

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**  
**Харківський національний медичний університет**

# **MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS**

**Management of patients with weight loss**

*Guidelines for students and interns*

## **СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ**

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## **Management of patients with weight loss**

### **General Outcome**

The students should be able to describe main links of pathogenesis, clinical features, diagnostic and treatment of different conditions which associated with weight loss.

### **The aim of this topic is to provide the student with an opportunity to:**

- Provide a basic overview of the pathophysiology, diagnosis, and classification of weight loss.
- Discuss the role of ammonia hypothesis, GABA hypothesis in etio-pathogenesis of weight loss.
- Evaluate guideline-based management strategies for the treatment of weight loss.
- Develop an individualized pharmacotherapy and monitoring plan for the management of weight loss, when given specific patient information.

### **Specific Learning Outcomes:**

- Upon successful completion of this unit, the students should be able to:
- Describe different conditions which associated with weight loss classifications.
- Describe the main mechanism of different conditions which associated with weight loss.
- Describe the main clinical features of weight loss.
- List and describe the group of drugs that are used in the treatment of weight loss and give specific examples of each.
- Make a treatment plan of patient with weight loss.

### **Students should be able to describe and define:**

1. What is meant by the term weight loss?
2. The basic mechanisms of weight loss.
3. The student should have an understanding of the pathophysiology of these diseases and be able to develop a comprehensive differential diagnosis. The student will understand the appropriate diagnostic testing. The assessment, diagnosis and management of the patient with weight loss.
4. Clinical manifestations of systemic lupus erythematosus.
5. Diagnosis of systemic lupus erythematosus.
6. Treatment of systemic lupus erythematosus.
7. Clinical manifestations of dermatomyositis.
8. Diagnosis of dermatomyositis.
9. Treatment of dermatomyositis.
10. Clinical manifestations of scleroderma.
11. Diagnosis of scleroderma.
12. Treatment of scleroderma.
14. Clinical manifestations of inflammatory bowel disease.

15. Diagnosis of inflammatory bowel disease.
16. Treatment of inflammatory bowel disease.
17. Clinical manifestations of inflammatory bowel disease.
18. Diagnosis of inflammatory bowel disease.
19. Treatment of inflammatory bowel disease.
20. Clinical manifestations of ulcerative colities.
21. Diagnosis of inflammatory ulcerative colities.
22. Treatment of inflammatory ulcerative colities.
23. Clinical manifestations of Crohn disease.
24. Diagnosis of inflammatory Crohn disease.
25. Treatment of inflammatory Crohn disease.
26. Clinical manifestations of irritable bowel disease.
27. Diagnosis of inflammatory irritable bowel disease.
28. Treatment of inflammatory irritable bowel disease.
29. Clinical manifestations of cancer.
30. Diagnosis of inflammatory cancer.
31. Treatment of inflammatory cancer.
32. Differential diagnosis.
33. Treatment of weight loss.

## **DEFENITION**

There are a number of different disease wich conducting with weight loss. Such as systemic lupus erythematosus (SLE), dermatomyositis, systemic sclerosis, inflammatory bowel disease (Chron's disease, ulcer colitis, irritable bowel disease, celiac disease) and cancer. All of the disease have different mechanic of pathophysiology accoding to the etiology of their.

In addition to psychosocial distress, anorexia/cachexia limits therapeutic options. Weight loss correlates with treatment toxicity and poor tumor response. Recent studies suggest that inflammatory cytokines associated with primary anorexia/cachexia interfere with hepatic medication metabolism and may even block chemotherapeutic anti tumor effects directly or through induction of acute-phase proteins.

Anorexia/cachexia and the frequently associated problem of fatigue are among the most common symptoms encountered in patients with advanced cancer. In some malignancies, notably non small-cell lung cancer, pancreatic cancer, and upper gastrointestinal cancers, weight loss is often present at first diagnosis. Patients with cancers not characterized by early onset of cachexia (e.g., breast, lymphoma, and colorectal cancer), may experience the syndrome in their last weeks of life.

At the first patient contact, record weight, appetite, and factors affecting food intake. Note variations in taste and smell (commonly disturbed), swallowing difficulties, and evidence of early satiety. As patients are subject to numerous secondary problems contributing to anorexia/cachexia, physicians may use an aide-memoir to ensure these problems are covered.

The profile of factors causing anorexia/cachexia no doubt varies from patient to patient. Moreover, genetic background may influence cachexia risk and response to therapy. While an etiology-based anorexia/cachexia classification system would be helpful, it remains to be defined. Definitive studies on genetic disposition are also awaited.

Specific biochemical markers of the anorexia/cachexia syndrome are not available, but less specific markers may be helpful. Patients with primary anorexia/cachexia usually have a low serum albumin and high C-reactive protein (CRP). Increasing levels of CRP provide a rough measure of chronic inflammation. Commonly, these patients are anemic with decreased lymphocyte counts. Symptoms of early satiety may be linked to abnormalities in autonomic function such as tachycardia.

In a weight-losing patient with a normal albumin and a normal or slightly elevated CRP, the physician should be particularly alert for alternate causes for weight loss.

### **The basic mechanisms of weight loss**

The anorexia/cachexia syndrome is a multi-factorial entity. While the association between contributing factors is not clearly understood, chronic inflammation has been identified as a core mechanism. Lipolysis, muscle protein catabolism, increases in acute-phase proteins (including C-reactive protein), and a rise in pro-inflammatory cytokines (notably IL-1 [interleukin-1], IL-6 [interleukin-6], TNF $\alpha$  [tumor necrosis factor alpha], and LIF [leukemia inhibitory factor]) are associated with the syndrome and are similar to the processes and substances found in the metabolic response to an acute injury.

Anorexia may be due to the effects of inflammatory cytokines on the hypothalamus with consequent changes in the balance of neurotransmitters stimulating or inhibiting food intake. Neuropeptide Y and Agouti Related Peptide (AGRP) are appetite-stimulating neurotransmitters; conversely the Opio-melanocortin and the Cocaine Amphetamine Related Factor (CART) neurotransmitter systems inhibit food intake. The "yin" and "yang" of appetite depend on the interplay between these two forces. In health, leptin, which is produced in fatty tissue, inhibits appetite, while ghrelin, a hormone mainly produced in the stomach, stimulates appetite; both act through their influence on the neurotransmitter systems described above. These physiologic regulators seem overwhelmed in cachectic patients; leptin levels are low and ghrelin levels are high, but all to no avail. The afferent loop of the appetite-satiety cycle, as described above, is better understood than the efferent loop. Relatively little is known about the translation of hypothalamic drive to energy intake and processing.

### **SYSTEMIC LUPUS ERYTHEMATOSUS**

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has protean manifestations and follows a relapsing and remitting course. More than 90 % of cases of SLE occur in women, frequently starting at childbearing age.

## Signs and symptoms

SLE is a chronic autoimmune disease that can affect almost any organ system; thus, its presentation and course are highly variable, ranging from indolent to fulminant.

In childhood-onset SLE, there are several clinical symptoms more commonly found than in adults, including malar rash, ulcers/mucocutaneous involvement, renal involvement, proteinuria, urinary cellular casts, seizures, thrombocytopenia, hemolytic anemia, fever, and lymphadenopathy.

In adults, Raynaud pleuritis and sicca are twice as common as in children and adolescents.

The classic presentation of a triad of fever, joint pain, and rash in a woman of childbearing age should prompt investigation into the diagnosis of SLE.

Patients may present with any of the following manifestations:

- Constitutional (eg, fatigue, fever, arthralgia, *weight changes*).
- Musculoskeletal (eg, arthralgia, arthropathy, myalgia, frank arthritis, avascular necrosis).
- Dermatologic (eg, malar rash, photosensitivity, discoid lupus).
- Renal (eg, acute or chronic renal failure, acute nephritic disease).
- Neuropsychiatric (eg, seizure, psychosis).
- Pulmonary (eg, pleurisy, pleural effusion, pneumonitis, pulmonary hypertension, interstitial lung disease).
- Gastrointestinal (eg, nausea, dyspepsia, abdominal pain).
- Cardiac (eg, pericarditis, myocarditis).
- Hematologic (eg, cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia).

In patients with suggestive clinical findings, a family history of autoimmune disease should raise further suspicion of SLE.

## Diagnosis

The diagnosis of SLE is based on a combination of clinical findings and laboratory evidence. Familiarity with the diagnostic criteria helps clinicians to recognize SLE and to subclassify this complex disease based on the pattern of target-organ manifestations.

The presence of 4 of the 11 American College of Rheumatology (ACR) criteria yields a sensitivity of 85 % and a specificity of 95 % for SLE.

When the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria in 2012, they classified a person as having SLE in the presence of biopsy-proven lupus nephritis with ANA or anti-dsDNA antibodies or if 4 of the diagnostic criteria, including at least 1 clinical and 1 immunologic criterion, have been satisfied.

## ACR mnemonic of SLE diagnostic criteria

The following are the ACR diagnostic criteria in SLE, presented in the «SOAP BRAIN MD» mnemonic:

- Serositis.
- Oral ulcers.
- Arthritis.
- Photosensitivity.
- Blood disorders.
- Renal involvement.
- Antinuclear antibodies.
- Immunologic phenomena (eg, dsDNA; anti-Smith [Sm] antibodies).
- Neurologic disorder.
- Malar rash.
- Discoid rash.

### *Testing*

The following are useful standard laboratory studies when SLE is suspected:

- CBC with differential.
  - Serum creatinine.
  - Urinalysis with microscopy.
- Other laboratory tests that may be used in the diagnosis of SLE are as follows:
- ESR or CRP results.
  - Complement levels.
  - Liver function tests.
  - Creatine kinase assay.
  - Spot protein/spot creatinine ratio.
  - Autoantibody tests.

### *Imaging studies*

The following imaging studies may be used to evaluate patients with suspected SLE:

- Joint radiography.
- Chest radiography and chest CT scanning.
- Echocardiography.
- Brain MRI/ MRA.
- Cardiac MRI.

### *Procedures*

Procedures that may be performed in patients with suspected SLE include the following:

- Arthrocentesis.
- Lumbar puncture.
- Renal biopsy.

See Workup for more detail.

## Management

Management of SLE often depends on the individual patient's disease severity and disease manifestations, although hydroxychloroquine has a central role for long-term treatment in all SLE patients.

### *Pharmacotherapy*

Medications used to treat SLE manifestations include the following:

- Biologic DMARDs (disease-modifying antirheumatic drugs): Belimumab, rituximab, IV immune globulin.
- Nonbiologic DMARDs: Cyclophosphamide, methotrexate, azathioprine, mycophenolate, cyclosporine.
- Nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen, naproxen, diclofenac).
- Corticosteroids (eg, methylprednisolone, prednisone).
- Antimalarials (eg, hydroxychloroquine).

See Treatment and Medication for more detail.

The classic malar rash, also known as a butterfly rash, with distribution over the cheeks and nasal bridge. Note that the fixed erythema, sometimes with mild induration as seen here, characteristically spares the nasolabial folds.



## DERMATOMYOSITIS

*Imagen 1*

Dermatomyositis is an idiopathic inflammatory myopathy with characteristic cutaneous findings that occur in children and adults. This systemic disorder most frequently affects the skin and muscles but may also affect the joints; the esophagus; the lungs; and, less commonly, the heart. Dystrophic calcinosis may complicate dermatomyositis and is most often observed in children and adolescents.

## Signs and symptoms

Persons with dermatomyositis often present with skin disease as one of the initial manifestations, and it may be the sole manifestation at onset in perhaps as many as 40 % of individuals with this condition. Cutaneous involvement may manifest as follows:

- Eruption predominantly on photo-exposed surfaces.
- Pruritus of skin lesions, sometimes intense enough to disturb sleep.
- Erythema of the mid-face.
- Eruption along the eyelid margins, with or without periorbital edema.
- Eruption on the dorsal hands, particularly over the knuckles.
- Changes in the nailfolds of the fingers.
- Eruption of the upper outer thighs.
- Scaly scalp or diffuse hair loss.



Muscle disease may occur concurrently, may precede the skin disease, or may follow the skin disease by weeks to years. Muscle involvement manifests as the following:

- Proximal muscle weakness.
- Muscle fatigue/weakness when climbing stairs, walking, rising from a seated position, combing hair, or reaching for items above shoulders.
- Muscle tenderness: May occur, but not a typical feature of dermatomyositis.

**Systemic manifestations that may occur include the following:**

- General systemic disturbances, fever, arthralgia, malaise, *weight loss*, Raynaud phenomenon.
- Dysphagia due to esophageal skeletal muscle involvement
- Gastroesophageal reflux due to esophageal smooth muscle involvement.
- Dysphonia.
- Atrioventricular defects, tachyarrhythmias, dilated cardiomyopathies.
- Gastrointestinal ulcers and infections, more common in children.
- Pulmonary involvement due to weakness of thoracic muscles, interstitial lung disease.
- Subcutaneous calcification,<sup>[4]</sup> which may result in contracture of joints; more common in children.
- Children may also develop a tiptoe gait secondary to flexion contracture of the ankles in early childhood.
- Malignancy in adult patients.

Persons with dermatomyositis often present with skin disease as one of the initial manifestations. In perhaps as many as 40 % of individuals with dermatomyositis, the skin disease is the sole manifestation at onset. Muscle disease may occur concurrently, may precede the skin disease, or may follow the skin disease by weeks to years.

Muscle involvement manifests as proximal muscle weakness. Affected patients often begin to note muscle fatigue or weakness when climbing stairs, walking, rising from a sitting position, combing their hair, or reaching for items in cabinets that are above their shoulders. Muscle tenderness may occur but is not a regular feature of dermatomyositis.

Systemic manifestations may occur; therefore, the review of systems should assess for the presence of arthralgia, arthritis, dyspnea, dysphagia, arrhythmia, and dysphonia.

Malignancy is possible in any adult patient with dermatomyositis, but it is more common in adults older than 60 years. Only a handful of children with dermatomyositis and malignancy have been reported, and malignancy does not appear to be over-represented in the pediatric (ie, <16 years) population.

A thorough history, review of systems, and assessment for previous malignancy should be performed in all patients with dermatomyositis to aid in evaluation for an associated malignancy. In the pediatric population, no further

screening is recommended, whereas in the adult population, most experts support a thorough search for malignancy with age-related malignancy screening as well as blind imaging to rule out underlying malignancy.

Dermatomyositis in children is characterized by muscle weakness and resembles the adult form of the disease. Children commonly develop a tip-toe gait secondary to flexion contracture of the ankles in early childhood. Children tend to have extramuscular manifestations, especially gastrointestinal (GI) ulcers and infections, more frequently than adults. Extramuscular manifestations of the disease may include the following:

General systemic disturbances, fever, arthralgia, malaise, *weight loss*, Raynaud phenomenon:

- Dysphagia.
- Gastroesophageal reflux.
- Atrioventricular defects, tachyarrhythmias, dilated cardiomyopathies.
- GI ulcers and infections.
- Contracture of joints.
- Pulmonary involvement due to weakness of thoracic muscles, interstitial lung disease.

Na et al found the frequency of subcutaneous calcifications to be significantly higher in juvenile dermatomyositis than adult dermatomyositis.

Several reports describe drug-induced dermatomyositis or existing dermatomyositis exacerbated by certain drugs, including statins and interferon therapy. Consequently, a medication history should be elicited in all patients.

### **Diagnosis**

Examination for cutaneous dermatomyositis may reveal the following findings:

- Characteristic, possibly pathognomonic cutaneous features: Heliotrope, Gottron papules.

- Characteristic but not pathognomonic features: Malar erythema, violaceous erythema or poikiloderma in a photosensitive distribution, violaceous erythema on the extensor surfaces, and periungual and cuticular changes.

- Violaceous erythema or poikiloderma involving the anterior chest is referred to as the "V-neck sign" whereas involvement of the upper back and shoulders is referred to as the "shawl sign"

- Rare cutaneous manifestations include vesiculobullous erosive lesions and an exfoliative erythroderma, which may be more common in patients with an associated malignancy than in those without a malignancy; biopsy samples of these manifestations reveal an interface dermatitis similar to that seen in biopsy samples of heliotrope rash, Gottron papules, poikiloderma, or scalp lesions.

Examination for muscle disease in dermatomyositis may demonstrate the following:

- Quadriparesis involving proximal musculature.

- Difficulty rising from a seated or supine position without support.
- Extensor muscles often more affected than the flexor muscles.
- Neck flexor muscle weakness.
- Distal strength, sensation, and tendon reflexes maintained (unless the patient has severely weak and atrophic muscle).

### **Testing**

Laboratory and other studies that may be helpful include the following:

- Muscle enzyme levels (eg, creatine kinase, aldolase, aspartate aminotransferase, lactic dehydrogenase).
- Myositis-specific antibodies.
- Antinuclear antibody levels.
- Pulmonary function studies with diffusion capacity.
- Electrocardiography.
- Esophageal manometry.
- Colonoscopy to screen for underlying malignancy.
- Papanicolaou smear in women for malignancy screening.
- CA-125 and CA-19-9 for malignancy screening.

### **Imaging studies**

The following imaging studies may be used in the evaluation of dermatomyositis:

- MRI or ultrasonography of the muscles.
- Chest radiography.
- Barium swallow.
- Electromyography.
- Imaging to screen for underlying malignancy, including CT scanning of the chest, abdomen, and pelvis, as well as transvaginal ultrasound and mammography for women.

### **Procedures**

The following procedures may be helpful in the evaluation of dermatomyositis:

- Skin biopsy.
- Muscle biopsy (open or via a needle): Findings can be diagnostic (perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration).

### **Differential diagnoses**

- Discoid Lupus Erythematosus.
- Graft Versus Host Disease.
- Lichen Myxedematosus.
- Lichen Planus.
- Multicentric Reticulohistiocytosis.
- Parapsoriasis.

- Pityriasis Rubra Pilaris.
- Polymorphous Light Eruption.
- Psoriasis.
- Rosacea.
- Sarcoidosis.
- Subacute Cutaneous Lupus Erythematosus (SCLE).
- Systemic Lupus Erythematosus (SLE).
- Tinea Corporis.

### **Management**

Therapy for the muscle component of dermatomyositis involves the use of corticosteroids, typically with an immunosuppressive agent. Therapy for the skin disease includes the following, among other options:

- Sun avoidance.
- Sunscreens and photoprotective clothing.
- Topical corticosteroids.
- Antimalarial agents.
- Methotrexate.
- Mycophenolate mofetil.
- Immune globulins.

### **Pharmacotherapy**

Medications used in the management of dermatomyositis include the following:

- Corticosteroids (eg, prednisone): Prednisone is a first-line therapy for muscle involvement in dermatomyositis.
- Immunosuppressive agents (eg, methotrexate, mycophenolate mofetil, azathioprine, rituximab, sirolimus).
- Immune globulins (eg, intravenous or subcutaneous immunoglobulin).
- Antimalarial agents (eg, hydroxychloroquine, chloroquine).

In addition to the medications listed above, diltiazem, colchicine, alendronate, and warfarin are among the medications that have shown potential benefit in treating calcinosis. Surgical excision of focal, tender calcinotic lesions is also considered a therapeutic option.

### **Nonpharmacotherapy**

General therapeutic measures may include the following:

- Physical therapy and rehabilitative measures.
- Sun avoidance.
- Sun-protection (eg, broad-spectrum sunscreens, sun protective clothing).
- Elevation of head of bed.
- Avoidance of eating before bedtime.

## **Surgery**

Surgical care is usually unnecessary in the management of dermatomyositis. However, some patients may benefit from surgical removal of localized areas of calcinosis, particularly those that are painful.

The mainstay of therapy for the muscle disease is systemically administered corticosteroids. Traditionally, prednisone (0.5–2 mg/kg/d) up to a dose of 60 mg/d is given as initial therapy. The drug should be slowly tapered to avoid relapse of the disease. Because most patients develop steroid-related toxic effects, most authorities administer a steroid-sparing immunosuppressive or cytotoxic agent early in the course. Drugs reported to be steroid-sparing in some patients or in small open-label studies have included the following:

1. Methotrexate.
2. Azathioprine.
3. Cyclophosphamide.
4. Cyclosporine.
5. Mycophenolate mofetil.
6. Leflunomide.
7. Chlorambucil.

Generally, methotrexate, mycophenolate mofetil, or azathioprine are used first line as glucocorticoid-sparing agents for muscle involvement. Response rates to methotrexate have been reported to be between approximately 70–80 %. In addition, one small, randomized trial supported the long-term benefits of azathioprine as compared with prednisone monotherapy. Results with cyclophosphamide in severe cases have been disappointing.

For refractory cases, the use of monthly high-dose intravenous immune globulin (IVIG) for 6 months has proved beneficial in the short term. In addition to its positive effects on refractory muscle and skin disease, IVIG has been reported to be beneficial for other systemic manifestations, including severe esophageal dysfunction.

Rituximab, a chimeric antibody directed against CD20+ B cells, may be effective, but results have been mixed. In a recent multicenter, randomized, double-blind placebo-controlled trial of 44 weeks of rituximab therapy in patients with dermatomyositis and polymyositis, most patients experienced improvement in muscle disease activity; however, no significant differences were noted between groups based on muscle parameters. The study had a delayed-start design, with rituximab started immediately in one arm and after 8 weeks in the second arm, which is speculated to have influenced the results.

Recently, an analysis of 195 patients with polymyositis and dermatomyositis looked to determine predictors of response to rituximab, and found that antisynthetase and anti-Mi2 autoantibodies, as well as lower disease damage and juvenile-onset disease, were predictors of clinical improvement with rituximab.



**Image 2.** These lesions on dorsal hands demonstrate photodistribution of dermatomyositis. Note sparing of interdigital web spaces

## SYSTEMIC SCLEROSIS

Systemic sclerosis is a complex and heterogeneous disease with clinical forms ranging from limited skin involvement (limited cutaneous systemic sclerosis) to forms with diffuse skin sclerosis and severe and often progressive internal organ involvement (diffuse cutaneous systemic sclerosis), and occasionally a fulminant course (fulminant systemic sclerosis).

Limited cutaneous systemic sclerosis involves areas distal to the elbows and knees but may involve the face and neck. CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias – although not all are needed for the disorder to be called CREST) is an older term used to describe this subset of limited cutaneous systemic sclerosis.

Diffuse cutaneous systemic sclerosis refers to skin thickening affecting the trunk and the skin of the extremities proximal to the elbows and knees besides involvement of the face. There are rare cases of typical systemic sclerosis internal organ involvement in the absence of clinically apparent cutaneous involvement, a clinical subset known as "scleroderma sine scleroderma".

Systemic sclerosis involvement is most obvious in the skin; however, the gastrointestinal tract as well as the respiratory, renal, cardiovascular, musculoskeletal, endocrine, and genitourinary systems are frequently involved.

In 2013, a joint committee of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) published a revised classification criteria for systemic sclerosis, to improve the sensitivity of the widely used previous classification criteria. The revised criteria for the classification of systemic sclerosis are listed in *table 1, below*.

The purpose of classification criteria is to enroll a uniform population of patients in research studies and it is based on various parameters that are commonly used for systemic sclerosis diagnosis. It is important to emphasize that these criteria are not diagnostic criteria and are not applicable to patients with scleroderma-like disorders or to patients with skin thickening sparing the fingers.

Table 1

**ACR/EULAR Revised Systemic Sclerosis Classification Criteria**

Item	Sub-item(s)	Score*
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints ( <i>presence of this criterion is sufficient criterion for SSc classification</i> )	None	9
Skin thickening of the fingers ( <i>count the higher score only</i> )	Puffy fingers	2
	Sclerodactyly (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions ( <i>count the higher score only</i> )	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	None	2
Abnormal nailfold capillaries	None	2
Pulmonary arterial hypertension and/or interstitial lung disease ( <i>maximum score is 2</i> )	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon	None	3
Systemic sclerosis–related autoantibodies ( <i>maximum score is 3</i> )	Anticentromere	3
	Anti–topoisomerase I	3
	Anti–RNA polymerase III	3
*The total score is determined by adding the maximum score in each category. Patients with a total score equal to or greater than 9 are classified as having definite systemic sclerosis (modified from van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. <i>Arthritis Rheum.</i> Nov 2013;65(11):2737-47.)		

Signs and symptoms of systemic sclerosis may involve the following systems:

- Skin.
- Vascular.
- Gastrointestinal (GI).
- Respiratory.
- Musculoskeletal.
- Cardiac.
- Renal.
- Genitourinary.
- Eyes, ears, nose, and throat.
- Endocrine – Hypothyroidism.
- Neurologic/psychiatric.
- Constitutional.

**Skin manifestations**

Skin manifestations of systemic sclerosis are as follows:

- Progressive skin tightness and induration, often preceded by swelling and puffiness (edematous stage) that does not respond to diuretic therapy.
- Skin induration initially affects the fingers (sclerodactyly) and extends proximally (see image below).



**Imagen 3.** Tightening of the skin in the face, with a characteristic beaklike facies and paucity of wrinkles

- Tightening of the skin in the face is often noted very early in the course of the disease (see image below).



**Image 4.** Sclerodactyly with digital ulceration, loss of skin creases, joint contractures, and sparse hair

- Prominent skin pigmentary changes both hyperpigmentation and hypopigmentation (see image below).



**Image 5.** Anterior chest demonstrating salt-and-pepper hypopigmentation and diffuse hyperpigmentation in a white woman

- Diffuse pruritus

### **Vascular manifestations**

Raynaud phenomenon is part of the initial presentation in 70 % of patients with systemic sclerosis; 95 % eventually develop it during the course of their disease. Raynaud phenomenon may precede obvious systemic sclerosis features by months or even years.

Raynaud phenomenon that is not associated with systemic sclerosis or other autoimmune diseases is known as primary Raynaud phenomenon. It occurs in 5–15 % of the general population. The female-to-male ratio is 4:1, with onset occurring usually during adolescence.



Other vascular manifestations of systemic sclerosis include the following:

- Healed pitting ulcers in fingertips.
- Large fingertip ulcers may lead to finger amputation.
- Cutaneous and mucosal telangiectasias.
- Evidence of macrovascular involvement including non-atherosclerotic myocardial infarction.

### **Gastrointestinal manifestations**

GI findings in systemic sclerosis include the following:

• Gastroesophageal reflux caused by lower esophageal sphincter (LES) incompetence and decreased or absent peristalsis in the lower two thirds of the esophagus (may lead to hoarseness, dysphagia and aspiration pneumonia).

- Dyspepsia, bloating, and early satiety.
- Intestinal pseudo-obstruction.
- Constipation alternating with diarrhea from bacterial overgrowth (may lead to malabsorption).
- Fecal incontinence.

• Malnutrition from inadequate caloric intake.

• Chronic iron deficiency anemia from occult blood loss.

### **Respiratory manifestations**

Respiratory complaints in systemic sclerosis include the following:

- Progressive dyspnea
- Chest pain (precordial) due to pulmonary artery hypertension
- Dry persistent cough due to restrictive lung disease

### **Musculoskeletal manifestations**

Musculoskeletal complaints in systemic sclerosis include the following:

- Arthralgia.
- Myalgia.
- Loss in joint range of motion and joint flexion contractures.
- Tendon friction rubs.
- Symptoms of carpal tunnel syndrome.
- Muscle weakness.

### **Cardiac manifestations**

Cardiac signs and symptoms in systemic sclerosis include the following:

- Dyspnea due to congestive heart failure or myocardial fibrosis.
- Palpitations, irregular heart beats, and syncope due to arrhythmias or conduction abnormalities.
- Symptoms of congestive heart failure or right sided heart failure.
- Systemic sclerosis is an independent risk factor for acute myocardial infarction.

## **Renal manifestations**

Renal signs and symptoms in systemic sclerosis include the following:

- Hypertension.
- Renal crisis.
- Chronic renal insufficiency.
- History of high dose corticosteroid use.

## **Genitourinary manifestations**

Patients with systemic sclerosis may present with the following:

- Erectile dysfunction.
- Bladder fibrosis.
- Dyspareunia (if introitus is affected).
- Vaginal narrowing, dryness and pain caused by vaginal fibrosis.

## **Eyes, ears, nose, and throat manifestations**

Patients may present with the following:

- Sicca syndrome.
- Poor dentition secondary to sicca syndrome.
- Loosening of dentition caused by alterations in the tooth suspensory ligament and thickening of the periodontal membrane.
- Hoarseness due to acid reflux with vocal cord inflammation or fibrosis.
- Increased risk for tongue cancer.
- Decreased oral aperture.
- Blindness caused by retinal artery occlusion.

## **Neurologic/psychiatric manifestations**

Patients may present with the following:

- Facial pain and decreased sensation due to trigeminal neuralgia.
- Hand paresthesias and weakness due to carpal tunnel peripheral entrapment neuropathy.
- Headache and stroke during hypertensive renal crisis.
- Depression and anxiety.

## **Constitutional manifestations**

Constitutional complaints in systemic sclerosis include the following:

- Fatigue.
- Weight loss.
- Loss of appetite.

The following disorders may present clinical similarities with systemic sclerosis ("scleroderma mimics") and need to be included in the differential diagnosis:

- Nephrogenic Systemic Fibrosis.
- Eosinophilic Fasciitis.
- Eosinophilia-Myalgia Syndrome.

- Graft Versus Host Disease.
- Reflex Sympathetic Dystrophy.
- Generalized morphea.
- Diabetic cheiroarthropathy.
- Porphyria cutanea tarda.
- Morphea.
- Linear scleroderma.
- Radiation exposure.
- Scleromyxedema (generalized lichen myxedematosus).
- Scleredema adultorum of Buschke.
- Scleredema diabeticorum.

Gadolinium-based contrast agents, bleomycin, pentazocine, and several other drugs and chemicals have been shown to cause disorders resembling systemic sclerosis. These must be considered in the differential diagnosis.

The diagnosis of systemic sclerosis is based on the clinical manifestations. Nevertheless, a number of tests and procedures may be used in the initial diagnosis (eg, to exclude alternative diagnoses), the assessment of organ involvement, and monitoring of disease progression.

Laboratory testing may include the following:

- Complete blood cell count (CBC).
- Serum muscle enzyme levels.
- Erythrocyte sedimentation rate.
- Serum CXCL4 level.
- N-terminal pro-brain natriuretic peptide.
- Autoantibody assays.

### **Assessment of gastrointestinal involvement**

Conventional radiography is the principal imaging study for assessment of gastrointestinal involvement in systemic sclerosis. Plain abdominal radiographs may reveal pseudointestinal obstruction, or rarely pneumatosis cystoides intestinalis. Esophagogastroduodenoscopy with appropriate biopsies, esophageal manometry assessment, and pH monitoring studies should be performed to survey and evaluate the upper gastrointestinal system, including documentation of esophageal dysmotility and an incompetent lower esophageal sphincter. A gastric emptying study should be performed to document delayed gastric emptying. Colonoscopy can identify wide-mouth colonic diverticula, which are uniquely characteristic for systemic sclerosis.

### **Assessment of pulmonary involvement**

Chest radiography is an insensitive imaging procedure that typically shows only late findings of pulmonary fibrosis, such as increased interstitial markings. High-resolution computerized tomography (HRCT) is highly sensitive

for revealing pulmonary involvement. HRCT scanning should be performed every 6 months if active alveolitis or interstitial pulmonary fibrosis is present and every year if these abnormalities are not present. For more information, see Thoracic Scleroderma Imaging.

Pulmonary function testing is important in all patients with systemic sclerosis, although lung volumes may correlate poorly with the extent of interstitial lung disease. Results of pulmonary function testing are ultimately abnormal in 80 % of the patients. Pulmonary function tests should be performed every 6 to 12 months to detect early abnormalities indicative of development and/or progression of pulmonary hypertension or pulmonary fibrosis.

Bronchoscopy with bronchoalveolar lavage is used to differentiate active infections from progressive interstitial lung disease.

### **Assessment of cardiovascular involvement**

Elevated CXCL4 serum levels correlate with the severity of pulmonary fibrosis and progression of pulmonary hypertension. Elevated serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) may correlate with early pulmonary hypertension.

Electrocardiograms (ECGs) should be performed routinely to identify arrhythmias and conduction defects. ECGs can identify early changes of right ventricular strain caused by pulmonary hypertension, and in advanced states, right atrial hypertrophy. Perform 24-hour ambulatory Holter monitoring to evaluate arrhythmias and serious conduction defects.

Transthoracic echocardiography is a noninvasive study for assessing pulmonary artery pressure. Conduct this test to evaluate the patient's pulmonary artery pressure at initial evaluation and during serial follow ups and to assess septal fibrosis or pericardial effusions.

Right-heart catheterization is the standard criterion and only definitive test for diagnosing pulmonary hypertension. It is usually performed after an elevated pulmonary artery pressure is found on echocardiographic screening.

## **INFLAMMATORY BOWEL DISEASES**

### **Classification**

In recent years, investigators have readdressed the complex issues involved in the classification of inflammatory bowel diseases.

The perspectives of basic scientists have been subtly different, driven by an attempt to understand the pathophysiology of the different manifestations of Crohn's disease, ulcerative colitis, and indeterminate colitis.

In 2003, a Working Party of investigators with an interest in the issues involved in disease subclassification was formed, with the objective of summarising recent developments in disease classification and examining the practicability of developing an integrated clinical, molecular, and serological classification of inflammatory bowel disease. The results of the Working Party were reported at

the 2005 Montreal World Congress of Gastroenterology. There are two classification for Crohn's disease and ulcerative colitis.

**Table 2**

**Vienna and Montreal classification for Crohn's disease**

	Vienna	Montreal
Age at diagnosis	A1 below 40 y	A1 below 16 y
	A2 above 40 y	A2 between 17 and 40 y
		A3 above 40 y
Location	L1 ileal	L1 ileal
	L2 colonic	L2 colonic
	L3 ileocolonic	L3 ileocolonic
	L4 upper	L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating	B1 non-stricturing, non-penetrating
	B2 stricturing	B2 stricturing
	B3 penetrating	B3 penetrating
		p perianal disease modifier†

*\*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present; †"p" is added to B1–B3 when concomitant perianal disease is present.*

**Table 3**

**Montreal classification of extent of ulcerative colitis (UC)**

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

**CROHN'S DISEASE AND ULCERATIVE COLITIS**

Crohn's disease is a lifelong disease arising from an interaction between genetic and environmental factors, but observed predominantly in developed countries of the world. The precise aetiology is unknown and therefore a causal therapy is not yet available.

Symptoms suggestive of CD can be caused by motility disturbances or bile malabsorption, which underscores the need for confirmation of inflammatory, penetrating or fibrotic lesions. Intestinal Crohn's disease affecting b30 cm in extent. This usually applies to an ileocaecal location (b30 cm ileum±right colon), but could apply to isolated colonic disease, or conceivably to proximal small intestinal disease.

Symptoms of CD are heterogeneous, but commonly include diarrhoea for more than 6 weeks, abdominal pain and / or weight loss. These symptoms

should raise the suspicion of CD, especially in patients at a young age. Systemic symptoms of malaise, anorexia, or fever are common.

Chronic diarrhoea is the most common presenting symptom a definition of a decrease in faecal consistency for more than 6 weeks may be adequate to differentiate this from self limited, infectious diarrhoea. More acute presentations may occur, and acute terminal ileal Crohn's disease may be mistaken for acute appendicitis. Chronic non-specific symptoms mimicking irritable bowel syndrome (IBS), unexplained anaemia and growth failure in children should also be considered to avoid delayed diagnosis. Abdominal pain and *weight loss* are seen in about 70 and 60 % respectively of patients before diagnosis. Although the irritable bowel syndrome is more common than CD, associated systemic symptoms, blood in stools and weight loss, should always trigger further investigations. Blood and/or mucus in the stool may be seen in up to 40 to 50 % of patients with Crohn's colitis, but less frequently than in ulcerative colitis (UC). Patients may present with extraintestinal manifestations of Crohn's disease before the gastrointestinal symptoms become prominent. Abnormalities of the musculoskeletal system are the most common extraintestinal manifestations of IBD, encompassing peripheral and axial joints. Extraintestinal manifestations are most common when CD affects the colon. Perianal fistulas are present in 10 % of patients at the time of diagnosis, and may be the presenting complaint.

The macroscopic diagnostic tools include physical examination, endoscopy, radiology, and examination of an operative specimen. Microscopic features can be only partly assessed on mucosal biopsy, but completely assessed on an operative specimen. The diagnosis depends on the finding of discontinuous and often granulomatous intestinal inflammation. The current view is that the diagnosis is established by a nonstrictly defined combination of clinical presentation, endoscopic appearance, radiology, histology, surgical findings and, more recently, serology. This still results in diagnostic obstacles. A change in diagnosis to UC during the first year occurs in about 5 % of cases. IBD restricted to the colon that cannot be allocated to the CD or UC category is best termed colitis unclassified and the term indeterminate colitis confined to operative specimens as originally described. A single gold standard for the diagnosis of CD is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Genetic testing is currently not recommended for routine diagnosis or management of CD.

A full history should include detailed questioning about the onset of symptoms, recent travel, food intolerances, medication (including antibiotics and non-steroidal anti-inflammatory drugs), and history of appendicectomy. Particular attention should be paid to well proven risk factors including smoking, family history, and recent infectious gastroenteritis.

Careful questioning about nocturnal symptoms, features of extraintestinal manifestations involving the mouth, skin, eye, or joints, episodes of perianal abscess, or anal fissure is appropriate. General examination includes general wellbeing, pulse rate, blood pressure, temperature, abdominal tenderness or distension, palpable masses, perineal and oral inspection, and rectal digital examination. Measurement of body weight and calculation of body mass index are recommended.

Check for signs of acute and/or chronic inflammatory response, anaemia, fluid depletion, and signs of malnutrition or malabsorption. Initial laboratory investigations should include CRP, and full blood count. If C-reactive protein is not available, then measurement of the erythrocyte sedimentation rate (ESR) may be used. Other biochemical markers may also be used to identify gut inflammation, in particular faecal calprotectin. Microbiological testing for infectious diarrhea including *Clostridium difficile* toxin is recommended. Additional stool tests may be needed for patients who have travelled abroad.

For suspected CD, ileocolonoscopy and biopsies from the terminal ileum as well as each colonic segment to look for microscopic evidence of CD are first line procedures to establish the diagnosis. Irrespective of the findings at ileocolonoscopy, further investigation is recommended to examine the location and extent of any CD in the upper gastrointestinal tract or small bowel.

Anaemia and thrombocytosis represent the most common changes in the full blood count of patients with CD. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are standard laboratory surrogates of the acute phase response to inflammation. The CRP broadly correlates with disease activity of CD assessed by standard indices and indicates serial changes in inflammatory activity because of its short half life of 19 h. The ESR less accurately measures intestinal inflammation in CD by reflecting changes of plasma protein concentration and packed cell volume. The ESR increases with disease activity, but correlates better with colonic rather than ileal disease. Estimation of faecal markers of inflammation have been shown to correlate well with intestinal inflammation, particularly faecal calprotectin, which has a positive predictive value of 85–90 % in distinguishing IBD from irritable bowel syndrome 36–40 and lactoferrin. However, while these markers have been tested in relatively small populations as diagnostic markers, most evidence comes from studies performed on patients with CD predicting relapse rather than in initial diagnosis. Improved diagnostic accuracy may come from newer tests including faecal S100A12. None of the above parameters is specific enough to permit differentiation from UC or enteric infection. Evidence for a pathophysiological role of certain strains of luminal bacteria in genetically susceptible hosts in CD comes from animal models and studies on innate immunity. None yet have a diagnostic role. The value of routine stool examination in patients with suspected CD or exacerbations of disease arises from both the differential diagnosis and high concordance with enteric infections such as *C. difficile*.

Colonoscopy with multiple biopsy specimens is well established as the first line procedure for diagnosing colitis. Ileoscopy with biopsy can be achieved with practice in at least 85 % of colonoscopies and increases the diagnostic yield of CD in patients presenting with symptoms of IBD. The most useful endoscopic features of CD are discontinuous involvement, anal lesions and cobblestoning. Colonoscopy assesses the anatomical severity of CD colitis with a high specificity. Anatomical criteria of severity are defined as deep ulcerations eroding the muscle layer, or mucosal detachments or ulcerations limited to the submucosa but extending to more than one third of a defined colonic segment (right, transverse, and left colon). When there is severe, active disease, the value of full colonoscopy is limited by a higher risk of bowel perforation and diagnostic errors are more frequent. In these circumstances initial flexible sigmoidoscopy is safer and ileocolonoscopy postponed until the clinical condition improves. The scoring of endoscopic disease activity in CD is reserved for clinical studies. 10 Ileoscopy is superior for the diagnosis of CD of the terminal ileum when compared with radiology techniques, including MR and CT, specially for mild lesions. Capsule endoscopy and enteroscopy with biopsy by a push endoscope are safe and useful procedures for diagnosis of CD in selected patients with suggestive symptoms after failure of radiologic examinations. A plain abdominal radiograph is valuable in the initial assessment of patients with suspected severe CD by providing evidence of small bowel or colonic dilatation, calcified calculi, sacroiliitis, or the impression of a mass in the right iliac fossa. It is not a diagnostic test for CD.

MR and CT enterography or enteroclysis is an imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement and penetrating lesions in CD [EL1b, RGB]. Radiation exposure should be considered when selecting techniques. Because of the lower sensitivity of barium studies, alternative techniques are preferred if available. Transabdominal ultrasonography is a useful additional technique for assessing bowel inflammation.

CT and MR are the recommended techniques for detection of extramural complications of CD. Transabdominal ultrasonography may also be used, but diagnostic accuracy is lower.

Small bowel capsule endoscopy (SBCE) should be reserved for patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileocolonoscopy and radiological examinations (SBE/SBFT or CTE or MRE). Double balloon enteroscopy (DBE) should be reserved for specific situations in which biopsy samples from suspected involved areas are important for diagnosis or in which a dilatation of strictures is reasonable.

### **Combined microscopic features**

Focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation and patchy chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas (not related to crypt injury) are the generally



accepted microscopic features which allow a diagnosis of Crohn's disease. The same features and, in addition, an irregular villous architecture, can be used for analysis of endoscopic biopsy samples from the ileum. If the ileitis is in continuity with colitis, the diagnostic value of this feature should be used with caution.

The microscopic features for the diagnosis and grading of dysplasia – intraepithelial neoplasia of the colon in Crohn's disease are the same as those proposed for ulcerative colitis and, similarly, a second opinion is recommended for a firm diagnosis.

As for ulcerative colitis, sporadic adenomas may be difficult to distinguish from dysplasia-associated lesions or masses (DALM). The distinction is however important, because the management of sporadic adenomas differs from that of colitis-associated dysplasia. The patient's age, the site and morphology of the lesion, along with biopsies of flat surrounding mucosal, may be helpful in this distinction.

Histology is routinely used for the diagnosis of ulcerative colitis (UC) and Crohn's disease (CD). The occurrence of healing of mucosal inflammation has already been noted as a feature of resolution in UC. Therefore, biopsies are used to discriminate between quiescent disease, inactive disease and different grades of activity in UC. This has led to the introduction of scoring systems for the assessment of disease activity in UC and their use in clinical drug trials.

### **Management patient with CD**

The early use of azathioprine/mercaptopurine or methotrexate in combination with steroids is an appropriate option in moderately active localized ileocaecal CD. Anti-TNF therapy should be considered as an alternative for patients with objective evidence of active disease who have previously been steroid refractory, steroid-dependent, or steroid-intolerant. For those patients with severely active localised ileocaecal Crohn's disease and objective evidence of active disease who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option [for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. All currently available anti-TNF therapies appear to have generally similar efficacy and adverse-event profiles for inflammatory ("luminal") Crohn's disease, so the choice depends on availability, route of delivery, patient preference, cost and national guidelines. Patients receiving azathioprine or mercaptopurine who relapse should be evaluated for adherence to therapy and have their dose optimised. Changing their maintenance therapy to methotrexate or anti-TNF therapy should be considered. Surgery should always be considered as an option in localised disease.

Mildly active localised ileocaecal Crohn's disease. Budesonide 9 mg daily is the preferred treatment. The benefit of mesalazine is limited. Antibiotics cannot be recommended. No treatment is an option for some patients

with mild symptoms. Antibiotics (metronidazole, ciprofloxacin), with or without mesalazine, are not recommended, because side-effects are commonplace. The same applies to nutritional therapy, which is often poorly tolerated by adults, although there are case series or small trials that have shown these treatments to be modestly effective.

Moderately active localised ileocaecal Crohn's disease. Moderately active, localised ileocaecal Crohn's disease should preferably be treated with budesonide 9 mg/day, or with systemic corticosteroids. Antibiotics can be added if septic complications are suspected. Azathioprine/6-mercaptopurine or methotrexate in combination with steroids is also an appropriate option. Anti-TNF therapy should be considered as an alternative for patients with objective evidence of active disease, who have previously been steroid-refractory, -dependent, or-intolerant. Risks should be carefully considered and discussed with patients. An effective approach to minimizing steroid therapy is the early introduction of anti-TNF agents. Selection of patients appropriate for biological therapy depends on clinical characteristics, previous response to other medical therapies, phenotype and co-morbid conditions. Certain patient populations may derive greater benefit from the early introduction of biological therapy, including steroid-refractory.

Severely active localised ileocaecal Crohn's disease. Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of active disease [for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Surgery is a reasonable alternative for some patients and should also be considered and discussed.

Colonic disease. Active colonic CD may be treated with sulfasalazine if only mildly active, or with systemic corticosteroids. For those who have relapsed, anti-TNF therapy with or without an immunomodulator is an appropriate option for patients with objective evidence of moderate or severely active disease [for infliximab]. For some patients who have infrequently relapsing disease, restarting steroids with an immunomodulator may be appropriate. Before initiating immunomodulator or anti-TNF therapy, surgical options should also be considered and discussed.

Extensive small bowel disease. Extensive small bowel Crohn's disease should be treated with systemic corticosteroids and thiopurines or methotrexate. For patients who have relapsed, anti-TNF therapy with or without azathioprine is an appropriate option if there is objective evidence of moderate or severely active disease. Adjunctive nutritional support is appropriate. Surgical options should also be considered and discussed at an early stage.

## **CANCER**

Cancer cachexia is not due to reduced nutritional intake. Enteral/parenteral feeding does not reverse the syndrome. Associated metabolic abnormalities often precede rather than follow initial weight loss.

Malignancies produce chemicals that also contribute to cachexia in some patients. Both lipolytic and proteolytic substances have been discovered in rodents and humans with cancer. Some tumors also directly produce inflammatory cytokines. Raised basal metabolism, changes in autonomic control mechanisms (favoring increased sympathetic activity), and alterations in hormone production (e.g., reduced testosterone levels) are often observed. The interaction between chronic inflammation, tumor cachectic products, and other associated pathophysiologic features is unclear. The panoply of abnormalities suggests common root causes with a cascade of imbalances within the neuro-hormonal immune axis. There is not yet one mediator of the anorexia/cachexia syndrome that clearly explains all its features. Inflammatory cytokines, specifically TNF $\alpha$ , IL-1 $\beta$ , IL-6, as well as others, may play a causative role.

## **PROGNOSIS**

Loss of greater than 5 % of pre-morbid weight prior to chemotherapy predicts a significantly shorter survival. This is independent of disease stage, tumor histology, and patient performance status. There is also a trend towards lower chemotherapy response rates among weight-losing cancer patients. Anorexia is also a powerful predictor of early death. Patients with a loss of appetite have a far worse prognosis than those who maintain their appetite. This observation persists even after adjusting for several other prognostic parameters. Thus, both weight loss and anorexia predict a poor prognosis for patients with advanced cancer.

## **TREATMENT OF WEIGHT LOSS**

Treat reversible cause such as anxiety-depression, oral thrush, constipation, poorly controlled pain, and early satiety, each of which, if present, strongly influences appetite, motivation, and mobility.

### **Anorexia**

Strong evidence suggests that corticosteroids and progestational agents are effective at improving appetite if appropriate doses are used.

### **Corticosteroids**

The relative efficacy of various corticosteroids is also thought to be equivalent. Dexamethasone is often selected because of its absence of mineralocorticoid effects. Dexamethasone has been demonstrated to improve appetite on a short-term basis in patients with advanced disease. Subsequent placebo-controlled clinical trials have replicated this finding. A common dosing regimen is:

Dexamethasone 2–8 mg PO q AM.

While corticosteroids increase appetite, they are catabolic and reduce muscle mass and function. Appetite stimulation is usually transient and ceases to be helpful after 3–4 weeks. Moreover, fluorinated corticosteroids (e.g., dexamethasone) are particularly prone to cause muscle breakdown. Long-term use is therefore not recommended in mobile patients. If longer term use is deemed necessary, consider switching from dexamethasone to an alternate corticosteroid (e.g., prednisolone). A common dose range is:

Prednisolone 20–40 mg PO q AM.

Progestational agents increase appetite and weight in 35–60 % of patients. Megestrol acetate is the best-studied progestational agent. Megestrol acetate oral suspension has gained popularity because of its improved bio-availability. There is, however, a significant food effect. The medication is best absorbed when taken along with a high-fat meal.

Start with megestrol acetate 400 mg/day. If appetite has not improved within approximately 2 weeks, escalate to megestrol acetate 600–800 mg/day.

The length of response to megestrol is longer than to corticosteroids. The weight gained is primarily as fat (not a bad outcome in its own right). A recent geriatric study suggests that megestrol also has catabolic effects on muscle. Adrenal suppression may also occur, as with any agent with glucocorticoid effects.

The mode of action of corticosteroids and progestational agents is not fully established. They both reduce the production of inflammatory cytokines. Whether direct positive effects on the hypothalamic feeding centers occur is not certain.

Both megestrol acetate and dexamethasone are relatively well tolerated overall. There is a slight risk of thromboembolic episodes with megestrol acetate. This risk is higher in patients receiving concomitant chemotherapy. A history of thrombophlebitis is a relative contraindication for prescribing megestrol acetate or another progestational agent.

Patients on megestrol acetate may need to receive corticosteroid repletion in the face of serious infections, trauma, or surgery because of the adrenal suppression.

In contrast, dexamethasone puts patients at risk for myopathy, cushingoid body habitus, and peptic ulcer disease. These side effect profiles play some role in determining which agent might be better for a specific patient.

In general, patients with a life expectancy of a few months or more may do better with megestrol acetate. Those with a life expectancy of only a few weeks, or those with a history of thrombophlebitis, may be able to get by with dexamethasone, as they are less likely to suffer side effects from corticosteroids in the short term.

### **Increase gastric emptying**

Patients may attribute their poor appetite to "feeling full", either all of the time or shortly after eating. Early satiety may stem from abnormal hypothalamic signals and/or autonomic abnormalities with consequent delay in gastric emptying. Metoclopramide and domperidone may relieve early satiety through stimulation of gastric emptying. The 14-ring macrolide antibiotics (e.g., erythromycin and clarithromycin) also stimulate gastric emptying. Their use in cancer patients has only been studied in a few small Japanese trials. Common dosing regimens are:

- Metoclopramide, 10–20 mg PO q 6 h (ac & HS).
- Domperidone 10–20 mg PO q 6 h (ac & HS).

Many pharmacologic agents for the cancer anorexia/weight loss syndrome have been tried. Among the medications that have been tested (*table 4*) and those that require further testing (*table 5*), two classes of agents stand out for their efficacy: progestational agents and corticosteroids.

**Table 4**

#### **Agents Tested That Do Not Benefit Anorexia/Cachexia Syndrome**

Cyproheptadine	Fluoxymesterone
Dronabinol	Hydrazine sulfate
Eicosapentaenoic acid	Pentoxifylline

**Table 5**

#### **Potentially Effective Agents for Anorexia That Require Further Study**

Adenosine triphosphate	Thalidomide
Creatine	TNF alpha inhibitors
Oxandrolone	

The question of whether or not we can increase appetite and sustain muscle has only recently been addressed, and results from small trials are encouraging but not definitive.

Muscle maintenance is dependent upon:

- Maintaining an adequate supply of efficient nutrients.
- Ability to process sources of energy.
- Ability to balance muscle synthesis and proteolysis.

Based on this triad, a variety of single-agent trials have recently reported promising results.

### **Anabolic agents-androgens**

Athletes have known for years that androgens build muscle. The medical profession has been slow to turn this observation to patient advantage, possibly because of the stigma associated with medications of abuse or because of adverse event concerns.

Fluoxymesterone can increase appetite, although not to the level achieved with megestrol. More recent reports show that oxandrolone, a steroid thought to be

more anabolic with less androgenic properties, will boost appetite, lean body mass, and function. Not surprisingly, as illustrated by some Olympic and professional athletes, combining exercise with androgen intake strongly enhances muscle size and function. Safer anabolic medications may include oxandrolone and testosterone undecenoate (less risk of hepatic toxicity). In hypogonadal patients, consider testosterone replacement.

### **Omega-3 fatty acids**

The omega-3 fatty acids that we find in dark, fatty fish (e.g., salmon, tuna, sardines, and herring) have anti-inflammatory cytokine effects. They may also limit muscle proteolysis. In rodent studies, anti-tumor effects and reduction of chemotherapy toxicity are also commonly reported.

Phase II trials in pancreatic cancer patients and one small, randomized trial enrolling patients with various cancers have shown that omega-3s, if taken in doses providing at least 2 grams of eicosapentaenoic acid (EPA) daily, had favorable effects on inflammation, appetite and lean body mass. It has also been suggested that this dose of EPA may prolong life. More recent, larger double-blind trials in humans did not show a survival effect or demonstrate good appetite stimulation when omega-3 preparations were compared with megestrol. They may, however, sustain or improve lean body mass.

### **Amino acids**

Protein intake should be assured, and amino acid mixtures, which are readily available in the form of whey protein, should be offered to weight-losing patients. Do specific amino acid combinations hold particular value? A combination of glutamine, arginine, and  $\beta$  hydroxyl methyl butyrate (the latter is a metabolite of leucine) has been studied in small controlled trials in both AIDS and cancer populations. Evidence of weight gain and increased lean body mass was noted. Comparisons of whey protein with specific amino acid mixtures have not been carried out.

### **NSAIDs**

Eicosanoid production is enhanced in chronic inflammatory states. A specific eicosanoid, 5 hydroxyeicosatetraenoic acid (15-HETE), may modulate the activity of proteolysis-inducing factor (PIF). NSAIDs can reduce tumor growth and tumor wasting in some animal models. Swedish and British work supports the benefits of indomethacin or ibuprofen in reducing cachexia in cancer patients. A recent phase III trial in humans comparing megestrol acetate, given with or without ibuprofen, did not show improved appetite or weight gain with the addition of the anti-inflammatory agent. While COX-2 inhibitors have been commonly used for pain control in North America, only modest COX-2 laboratory or clinical studies on cachexia are available.

## **Multivitamins**

The geriatric literature supports the routine use of multivitamin supplementation for institutionalized patients. Malnourished cancer patients are at risk for developing unrecognized deficiencies. Studies on vitamin use in cachectic patients are not available. Studies on the use of antioxidants in combination with other anti-cachexia measures are ongoing.

## **Exercise-rehabilitation**

"If you don't use it, you lose it". Muscles require stimulation in order to thrive. Common sense dictates that we encourage muscular activity as long as it is safe. A growing body of evidence supports the notion that exercise may fundamentally affect cancer incidence and course, the adverse effects of therapy, and fatigue. Borrowing from the geriatric literature, tailored exercise may even benefit fragile patients. As a result, it is reasonable to advise weight-losing patients to begin, or maintain, a rehabilitation program unless contraindicated by dangerous bone metastases and/or reduced cardiovascular capacity.

It is important to include physiotherapists on the comprehensive cancer care team. They will greatly enhance the ability to include exercise as part of an overall patient prescription for functional assessment and rehabilitation.

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*Навчальне видання*

# **СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ**

## **Ведення хворих зі схудненням**

*Методичні вказівки для студентів та лікарів-інтернів*

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Відповідальний за випуск Бабак О.Я.



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# **MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS**

**Management of patients with weight loss**

*Guidelines for students and interns*