Immunonutrition in (Sarcoma) Surgery

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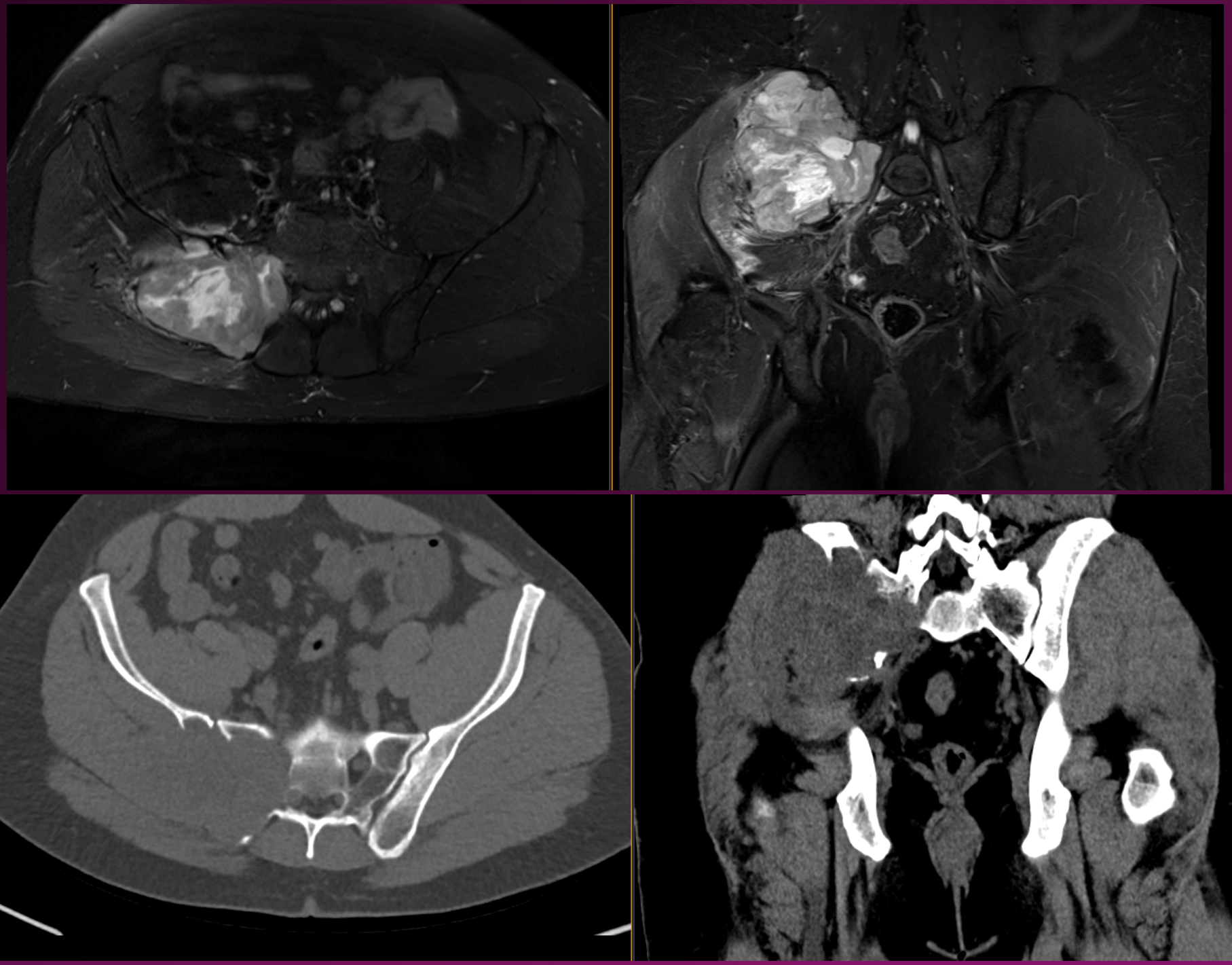
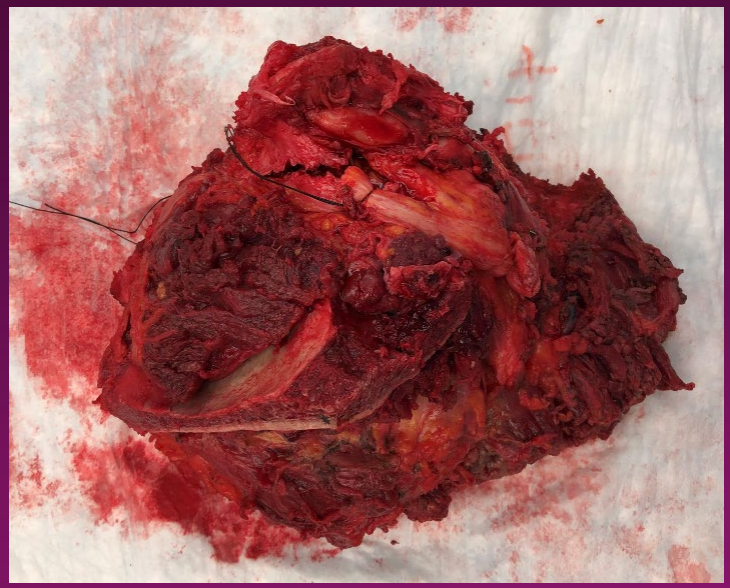
CASE

- 43y M with Neurofibromatosis type 1 presents with aggressive right pelvic lesion. Biopsy confirmed as high grade malignant peripheral nerve sheath tumor
- Enrolled in clinical trial
  - Interdigitated dual immunotherapy/radiation
    - DURVALUMAB, TREMELIMUMAB
    - 50.4 Gy in 28 fractions IMRT
- Preoperatively- developed immunotherapy related colitis, diarrhea, anorexia, elevation in LFTs, weight loss
  - Treated with steroids, allowed labs/symptoms to improve



Staged Resection

- 1/4/2021: Anterior approach
  - Enterolysis, right ureterolysis, R internal iliac artery/vein ligation, omental flap, anterior sacral osteotomies, placement gortex barrier and harvest of VRAM flap
- Posterior approach planned for 1/7, developed ileus and aspiration pneumonia.
  - TPN begun
- 1/12/2021: Posterior approach
  - Type I/IV internal hemipelvectomy
  - Radical resection right sacropelvis for MPNST



Postop Course

- Wound infection
- C.Diff colitis
- Postop ileus
- Edema
- Deconditioning

- TPN: 18 days
- LOS: 1 month

- Has resumed single agent DURVALUMAB
- Ongoing local wound management
- Protein supplementation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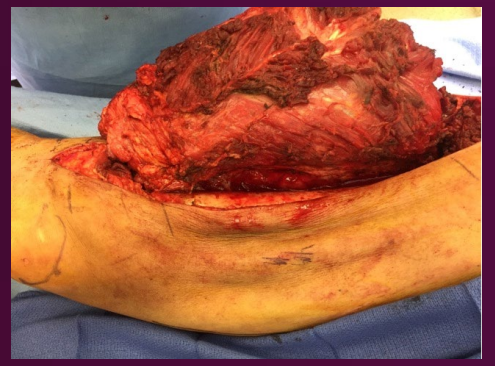
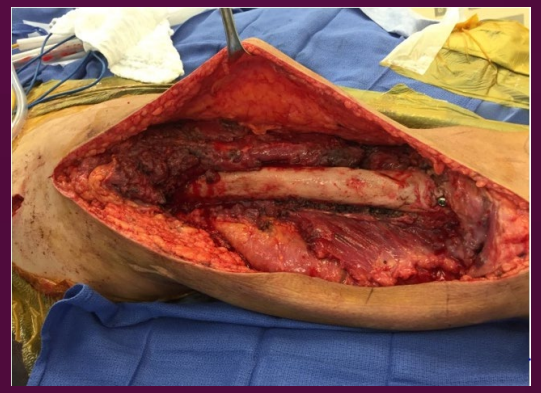
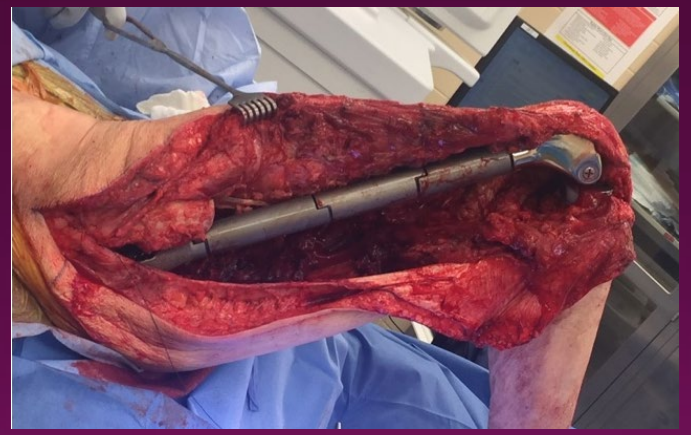
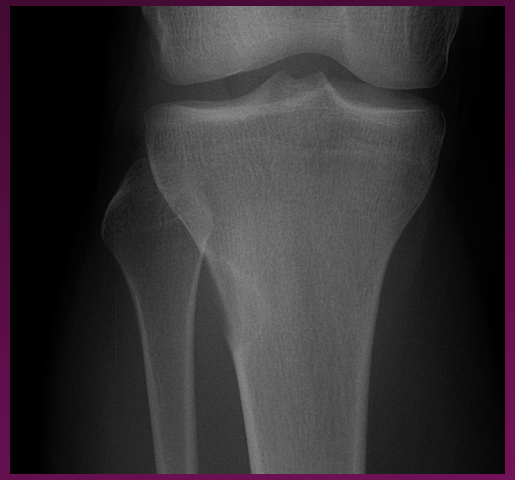
Typical Uphill Battle

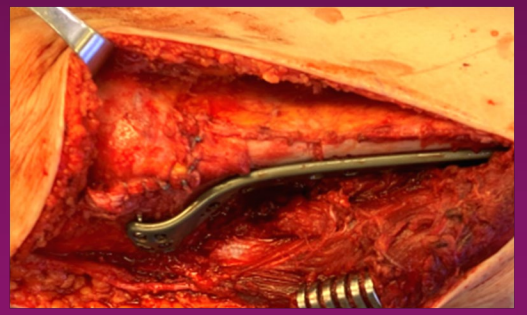
- Radiation therapy
- Chemotherapy
- Systemic therapy
- Older patients
- Large dead space
- Devascularized tissue
- Baseline/Iatrogenic malnutrition











Nutrition as WE know it…

- Albumin
- Prealbumin
- Transferrin

- BMI

The direct and indirect cost of poor nutrition is great

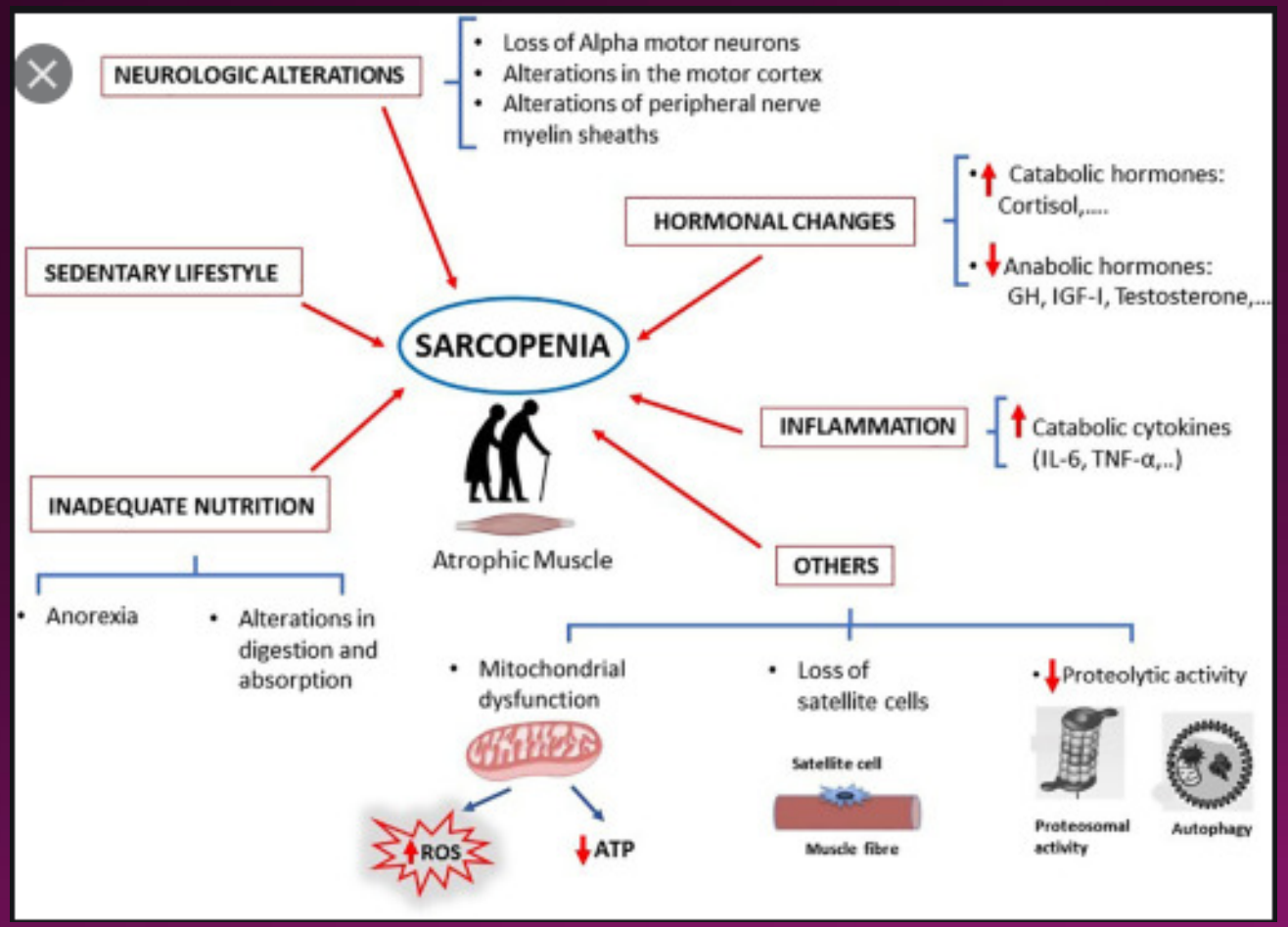
- Prevalence 30-50%, up to 85% in long-term care facilities
- Increased hospital costs, LOS, readmission rates, major and minor complications, requirements of ongoing services (home health, etc)
- Increased mortality
- Increased missed days from work
- 8 diseases (COPD, breast ca, colorectal ca, depression, dementia, stroke and MSK disorders) → economic burden of associated malnutrition estimated at $157 billion

Malnutrition

- Definition ????
- No standard method for screening and diagnosing
- Broadly → Jenson et al: “decline in lean body mass with the potential for functional impairment”
- Role of inflammation leading to acute or chronic disease related malnutrition vs. non-inflammatory categories of malnutrition (chronic starvation, anorexia nervosa)
- Understanding that obesity often coexists with malnutrition
- The problems with serum lab values as definitions

Sarcopenia

Gradual reduction in muscle mass, simultaneous decrease in muscle strength
→ reduced mobility, fragility, loss of independence



Vitamins and Hormones Volume 115, 2021, Chapter 20, Pages 535-570

Why the labs aren't so helpful

- Albumin
  - Hepatic protein
  - Negative acute phase protein
  - ½ life 14-20 days
  - Carrier molecule for various minerals, hormones and Fatty acids
  - Maintains oncotic pressure in the capillaries
  - >50% is in extravascular compartment, only about 5% produced daily in liver

- Daily consumption doesn't sig affect levels
- Pool affected by inflammatory conditions and drugs
  - Liver failure, burns, sepsis, trauma, post-surgery states, cancer
  - "stress-induced hypoalbuminemia"
- Not reliable/sensitive enough for diagnosing protein-calorie (non-inflammatory) malnutrition
- Poor specificity for functionally impaired elderly
  - Posture-related effects related to hydrostatic and oncotic pressures with changes in body positions
- May be ok for preop screen for elective orthopaedic surgery

Prealbumin

- Negative acute phase reactant made by liver
- Degraded by kidney
- ½ life 2-3 days
- Total body pool sig less than albumin
- Transports thyroxine

- Theoretically a more reliable indicator of acute changes in nutritional status
- Subject to same variations related to inflammatory states
- Renal and thyroid dysfunction

- May be helpful to **TREND** in those being given nutritional therapy

Other Serum Markers

Transferrin

- Negative phase reactant
- Role in iron transport
  - Anemia = elev transferrin
- Increase in renal failure
- OCPs/estrogen alter levels
- No correlation found between fat-free mass and transferrin levels

Retinol Binding Protein

- Vitamin A and zinc
- Degraded in kidneys
- Rapid turnover, similar to PAB
  - But similarly, not useful post-surgically d/t metabolic stress

Other Serum Markers

- CRP
  - Positive acute phase reactant
  - Mildly elevated in 1/3 of the population
  - Non-nutritional and inflammatory states affect
- TLC
  - More reflective of age than nutritional status
    - Less helpful in elderly
- Nitrogen balance
  - Urea concentration
  - Urinary creatine/height index

Better Techniques for Malnutrition Dx

- **Subjective Global Assessment**
  - Well validated, noninvasive bedside tool for geriatric patients
  - Good reliability
  - Cost-effective
  - **Patient Generated-SGA** for cancer, ischemic stroke and hemodialysis patients

- **MST**
  - Simple, fast

Table 1. Subjective global assessment

History
Weight loss in last six months
Changes in dietary intake
Gastrointestinal symptoms
Functional capacity
Disease and its relation to nutritional requirements
Physical examination
Subcutaneous fat
Muscle wasting
Ankle edema
Sacral edema
Ascites

Malnutrition Screening Tool (MST)[1]

1. Has the patient lost weight recently without trying?

Yes (0)
No (0)
Unsure (2)

Within the last 6 months

If unsure, ask if they suspect they've lost weight eg. clothes looser

If YES, how much weight has the patient lost?

0.5-5 kg (1)
>5-10 kg (2)
>10-15 kg (3)
> 15 kg (4)
Unsure (2)

For e.g. less than ¾ usual intake

2. Has the patient been eating poorly because of decreased appetite?

Yes (1)
No (0)

May also be eating poorly due to chewing and swallowing difficulties

Patients receive a score from 0-5 on MST:
→ Score <2 (0-1) = not at risk of malnutrition
→ Score ≥2 (2-5) = at risk of malnutrition

[1] Ferguson M, Capra S, Bauer J, Banks M. (1999). Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. *Nutrition*, 15, 458-64.

Better Techniques for Malnutrition Dx

- Assessment of muscle mass and subcutaneous fat
  - Triceps skinfold thickness
    - Account for age/sex
- Hand Grip Strength
  - Validated, reliable, responsive to therapy

Nutritional Risk Screening (NRS 2002)

Table 1 Initial screening

		Yes	No
1	Is BMI <20.5?		
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		

Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed.
No: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

Table 2 Final screening

Impaired nutritional status		**Severity of disease (≈ increase in requirements)**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss >5% in 3 mths 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**	Wt loss >5% in 2 mths or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss >5% in 1 mth (>15% in 3 mths) or BMI <18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe **Score 3**	Head injury* Bone marrow transplantation* *Intensive care patients (APACHE>10).*
Score:	+	**Score**:	**= Total score**
Age	if ≥70 years: add 1 to total score above	**= age-adjusted total score**	

Score ≥3: the patient is nutritionally at-risk and a nutritional care plan is initiated
Score <3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

NRS-2002 is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.
Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to **increased requirements** caused by stress metabolism of the clinical condition.

A nutritional care plan is indicated in all patients who are

(1) severely undernourished (score = 3), or (2) severely ill (score = 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).

Prototypes for severity of disease
Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.

Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

Table. Academy of Nutrition and Dietetics (Academy)/American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) clinical characteristics that the clinician can obtain and document to support a diagnosis of malnutrition[ab]

	Malnutrition in the Context of Acute Illness or Injury				Malnutrition in the Context of Chronic Illness				Malnutrition in the Context of Social or Environmental Circumstances			
Clinical characteristic	Non-severe (moderate) malnutrition		Severe malnutrition		Non-severe (moderate) malnutrition		Severe malnutrition		Non-severe (moderate) malnutrition		Severe malnutrition	
(1) Energy intake (reference 30)	< 75% of estimated energy requirement for > 7 days		≤ 50% of estimated energy requirement for ≥ 5 days		< 75% of estimated energy requirement for ≥ 1 month		< 75% of estimated energy requirement for ≥ 1 month		< 75% of estimated energy requirement for ≥ 3 months		≤50% of estimated energy requirement for ≥ 1 month	
Malnutrition is the result of inadequate food and nutrient intake or assimilation; thus, recent intake compared to estimated requirements is a primary criterion defining malnutrition. The clinician may obtain or review the food and nutrition history, estimate optimum energy needs, compare them with estimates of energy consumed and report inadequate intake as a percentage of estimated energy requirements over time.												
(2) Interpretation of weight loss (references 33-36)	%	Time	%	Time	%	Time	%	Time	%	Time	%	Time
The clinician may evaluate weight in light of other clinical findings including the presence of under- or over- hydration. The clinician may assess weight change over time reported as a percentage of weight lost from baseline.	1-2	1 wk	>2	1 wk	5	1 mo	>5	1 mo	5	1 mo	>5	1 mo
	5	1 mo	>5	1 mo	7.5	3 mo	>7.5	3 mo	7.5	3 mo	>7.5	3 mo
	7.5	3 mos	>7.5	3 mos	10	6 mo	>10	6 mo	10	6 mo	>10	6 mo
					20	1y	>20	1y	20	1y	>20	1 y
Physical findings (references 36,37)												
Malnutrition typically results in changes to the physical exam. The clinician may perform a physical exam and document any one of the physical exam findings below as an indicator of malnutrition.												
(3) Body fat	Mild		Moderate		Mild		Severe		Mild		Severe	
Loss of subcutaneous fat (eg, orbital, triceps, fat overlying the ribs).												

Table. Academy of Nutrition and Dietetics (Academy)/American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) clinical characteristics that the clinician can obtain and document to support a diagnosis of malnutrition[ab] (*continued*)

	Malnutrition in the Context of Acute Illness or Injury		Malnutrition in the Context of Chronic Illness		Malnutrition in the Context of Social or Environmental Circumstances	
Clinical characteristic	Non-severe (moderate) malnutrition	Severe malnutrition	Non-severe (moderate) malnutrition	Severe malnutrition	Non-severe (moderate) malnutrition	Severe malnutrition
(4) Muscle mass Muscle loss (eg, wasting of the temples [temporalis muscle]; clavicles [pectoralis and deltoids]; shoulders [deltoids]; interosseous muscles; scapula [latissimus dorsi, trapezious, deltoids]; thigh [quadriceps] and calf [gastrocnemius]).	Mild	Moderate	Mild	Severe	Mild	Severe
(5) Fluid accumulation The clinician may evaluate generalized or localized fluid accumulation evident on exam (extremities; vulvar/scrotal edema or ascites). Weight loss is often masked by generalized fluid retention (edema) and weight gain may be observed.	Mild	Moderate to severe	Mild	Severe	Mild	Severe
(6) Reduced grip strength (reference 42) Consult normative standards supplied by the manufacturer of the measurement device.	N/A[c]	Measurably reduced	N/A	Measurably reduced	N/A	Measurably Reduced

[a]A minimum of two of the six characteristics above is recommended for diagnosis of either severe or non-severe malnutrition. Height and weight should be measured rather than estimated to determine body mass index. Usual weight should be obtained in order to determine the percentage and to interpret the significance of weight loss. Basic indicators of nutritional status such as body weight, weight change, and appetite may substantively improve with refeeding in the absence of inflammation. Refeeding and/or nutrition support may stabilize but not significantly improve nutrition parameters in the presence of inflammation. The National Center for Health Statistics defines "chronic" as a disease/condition lasting 3 months or longer (reference 12). Serum proteins such as albumin and prealbumin are not included as defining characteristics of malnutrition because recent evidence analysis shows that serum levels of these proteins do not change in response to changes in nutrient intake (references (22,23,52,53).

Paradigm Shift

- Prepare, “prehabilitate” the patient for the *INSULT OF SURGERY*.
  - Hyperinflammation
  - Oxidative stress
  - Immune impairment
  - Insulin resistance
  - Resultant exposure to infection
- Not just to prevent malnutrition but also to attenuate oxidative stress, reduce inflammation & modulate the metabolic response to planned surgical stress.

- Preoperative Assessment: identify patients, evaluate their nutritional status, intervene as appropriate
  - BMI <35, Hgb A1c <7.5, smoking cessation, EDUCATION
  - Malnourished
  - Well nourished undergoing major surgery
    - GI, colorectal, PHB, H&N, **hip arthroplasty & spine**
- Perioperative
  - ERAS (Enhanced Recovery After Surgery)
    - Preop carbohydrate loading
- Postoperative
  - Early return to EN/regular diet
  - Adequate resuscitation and glucose control, electrolyte/pH balance
  - Probiotics

ERAS

- Conservative fluid management
- Patient education
- Epidural anesthesia
- Warming
- Early mobilization
- No bowel prep, preop fasting, NG tube
- Early enteral access/return to oral nutrition

Immunonutrition

- Perioperative nutritional supplementation
  - Increased protein intake
  - Carbohydrate loading
    - 100g multidextrose night before surgery/50mg multidextrose AM of surgery
    - Less postop nausea & improved blood sugar control
  - Immunonutrition
- IMN: Simple definition: Nutrition (calories and protein) with *supplemental arginine and omega 3 fatty acids*
  - other elements: RNA, nucleotides, antioxidants
  - So also important for <u>modulating stress response</u>

- Biology/chemistry
- Timing may be important
  - 5-7 days preop and continuing into postop period ideal
- Fish Oil Omega 3s:
  - Modulates host immune system and inflammatory response
  - Attenuate production of inflammatory PGs and prostacyclins, reduce cytotoxicity of inflammatory cells
  - Eicosapentanoic and docohexanoic acids precursors of resolvins → reduce cellular inflammation
- Arginine:
  - Essential AA, precursor to proline and polyamines → essential for tissue repair & wound healing
  - Integrity and function of immune cells, precursor of NO synthesis
  - Rapidly depleted in surgery and after metabolic stress

Summary of Literature

- Most – surgical oncology
- Few studies- orthopaedics

- Not all studies show clinical benefit or have **contradicting results**
- Several systematic reviews and meta-analyses
  - Many variables and inherent limitations , lack of standardization, variable definitions
- Perioperative IN in elective curative surgery for **solid malignant tumors**
  - Reduced overall infectious complications and surgical site infections
  - No diff 30day mortality
- Perioperative IN in **GI cancer** patients
  - Reduced surgical site infections, LOS, wbc count, CRP
  - No difference in CD4+, IL-6, TNFa
- Perioperative nutritional supplementation effect on postop complications in **GI cancer surgery**
  - Periop nutritional supplementation: **reduced risk of postop complications, infections, and non-infectious complications** as well as **decreased LOS**
- Preop IN vs. standard ONS vs. regular diet without supplements **(GI, colorectal, liver, HBP cancer)**
  - Analyzed outcomes: wound infection, infectious and noninfectious complications, LOS
    - *IMN vs. ONS* → no benefit
    - IMN versus no supp → **decreased infectious complications and decreased LOS**
- Postop enteral/parental IN in **gastric or pancreatic** resection patients
  - Malnourished patients also got PREOPERATIVE parental nutrition
  - *No difference in outcomes for well nourished*
  - Malnourished receiving IN had **decreased postop complications and decreased LOS**

Randomized Prospective Literature

- Periop IMN modulates inflammatory response after **radical cystectomy**
  - IMN group: maintained Th1-Th2 balance, lower IL-6, maintenance of arginine postop
- Periop IMN in **cancer surgery**
  - IMN group with decreased infections and LOS
- Preoperative IMN in patients undergoing **pancreatoduodenectomy**
  - Reduced complications/severity of complications
  - T-bet levels, serum eicosapentaenoic acid and eicosapentaenoic acid/arachidonic acid ratio greater in IMN group
  - PGE2 lesser in IMN group

Trauma Literature

- Severe trauma → hypercatabolism → hyperglycemia, hypoproteinemia, lactate acidosis, immunosuppression
- Early full enteral nutrition = decreased infection rate, shorter LOS, improved overall outcome
- Immunonutrition
  - **Glutamine** supplementation reduced MOF and death d/t infections in critically ill patients
  - TLC, IL-2, activated T helper cells return to normal faster in glutamine supplemented diets
  - Fish oil FAs anti-inflammatory effects

Orthopaedic Literature

- Elective **spine & TJA**
  - 125 patients over 12mos
  - IMN group (pre and postop) vs. no supp
    - Reduced complications, reoperations, readmission
- Multimodal periop care + IMN (& carb loading) vs traditional care in **THA**
  - 32 patients randomized
  - ACERTO +IMN group: decreased LOS, postop CRP
- Periop IMN in **elderly undergoing THA & TKA**
  - Retrospective
  - IMN group #1617 vs. control #1398
  - IMN group: shorter LOS, fewer infectious complications, noninfectious complications and need for ICU

Pilot Study in Sarcoma

- Cohort of 20 patients undergoing sarcoma resection +/- reconstruction given perioperative IMN + carb loading
  - Compared to 20 historical controls who rec'd standard protein-calorie supplementation

- IMN group: significantly lower operative time, lower EBL, shorter LOS
- No difference in wound complications or re-operation rates

Thank you!!


LOOK
What we are Lear


Nutrition
Serving size
160
Calories
ORAN
UPMC