Interprofessional Webinar Series
Management of Anorexia/Cachexia

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Disclosure Slide

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Objectives

• Discuss the prevalence and significance of anorexia/cachexia in patients receiving palliative care.

• Recognize the clinical features and assessment criteria for anorexia/cachexia.

• Identify the treatment options for anorexia/cachexia and recognize its impact on quality of life.
Cachexia: Definition

• Multifactorial syndrome that is defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and that leads to progressive functional impairment. Usually diagnosed when pts have weight loss more than 5% of preillness weight in previous 2 to 6 months.

• Pathophysiology: negative protein and energy balance that is driven by a variable combination of reduced food intake (anorexia) and abnormal metabolism.

Conditions Associated with Cachexia

- Occurs in ~ 70% of patients during the terminal course of disease
- Cancer
  - Cancer of the upper GI and lung have the highest prevalence of weight loss
- Acquired Immunodeficiency Syndrome
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Other chronic illness:
  - Dementia, rheumatoid arthritis, tuberculosis, malaria, chronic kidney disease

Anorexia:

- Loss of appetite or reduced caloric intake.
- It is a common complication of advance cancer and other terminal illnesses.

Phases of Cachexia

- Precachexia
- Cachexia
- Refractory cachexia

\[ \text{Partially reversible} \]

For example, a patient with small-cell lung cancer and severe B-type symptoms (such as pyrexia, sweating) and cachexia mainly due to hypermetabolism

Metabolic change

Reduced food intake

For example, a patient with pharyngeal cancer and cachexia mainly due to reduced food intake secondary to dysphagia

Mechanism of Cachexia

Effect on Patient Quality of Life

• Physical activity is impaired by the loss of muscle tissue

• Concentration and alertness are diminished by fatigue

• Mood is dominated by lethargy and increasing indifference

• Isolated owing to reduced physical, mental, and emotional activity

• Caregiver stress

Characteristics of Cachexia

- Anorexia
  - Lack of appetite signals, early satiety
- Asthenia
  - Weakness, fatigue, lethargy
- Unintended weight loss
  - >10% premorbid body weight
- Anemia
- Edema
Assessment

• The **objective measures**: serial measurement of body weight and assessment of dietary intake

• The **subjective measures**: malnutritional assessment tools

• The **laboratory measures**: e.g., albumin, transferrin are rarely needed
## Diagnostic Criteria for Cachexia

Unintentional weight loss \( \geq 5\% \)

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt; 20 in those aged &lt; 65 years old  &lt; 22 in those aged ≥ 65 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>&lt; 35 g/L (3.5 g/dL)</td>
</tr>
<tr>
<td>Low fat-free mass</td>
<td>Lowest 10%</td>
</tr>
<tr>
<td>Evidence of cytokine excess</td>
<td>E.g., elevated C-reactive protein</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Anorexia, fatigue, decreased muscle strength</td>
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Cachexia

- An international consensus group recommended that five domains be encompassed in cachexia assessment:
  1. stores depletion
  2. muscle mass and strength
  3. anorexia/reduced food intake
  4. catabolic drivers
  5. functional/psychosocial effects

- Malnutrition assessment tools are generally in use to assess cachexia.

Malnutrition Assessment Tools

• Several screening tests have been developed to assess for malnutrition, including:
  • Patient-Generated Subjective Global Assessment (PG-SGA)
  • Mini-nutritional assessment (MNA)
  • Malnutrition Universal Screening Tool (MUST)
  • Simplified Nutritional Appetite Questionnaire (SNAQ)

• No single screening tool has been universally agreed upon as the best way.
Appetite

- Although the reliability of subjective assessments of appetite is debated, they are probably the simplest and most practical measures available.

- The patient’s subjective loss of appetite can be assessed with a numeric rating scale, such as the Edmonton Symptom Assessment System (ESAS).


Secondary Nutrition Impact Symptoms (S-NIS)

- S-NIS: Other symptoms that may impact appetite and caloric intake, including symptoms:
  - May be related to the underlying illness
  - May contribute to reduced caloric intake
  - Might be the consequence of cachexia, e.g., pain, xerostomia, n/v, constipation, and depression
Other Reasons for Cachexia

• Potentially reversible metabolic abnormalities including:
  • hypothyroidism
  • adrenal insufficiency (bilateral adrenal metastasis)
  • hypogonadism (in male patients)

• Gastroparesis: multifactorial
  • chemotherapy-induced autonomic dysfunction
  • medications, such as opioids or anticholinergics
  • radiation enteritis
  • tumor infiltration
  • result of a paraneoplastic syndrome
Importance of Better Recognition and Treatment

• More ‘silent’ symptoms than pain or dyspnea; often go unrecognized, unaddressed

• Probably a common pathway for many diseases

• Targeted therapies may do much to improve QOL
Treatment and Supportive Care

- Pharmacotherapy
- Preparing favorite foods; the pleasure of tasting food should be emphasized over total caloric intake
- The social benefits of eating at the dining table with other family members should be encouraged
- Small, frequent meals that are dense in calories
- Ensuring optimal mouth care
- Providing a relaxed eating environment
- Avoiding strong odors or heavy spices
Treatment Approach

• Optimizing management of major contributors to anorexia

• Patients and families should be counseled that increasing caloric intake *does not* reverse the underlying process and that anorexia/cachexia is not an uncommon symptom. It is different from starvation and is a natural process that occurs at the end of life.
Treatment: Assessment of Other Causes

- M: Medications (digoxin, theophylline)
- E: Emotional (depression)
- A: Anorexia
- L: Late-life paranoia
- S: Swallowing disorders
- O: Oral problems
- N: Nosocomial infections (tuberculosis, H. pylori)
- W: Wandering and other dementia-related behavior
- H: Hyperthyroidism/hypercalcemia/hypoadrenalism
- E: Enteric problems (malabsorption)
- E: Eating problems
- L: Low-salt, low-cholesterol diets
- S: Stones (gallstones)
Pharmacological Approaches

• Megestrol acetate
• Glucocorticoids
• Mirtazapine
• Dronabinol
• Anabolic steroids

• Cyproheptadine
• Others:
  • Thalidomide
  • Amino Acids/L-Carnitine
  • Celecoxib
  • Fish Oil (EPA)
Megestrol Acetate

• Synthetic derivative of progesterone

• Acts as progestational, anti-inflammatory and intrinsic androgen agent

• Approved by the FDA for the treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS

• Should be used no more than 8-12 weeks at a time

• *No effect* on overall quality of life or lean body mass
Megestrol Acetate (Cont’d)

- Many randomized placebo-controlled trials
  - Improved appetite and weight gain in patients with cancer and AIDS
  - Increased appetite and body weight in patients with COPD

- Dose-related effect appetite, food intake, weight, and subjective sensation of well-being

- Dosing range: 160-1600 mg/day
  - Dose-related side effect profile
  - Thromboembolic events, peripheral edema, hyperglycemia, hypertension, breakthrough bleeding, increased liver enzymes

Corticosteroids

• A 2005 systematic review of six double-blind randomized controlled studies of glucocorticoids (dexamethasone, prednisolone, and methylprednisolone) in cancer patients concluded that, compared to placebo, they improved appetite and quality of life, but the beneficial effects diminished over time.

• Produce temporary appetite stimulation
  • No studies have shown a beneficial effect on body weight

• Optimal dose not clearly defined

Cannabinoids

• Increased appetite is a well-known side effect of the cannabinoids

• Synthetic agents include dronabinol

• Dronabinol is FDA approved for anorexia/weight loss associated with AIDS

• One comparative trial published in patients with cancer-induced anorexia/cachexia comparing dronabinol to megestrol
  • Megestrol was significantly better in terms of both stimulating appetite and weight, and the combination of both agents was not better than megestrol alone.

Anabolic Steroids

• The Endocrine Society has published clinical practice guidelines for replacing testosterone in chronic illnesses with hypogonadism, such as advanced HIV/AIDS, type 2 DM, ESRD, and COPD, and not in cancer.

• In such men, physiologic testosterone supplementation has been shown to increase lean body mass, and in some studies, improve muscle strength.

Cyproheptadine

• Histamine antagonist

• Shown to produce slight improvement in appetite in patients with cancer cachexia
  • No effect on body weight

• Produce significant sedation limiting use

Mirtazapine

• Antidepressant approved by the FDA for the treatment of major depressive disorder. It is known to cause appetite stimulation and weight gain at standard treatment doses.

• In controlled trials, 17% of patients taking mirtazapine reported an increase in appetite, compared with 2% of patients receiving placebo. Almost 8% of patients receiving mirtazapine had weight gain ≥ 7% of body weight, whereas patients receiving placebo had 0% weight gain.

• Most studies involved geriatric patients with established diagnosis of depression or dementia with depression.

Others

Thalidomide

• Potent inhibitor of TNF-alpha production
• Associated with weight gain in patients with TB or HIV infection
• Possible role in cancer patients
• Cochrane Review: insufficient evidence to support or refute in cancer-associated cachexia

Amino Acids/L-carnitine

- Required for the transport of fatty acids to the mitochondria where they are utilized to generate metabolic energy

- An RCT showed a trial of L-carnitine (4 g daily) in 72 patients with advanced pancreatic cancer reported an increase in body mass index (BMI), quality of life, and a trend toward improved survival

Others (Cont’d)

Celecoxib

- Placebo-controlled pilot study of cachectic cancer patients; celecoxib (200 mg BID) was associated with weight gain, increased body mass index (BMI), improved quality of life

- Larger prospective randomized study reported those on both megestrol and ibuprofen had gain in weight and improvements in QOL scores

Others (Cont’d)

Fish Oil (EPA)

• Alpha 3-omega fatty acid, stimulates adenylate cyclase activity and lipolysis

• Evidence is inconclusive on cancer-associated cachexia

• A 2007 Cochrane database meta-analysis concluded that there were insufficient data to establish that EPA was better than placebo

Investigational: Combination Therapies

• Incorporate multimodal therapy, targeting multiple underlying pathophysiological processes

• Large randomized study of 332 cachectic cancer; patients were given either: megestrol acetate, fish oil, L-carnitine, thalidomide OR a combination of all of the above. Most effective treatment in attaining primary endpoints was the combination arm.


Future Drugs: Growth Hormone and Ghrelin

• Promising results have been seen with ghrelin, a growth hormone (GH)-releasing peptide that induces positive energy.
  • Some studies in cachectic patients with COPD suggest that repeated intravenous administration of ghrelin lessens muscle wasting and improves body composition, functional capacity, and sympathetic augmentation.

• A preliminary report of two large double-blind placebo-controlled trials of anamorelin in patients with lung cancer-related cachexia (the ROMANA 1 and ROMANA 2 studies) noted significantly increased lean body weight and clinically meaningful improvements in appetite with anamorelin compared to placebo.

Artificial Nutritional Support

• No evidence that artificial nutrition, including hyperalimentation, prolongs life or improves functional status, and it is **not indicated**, with some exceptions.

• For highly selected patients (e.g., high-grade bowel obstruction or malabsorption from advanced cancer)
  - Good functional status, good prognosis

• Other disease: controversial

A 53-year-old woman with advanced hepatocellular carcinoma, currently receiving oral chemotherapy, is seen in your outpatient palliative care clinic. Her pain is controlled, but both the patient and her husband are concerned that she has had little appetite and has lost 10 pounds since her last visit. She is still ambulatory and enjoying most of her former activities, but she misses the enjoyment of eating. On physical examination, you find that she is a thin woman with normal vital signs. She has no signs of candida infection or other lesions in her oropharynx. She has normal dentition, minimal ascites, and no lower-extremity edema.

Of the following medications, which has the best evidence supporting effectiveness in treating her anorexia and helping her gain weight?

A. Dronabinol
B. Dexamethasone
C. Mirtazapine
D. Megestrol acetate
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CASE 2

GF is a 68-year-old woman with metastatic colorectal cancer who is receiving palliative care only. She reports a decreased appetite and a weight loss corresponding to 8% of her body weight over the past 2 months. In providing education to this patient about her conditions and/or possible treatment options, which of the following statements would be most appropriate?

A. Cancer-related cachexia is associated with increased mortality, so she should try to increase her food intake.

B. It is likely that the muscle mass in her body is declining, so she should consider hospitalization to receive parenteral nutrition.

C. Most patients with advanced cancer who have decreased appetite and weight loss should receive a corticosteroid, such as dexamethasone.

D. Megestrol acetate may increase her appetite but has not been associated with an improvement in survival.
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A. Somnolence
B. Constipation
C. Drowsiness
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Conclusion

• Cachexia is a core clinical feature of many advanced illnesses.

• Cachexia too often goes undiagnosed or untreated, with adverse consequences for patients.

• Feeding is not the answer, especially with advanced illness.

• Pharmacological options are available, but require risk vs. benefit assessment.
Management of Anorexia/Cachexia

Q/A