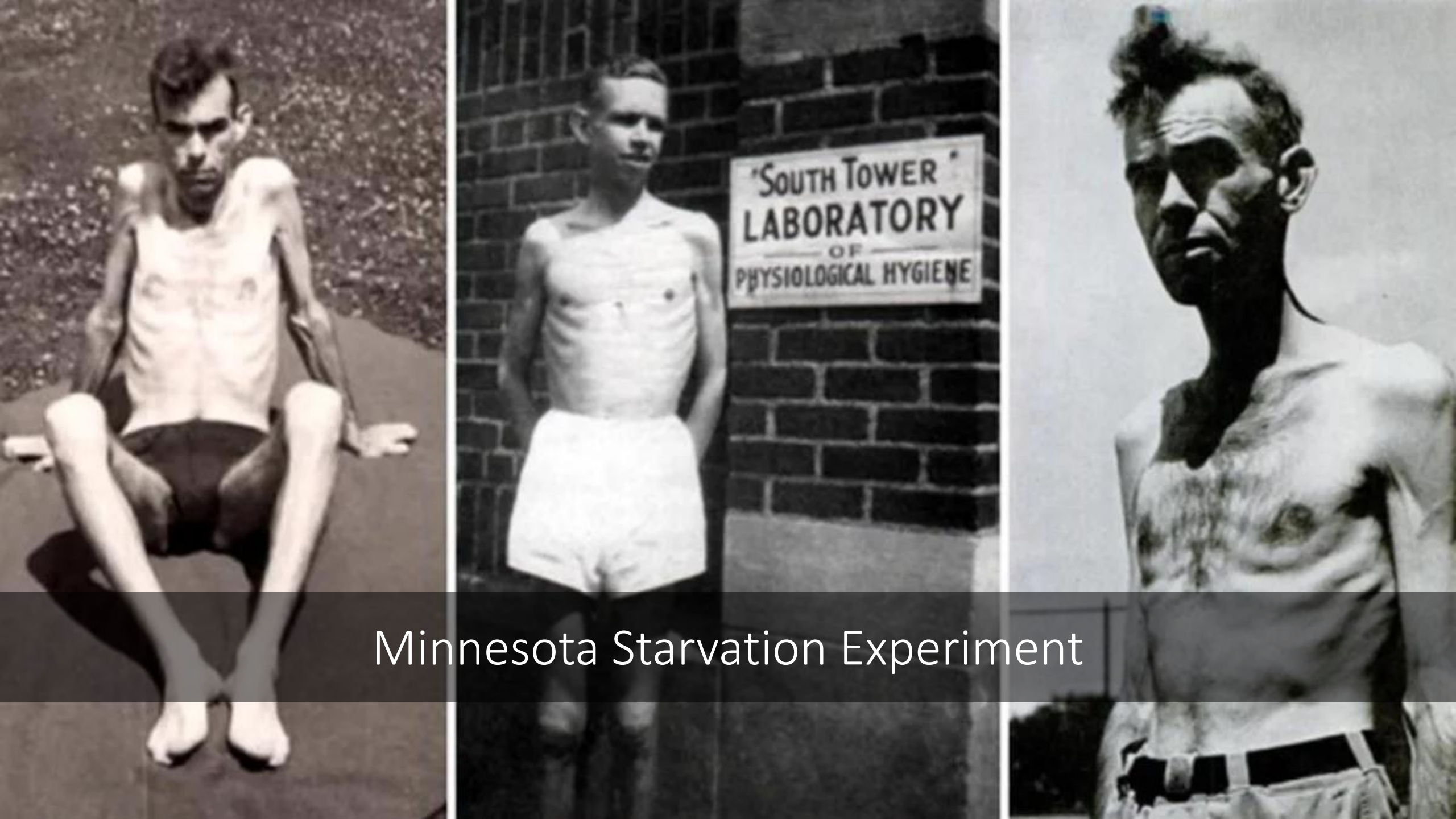
Thiamine deficiency

Na+/water retention

+/- Hyperglycemia

REFEEDING SYNDROME

Kraft MD, et. al. Nutr Clin Pract 2005; Stanga Z, et. al. Eur J Clin Nutr 2008



Minnesota Starvation Experiment

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Nutrition in Clinical Practice
Volume 35 Number 2
April 2020 178–195

DOI: 10.1002/ncp.10474
wileyonlinelibrary.com
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ASPEN Consensus Recommendations for Refeeding Syndrome

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At Risk:

Acquired immunodeficiency syndrome
Chronic alcohol or drug use disorder
Dysphagia and esophageal dysmotility (eg, eosinophilic esophagitis, achalasia, gastric dysmotility)
Eating disorders (eg, anorexia nervosa)
Food insecurity and homelessness
Failure to thrive, including physical and sexual abuse and victims of neglect (particularly children)
Hyperemesis gravidarum or protracted vomiting
Major stressors or surgery without nutrition for prolonged periods of time
Malabsorptive states (eg, short-bowel syndrome, Crohn's disease, cystic fibrosis, pyloric stenosis, maldigestion, pancreatic insufficiency)
Cancer
Advanced neurologic impairment or general inability to communicate needs
Post bariatric surgery
Postoperative patients with complications
Prolonged fasting (eg, individuals on hunger strikes, anorexia nervosa)
Refugees
Protein malnourishment

(NutrClinPract.2020;35:178– 195)

Amyotrophic Lateral Sclerosis (ALS)

- Common Barriers to Consuming Adequate Nutrition
  - Dysphagia
  - Hypermetabolic
  - Difficulty self-feeding
  - Fatigue
  - Shortness of Breath
  - Constipation
  - Sialorrhea
  - Depression
  - Decreased appetite

Dobak S, Practical Gastroenterology, April 2022

Amyotrophic Lateral Sclerosis (ALS)

- Gastrostomy Tubes
  - RCT are lacking
  - Observational studies suggest a survival benefit
- Gastrostomy Tube Indications
  - Insufficient nutrition or hydration (weight loss, clinical signs)
  - Chewing or swallowing difficulty
  - Fatigue preventing adequate intake
  - Prolonged mealtime (>45 minutes)

Dobak S, Practical Gastroenterology, April 2022

Refeeding Syndrome Signs and Symptoms

Table 2. Signs and Symptoms of Severe Refeeding Syndrome.[a]

Hypophosphatemia	Hypokalemia	Hypomagnesemia	Thiamin Deficiency	Sodium Retention
Neurological	Neurological	Neurological	Encephalopathy	Fluid overload
Paresthesias	Paralysis	Weakness	Lactic acidosis	Pulmonary edema
Weakness	Weakness	Tremor	Nystagmus	Cardiac decompensation
Delirium	Cardiac	Muscle twitching	Neuropathy	
Disorientation	Arrhythmias	Changed mental status	Dementia	
Encephalopathy	Contraction changes	Tetany	Wernicke's syndrome	
Areflexic paralysis	Respiratory failure	Convulsions	Korsakoff psychosis	
Seizures	Gastrointestinal	Seizures	Wet and dry beriberi	
Coma	Nausea	Coma		
Tetany	Vomiting	Cardiac		
Cardiac	Constipation	Arrhythmias		
Hypotension	Other	Gastrointestinal		
Shock	Rhabdomyolysis	Anorexia		
Decreased stroke volume	Muscle necrosis	Nausea		
Decreased mean arterial Pressure		Vomiting		
Increased wedge pressure		Constipation		
Pulmonary				
Diaphragmatic weakness				
Respiratory failure				
Dyspnea				
Hematologic				
Hemolysis				
Thrombocytopenia				
Leukocyte dysfunction				

Adapted with permission from Reference 96. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. *Nutr Clin Pract*. 2005;20(6):625-633.

Table 1. Published Recommendations for Initiation and Advancement of Nourishment for Patients at Risk for RS.

	Initial Calories	Feeding Advancement	Other Recommendations
NICE[44]	• Maximum 10 kcal/kg/d • 5 kcal/kg/d in "extreme" cases (examples, BMI < 14 kg/m^2 or negligible intake for >15 days)	• Slowly to meet or exceed full needs by 4–7 days	• Restore circulatory volume
IrSPEN[98]	• Extreme risk: 5 kcal/kg/d • High risk: 10 kcal/kg • Moderate risk: 20 kcal/kg	• Slow initiation of feeding according to risk category	• Check electrolyte levels • Electrolyte replacement to correct deficiencies • Monitor fluid balance
CNSG[99]	• Extreme risk: consider providing only 5 kcal/kg/d • High risk: commence nutrition support at a maximum of 10 kcal/kg body weight • Moderate risk: introduce at a maximum of 50% of requirements for the first 2 days	• Extreme or high risk: slowly over 4–7 days as clinical and biochemical monitoring allows • Moderate risk: increase energy intake only as clinical conditions and electrolyte results allow	• Energy and fluid must be introduced very gradually • Check potassium, magnesium, phosphorus • Do not discontinue feeding if electrolyte levels fall • When serum potassium, magnesium, or phosphorus levels are significantly low, feeding should not be advanced further until supplementation has occurred
Cray[96]	• ≈10 kcal/kg/d for severe cases • 15–20 kcal/kg for others	• Increase calories cautiously in a stepwise manner by 200–300 kcal every 2–3 days	• Consider all sources of calories and fluids in your calculations (including dextrose) • Check baseline electrolytes (especially phosphorus, potassium, and magnesium) before initiating nutrition support, and replace any low levels promptly • Unless hemodynamically unstable, keep sodium-containing IV fluids to ≈1 L/d initially in severely malnourished patients, such as those with anorexia nervosa, who may have a component of cardiomyopathy
Friedli [100]	• Ranging from 5 to 25 kcal/kg/d depending on severity of RS risk	• Nutrition therapy should be started with reduced caloric targets and slow increase to the full caloric amount over 5–10 days according to the individual risk category for RS • Fluid overload should be prevented by restricted use of fluid and sodium restrict diet within the first 7 days	• Patients at high risk for RS should receive electrolytes substitution of lower than normal/in low normal range • Prophylactic supplementation of electrolytes

ASPEN Consensus Criteria for Identifying at Risk Patients

Table 3. ASPEN Consensus Criteria for Identifying Adult Patients at Risk for Refeeding Syndrome.[49,71,110]

	Moderate Risk: 2 Risk Criteria Needed	Significant Risk: 1 Risk Criterion Needed
BMI	16–18.5 kg/m^2	<16 kg/m^2
Weight loss	5% in 1 month	7.5% in 3 months or >10% in 6 months
Caloric intake	None or negligible oral intake for 5–6 days **OR** <75% of estimated energy requirement for >7 days during an acute illness or injury **OR** <75% of estimated energy requirement for >1 month	None or negligible oral intake for >7 days **OR** <50% of estimated energy requirement for >5 days during an acute illness or injury **OR** <50% of estimated energy requirement for >1 month
Abnormal prefeeding potassium, phosphorus, or magnesium serum concentrations[a]	Minimally low levels or normal current levels with recent low levels necessitating minimal or single-dose supplementation	Moderately/significantly low levels or minimally low/normal levels with recent low levels necessitating significant or multiple-dose supplementation
Loss of subcutaneous fat	Evidence of moderate loss	Evidence of severe loss
Loss of muscle mass	Evidence of mild or moderate loss	Evidence of severe loss
Higher-risk comorbidities (see Table 4)	Moderate disease	Severe disease

ASPEN, American Society for Parenteral and Enteral Nutrition; BMI, body mass index.
[a]Please note that electrolytes may be normal despite total-body deficiency, which is believed to increase risk of refeeding syndrome.

(NutrClinPract.2020;35:178– 195)

Table 6. ASPEN Consensus Recommendations for Avoidance and Treatment of RS in At-Risk Adults.

Aspect of Care	Recommendations
Initiation of calories	• 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. This includes enteral as well as parenteral glucose. • In patients with moderate to high risk of RS with low electrolyte levels, holding the initiation or increase of calories until electrolytes are supplemented and/or normalized should be considered. • Initiation of or increasing calories should be delayed in patients with severely low phosphorus, potassium, or magnesium levels until corrected. • Calories from IV dextrose solutions and medications being infused in dextrose should be considered in the limits above and/or initiated with caution in patients at moderate to severe risk for RS. If a patient has received significant amounts of dextrose for several days, from maintenance IV fluids and/or medications in dextrose, and has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount than recommended above.
Fluid restriction	• No recommendation.
Sodium restriction	• No recommendation.
Protein restriction	• No recommendation.
Electrolytes	• Check serum potassium, magnesium, and phosphorus before initiation of nutrition. • Monitor every 12 hours for the first 3 days in high-risk patients. May be more frequent based on clinical picture. • Replete low electrolytes based on established standards of care. • No recommendation can be made for whether prophylactic dosing of electrolytes should be given if prefeeding levels are normal. • 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. Recommendations may be changed based on practitioner judgment and clinical presentation, and cessation of nutrition support may be considered when electrolyte levels are severely and/or life-threateningly low or dropping precipitously.

Thiamin and multivitamins	• Supplement thiamin 100 mg before feeding or before initiating dextrose-containing IV fluids in patients at risk. • Supplement thiamin 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 thiamin deficiency. • Routine thiamin levels are unlikely to be of value. • MVI is added to PN daily, unless contraindicated, as long as PN is continued. For patients receiving oral/enteral nourishment, add complete oral/enteral multivitamin once daily for 10 days or greater based on clinical status and mode of therapy.
Monitoring and long-term care	• Recommend vital signs every 4 hours for the first 24 hours after initiation of calories in patients at risk. • Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care. • Daily weights with monitored intake and output. • Evaluate short- and long-term goals for nutrition care daily during the first several days until the patient is deemed stabilized (eg, no requirement for electrolyte supplementation for 2 days) and then based on institutional standards of care.

Awareness of Refeeding Syndrome

- European Journal of Clinical Medicine 2019
- Questionnaire with case vignette concerning an older person who developed RS after initiation of nutritional therapy
- German physicians and fifth year medical students (281 participants)
- Seven centers in Germany

Janssen G, Pourhassan M, Lenzen-GroBimilinghaus, et al.
European Journal of Clinical Nutrition (2019) 73:1458-1463

Variables		Diagnosis of RFS			*p* Value
		n (%)	Correct and nearly correct (*n* = 61, 22%)	Not correct (*n* = 220, 78%)	
Gender	Male	123 (41.0)	19 (17.0)	94 (83.0)	0.136
	Female	178 (59.0)	40 (25.0)	122 (75.0)	
Age	21–30	130 (43.0)	17 (15.0)	97 (85.0)	0.011
	31–40	62 (20.0)	11 (18.0)	49 (82.0)	
	41–50	50 (17.0)	14 (28.0)	36 (72.0)	
	51–60	53 (17.0)	18 (39.0)	28 (61.0)	
	61–70	7 (2.0)	1 (14.0)	6 (86.0)	
	71–80	1 (1.0)	–	–	
	>80	–	–	–	
Medical position	Assistant physician	91 (30.0)	24 (28.0)	62 (72.0)	<0.001
	Senior physician	44 (15.0)	14 (36.0)	25 (64.0)	
	Chief	17 (5.0)	4 (25.0)	12 (75.0)	
	Private office	25 (8.0)	4 (16.0)	21 (84.0)	
	Retirement	1 (1.0)	–	–	
	Others	15 (5.0)	8 (57.0)	6 (43.0)	
	Student	108 (36.0)	4 (4.0)	91 (96.0)	
Professional experience	<5	169 (55.0)	21 (14.0)	131 (86.0)	<0.001
	5–10	45 (15.0)	12 (28.0)	31 (72.0)	
	10–20	33 (11.0)	16 (50.0)	16 (50.0)	
	>20	58 (19.0)	11 (21.0)	41 (79.0)	

Medical specialty	No	112 (36.0)	7 (7.0)	91 (93.0)	<0.001
	General practice	20 (6.0)	3 (16.0)	16 (84.0)	
	Anesthesia	5 (2.0)	0 (0.0)	5 (100.0)	
	Surgery	8 (2.0)	1 (12.5)	7 (88.0)	
	Geriatrics	42 (14.0)	17 (45.0)	21 (55.0)	
	Gynecology	–	–	–	
	Internal medicine	87 (28.0)	31 (36.0)	54 (64.0)	
	Neurology	11 (4.0)	1 (14.0)	6 (86.0)	
	Orthopedy	15 (5.0)	1 (7.0)	13 (93.0)	
	Pediatric	–	–	–	
	Psychiatry	1 (1.0)	0 (0.0)	1 (100.0)	
	Urology	–	–	–	
	Others	5 (2.0)	0 (0.0)	5 (100.0)	
Certified in nutritional medicine	Yes	12 (4.0)	6 (56.0)	5 (44.0)	0.014
	No	285 (96.0)	52 (20.0)	210 (80.0)	

Janssen G, Pourhassan M, Lenzen-GroBimilinghaus, et al.
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Questionnaire Results

- 281 participants
- 40 participants (14%) correctly diagnosed RS in the case vignette
- 21 participants (8%) gave nearly correct answers
  - description of a similar state such as electrolyte disturbances or metabolic derailment
- Majority of the participants did not diagnose RS

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Case Report

- 87 yo F with advanced Alzheimer's admit to the hospital with poor general condition and aspiration pneumonia.
  - 45kg, BMI 16
- Hypernatremia noted in ED. D5W initiated
- Day 2 PN (30kcal/kg/day) initiated
- Day 4, general condition deteriorated and severe electrolyte imbalance (primarily K)
- PN discontinued. EN 10 kcal/kg/day)

Asia Pac J Clin Nutr 2017;26(2):379-383

	Day 1	Day 2	Day 5	Day 7	Day 9	Day 12	Day 16	Day 22	Day 26	Normal range
Glucose (mg/dl)	141	-	118	119	101	152	126	119	128	70-105
BUN (mg/dl)	64	42	30	21	14	23	27	27	38	21-43
Creatinine(mg/dl)	0.8	0.6	0.36	0.33	0.36	0.45	0.36	0.43	0.43	0.4-1.2
AST (U/L)	11	8	9	9	13	13	10	17	24	5-34
ALT (U/L)	<6	7	<6	<6	9	13	10	13	27	0-55
Total protein (g/dL)	6.1	-	5.9	-	-	5.2	-	5.1	5.6	6.2-8
Albumin (g/dL)	2.9	2.5	2.4	2.4	2.4	2.6	3	3.1	3.1	3.5-5
K (mmol/L)	3.7	3.0	2.7	2.6	2.7	3.7	3.1	5	4.5	3.5-5.1
Ca (mg/dL)	8.5	8.1	7.8	6.7	7.3	7.9	8.6	8.7	8.7	8.4-10.2
Phosphate (mmol/L)	-	0.8	0.8	0.8	0.6	0.8	1	1.2	1.3	0.9-1.3
Na (mEq/L)	147	140	133	130	126	130	135	138	137	136-145
Chloride (mmol/L)	-	-	99	-	94	-	101	-	-	96-105
Mg (mg/dl)	-	1.47	1.57	1.47	1.88	1.36	1.35	1.58	1.84	1.6-2.6
Folate (ng/mL)	1									3-20
B-12 (pg/mL)	312									137-883

BUN: blood urea nitrogen; AST: alanine aminotransferase; ALT: aspartate aminotransferase; K: Potassium; Ca: Calcium; Na: Sodium; Mg: Magnesium.

Asia Pac J Clin Nutr 2017;26(2):379-383

NSS consulted to initiate PN in a 72 yoM s/p total colectomy/ileostomy. NG to suction. PICC in place
PMH/PSH: Colon Cancer, HTN, DM, SBR x 3,
Ht 70 in WT 50kg

Na	135	(135-145meq/L)
K	3.2	(3.6-5meq/L)
Cl	99	(98-107meq/L)
CO_2	24	(22-31meq/L)
Ca	9	(8.4-10.2mg/dL)
Ion Ca	1.2	(1.13-1.32mmol/L)
PO_4	2	(2.5-4.5mg/dL)
Mg	1.5	(1.7-2.2mg/dL)
Glucose	230	(70-110mg/dL)
BUN	12	(7-20mg/dL)
SCr	0.5	(0.7-1.5mg/dL)

Concerns

- BMI-16.5
- K, Mg, Phos are low
- Glucose is > 200mg/dL
- Recent weight loss?
- Dextrose containing IV fluids post-op?

Questions