Involuntary Weight Loss

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KEYWORDS
- Involuntary weight loss
- Unintentional weight loss
- Unintended weight loss
- Unexplained weight loss
- Malignancy
- Diagnosis
- Prognosis
- Etiology

KEY POINTS
- Involuntary weight loss is a common clinical problem that frequently is a sign of underlying illness.
- The most common identified causes of involuntary weight loss are malignancy, gastrointestinal disorders, and psychiatric conditions; unknown etiologies represent a significant portion.
- Patients with normal history, physical examination, laboratory tests, and basic imaging studies are less likely to have a malignancy as the cause of involuntary weight loss; however, malignancy cannot be completely excluded.
- Treatment of involuntary weight loss is directed at the underlying causes.

INTRODUCTION

Involuntary weight loss is truly a generalist’s syndrome. There is no specialty for it, and the differential diagnosis is as broad as any. It may be present as a patient’s chief complaint but also may be found by astute observation by a clinician or family member. It requires a comprehensive evaluation to determine its cause. Involuntary weight loss poses a clinical problem of opposing tensions: on one hand, the specter of malignancy urges the clinician to undertake extensive workup so as not to miss it; on the other, most patients who present with involuntary weight loss do not have a malignancy, and these patients may incur the cost of the diagnostic workup, including the risk of invasive tests and procedures that may follow incidental findings. Frequently patients with involuntary weight loss are elderly and already have comorbid medical conditions, and the prognostic implications may be serious.

IS INVOLUNTARY WEIGHT LOSS A CONCERN? INSIGHTS FROM EPIDEMIOLOGY

It is often now presumed that intentional weight loss is desirable, whereas unintentional weight loss is a marker for serious illness. However, the relationship between
weight and health has had a storied epidemiologic history. The Metropolitan Life Insurance Company was one of the early pioneers in identifying obesity as a risk factor for mortality in its actuarial life tables from the 1950s. Although there remain concerns regarding measurement standardization and smoking status in that data set, the concept of obesity as a risk factor for mortality eventually became consensus. The range of body mass index at which mortality is increased is still a subject of research and controversy.2

The next epidemiologic question was whether changes in weight were associated with positive or negative health outcomes. In the 1980s and 1990s debate took place with the concern that weight loss may be harmful.3,4 Other approaches sought to associate health risk with weight fluctuation or “weight cycling” in general.5–7 However, studies that attempted to control for preexisting illnesses have not shown a definite risk from weight fluctuation alone.8,9 Several studies sought to demonstrate that intentional weight loss was favorable for health outcomes, and in doing so were able to show an association between unintentional weight loss and mortality in select populations.10,11 By contrast, a study of men in Israel beginning in the 1960s reported increased mortality with weight loss regardless of dieting status.12 An analysis of data of the more modern era from the Iowa Women’s Health Study showed that unintentional weight loss, but not intentional weight loss, of more than 20 lb (9 kg) was associated with increased mortality.13 After adjusting for comorbid conditions, this association appeared to be present in the 55-year and older age group. Wannamethee and colleagues14 sought to further explore intentional versus unintentional weight loss in a study of more than 4000 British men, and found that unintentional weight loss (over 4 years, mean 3.91 kg, as reported by participants) was associated with increased risk of total mortality, even after adjustment for preexisting disease. Of note, intentional weight loss was only associated with mortality if the weight loss was undertaken on the advice of a physician or if the patient was in ill health.

Finally, studies examining shorter-term weight loss are likely more relevant to the clinical problem of involuntary weight loss. In the United States, Gregg and colleagues15 found that intentional weight loss over the preceding year was associated with a decreased mortality rate over the ensuing 9 years, whereas unintentional weight loss was associated with an approximately 30% increase in mortality. Sahyoun and colleagues16 found an association between weight loss of 5% or more within the preceding 6 months and increased total mortality.

Thus despite the limitations in epidemiology-based methods to differentiate between voluntary and involuntary weight loss, there are at least moderate data suggesting that unintentional weight loss is harmful.

WHAT DEFINES INVOLUNTARY WEIGHT LOSS?

These epidemiology studies suggest that unintentional weight loss may be harmful. When approaching a patient, however, there is need to have a clinical definition for use in practice. Although there is as yet no consensus definition of involuntary weight loss, certain terms may still be reasonably defined (Table 1).

First, the term involuntary: in the literature, “involuntary” is used interchangeably with “unintended” or “unintentional.” These terms may be defined as the condition whereby the patient does not purposefully set out to lose weight for any reason, and excluding weight loss as an expected consequence of treatment of a known illness, such as diuretic therapy for heart failure. In addition, there are several terms used in the literature to describe weight loss of unknown etiology. For this review, the terms “unexplained” or “isolated” or “unknown” refer to weight loss without an
apparent cause after a workup has been performed. There is no consensus as to the amount of workup required to label the weight loss as unexplained, but one could reasonably consider such a workup to include history, physical examination, laboratory and imaging studies, and the passage of time without a diagnosis.

Second, one must consider the extent of weight loss to consider involuntary weight loss as a clinical entity or syndrome. There are 3 characteristics to consider: the degree of weight loss, how weight loss is assessed, and the time frame in which the weight loss occurs.

### Degree of Weight Loss

What is a normal and what is an abnormal amount of weight loss? Although it is widely believed that day-to-day fluctuations of up to 5 lb (2.2 kg) may be normal based on changes in intake and output and time of measurement, there are few data available to gauge what is normal fluctuation in weight in healthy people. In addition, weight may fluctuate throughout the day, as much as 1% to 2% in one small study of hospitalized patients. Involuntary weight loss, then, should merit a diagnostic workup when exceeding these thresholds. Most of the published case series of involuntary weight loss used an inclusion criteria of 5% or greater weight loss compared with usual body weight, with some studies using criteria up to 7.5% to 10%.

Wallace and colleagues assessed the degree of weight loss that is significant in a prospective cohort study of elderly veterans. Using a receiver-operator characteristic curve, they assessed the optimal weight-loss percentage to be 4% over the preceding year with regard to the balance of sensitivity (75%) and specificity (61%) associated with subsequent mortality. In another epidemiology study...
study, involuntary weight loss of 5% or more (but not <5%) over the preceding 6 months was associated with subsequent mortality. However, the optimal cutoff for weight-loss percentage described as pathologic that would apply broadly to all populations remains uncertain.

**Assessment of Weight Loss**

How weight loss is measured is also a matter of some discretion. Excessively stringent criteria such as requiring weights measured at the same time of day on a standardized office scale would miss patients who have not been previously followed regularly and frequently; these patients may nevertheless on presentation have a serious illness and would be harmed by a delay in diagnostic workup. Conversely, criteria that are too vague may result in unnecessary testing of patients without underlying illness. Published case series often replicated the measurement method of Marton and colleagues: either documented weight loss, or at least 2 of the following 3 criteria: change in clothing size, a friend or relative corroborating the weight loss, or the patient’s estimate of amount of weight lost. These criteria remain useful, although this method has not been validated as a prognostic tool.

In addition to the magnitude of weight loss, the duration is worth considering. Too short a time frame may select for only the most acute illnesses; too long a time frame may reflect other long-term physiologic changes rather than an underlying serious illness. From a clinical perspective, an intermediate time frame on the order of months to a year is likely to be most relevant. Published case series used criteria for weight loss occurring in the preceding 3 to 12 months (Table 2). One study had no duration requirement. Requiring a longer duration before a workup may miss a serious diagnosis that may progress. Involuntary weight loss that occurred many years prior with subsequent stabilization or reversal is not likely to reflect a progressive illness, although it may be the sign of a relapsing-remitting condition.

It is reasonable, therefore, to define the degree of weight loss as 5% or more of usual body weight within the preceding 6 to 12 months, to use weights measured in the clinic when available, and to use the criteria of Marton and colleagues if standardized measurements are unavailable (see Table 1).

**OTHER SYNDROMES**

Cachexia is not synonymous with involuntary weight loss; it is a clinical syndrome characterized by loss of muscle mass, and is caused by inflammatory metabolic derangements attributable to an underlying illness. The consensus definition as of 2008 is as follows: weight loss of at least 5% in 12 months or less, the presence of an underlying illness, and 3 of 5 of the following: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal laboratory testing consisting of increased inflammatory markers, anemia, or low serum albumin (see Table 1). Patients presenting with involuntary weight loss may have or may develop cachexia, depending on the cause of the weight loss.

Sarcopenia is a term used to describe a geriatric syndrome characterized by the loss of muscle mass and muscle function; although weight loss is not a criterion for sarcopenia, patients may have common underlying mechanisms causing both sarcopenia and cachexia.

**PATHOPHYSIOLOGY**

Weight homeostasis is a complex system affected by gastrointestinal hormones, hormones from adipose tissue, and the hypothalamus, as well as reward centers and
social factors. Involuntary weight loss is a striking problem in many nations when juxtaposed with epidemics of obesity. Much of the focus with regard to weight homeostasis has been either the pathophysiology of obesity or the mechanisms underpinning weight-losing syndromes such as cancer cachexia (Fig. 1).

In obesity, the long-term increase in weight is governed by numerous factors, including availability of high-calorie food and decrease in physical activity, with possible contributions from exposures to toxins, viruses, and medications. At the gastrointestinal level, satiety is sensed by gastric distension sending signals to the brain via the nervous system, and by release of peptides such as cholecystokinin, peptide YY, glucagon-like peptide 1 (GLP-1), and amylin, while feeding is stimulated by ghrelin. Leptin is responsible for decreased food intake, and is secreted by adipocytes in response to body fat mass, affecting receptors in the hypothalamus. Evolutionarily, it is thought that low leptin levels in response to low fat mass stimulate hunger and energy efficiency in an effort to return to the fat mass set point. Over time, the set point for the body’s fat mass may increase under the influence of multiple factors, leading to obesity.

Involuntary weight loss, however, is not merely the opposite aspect of pathologic weight gain in obesity. What happens to patients who lose weight involuntarily, when it is so difficult for others to lose weight intentionally or even to maintain weight without gaining? One such model is the weight loss associated with cancer, or cancer cachexia. Cancer cachexia is thought to be mediated by the production of cytokines such as tumor necrosis factor (TNF)-α and interleukin-6, and other factors including myostatin and activin, to a susceptible host. These factors suppress the appetite and promote muscle and fat breakdown. In addition, they may promote inefficient energy expenditure. The normal response to decreased energy intake is to reduce energy expenditure; in cancer cachexia, in the face of decreased energy intake resulting from multiple factors, instead of decreasing energy consumption, continued gluconeogenesis, lactate recycling, and protein turnover occur, driven in some models by TNF. The expected physiologic decrease in leptin in response to decreased fat mass does not occur in cancer cachexia. Weight loss in acute illnesses such as sepsis is also likely mediated by cytokines. The cachexia in other states is not just about losing total weight; rather, it is a transformation of body mass, as exemplified by cachexia resulting from chronic obstructive pulmonary disease (COPD). By contrast, the weight loss attributable to inadequate food intake alone has normal leptin signaling and is reversible with nutritional repletion.

**INCIDENCE AND PREVALENCE**

Estimates of the incidence of involuntary weight loss vary. The yearly incidence in case series from referral centers varies between 0.6% and 7.3% per year. These estimates depend on the particular patient populations and referral patterns, as well as the definition of involuntary weight loss used. A series of elderly veterans reported a higher incidence of 13% per year using a cutoff of 4% weight loss. In a general population, the incidence would be expected to be much lower than that in referral centers or in subsets of higher-risk patients. However, an epidemiology study of 5% or more weight loss over the preceding 6 months reported a 7% prevalence. Nursing home and home care populations may have increased prevalence of involuntary weight loss. Other epidemiology studies spanned a longer period of time. These prevalences vary, from a 4-year 11% prevalence in men in Great Britain to a 6-year 19% prevalence in women in the United States.
<table>
<thead>
<tr>
<th>Study, Ref. Year</th>
<th>Type of Study, No. of Patients</th>
<th>Setting</th>
<th>Patients</th>
<th>Follow-Up</th>
<th>Median Age (y)</th>
<th>Malignancy (%)</th>
<th>Gastrointestinal (%)</th>
<th>Infection (%)</th>
<th>Psychiatric (%)</th>
<th>Unknown (%)</th>
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<tbody>
<tr>
<td>Marton et al, 1981</td>
<td>Prospective N = 91</td>
<td>Veterans Administration, California, United States</td>
<td>≥5% weight loss over 6 mo 70% inpatient, 30% outpatient</td>
<td>6–12 mo</td>
<td>59</td>
<td>19</td>
<td>14</td>
<td>3</td>
<td>9</td>
<td>26</td>
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<tr>
<td>Rabinovitz et al, 1986</td>
<td>Retrospective N = 154</td>
<td>Internal medicine department, Israel</td>
<td>≥5% weight loss Inpatient</td>
<td>24–36 mo</td>
<td>64</td>
<td>36</td>
<td>17</td>
<td>4</td>
<td>10</td>
<td>23</td>
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<tr>
<td>Thompson &amp; Morris, 1991</td>
<td>Prospective N = 45</td>
<td>Family practice clinics, southeastern United States</td>
<td>≥63 y ≥7.5% weight loss over 6 mo Outpatient</td>
<td>24 mo</td>
<td>72</td>
<td>16</td>
<td>11</td>
<td>2</td>
<td>18</td>
<td>24</td>
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<tr>
<td>Lankisch et al, 2001</td>
<td>Prospective N = 158</td>
<td>Referral center, single site, Germany</td>
<td>≥5% weight loss within 6 mo Inpatient</td>
<td>12–36 mo</td>
<td>68</td>
<td>24</td>
<td>19</td>
<td>$^a$</td>
<td>11</td>
<td>16</td>
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<td>Design</td>
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<td>Criteria</td>
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<td>Bilbao-Garay et al, 2002</td>
<td>Prospective</td>
<td>78</td>
<td>Internal medicine referral clinic, Spain</td>
<td>≥5% weight loss over 3 mo, or ≥10% over 6 mo Outpatient Used diagnostic protocol</td>
<td>6 mo</td>
<td>59</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>Metalidis et al, 2008</td>
<td>Prospective</td>
<td>101</td>
<td>University general internal medicine clinic, Belgium</td>
<td>≥5% weight loss over 6–12 mo Inpatient and outpatient</td>
<td>6 mo</td>
<td>64</td>
<td>22</td>
<td>15</td>
<td>8</td>
<td>16</td>
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<tr>
<td>Wu et al, 2011</td>
<td>Retrospective</td>
<td>136</td>
<td>Veterans hospital, Taiwan</td>
<td>≥5% weight loss over 6–12 mo Elderly, inpatient</td>
<td>1 admission</td>
<td>80</td>
<td>17</td>
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<tr>
<td>Chen et al, 2010</td>
<td>Retrospective</td>
<td>50</td>
<td>Veterans hospital, Taiwan</td>
<td>≥5% weight loss, no time frame Elderly, inpatient.</td>
<td>12 mo</td>
<td>79</td>
<td>6</td>
<td>22</td>
<td>6</td>
<td>13</td>
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a Etiology listed by organ system; infectious causes not reportedly separately.
b Not reported separately.

Data from Refs. 20–27.
Fig. 1. (A) Homeostasis. (B) Obesity. (C) Involuntary weight loss.
DIFFERENTIAL DIAGNOSIS

The causes of involuntary weight loss are many (Table 3). In the literature, weight loss associated with clinical diseases may be reported as a symptom, a quantified amount of weight loss, or, in the case of certain diseases such as heart failure, COPD, and cancer, it may be characterized by extensive research into the phenomenon of cachexia (see Table 1).

Cardiovascular Disease

The most well-described condition is cardiac cachexia associated with advanced heart failure. This wasting process is likely mediated via inflammatory and hormonal mechanisms and is associated with increased mortality independent of New York Heart Association (NYHA) class, with a prevalence as high as 16%. Involuntary weight loss caused by cardiac cachexia presents as loss of muscle mass and fat, and is distinct from intentional weight loss such as produced by diuretic therapy. In most cases, one would expect the diagnosis of heart failure to be already known or evident on presentation.

Respiratory Disease

Advanced COPD can cause involuntary weight loss. Low body weight and, more specifically, low muscle mass (fat-free mass) is associated with mortality. Studies of COPD have generally used static measurements of weight or fat-free mass rather than measuring loss of weight per se; the prevalence of cachexia using these measurements is estimated at between 20% and 40%. Cachexia caused by advanced COPD is likely due to a combination of increased energy expenditure from work of breathing as well as neurohormonal changes. In most cases, the presence of severe COPD should be evident on history and physical examination, and readily confirmed

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Heart Failure/Cardiac Cachexia</th>
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<tbody>
<tr>
<td>Respiratory</td>
<td>COPD, interstitial lung disease, vasculitides, lung cancer</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Malabsorption, diarrhea, autoimmune/inflammatory, mesenteric ischemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Uremic cachexia</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Solid tumors, eg, lung, prostate, colorectal, pancreatic &gt; hematologic malignancies</td>
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<tr>
<td>Neurologic</td>
<td>Dementia, stroke, Parkinson disease, neuromuscular diseases, multiple sclerosis</td>
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<tr>
<td>Endocrine</td>
<td>Diabetes, adrenal insufficiency, hyperthyroidism</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Rheumatoid arthritis, sarcoidosis</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV, tuberculosis, other chronic infections</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression, anxiety, anorexia nervosa</td>
</tr>
<tr>
<td>Medications</td>
<td>Antiepileptics, antidepressants, antianxiety drugs, stimulants, diuretics, laxatives</td>
</tr>
<tr>
<td>Substance abuse and dependence</td>
<td>Alcohol, opiates; smoking as risk factor for malignancy</td>
</tr>
<tr>
<td>Social</td>
<td>Poverty, abuse, neglect; oral health</td>
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</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.
by imaging and pulmonary function testing. Other respiratory diseases that may pre-
sent with involuntary weight loss include malignancy, rheumatologic disease such as
antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, interstitial lung
disease, and infections such as tuberculosis. Because smoking is a common risk fac-
tor for both COPD and lung cancer, the patient with known COPD who presents with
involuntary weight loss should not be assumed to have COPD cachexia; rather,
workup of lung cancer should be considered.

**Gastrointestinal**

Gastrointestinal causes of weight loss include malabsorptive syndromes such as
pancreatic insufficiency and celiac disease, diarrheal illnesses, inflammatory bowel
disease, peptic ulcer disease, mesenteric ischemia, and protein-losing enteropathies.
An important cause, especially in the elderly, is dental disease, with difficulty chewing
leading to decreased caloric intake.

**Renal**

Renal failure may result in weight gain caused by inadequate renal excretion;
advanced renal failure may lead to protein energy malnutrition. Inflammatory cyto-
kines and neuropeptide signaling to the hypothalamus have been implicated in the
uremia cachexia syndrome. As with advanced heart failure, involuntary weight
loss in advanced chronic kidney disease must be distinguished from weight loss
resulting from medical treatments, including diuretic therapy and dialysis.

**Cancer**

Cancer is estimated to cause involuntary weight loss of at least 5% in approximately
one-third of patients, and becomes nearly universal when terminal. Weight loss
appears to be greater in patients with solid tumors, especially gastrointestinal, pancre-
atic, and lung cancers, and is associated with increased mortality. Unlike
advanced heart failure or COPD, cancer as the cause of weight loss may not be readily
apparent on initial history and physical, and may require additional laboratory testing
and imaging studies. Weight loss may be rapid in gastrointestinal and head and neck
cancers.

**Neurologic**

Neurologic conditions may cause weight loss from decreased functional status owing
to cognitive impairment such as dementia, reduced swallowing and gastrointestinal
function such as in Parkinson disease, multiple sclerosis, and neuromuscular
conditions.

**Endocrinopathies**

Weight loss is a common presenting feature of hyperthyroidism, occurring in 40% to
60% of those affected, even in elderly patients who may not have as many other
classic features of hyperthyroidism. Other endocrinopathies that may present
with weight loss include diabetes, adrenal insufficiency (25%–60%), hypopituita-

**Inflammatory and Rheumatologic Conditions**

Conditions such as rheumatoid arthritis, sarcoidosis, and ANCA-associated vascu-
litides may present with weight loss.
Infectious Diseases

Human immunodeficiency virus (HIV) may lead to weight loss and cachexia, from the virus itself as well as from the medications used to treat it. Other chronic infections such as tuberculosis may lead to chronic inflammatory states and consequent weight loss.

Psychiatric

Psychiatric conditions such as depression and anxiety may be associated with both weight gain and weight loss. These disorders must also be distinguished from adverse effects of medications used to treat these conditions.

Medications

Medications used to treat other conditions may inadvertently cause weight loss. The antiepileptic drugs topiramate and zonisamide have been shown to cause weight loss $^{53-55}$ and are often used for conditions other than epilepsy. Psychiatric medications commonly associated with weight loss include selective serotonin reuptake inhibitors, which can have variable effects on weight; bupropion; and stimulants such as those used for attention-deficit hyperactivity disorder. Many medications may have gastrointestinal side effects that may secondarily cause weight loss resulting from diarrhea. Metformin and GLP-1 agonists used to treat diabetes, and diuretics and laxatives through appropriate use or misuse all may cause weight loss. Antibiotics may cause weight loss through diarrhea or direct effects.

Substance Abuse and Dependence

Likely through multifactorial mechanisms, substance abuse can cause involuntary weight loss. Abuse of cocaine may lead to fat dysregulation in addition to appetite suppression. $^{56}$ Other substance dependence frequently leads to malnutrition, $^{57}$ including alcoholism, heroin dependence, and methamphetamine dependence.

Social

Just as ready access to high-calorie foods can be one factor in the development of obesity, inadequate access to food through poverty or neglect and abuse may be a factor in causing weight loss. Weight loss caused by inadequate intake produces appropriate downregulation of leptin and a decrease in energy expenditure, and, unlike the weight loss from cancer cachexia, is reversible by reinstituting proper nourishment.

ETIOLOGY OF INVOLUNTARY WEIGHT LOSS: INSIGHTS FROM CASE SERIES

Given such a wide differential diagnosis, it is useful to explore what is found in published case series of patients with involuntary weight loss.

What Causes are Found?

With the caveat that the different case series included different populations, countries, age groups, and inclusion criteria, the following overall representation is seen (see Table 2). $^{20-27}$ Malignancy represented 6% to 36% of cases, with all but one series being greater than 15%; nonmalignant gastrointestinal illnesses 6% to 19%; and psychiatric illnesses 9% to 33%. Infection was a relatively small percentage of cases (2%–8%) and in a significant portion of cases, no cause was found (11%–28%).
What Percentage of Patients are Unknown After an Initial Workup?

How often a diagnosis is found after the initial workup depends on the content of the initial workup and on the final percentage of unknown causes in the cohort. The aforementioned case series were heterogeneous in population, and only 2 of the studies used a protocol for the initial workup. Few series reported the percentage of patients able to be diagnosed after the initial workup (the extent of which varied by series), and this value was between 33% and 60%.

Hernandez and colleagues studied the characteristics and outcomes specifically of patients who had a negative initial workup. These patients initially received a complete blood count (CBC), basic metabolic panel (glucose, blood urea nitrogen, creatinine, potassium, sodium), chest radiograph, and abdominal radiograph, in addition to history and examination. After 6 months, no diagnosis was found in 25% of patients; these patients were considered to have “isolated involuntary weight loss.” Excluding those lost to follow-up, approximately 94% of these patients with a negative initial workup were eventually found to have a diagnosis. Malignancy represented 38%, followed by psychiatric (23%) and gastrointestinal diseases (10%). A smaller study in France, by contrast, had very few malignancies in a population who had already undergone workup.

Based on these limited data, one could expect to find a diagnosis after initial workup in most cases, with another 10% to 20% yield after additional workup, and subsequently leaving 10% to 25% of patients still without a diagnosis after extended follow-up.

What About Unintended Weight Loss in the Elderly?

Increasingly old age, loss of a spouse, disability, and previous hospital admission are being reported as risk factors for weight loss in the elderly. Unintentional weight loss in the elderly is very common, occurring in 15% to 20% of elderly patients. Older patients are at greater risk than younger patients for decreased caloric intake. Olfactory function declines with age, and increasing dental problems and dry mouth can cause decreased interest in food intake because of pain, difficulty chewing, and decreased enjoyment in the taste of food. Eating is usually a very social behavior, and elderly persons who are alone are less likely to eat adequate calories.

What Factors Portend a More Serious Diagnostic Etiology?

Various prediction rules have been described, but are mainly based on small case series. Marton and colleagues developed a discriminant function score for weight loss being due to a physical cause, but did not specifically assess prediction of malignancy. The variables that were associated with less likelihood of a physical cause of weight loss were a smoking history of less than 20 pack-years and a lack of decrease in activity. Factors that were more predictive were nausea/vomiting, recent increase in appetite, recently changed cough, or positive physical examination findings.

Hernandez and colleagues found that age greater than 80 years, white blood cell count greater than 12,000, alkaline phosphatase greater than 300 IU/L, and lactate dehydrogenase (LDH) greater than 500 IU/L were predictive of malignancy in a multivariate analysis, with albumin greater than 3.5 g/dL being negatively associated. The amount of weight loss was associated with a diagnosis of malignancy in the univariate analysis, but not in the multivariate analysis. A clinical predictive rule was developed and validated using point scores for these variables: likelihood ratios were 0.07, 1.2, and 28 for scores of less than 0, 0 to 1, and greater than 1, respectively. Therefore,
a score less than 0 or greater than 1 is clinically useful. However, the overall negative predictive value of this prediction model was 85%, not necessarily enough to exclude malignancy in a clinical situation.

Baicus and colleagues\(^3\) assessed inpatients with involuntary weight loss and derived a formula for the risk of cancer based on age older than 62 years, hemoglobin less than 10 g/dL, and erythrocyte sedimentation rate (ESR) greater than 29 mm/h. The risk for all 3 factors not being present was 9%, compared with 64% if all 3 were positive.

From the other case series, there are some associative data regarding malignancy risk. In the case series of Metalidis and colleagues,\(^2\) no patients with malignancy had a completely normal baseline evaluation, which consisted of history, examination, chest radiograph, abdominal ultrasonogram, and laboratory tests that included CBC, C-reactive protein (CRP), aspartate aminotransferase, alanine aminotransferase, LDH, alkaline phosphatase, albumin, ferritin, thyroid function tests, fasting glucose, and a urinalysis. However, the number of patients with malignancy was relatively small (n = 22). Rabinovitz and colleagues\(^2\) showed that patients with malignancy were more likely to have a low albumin level or elevated alkaline phosphatase.

**What is the Prognosis for Patients Who Present with Involuntary Weight Loss?**

In the published case series, overall mortality was high, at 16% to 38%.\(^1\)\(^9\)\(^–\)\(^2\)\(^4\) Mortality tended to be higher in patients diagnosed with malignancy. The amount of weight loss may be predictive: Chen and colleagues\(^2\) reported that of elderly patients with unexplained, unintentional weight loss, those with cancer had the most rapid weight loss, of approximately 6.5% per month. However, this study had fewer patients with

### Table 4

<table>
<thead>
<tr>
<th><strong>Diagnostic models for patients presenting with involuntary weight loss</strong></th>
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<tbody>
<tr>
<td><strong>Marton</strong></td>
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<td><strong>Developed a discriminant function model using these factors</strong></td>
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<td><strong>Hernandez</strong></td>
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<td><strong>Malignancy less likely:</strong></td>
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<td><strong>Prediction rule developed, +1 for age and WBC, +2 for alkaline phosphatase, +3 for LDH, −2 for albumin</strong></td>
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<td><strong>Baicus</strong></td>
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<td><strong>All 3 present: 9% risk</strong></td>
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<tr>
<td><strong>All 3 absent: 64% risk</strong></td>
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</table>

*Abbreviations: ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LR, likelihood ratio; WBC, white blood cells.*

*Data from Refs.\(^2\)\(^1\),\(^3\)\(^6\),\(^5\)*
malignancy in comparison with other studies. Conversely, Rabinovitz and colleagues\textsuperscript{24} did not find a difference in degree of weight loss with respect to etiology.

**SUGGESTED ALGORITHM**

A suggested algorithm is shown in Fig. 2. Patients who present with involuntary weight loss have serious illness, including malignancy, a significant percentage of the time. All

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**Fig. 2.** Suggested algorithm. CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; TSH, thyroid-stimulating hormone.
patients who present with involuntary weight loss should be evaluated, whether it is the patient’s chief complaint or is incidentally found. A working definition of 5% or greater loss of usual weight within the preceding 6 to 12 months is a reasonable starting point for evaluation. Failing to precisely meet this criterion should not preclude a workup if the clinical suspicion is high; as noted earlier, Wallace and colleagues found a 4% cutoff to be optimal in a sample of elderly veterans. In addition, weight loss over a period longer than 12 months may still be of importance to merit a workup. If weight measurements are not known, the methodology of Marton and colleagues remains reasonable (see earlier discussion). Note should be made of the obese patient for whom intended weight loss changes unexpectedly from difficult to easy; although there are few data to support it, it is reasonable to investigate whether this presentation represents involuntary weight loss.

Workup should include a discussion of the risks of the testing in the context of the patient’s overall goals of care.

A thorough history should include assessment of cardiac, respiratory, and gastrointestinal symptoms, as well as systemic signs of infection or malignancy. Assessment of depression, anxiety, or other psychiatric causes of weight loss should be undertaken, as well as screening for substance abuse and dependence. Risk factors for infection should be identified. Identification of social factors and a comprehensive medication/supplement history should be compiled.

Examination should be complete, to include the major cardiovascular, respiratory, gastrointestinal, genitourinary, dermatologic, and musculoskeletal organ systems, as well as a neurologic examination, mental status examination, and assessment for lymphadenopathy. Breast and prostate examinations should be considered.

The workup should be conducted according to a patient-centered approach. Many patients who present with involuntary weight loss are elderly with significant comorbid conditions. Elderly patients are more likely to have complex causes including social isolation, depression, and underlying frailty. Appropriate history should be taken (focusing on sense of smell, food intake, swallowing, dental pain, social support systems, and symptoms of depression) and physical examination carried out, focusing on oral-cavity examination in elderly patients with unintended weight loss.

If a leading diagnosis is suggested at the initial presentation, patients should receive confirmatory testing, if needed, and treatment begun. If treatment does not result in weight gain the workup should be reassessed, with consideration for additional testing. It is important not to provide premature diagnostic closure; though some patients with progressive chronic disease may develop weight loss as a result, there may be a separate illness that precipitates the involuntary weight loss.

If the cause is not evident after the initial history and examination, a reasonable laboratory testing strategy includes a CBC, liver function panel, renal function, blood sugar, electrolytes, calcium, thyroid-stimulating hormone, ESR, CRP, and LDH; although not specific, these are reasonable screening tests. An HIV test is now recommended as universal screening and should be ordered if a patient’s status is not known. A prostate-specific antigen test in male patients should be considered, although other tumor markers should not be routinely ordered. Appropriate imaging studies start with a chest radiograph.

Although some clinicians, in light of the case series results discussed here, would favor only performing imaging interventions if there are directed abnormalities in the initial workup, one must recognize that the case series are varied and have small sample sizes. In a patient with ongoing weight loss, it is reasonable to add abdominal imaging even if the initial laboratory tests are not revealing—either with ultrasonography, as was used in some case series, or an abdomen/pelvis computed tomography (CT)
scan. The increased sensitivity of the CT must be weighed against the risks of radiation and contrast exposure. In addition, one should consider age-appropriate cancer screening if it has not already been done, to include colorectal cancer screening, breast cancer screening, and cervical cancer screening. One must balance whether screening has already been discontinued in the elderly or medically frail patient, and whether the advent of involuntary weight loss would alter the decision making regarding the potential findings of these screening tests.

If no cause is found initially, during the course of follow-up it might be expected that a diagnosis will be found in another 10% to 20% of patients. Patients should be followed closely for ongoing weight loss, and for localizing symptoms or signs that may suggest a diagnosis.

TREATMENT

Treatment of involuntary weight loss is generally directed toward identifying and treating the underlying illness, with the presumption that treating this illness will reverse the weight loss. A systematic review of megestrol treatment for patients with cachexia caused by HIV, cancer, COPD, cystic fibrosis, and in the elderly found an increase in weight but no effect on quality of life. Another review found that there may be a small increase in weight in patients with advanced HIV treated with anabolic steroids and resistance exercise. The question is whether there is an effective treatment for involuntary weight loss of unknown etiology or while the workup is proceeding. Performing a nutritional assessment is a reasonable step, but there is as yet no conclusive data pertaining to interventions such as megestrol, cannabinoids, nutritional supplements, or enteral or parenteral feeding, in the setting of involuntary weight loss without an etiologic diagnosis.

SUMMARY

Involuntary weight loss remains an important and challenging clinical problem, with a high degree of morbidity and mortality. Because of the frequency of finding a serious underlying diagnosis, clinicians must be thorough in assessment, keeping in mind a broad range of possible causes. Although prediction scores exist, they have not been broadly validated; therefore, clinical judgment remains ever essential.

REFERENCES