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Heterogeneous group of muscular disorders characterised by progressive muscle weakness.

Presentation is sub-acute or chronic and rarely acute.

May be associated with dysphagia, fatigue, difficulties with breathing, and skin lesions.

Diagnosis is confirmed by elevated serum muscle-derived enzymes, typical electromyography (EMG) findings, and inflammation on muscle biopsy.

Corticosteroids are first-line therapy. Intravenous immunoglobulin, methotrexate, and azathioprine are used as second-line therapy. Third-line therapies include cyclophosphamide, mycophenolate, ciclosporin, and tacrolimus.
Definition

Idiopathic inflammatory myopathies constitute a heterogeneous group of sub-acute, chronic, and, rarely, acute diseases of skeletal muscle that have in common the presence of moderate-to-severe proximal muscle weakness and inflammation on muscle biopsy.\[1\] Based on distinct features, they are divided into 3 groups: polymyositis, dermatomyositis, and inclusion body myositis. Polymyositis and dermatomyositis seem to have an autoimmune pathogenesis, whereas inclusion body myositis seems to have an autoimmune and degenerative pathogenesis.\[1\] [2]

Epidemiology

In the US the annual incidence of idiopathic inflammatory myopathies is 5.5 to 10 cases per million.\[1\] [11] Annual incidence rates increase with age, ranging from 2.5 cases per million under the age of 15 years to 10.5 cases per million over the age of 65 years.\[12\] The prevalence is between 25 and 35.3 cases per million.\[13\] [14]

In the UK there were a total of 1819 hospital admissions with dermatomyositis in the 1-year period between 2006 and 2007.\[15\] Dermatomyositis affects both children and adults. About half of the UK hospital cases were in patients aged between 15 and 59. The condition also affects women more often than men.\[1\] [16]

Incidence data from Spain suggest that the condition affects between 2.2 to 10.6 people per million population per year.\[17\]

Polymyositis is seen after the second decade of life and very rarely in childhood. Its incidence is higher in women.\[1\] [16] [5] The incidence of polymyositis in Spain has been estimated to be between 2.9 and 8.6 cases per million population per year.\[17\] In Australia the incidence of inflammatory myopathies is 7.4 per million person-years.\[18\]

Epidemiological data on inclusion body myositis are rare. A prevalence of 4.9 cases per million population has been reported in the Netherlands.\[19\] Inclusion body myositis is 3 times more common in men than in women and is more likely to affect people >50 years of age. It is more common in the white population compared with the black population, whereas polymyositis and dermatomyositis are more common in black people than white people.\[1\] [2] [11] [12]

Aetiology

Aetiology is unknown at present. However, several factors have been suggested.

- Infection: several viruses including coxsackievirus, influenza virus, retroviruses, cytomegalovirus, and Epstein-Barr virus (EBV) seem to be associated with these myopathies.\[1\] [2] [20] [21] [22] [23] Other associated infectious agents include protozoa, cestodes, nematodes, and Borrelia species.\[1\]
- Genetic: specific human leukocyte antigen (HLA) subtypes are believed to confer increased risk of development of idiopathic inflammatory myopathies.\[24\]
- Environmental: UV radiation intensity has been shown to be the strongest contributor, out of 13 geoclimatic variables, to the relative proportion of dermatomyositis in a population.\[25\] Hydroxyurea has also been implicated in cases of dermatomyositis.\[26\]
• Immunological: various autoantibodies have been found in up to 20% of patients. Among them, the antisynthetases anti-Jo-1 antibodies have been associated with a high incidence of interstitial lung disease.[27]

Pathophysiology

In dermatomyositis, the primary antigen target consists of components of the vascular endothelium of the larger endomysial blood vessels.[1] [28] [29] Activation of complement leads to the deposition of a membranolytic attack complex on the endomysial microvasculature. This results in capillary necrosis, microinfarction, inflammation, endofascicular hypoperfusion, and, finally, perifascicular atrophy.[30] [31] This is most prominent at the periphery of the fascicles where the capillary network is less dense.[30] Lymphocytic cells infiltrate the perimysial and perivascular regions of affected muscles, supporting the humoral-mediated process in the pathogenesis of dermatomyositis.[30]

In polymyositis and inclusion body myositis, there is evidence of antigen-directed and major histocompatibility complex-1 (MHC-1)-restricted cytotoxicity mediated by CD8 T cells.[30] In polymyositis, immunological synapses form between CD8 T cells and MHC-1 expressed on muscle fibres.[30] In polymyositis and inclusion body myositis, inducible costimulator (ICOS) ligand expressed on muscle fibres interacts with ICOS receptors located on the autoinvasive T cells. This facilitates clonal expansion and the co-stimulation of memory T cells.[30] A programmed death ligand that mediates the inhibition of T-cell activation is also expressed in muscle fibres.[30] These findings suggest that:

• The muscle fibres behave as antigen-presenting cells
• There is a balance of inflammatory stimuli within the immunological synapse of muscle/CD8 cells, to protect the muscle from excessive immune aggression.[30]

Adhesion to muscle fibres by activated T cells is facilitated by cytokines, chemokines, and adhesion molecules.[30] [31] [32] [33]

An alternative theory for the pathogenesis of dermatomyositis suggests that endothelial cells and myofibres are injured by the chronic overproduction intracellularly of one or more interferon 1 inducible proteins. This is based on observations of the association of tissue pathology with interferon 1-related pathology. The plasmacytoid dendritic cells are typically found in their plasmacytoid morphology (active form that produces interferon 1) in perimysial regions. This results in higher concentration of interferon 1 in perimysial perifascicular regions and may contribute, through unidentified mechanisms, to perifascicular atrophy.[34] [35] [36]

Classification

Classification of idiopathic inflammatory myopathies[3]

1. Primary idiopathic polymyositis
2. Primary idiopathic dermatomyositis
3. Polymyositis or dermatomyositis with malignancy
4. Juvenile dermatomyositis (or polymyositis)
5. Polymyositis or dermatomyositis associated with other connective tissue diseases
6. Inclusion body myositis
7. Rare forms of idiopathic myositis:
• Granulomatous myositis
• Eosinophilic myositis
• Focal myositis
• Orbital myositis.

Immune-mediated necrotising myopathies (in the past treated as a subset of polymyositis) are likely to be a distinct group.
Secondary prevention

- H2 antagonists are recommended while on corticosteroid therapy if the patient has a history of peptic ulcer disease.
- Bisphosphonates are used for the prevention of corticosteroid-induced osteoporosis in postmenopausal women.
- Patients with a history of TB or a positive tuberculin test may need prophylactic treatment with isoniazid.
Idiopathic inflammatory myopathies

Diagnosis

Case history

Case history #1

A 57-year-old man presents with a 5-year history of slowly progressive leg weakness. Recently he has had multiple falls and experiences difficulties with fine tasks using his hands. Neurological examination shows atrophy of ilioptosas, quadriceps, and finger flexors bilaterally. Manual muscle strength test finds predominant weakness in finger/wrist flexors compared with finger/wrist extensors. Additionally, it demonstrates neck flexion 3/5, neck extension 4/5, arm abduction 4/5, forearm flexion 4/5, hip extension 3/5, hip flexion 2/5, knee extension 2/5, knee flexion 2/5, ankle dorsiflexion 4/5, and ankle plantar flexion 5/5. The rest of the neurological examination is unremarkable except for reduced patellar reflexes.

Case history #2

A 42-year-old woman presents with progressive muscular weakness and recurrent facial oedema. The oedema started 3 months ago and worsened to the point that she was unable to open her mouth or eyes. Concomitant to her facial rash, she experiences intermittent difficulty in swallowing. Her weakness results in an inability to rise from a chair or ascend stairs. Skin examination demonstrates blue-purple discoloration on the upper eyelids with oedema. Her muscle strength is 3/5 on bilateral hip flexion and 3/5 on bilateral shoulder abduction. The rest of the neurological examination is normal.

Other presentations

Extramuscular manifestations may be predominant. Dysphagia is most prominent in dermatomyositis and inclusion body myositis. Cardiac involvement (e.g., heart failure, arrhythmias, and MI) is recognised as an important prognostic factor of death. Interstitial lung disease may precede muscular symptoms. Other pulmonary manifestations include drug-induced pneumonitis, pulmonary capillary angitis, and pulmonary failure due to thoracic muscle weakness. Systemic features such as fever and weight loss occur especially with co-existent associated connective tissue disease.

IIM may be associated with malignancy. The highest risk is near the time of diagnosis and up to 3 years after the diagnosis of myositis and is equal in males and females. Patients with dermatomyositis have a higher risk of developing malignancy than patients with polymyositis. There is 3 to 6 times increased risk of developing cancer in dermatomyositis, with 58% of neoplasms occurring after myositis diagnosis. The most frequent malignancies are ovarian cancer, pancreatic cancer, and non-Hodgkin's lymphoma. Patients with polymyositis have a 1.4 to 2 times increased risk of developing cancer compared with the general population. The most frequent malignancies observed with polymyositis are non-Hodgkin's lymphoma, lung cancer, and bladder cancer.

Step-by-step diagnostic approach

Typically presents with a myopathy syndrome characterised by proximal symmetrical muscle weakness, although in inclusion body myositis there is usually more distal weakness. It frequently develops over weeks to months, but may develop insidiously, as in inclusion body myositis, or, occasionally, much more acutely.
History

Polymyositis occurs most commonly between the ages of 40 and 60 years, and inclusion body myositis usually in people >50 years of age. Dermatomyositis incidence has two age peaks: one between the age of 40 and 70 years and the other one in childhood at around 9 years.

Specific questioning concerning risk factors known to be associated with the development of an inflammatory myopathy (e.g., history of exposure to high intensity of global UV radiation; genetic predisposition; treatment with lipid-lowering agents, D-penicillamine, or other drugs or toxins known to be risk factors; presence of HIV infection; history of preceding other viral or non-viral infection; and preceding vaccination) is important.

History may reveal increased difficulties in performing motor tasks predominantly requiring proximal muscles, such as getting up from a chair, climbing steps, and combing hair.

Fine motor tasks that depend on distal muscles, such as sewing, knitting, or writing, are affected late in the course of dermatomyositis and polymyositis, but earlier in inclusion body myositis. Falling is commonly reported in patients with inclusion body myositis, because of early quadriceps involvement.

Other extramuscular symptoms include arthralgia, dysphagia, shortness of breath, palpitations, syncope, and MI symptoms.

IIM may be associated with malignancy.[4] [5] [6] [7] [8] [9] The highest risk is near the time of diagnosis and up to 3 years after the diagnosis of myositis and is equal in males and females. Patients with dermatomyositis have a higher risk of developing malignancy than patients with polymyositis.[4] [6] There is 3 to 6 times increased risk of developing cancer in dermatomyositis, with 58% of neoplasms occurring after myositis diagnosis. The most frequent malignancies are ovarian cancer,[8] [10] pancreatic cancer, and non-Hodgkin's lymphoma.[8] Patients with polymyositis have a 1.4 to 2 times increased risk of developing cancer compared with the general population. The most frequent malignancies observed with polymyositis are non-Hodgkin's lymphoma, lung cancer, and bladder cancer.[8]

Physical examination

Physical examination reveals proximal muscle weakness. One third of patients with polymyositis have pain and muscle tenderness.

Weakness in inclusion body myositis may be asymmetrical, with early quadriceps weakness. It occurs predominantly in shoulder abductors, and finger/wrist flexors when compared with finger/wrist extensors, and knee extensors compared with hip flexors. The arm weakness in inclusion body myositis is often limited to the ulnar flexors. Mild facial weakness sparing extra-ocular muscles may occur in up to 60% of patients with inclusion body myositis.[1] This is seen to a lesser extent in polymyositis and dermatomyositis. Patellar reflexes are lost in inclusion body myositis.

Weight loss, fatigue, and generalised malaise are common.

In dermatomyositis, the following skin lesions are characteristic:

- Heliotrope rash with eyelid oedema
- Facial rash
- Gottron's papules, which are erythema of knuckles accompanied by a raised violaceous scaly eruption
Idiopathic inflammatory myopathies

Diagnosis

• Erythematous rash over the knees, elbows, malleoli, and at the base of the neck and upper chest, forming a V sign
• Nail fold changes such as dilation of capillary loops of periungual area.

Other extramuscular signs include skin calcinosis, joint swelling, abnormal pulmonary breath sounds, arrhythmias, signs of heart failure (e.g., with cardiomyopathy) and MI, and physical findings of associated malignancy. Peripheral neuropathy may be seen in inclusion body myositis. Signs of systemic autoimmune disease may be seen in at least 20% of patients.[1]

Initial investigations

The three most important initial tests to perform on all patients with suspected disease are:

• Muscle-derived serum enzyme evaluation
• EMG
• Muscle biopsy.

Muscle-derived serum enzymes may be elevated. The most sensitive indicator enzyme is creatinine kinase (CK). Although its level usually parallels the disease activity, it can be normal in active disease and is not helpful in inclusion body myositis.

Lactate dehydrogenase (LDH), aldolase, myoglobin, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are part of the initial work-up and may be elevated, but they are less specific for muscle injury. These markers may help in disease diagnosis but should not be used alone to assess disease severity and to monitor response to treatment.

EMG is performed next, to confirm the myopathic pattern of the disorder and for the exclusion of a primary neurogenic disorder. Typical EMG recordings include:

• Myopathic motor unit potentials characterised by early recruitment
• Short duration and low amplitude polyphasic motor units on voluntary activation
• Increased spontaneous activity at rest.

These findings are not specific for idiopathic inflammatory myopathies and may be seen in a variety of myopathies.

Muscle biopsy is required next for definitive diagnosis.

In polymyositis, muscle biopsy shows:

• Endomysial inflammatory infiltrates[1]
• Muscle fibre necrosis
• Scattered atrophy
• Regeneration of muscle fibres.

In dermatomyositis, muscle biopsy shows:
Idiopathic inflammatory myopathies

**Diagnosis**

- Perivascular, perimysial inflammatory infiltrate[1]
- Perifascicular atrophy (but may be absent in 50% or more of cases).

In inclusion body myositis, muscle biopsy shows:

- Endomysial inflammation surrounding and invading non-necrotic fibres
  [Fig-4]
- Necrosis
- Eosinophilic inclusions
- One or more rimmed vacuoles (often prominent and the feature that is most typically used to distinguish inclusion body myositis from polymyositis) containing amyloid deposits revealed by Congo red staining under polarised light.[1]

**Ancillary investigations**

Once the diagnosis has been confirmed by muscle biopsy, testing for the following antibodies sometimes helps to determine the prognosis.

- Anticytoplasmic myositis-specific antibodies against translational components, such as antisynthetase antibodies and anti-signal recognition particle (anti-SRP) antibodies, are usually associated with relatively severe muscle disease. Up to 25% of patients with polymyositis have antisynthetase antibodies (also called anti-Jo-1 antibodies). Up to 75% of polymyositis patients with anti-Jo-1 antibodies have interstitial lung disease (ILD).[5]
- Antibodies against Mi-2 and Mas antigens are usually associated with relatively mild muscle disease.

Further tests, performed after the diagnosis has been made, include:

- Soluble CD30 and antinuclear antibodies (ANA). May be elevated in dermatomyositis and polymyositis.
- Erythrocyte sedimentation rate (ESR). May be elevated but is an inaccurate indicator of disease activity.
- Type 1 interferon. Increased levels in patients with dermatomyositis and, to a lesser extent, polymyositis, and correlated with disease activity; but assays not commercially available as yet.
- MRI. Performed to assess inflammation in muscles. If there is any doubt about the most appropriate site for muscle biopsy, an MRI may help to determine best site, either at the initial stage or for any subsequent biopsies.[50]
- Muscle ultrasonography. This is an emerging non-invasive and low-cost technique performed for similar reasons to those for MRI.[51][52]

**Risk factors**

**Strong**

- children and age >40 years
  - Polymyositis is a disease of adulthood, with peak incidence between the ages of 40 and 60 years.
  - Dermatomyositis incidence has 2 age peaks: one between the ages of 40 and 70 years, and the other one in childhood at around 9 years. Childhood diagnosis is not covered in detail in this topic.
  - Inclusion body myositis usually presents in people >50 years of age.[1]
Idiopathic inflammatory myopathies

Diagnosis

**Exposure to high intensity of global UV radiation**
- A study of 919 people with myositis based at 15 locations around the world found that, out of 13 geoclimatic variables, UV radiation intensity was the strongest contributor to the relative proportion of dermatomyositis and was strongly related to the proportion of anti-Mi2 autoantibodies.[25]

**Genetic predisposition**
- Specific HLA subtypes appear to confer increased risk for polymyositis and dermatomyositis. These include HLA-DRB1-03 in white people and HLA-DRB1-14 in Korean people.[24] [37] [38]
- A study of 47 patients with sporadic inclusion body myositis found a significant increase in the frequency of several HLA alleles compared with control patients.[39]
- Preliminary data suggest tumour necrosis factor (TNF A2) allele AA is associated with juvenile dermatomyositis.[40]
- Other non-HLA immune response genes have been implicated in idiopathic inflammatory myopathies, including cytokine genes and their receptors, adhesion molecules, T-cell receptor genes, and immunoglobulin genes. Most of the associations originate from small studies, which have not been repeated or confirmed.[41]

**Female sex and/or black ethnicity (polymyositis and dermatomyositis)**
- Polymyositis and dermatomyositis have a female predominance, with a female: male ratio of 2:1.[11] [12] [42]
- Polymyositis and dermatomyositis are found more commonly in black people compared with white people, in a ratio of 2.8:1.[11] [12] [5] [43]

**Male sex and/or white ethnicity (inclusion body myositis)**
- Inclusion body myositis affects men more than women, with a ratio of between 1.4:1 and 3:1.[44] [45] It is more common in white patients than in black patients.[1]

**Weak**

**Lipid-lowering agents**
- Lipid-lowering agents have been associated with a spectrum of muscle toxicity ranging from myalgia to inflammatory myopathy or rhabdomyolysis.[41]

**HIV**
- In HIV-positive patients, an inflammatory myopathy can occur either as the first clinical manifestation of HIV infection or concurrently with other manifestations of AIDS.[1]

**Viral infections (excluding HIV)**
- Coxsackievirus, influenza, paramyxoviruses, cytomegalovirus, and EBV have been directly associated with acute and chronic myositis.[1]
- Molecular mimicry has been proposed as a mechanism of action of coxsackieviruses because of structural homology between Jo-1 antibody and the genomic RNA of animal picornavirus and the encephalomyocarditis virus.[1]
- In human T-cell lymphotropic virus type 1 infection (HTLV-I), inflammatory myopathy may occur in isolation or concomitant to myeloneuropathy.[1]
non-viral infection

- Non-viral infectious agents have been associated with inflammatory myopathy, such as protozoa, cestodes, nematodes, *Staphylococcus aureus*, *Legionella pneumophila* (Legionnaires' disease), and *Borrelia burgdorferi* (Lyme disease).[1]

vaccination

- Studies in defined populations have failed to demonstrate an association between immunisation and myositis.[41] [46]
- There have been case reports of post-vaccination dermatomyositis following tetanus, BCG, and diphtheria vaccination.[47] [48] [49]
- Macrophagic myofasciitis has occurred following tetanus and hepatitis vaccination, probably triggered by aluminium hydroxide used as an adjuvant in the vaccine.[46]

D-penicillamine

- About 1.2% of patients with rheumatoid arthritis treated with D-penicillamine may develop inflammatory myopathy, which appears, on average, 16 months after treatment onset. It may improve rapidly after withdrawal of the drug.[41]

other drugs or toxins

- Interferon alfa, growth hormone, and local anaesthesia have been associated with inflammatory myopathies.[41]
- Other agents have been linked to inflammatory myopathies, including silica, ingestion of tryptophan, ciguatera poisoning, collagen and silicone implants, and cyanoacrylate glue exposure.[41]

History & examination factors

**Key diagnostic factors**

**presence of risk factors (common)**

- Key risk factors include: children and age >40 years, exposure to high intensity of global UV radiation, female sex and/or black ethnicity, male sex and/or white ethnicity, and genetic predisposition.

**difficulty with motor tasks (common)**

- All forms result in difficulties with tasks requiring the use of proximal muscles (e.g., getting up from a chair, climbing steps, lifting objects, and combing hair).
- However, fine motor movements that depend on the strength of distal muscles (e.g., sewing, knitting, or writing) could be affected late in the course of dermatomyositis and polymyositis, and earlier in the course of inclusion body myositis.[21]

**muscle weakness (common)**

- Having the patient stand from the sitting position (especially from a low foot stool) with the arms crossed is a good way to examine proximal leg muscle strength. Often a patient with a myopathy is unable to do this.
- Distal muscles could be affected late in the course of dermatomyositis and polymyositis, and earlier in the course of inclusion body myositis.[1]

**muscle atrophy (common)**
Idiopathic inflammatory myopathies

Diagnosis

- Severe muscle weakness is usually associated with muscle atrophy.
- In inclusion body myositis, quadriceps and distal wrist and finger flexor atrophy is common.[1]

Heliotrope rash with eyelid oedema (uncommon)

- A blue-purple discoloration of the upper eyelids, with oedema.
- Highly suggestive of dermatomyositis.
- Rarely observed in other disorders.

Gottron’s papules (uncommon)

- Erythema over the knuckles, accompanied by raised violaceous scalp eruption, seen in dermatomyositis.

Other diagnostic factors

Frequent falls (common)

- Falling is frequent, particularly in the course of inclusion body myositis, because of early involvement of the quadriceps muscle.[1]

Fatigue and generalised malaise (common)

- A non-specific symptom when the disease is active.

Weight loss (common)

- A non-specific symptom when the disease is active.
- May also occur in association with concomitant malignant disease. This is most likely in dermatomyositis.

Shortness of breath (common)

- Results from cardiopulmonary complications. Cardiac involvement includes conduction defects, tachyarrythmias, cardiomyopathy, and low ejection fractions.
- Pulmonary abnormalities result from primary weakness of thoracic muscles, drug-induced pneumonitis, and interstitial lung disease (ILD).
- ILD develops in 10% of patients with dermatomyositis and polymyositis, the majority of whom have anti-Jo-1 antibodies.[1]
- It is not a feature of inclusion body myositis.

Mild fever (common)

- A common symptom when the disease is active or associated with a connective tissue disorder.[1]
- However, this is not the case in inclusion body myositis.

Abnormal breath sounds (common)

- Due to pulmonary or cardiac involvement.

Dysphagia (uncommon)

- Results from weakness of the oropharynx and distal oesophagus.
- May occur in all forms.
- In inclusion body myositis, dysphagia has been reported in 9% of patients at presentation[1] [44] [53] and 40% to 66% of patients with well-established disease.
myalgia (uncommon)
- Prominent muscle pain and tenderness may occur in one third of patients with polymyositis, especially early on in the disease course.
- Muscle pain has been reported in 73% of patients with childhood dermatomyositis.[1] [5]
- It is not a feature of inclusion body myositis.

arthralgia (uncommon)
- May be associated with general systemic disturbance, especially in inflammatory myopathy occurring with a connective tissue disorder.[1]

palpitations (uncommon)
- Due to cardiac involvement.

syncope (uncommon)
- Arrhythmias due to cardiac involvement may present in this way.

symptoms of MI (uncommon)
- Cardiac involvement is recognised as an important prognostic factor of death.

facial rash (uncommon)
- Often red or bluish-purple, accompanied by pruritus or burning sensation.

erthematosus rash (uncommon)
- Over the knees, elbows, malleoli, and at the base of the neck and upper chest, forming a V sign, in patients with dermatomyositis.

nail fold changes (uncommon)
- Dilation of capillary loops of periungual area in dermatomyositis.

facial muscle weakness (uncommon)
- Facial weakness sparing the extra-ocular muscles may occur in advanced disease; however, up to 60% of patients with sporadic inclusion body myositis may develop mild facial weakness.[1]

skin calcinosis (uncommon)
- Mostly affecting children with dermatomyositis in the later stages.

joint swelling (uncommon)
- Especially when polymyositis or dermatomyositis occurs with a connective tissue disorder.[1]
- Not in inclusion body myositis.

arrhythmias (uncommon)
- May complicate polymyositis and dermatomyositis.[5]

signs of heart failure and/or MI (uncommon)
- Cardiac involvement (e.g., cardiomyopathy) is recognised as an important prognostic factor of death.
Diagnosis

In up to 45% of patients with dermatomyositis, it has been associated with a malignancy. Recent research suggests an association between polymyositis and cancer.

**Systemic signs of autoimmune disease (uncommon)**
- May be seen in at least 20% of patients.

**Peripheral neuropathy (uncommon)**
- May be seen in inclusion body myositis.

## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CK</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>- The most sensitive and specific muscle-derived serum enzyme of disease activity.</td>
<td></td>
</tr>
<tr>
<td>- Can be elevated as much as 50 times above normal, especially in polymyositis.</td>
<td></td>
</tr>
<tr>
<td>- Can be normal in active dermatomyositis and rarely in active polymyositis.</td>
<td></td>
</tr>
<tr>
<td>- Normal or only mildly elevated in inclusion body myositis.</td>
<td></td>
</tr>
<tr>
<td>- When elevated, serial evaluation represents the most effective laboratory guide for monitoring disease progression in polymyositis and dermatomyositis, as well as treatment response.</td>
<td></td>
</tr>
<tr>
<td>- Not helpful in inclusion body myositis.</td>
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</tr>
<tr>
<td>- The CK level may normalise with treatment, yet objective clinical examination does not typically reveal any improvement.</td>
<td></td>
</tr>
</tbody>
</table>

| **EMG** | short duration, low amplitude, polyphasic units with early recruitment on voluntary activity; diffuse spontaneous activity with fibrillation and positive sharp waves at rest |
| - May show myopathic motor units on voluntary activity. | |
| - Typical pattern at rest may be present. | |
| - Mixed long and short duration, small and large amplitude, polyphasic early firing units, and increased amplitude of motor units pattern may be present in any type, more often in inclusion body myositis due to muscle fibre regeneration and disease chronicity. | |
| - EMG pattern described above is not specific for idiopathic inflammatory myopathies and can be seen in a variety of other myopathies. | |
### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>muscle biopsy</strong></td>
<td><strong>polymyositis:</strong> endomysial inflammatory infiltrates, muscle necrosis, atrophy, muscle fibre regeneration; dermatomyositis: perifascicular atrophy, perivasculare/perimysial inflammation; inclusion body myositis: endomysial inflammatory infiltrate, fibre size variability, fibre necrosis, rimmed vacuoles</td>
</tr>
<tr>
<td>• Mandatory for definitive diagnosis.</td>
<td></td>
</tr>
<tr>
<td>• For accurate results there are 3 essential prerequisites: proper choice of muscle; appropriate staining; and interpretation of results by an expert in myopathology.</td>
<td></td>
</tr>
<tr>
<td>• A very weak muscle should be avoided because of the high risk of loss of the distinguished characteristics of idiopathic inflammatory myopathies, yielding non-specific end-stage myopathic changes. A moderately weak muscle offers the best chance of a positive biopsy.</td>
<td></td>
</tr>
<tr>
<td>• In inclusion body myositis, inclusion bodies contain beta-amyloid that can be revealed by Congo red staining.[1]</td>
<td></td>
</tr>
<tr>
<td><strong>aldolase</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Less specific than CK for monitoring disease activity, because it is present not only in the muscle but also in the liver.</td>
<td></td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Elevated level may be erroneously interpreted as a sign of liver disease.</td>
<td></td>
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<tr>
<td>• Present in muscle, liver, and erythrocytes.[5]</td>
<td></td>
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<tr>
<td><strong>alanine transaminases</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Less specific for muscle injury than CK.</td>
<td></td>
</tr>
<tr>
<td><strong>myoglobin</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• A sensitive index of the integrity of muscle fibres.</td>
<td></td>
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<tr>
<td>• Useful in the assessment of disease activity and serves as a guide during treatment.[5]</td>
<td></td>
</tr>
</tbody>
</table>

### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESR</strong></td>
<td>elevated</td>
</tr>
<tr>
<td>• Normal in about half of patients with polymyositis and dermatomyositis.</td>
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</tr>
<tr>
<td>• Inaccurate indicator of disease activity; in most cases there is no correlation between ESR and degree of weakness.[5]</td>
<td></td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• A positive result is common in dermatomyositis and polymyositis.[5]</td>
<td></td>
</tr>
<tr>
<td><strong>myositis-specific antibodies</strong></td>
<td>type-specific antibodies</td>
</tr>
<tr>
<td>• Two major groups exist.</td>
<td></td>
</tr>
<tr>
<td>• Anticytoplasmic antibodies against translational components (e.g., antisynthetase antibodies and anti-SRP antibodies) are usually associated with relatively severe muscle disease.</td>
<td></td>
</tr>
<tr>
<td>• Antibodies against Mi-2 and Mas antigens are usually associated with relatively mild muscle disease. Up to 79% of patients with dermatomyositis have Mi-2 antibodies.[5]</td>
<td></td>
</tr>
</tbody>
</table>
Idiopathic inflammatory myopathies

Diagnosis

Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>soluble CD30</td>
<td>elevated</td>
</tr>
<tr>
<td>• Expressed mainly by activated CD+ T cells.</td>
<td></td>
</tr>
<tr>
<td>• Elevated in dermatomyositis and polymyositis.</td>
<td></td>
</tr>
<tr>
<td>type 1 interferon</td>
<td>elevated</td>
</tr>
<tr>
<td>• Increased levels of type 1 interferon are evident in blood in patients with dermatomyositis and, to a lesser extent, polymyositis, and are correlated with disease activity.</td>
<td></td>
</tr>
<tr>
<td>• Assays are not yet commercially available but may be in the future, and may be better than CK for monitoring activity.</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>increased signal or oedema that can be seen in inflammatory processes; the changes are not specific</td>
</tr>
<tr>
<td>• Performed to assess inflammation in muscles.</td>
<td></td>
</tr>
<tr>
<td>• May be helpful in selecting site for muscle biopsy.[50]</td>
<td></td>
</tr>
<tr>
<td>ultrasound scan</td>
<td>image suggestive of inflammatory processes</td>
</tr>
<tr>
<td>• Non-invasive and low-cost imaging technique.[51] [52]</td>
<td></td>
</tr>
</tbody>
</table>

Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary inclusion body myositis</td>
<td>• Quadriceps more likely to be spared but not always.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• May be associated with leukoencephalopathy.</td>
<td>• Absence of inflammation on muscle biopsy more likely in hereditary inclusion body myositis.[1]</td>
</tr>
<tr>
<td>Oculopharyngeal muscular dystrophy</td>
<td>• Clinical features include ptosis and dysphagia, occasionally with proximal limb weakness.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Muscle biopsy shows rimmed vacuoles and tubular filaments with an absence of inflammatory features.[54]</td>
</tr>
<tr>
<td>Late-onset distal myopathy</td>
<td>• Progressive muscular weakness and atrophy beginning in hands or feet.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Muscle biopsy may show rimmed vacuoles and tubulofilamentous inclusions in several types of distal myopathy (e.g., Welander's, Udd's, Markesbery-Griggs, Laing's, distal myopathy), but there is an absence of inflammation.[5]</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Overlap myositis                         | • Symptoms of polymyositis or dermatomyositis associated with some other connective tissue disorders.  
• Diagnostic criteria for the two different disorders are fulfilled. | • Additional serological features diagnostic of an underlying connective tissue disease (e.g., SLE, rheumatoid arthritis, scleroderma, or mixed connective tissue disease).[5] |
| Amyotrophic lateral sclerosis (motor neuron disease) | • Upper motor neuron signs (not present in idiopathic inflammatory myopathies). | • EMG shows fasciculation potentials (rare in idiopathic inflammatory myopathies), and neurogenic changes are more apparent.  
• Muscle biopsy shows neurogenic changes. |
| Myasthenia gravis                        | • Weakness more likely to fluctuate, increasing with repeated or sustained exertion.  
• Involvement of extra-ocular muscles is common.  
• Spontaneous remissions can occur. | • EMG typically shows abnormal decrement in repetitive nerve stimulation and increased jitter in single-fibre EMG.  
• Presence of antibodies to acetylcholine receptors or muscle-specific kinase. |
| Drug-induced myopathy                    | • History of medication associated with development of myopathy (e.g., lipid-lowering drugs, D-penicillamine, laxative abuse).  
• Withdrawal of implicated drug may reverse the myopathic damage. | • No differentiating tests. |
| Acid maltase deficiency                  | • More likely to develop respiratory failure (occurs in approximately one third of patients, may be the presenting symptom). | • At rest, EMG may show myotonic discharges.  
• Muscle biopsy tissue or cultured skin fibroblasts show a reduction of acid alpha-glucosidase activity. |
### Idiopathic inflammatory myopathies

#### Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
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</tr>
</thead>
</table>
| **Secondary metabolic myopathy**              | • Muscle weakness co-exists with systemic manifestations of specific metabolic or endocrine abnormalities, such as hypokalaemia, hypophosphataemia, hypothyroidism, hyperthyroidism, and hyperparathyroidism.  
  • Restoration of muscle strength may occur after correction of the metabolic or endocrine condition. | • Abnormal blood tests indicating the presence of endocrine or metabolic diagnosis (e.g., low serum potassium or abnormal thyroid function tests). |
| **Chronic inflammatory demyelinating polyneuropathy** | • Weakness is usually both proximal and distal, and mildly asymmetrical.  
  • Sensory symptoms and signs and diffuse hypo-/ areflexia are prominent. | • Nerve conduction studies show signs of primary demyelination.  
  • Needle EMG shows neurogenic pattern and no signs of myopathy.  
  • Serum CK is typically normal. |
| **Scleroderma**                               | • Muscle weakness more likely to be low-grade if present.                                         | • Mostly mild or absent elevation of serum CK.  
  • EMG shows no or little spontaneous activity.  
  • Muscle biopsy may reveal perimysial fibrosis, scleroderma vasculopathy, and type 2 fibre atrophy with little muscle fibre destruction.[5] |

#### Diagnostic criteria

**Commonly used severity criteria for idiopathic inflammatory myopathies**

- Severe disease: includes those with severe muscle weakness (e.g., quadriplegia), interstitial lung disease, myocarditis, respiratory failure, severe dysphagia, or other life-threatening complications.
- Non-severe disease: includes those with muscle strength of 4/5 or above and none of the life-threatening complications of severe disease.
Step-by-step treatment approach

The main objective of treatment is to improve muscle strength and to obtain remission or clinical stabilisation.

Despite the paucity of good evidence, it is clear that various types of immunotherapy are helpful in polymyositis and dermatomyositis. In contrast, patients with inclusion body myositis may receive trials of the following therapies, but the condition is usually resistant to most treatment options.[55]

**Initial pharmacotherapy in people with severe muscle weakness or life-threatening complications**

Includes those with severe muscle weakness (e.g., quadriplegia), interstitial lung disease (ILD), myocarditis, respiratory failure, severe dysphagia, or other life-threatening complications.

An initial short course of IV corticosteroids for 3 consecutive days is used to achieve rapid disease control.[55]

Patients are subsequently transferred to high-dose oral corticosteroids. In this group of patients, tapering of corticosteroid dose is slow, often over several months.

Although this is a common initial approach, some physicians may start intravenous immunoglobulin (IVIG) early on in this group, in combination with corticosteroids.[55] [56]

**Initial pharmacotherapy in people following acute stabilisation or without severe or life-threatening symptoms**

Includes those with mild-to-moderate muscle weakness without any life-threatening complication.

Oral corticosteroids are the first-line treatment for dermatomyositis and polymyositis.[55]

A high dose of oral corticosteroid reduces morbidity and improves muscle strength and function in a considerable proportion of people.[57] [58] Noticeable clinical improvement occurs within 3 to 6 months in most patients.[59] Monitoring for adverse effects is necessary.

Muscle strength usually returns to normal or reaches a plateau within 4 to 6 months, and a minimal level of oral corticosteroid may be maintained to sustain an adequate clinical response (normal or near-normal motor strength that enables the patient to perform activities of daily living independently).

A Cochrane review of available pooled evidence from several RCTs found that a significant improvement in functional performance was observed in patients with idiopathic inflammatory myopathy, among other muscle disorders, who were treated with creatine. Creatine was also well tolerated and may therefore be useful as adjunctive therapy.[60]

**Second-line pharmacotherapy in people following acute stabilisation or without severe or life-threatening symptoms**

When no improvement occurs after a trial of 4 to 6 months of high-dose oral corticosteroids, alternative diagnoses should be ruled out, such as inflammatory muscular dystrophy.

If the diagnosis of polymyositis or dermatomyositis is confirmed, second-line therapies should be considered. These are used primarily in patients who are refractory to corticosteroids or for their...
Idiopathic inflammatory myopathies

Treatment

corticosteroid-sparing potential.[55] [61] Agents include IVIG, methotrexate, or azathioprine.[62] [63] [64] [65] [66]

Limited evidence suggests that IVIG is effective in dermatomyositis and polymyositis.[42] [61] [67] [68] [69] [62] [63] It is often used in combination with oral corticosteroids or other immunosuppressive drugs. Availability and cost may limit its use.

Methotrexate is another initial choice therapy in this group. It has been found to be effective in up to 88% of dermatomyositis and polymyositis patients, including those refractory to prednisolone.[57] [70] [71] Methotrexate is often preferred over azathioprine in patients with dermatomyositis and polymyositis because it is considered to have a more rapid benefit.[55]

Azathioprine is the next choice of therapy. It can be as effective and well tolerated as methotrexate, but seems to take longer to take effect (6 months or more).[66]

All second-line agents may be used alone or in combination with oral corticosteroids.

**Third-line pharmacotherapy in people following acute stabilisation or without severe or life-threatening symptoms**

Third-line treatments are indicated in cases refractory to corticosteroids and second-line agents. They are either more toxic than corticosteroids and second-line agents or have not been used as extensively in the treatment of idiopathic inflammatory myopathies.[55]

There are few, if any, controlled studies and little consensus about how to use these therapies, so treatment choice will depend on the individual experience of the physician and any contraindications to particular therapies in each patient.

These treatments are used as monotherapies or sometimes combined with corticosteroids or other immunosuppressants.

- Cyclophosphamide is used in patients with refractory polymyositis and dermatomyositis, particularly when associated with vasculitis, ILD, and disease with bulbar or respiratory muscle involvement.[59] [72] Use should be reserved for patients with severe myopathy and ILD who are unresponsive to other agents, although there is potential for liver, bladder, and bone marrow toxicity.[64] [73]
- Chlorambucil has been used with some success in a few studies of refractory dermatomyositis.[55] [74]
- Ciclosporin has shown some benefit in polymyositis or dermatomyositis.[55] [75] Improvement may be noticed within 2 to 6 weeks after treatment onset, and corticosteroids can be reduced or discontinued in the majority of patients.[55] [76] [77] [78] Frequent monitoring of serum trough levels (optimal range 100-200 ng/mL), FBC, and renal and liver function is necessary.[73] [65]
- Ciclosporin alone or in combination with IVIG and corticosteroids may be effective in refractory or relapsing dermatomyositis or polymyositis.[79]
- Tacrolimus and mycophenolate have both been found to be effective in a small number of cases.[80] [81] [82] Case studies report that clinical improvement to tacrolimus is varied and may be observed over periods ranging from 3 to 13 months.[83] [84] Nephrotoxicity, hypertension, and reversible posterior leukoencephalopathy are potential side effects.[85] Mycophenolate inhibits de novo guanosine nucleotide synthesis, therefore impairing the function of T and B lymphocytes. It shows promising results for refractory dermatomyositis and polymyositis; however, controlled
Idiopathic inflammatory myopathies

Treatment trials are lacking.[86] [87] Benefit of mycophenolate is observed after 2-3 months, with length of treatment dependent on individual patient response.

Non-drug therapies are infrequently used as the next choice of treatment. Again, there have been few, if any, controlled trials to compare these treatments, and there is no consensus on the order of their use.

- Plasmapheresis and leukopheresis have been used, although more recent evidence found them to be ineffective.[88] [89]
- Total body irradiation has been reported to be effective in a few cases.[90] [91] In contrast, other studies found it ineffective and a possible aggravating factor in inclusion body myositis.[92] [93]
- Thymectomy has been performed in a few patients with dermatomyositis and polymyositis, with some improvement.[94]

**Juvenile dermatomyositis (JDM)**

Prednisolone is the initial treatment of choice. The maximum dose is tapered according to patient response.[95] [96] Subcutaneous methotrexate is added as a first-line therapy.[95] A controlled study demonstrated that combined treatment with prednisolone and either ciclosporin or methotrexate is more effective than prednisolone alone. However, the safety profile and corticosteroid-sparing effect favours the combination of prednisolone plus methotrexate.[97] For patients who are refractory to first-line therapy, methylprednisolone is recommended in combination with methotrexate and hydroxychloroquine.[95] Rituximab is gaining acceptance for severe refractory JDM.[98] Other therapies such as IVIG, cyclophosphamide, mycophenolate, ciclosporin, azathioprine, and tacrolimus have also been used in refractory disease; however, only small trials and case reports support the use of these drugs.

**Treatment details overview**

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

### Acute

<table>
<thead>
<tr>
<th>with severe muscle weakness or life-threatening complications: adult or child</th>
<th>1st intravenous corticosteroids</th>
<th>adjunct intravenous immunoglobulin (IVIG)</th>
</tr>
</thead>
</table>

### Ongoing

<table>
<thead>
<tr>
<th>following acute stabilisation or without severe or life-threatening symptoms: adult</th>
<th>1st oral corticosteroids</th>
<th>adjunct creatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd intravenous immunoglobulin (IVIG) or methotrexate or azathioprine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>adjunct</td>
<td>oral corticosteroids</td>
</tr>
<tr>
<td>adjunct</td>
<td>creatine</td>
</tr>
<tr>
<td>3rd</td>
<td>other immunosuppressive agents or procedures</td>
</tr>
<tr>
<td>adjunct</td>
<td>oral corticosteroids</td>
</tr>
<tr>
<td>adjunct</td>
<td>creatine</td>
</tr>
</tbody>
</table>

following acute stabilisation or without severe or life-threatening symptoms: child

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>prednisolone plus subcutaneous methotrexate</td>
</tr>
<tr>
<td>2nd</td>
<td>methylprednisolone plus methotrexate and hydroxychloroquine</td>
</tr>
<tr>
<td>3rd</td>
<td>other immunosuppressants</td>
</tr>
</tbody>
</table>
## Treatment options

### Acute

**with severe muscle weakness or life-threatening complications: adult or child**

<table>
<thead>
<tr>
<th>1st</th>
<th>intravenous corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td>» methylprednisolone: children: consult specialist for guidance on dose; adults: 0.5 to 1 g intravenously once daily or on alternate days for 3-6 doses (i.e., 3-12 days) -and-</td>
</tr>
<tr>
<td></td>
<td>» prednisolone: children: consult specialist for guidance on dose; adults: 0.75 to 1.5 mg/kg/day (maximum 100 mg/day) orally for 2-4 weeks following completion of intravenous methylprednisolone course, then taper dose to maintenance dose</td>
</tr>
<tr>
<td></td>
<td>» Includes those with severe muscle weakness (e.g., quadriplegia), interstitial lung disease (ILD), myocarditis, respiratory failure, severe dysphagia, or other life-threatening complications.</td>
</tr>
<tr>
<td></td>
<td>» An initial short course of IV corticosteroids for 3 consecutive days is used to achieve rapid disease control.[55]</td>
</tr>
<tr>
<td></td>
<td>» Patients are subsequently transferred to high-dose oral corticosteroids. In this group of patients, tapering of corticosteroid dose is slow, often over several months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>adjunct</th>
<th>intravenous immunoglobulin (IVIG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td>» normal immunoglobulin human: children: consult specialist for guidance on dose; adults: 1 g/kg/day intravenously for 2 days</td>
</tr>
<tr>
<td></td>
<td>» IVIG therapy combined with intravenous corticosteroids is sometimes used initially rather than corticosteroids alone, depending on the physician's experience.[55] [56]</td>
</tr>
</tbody>
</table>

### Ongoing

**following acute stabilisation or without severe or life-threatening symptoms: adult**

<table>
<thead>
<tr>
<th>1st</th>
<th>oral corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
</tbody>
</table>

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# Treatment

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» prednisolone: 0.75 to 1.5 mg/kg/day orally for 2-4 weeks, maximum 60 mg/day, then taper dose to maintenance dose</td>
</tr>
<tr>
<td></td>
<td>» High-dose oral corticosteroids reduce morbidity and improve muscle strength and motor function in polymyositis and dermatomyositis.[55] [57] [58]</td>
</tr>
<tr>
<td></td>
<td>» Effectiveness in inclusion body myositis is poor compared with other types of inflammatory myopathy.</td>
</tr>
<tr>
<td></td>
<td>» To reduce adverse effects, the daily dose of oral corticosteroid is switched to alternate days after 2 to 4 weeks and gradually tapered to appropriate maintenance dose.[55] [99] The tapering period is variable and will depend on individual patient response.</td>
</tr>
<tr>
<td></td>
<td>» Alternate-day dosing is not appropriate in certain people (e.g., diabetic patients) who require daily dosing.[55]</td>
</tr>
<tr>
<td>adjunct</td>
<td>creatine</td>
</tr>
<tr>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» creatine: consult specialist on dose</td>
</tr>
<tr>
<td></td>
<td>» A Cochrane review of available pooled evidence from several RCTs found that a significant improvement in functional performance was observed in patients with idiopathic inflammatory myopathy, among other muscle disorders, who were treated with creatine. Creatine was also well tolerated and may therefore be useful as adjunctive therapy.[60]</td>
</tr>
<tr>
<td>2nd</td>
<td>intravenous immunoglobulin (IVIG) or methotrexate or azathioprine</td>
</tr>
<tr>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» normal immunoglobulin human: 1 g/kg/day intravenously for 2 days</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>» methotrexate: 7.5 mg orally once weekly on the same day of each week initially (alternatively, dose can be given as 2.5 mg orally every 12 hours for 3 doses), may increase by 2.5 mg/week increments according to response, maximum 25 mg/week</td>
</tr>
</tbody>
</table>
Ongoing

Secondary options

- **azathioprine**: 50 mg orally once daily initially, increase every 1-2 weeks according to response, maximum 2-3 mg/kg/day

  - When no improvement occurs after a trial of 4 to 6 months of high-dose oral corticosteroids, second-line therapies should be considered.[55] [61] These include IVIG, methotrexate, or azathioprine.[62] [63] [64] [65] [66]

  - Limited evidence suggests that IVIG is effective in dermatomyositis and polymyositis.[42] [61] [67] [68] [69] [62] [63] It is often used in combination with oral corticosteroids or other immunosuppressive drugs. Availability and cost may limit its use.

  - Methotrexate has been found to be effective in up to 88% of dermatomyositis and polymyositis patients, including those refractory to prednisolone.[57] [70] [71] Methotrexate is often preferred over azathioprine in patients with dermatomyositis and polymyositis because it is considered to have a more rapid benefit.[55]

  - Azathioprine is the next choice of therapy. It can be as effective and well tolerated as methotrexate, but seems to take longer to take effect (6 months or more).[66] Monitoring of liver enzymes is necessary and length of treatment is variable, according to patients’ clinical course.

  - All second-line agents may be used alone or in combination with oral corticosteroids.

  - There are no specific guidelines regarding the duration of immunosuppressive therapy in inflammatory myopathies, as it depends on the patient response. Treatments are generally used long-term at the lowest and most effective dose possible.

adjunct oral corticosteroids

Primary options

- **prednisolone**: 5-40mg orally once daily

  - Immunosuppressive agents may be used alone or in combination with oral corticosteroids.

adjunct creatine

Primary options

- **creatine**: consult specialist on dose
<table>
<thead>
<tr>
<th>Ongoing</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>» A Cochrane review of available pooled evidence from several RCTs found that a significant improvement in functional performance was observed in patients with idiopathic inflammatory myopathy, among other muscle disorders, who were treated with creatine. Creatine was also well tolerated and may therefore be useful as adjunctive therapy.[60]</td>
<td></td>
</tr>
</tbody>
</table>

3rd other immunosuppressive agents or procedures

**Primary options**

» cyclic phosphamide: 1-2 mg/kg/day orally once daily for 6-12 months; 500-1000 mg/square metre of body surface area intravenously once monthly for 6-12 months

OR

» chlorambucil: see local consultant protocol for dosing guidelines

OR

» ciclosporin: 3-4 mg/kg/day orally in 2 divided doses, increase gradually according to response, maximum 5 mg/kg/day

Bioavailability may differ between brands.

OR

» tacrolimus: 0.1 to 0.2 mg/kg/day orally given in 2 divided doses

OR

» mycophenolate mofetil: 1 to 1.5 g orally twice daily

**Secondary options**

» plasmapheresis

OR

» total body irradiation

OR

» thymectomy

» Indicated in cases refractory to corticosteroids and second-line agents.
<table>
<thead>
<tr>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>» These people are more likely to have severe symptoms that have been stabilised to some extent.</td>
</tr>
<tr>
<td>» Each treatment may be used alone or combined with corticosteroids.</td>
</tr>
<tr>
<td>» Effectiveness in inclusion body myopathy is poor compared with other types of inflammatory myopathy.</td>
</tr>
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<td>» Cyclophosphamide is used in patients with refractory polymyositis and dermatomyositis, particularly when associated with vasculitis, ILD, and disease with bulbar or respiratory muscle involvement.[59] [72] [64] [73]</td>
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<td>» Non-drug therapies are infrequently used as the next choice of treatment. Again, there have been few, if any, controlled trials to compare these treatments, and there is no consensus on the order of their use. Plasmapheresis and leukopheresis have been used, although more recent evidence found them to be ineffective.[88] [89] Total body irradiation has been reported to be effective in a few cases.[90] [91] In contrast, other studies found it ineffective and a possible aggravating factor in inclusion body myositis.[92] [93] Thymectomy has been performed in a few cases.</td>
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</tr>
</tbody>
</table>

### following acute stabilisation or without severe or life-threatening symptoms: child

<table>
<thead>
<tr>
<th>1st</th>
<th>prednisolone plus subcutaneous methotrexate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» prednisolone: 2 mg/kg (maximum 60 mg/day) orally once daily initially, gradually taper dose over 2-4 weeks according to patient response</td>
<td></td>
</tr>
<tr>
<td>-and-</td>
<td></td>
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<tr>
<td>» methotrexate: 15 mg/square metre of body surface area once weekly</td>
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<tr>
<td>» Prednisolone is the initial treatment of choice for juvenile dermatomyositis (JDM). The maximum dose is tapered according to patient response.</td>
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<tr>
<td>» Subcutaneous methotrexate is added as a first-line therapy.</td>
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</table>
### Treatment

**Ongoing**

- There are no specific guidelines regarding the duration of immunosuppressive therapy in inflammatory myopathies, as it depends on the patient response. Treatments are generally used long-term at the lowest and most effective dose possible.

**2nd**

- **methylprednisolone** plus **methotrexate** and **hydroxychloroquine**

**Primary options**

- **methylprednisolone**: consult specialist for guidance on dose
  - **and**
  - OR

- **methotrexate**: consult specialist for guidance on dose
  - **and**
  - OR

- **hydroxychloroquine**: consult specialist for guidance on dose

- For patients who are refractory to first-line therapy, intravenous methylprednisolone is recommended in combination with methotrexate and hydroxychloroquine.[95]

**3rd**

- **other immunosuppressants**

**Primary options**

- **rituximab**: consult specialist for guidance on dose
  - OR

- **normal immunoglobulin human**: consult specialist for guidance on dose
  - OR

- **cyclophosphamide**: consult specialist for guidance on dose
  - OR
Ongoing

» mycophenolate mofetil: consult specialist for guidance on dose

OR

» ciclosporin: consult specialist for guidance on dose

OR

» azathioprine: consult specialist for guidance on dose

OR

» tacrolimus: consult specialist for guidance on dose

» Rituximab is gaining acceptance for severe refractory JDM.[98]

» Other therapies such as IVIG, cyclophosphamide, mycophenolate, ciclosporin, azathioprine, and tacrolimus have also been used in refractory disease; however, only small trials and case reports support the use of these drugs.

» There are no specific guidelines regarding the duration of immunosuppressive therapy in inflammatory myopathies, as it depends on the patient response. Treatments are generally used long-term at the lowest and most effective dose possible.
**Emerging**

**Rituximab**
A new agent for refractory cases of dermatomyositis.[75] A depleting chimeric monoclonal antibody against the B lymphocyte marker CD20. Adverse effects are usually mild. Studied in 5 patients with long-standing dermatomyositis previously treated with at least 3 immunosuppressive agents with incomplete response, and in 1 newly diagnosed patient. There was a sustained improvement in muscle strength and rash up to 1 year.[100]

**Eculizumab**
A high-affinity humanised monoclonal antibody to C5 that has the ability to inhibit the cleavage of the complement sequence C5 to C5a and C5b-9, implicated in the pathogenesis of dermatomyositis.[75] Some evidence of benefit in dermatomyositis.[75]

**Anti-T-lymphocyte globulin**
Studied in combination with methotrexate and prednisolone in patients with inclusion body myositis in a randomised controlled but unblinded pilot study of 10 patients. There was mild improvement of muscle strength, a slight decrease in serum CK levels, and minimal biopsy changes compared with methotrexate alone.[75] [101]

**Autologous haematopoietic stem cell transplantation**
Has been used as a rescue therapeutic option in the most severe cases of autoimmune disorders, but scant data exist about its use in myositis.[75]

**TNF-alpha antagonists**
Etanercept and infliximab are monoclonal antibodies that block the effect of TNF-alpha, a cytokine with a possible role in the pathogenesis of dermatomyositis and polymyositis. There have been several anecdotal and case reports of their safe use in refractory cases of dermatomyositis, polymyositis, and juvenile amyopathic dermatomyositis, with claims of rapid clinical improvement with a decrease in serum CK levels.[99]
**Recommendations**

**Monitoring**

Monitoring for complications

- Dermatomyositis is the type most commonly associated with malignancy, so a diagnosis of dermatomyositis warrants an extensive work-up (chest CT, GI endoscopy, pelvic CT). In addition, all patients treated with chronic immunosuppressive therapies should have periodic careful assessment for cancer.
- Periodic non-invasive studies such as ECG, echo, and scintigraphy with technetium-99 pyrophosphate are recommended to detect early cardiac dysfunction.[5]
- Periodic chest x-ray and pulmonary function tests (PFTs) are recommended in all patients. The frequency of these will depend on the severity of the disease.

Monitoring for corticosteroid treatment adverse effects

- Bone density is measured at baseline and every 6 months during corticosteroid treatment. Calcium and vitamin D supplementation is recommended when bone density score is <2.5 standard deviations below normal.[55] Bisphosphonate is used for osteoporosis treatment.
- Initial fasting blood glucose and regular blood glucose levels are recommended in chronic corticosteroid treatment.
- Chest x-ray is performed before starting corticosteroids, to detect pulmonary infections such as TB.
- Histamine H2-receptor antagonists may be prescribed if the patient develops GI discomfort or has a history of peptic ulcer disease.
- BP is measured on each visit, as accelerated hypertension and renal failure could occur particularly in patients with scleroderma or mixed connective tissue disease and overlap syndrome.[55] [56]
- Eye examinations are performed periodically to check for cataracts and glaucoma.
- Serum potassium levels are monitored. Potassium supplementation may be required if the patient becomes hypokalaemic.[55]

Monitoring for immunosuppressant treatment adverse effects

- Methotrexate. Measurement of baseline and periodic PFTs with diffusion is recommended. FBC and liver function tests (LFTs) including gamma-GT are checked every 1 to 2 weeks until on a stable dose, then once a month.[55]
- Azathioprine. Measurement of baseline and periodic PFTs with diffusion is recommended. FBC and LFTs including gamma-GT are checked every 1 to 2 weeks until on a stable dose, then once a month.[9]
- IVIG. Measurement of baseline renal function is recommended because of risk of IVIG-induced renal failure.[55]
- Chlorambucil. Requires monthly assessment of FBC and LFTs.
- Tacrolimus. Monitoring BP and checking electrolytes and renal function are recommended.
- Ciclosporin. Periodic monitoring of BP, electrolytes, renal function, and trough ciclosporin is recommended. Urinalysis and FBCs are checked every 1 to 2 weeks at onset, then at least monthly.

**Patient instructions**

Patients are instructed to start a low-sodium, low-carbohydrate, high-protein diet and counselled to prevent excessive weight gain.
In addition, physiotherapy and an aerobic exercise programme are recommended to reduce bone loss and prevent type 2 muscle fibre atrophy.

## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>corticosteroid-related osteoporotic fractures and avascular necrosis of bone</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>May complicate long-term corticosteroid treatment. Prophylaxis with calcium and vitamin D supplementation is recommended when bone density score is &lt;2.5 standard deviations below normal.^[55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroid myopathy</td>
<td>long term</td>
<td>medium</td>
</tr>
<tr>
<td>May complicate long-term corticosteroid administration, resulting in progressive muscle weakness, typically after an initial improvement in muscle strength. Normal CK levels and an absence of muscle irritability on needle EMG favour corticosteroid myopathy (a type 2 fibre myopathy) over myositis relapse.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroid-induced diabetes</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>May complicate long-term corticosteroid treatment. Initial fasting blood glucose and regular blood glucose levels are recommended prior to starting corticosteroid therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>immunosuppression-associated infection</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Serious routine and opportunistic infections and septicaemia from bacterial and fungal agents may complicate the course of immunosuppressive therapies. Early antibiotic or antifungal therapy should be initiated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac disease</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Arrhythmias and cardiomyopathies may complicate polymyositis and dermatomyositis.^[5] The patient may present with shortness of breath, syncope, or respiratory failure. ECG and cardiac ultrasound are key tests to document these conditions.</td>
<td></td>
<td></td>
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<tr>
<td>pulmonary disease</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>ILD may occur, especially in patients with Jo antibodies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dysphagia</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>May occur because of dysfunction of oropharyngeal muscles and/or oesophagus striated muscle fibres.^[111][112][113] Feeding via a percutaneous gastrostomy may be necessary in severe cases. In others, dysphagia may be improved by cricopharyngeal myotomy.^[5] Most common in inclusion body myositis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malignancy</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>In up to 45% of patients with dermatomyositis, it has been associated with a malignancy.^[5][6][7][8][9] In addition, recent research suggests an association between polymyositis and cancer.^[5][6][7][8][9]</td>
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Idiopathic inflammatory myopathies

Prognosis

Twenty-five percent of patients achieve complete remission with prednisolone.[57]

Inclusion body myositis responds poorly, whereas patients with antibodies to aminoacyl-tRNA synthetases or the signal recognition particle (SRP) generally respond partially to prednisolone.[102] The initial response to prednisolone may be a predictor of the subsequent response to other immunosuppressive agents.[102]

Factors affecting patient outlook

Five- and 10-year survival rates of 95% and 84%, respectively, have been reported.[102] [103] Factors associated with poor survival include older age, malignancy, delayed initiation of corticosteroid therapy, pharyngeal dysphagia with aspiration pneumonia, interstitial lung disease (ILD), and myocardial involvement.[102] [104] [105] [106] [107] [108] [109]

Among the serum autoantibodies, anti-SRP is the worst prognostic marker; the antisynthetases are also associated with recurrent disease flares and lower survival.

Conversely, 5-year survival rates among the subsets with antipolymyositis-Scl and anti-Mi-2 antibodies approach 95%.[102] [110]
## Treatment guidelines

### Europe

**EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases**

**Published by:** European Federation of Neurological Societies  
**Last published:** 2008

**Guidelines for the use of intravenous immunoglobulin in neurological diseases**

**Published by:** Association of British Neurologists  
**Last published:** 2005

### North America

**Guidelines on the use of intravenous immune globulin for neurologic conditions**

**Published by:** National Advisory Committee on Blood and Blood Products and Canadian Blood Services  
**Last published:** 2007
Key articles


References


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References


Idiopathic inflammatory myopathies

Images

Figure 1: Inclusion body myositis showing rimmed vacuoles

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Figure 2: Inclusion body myositis showing interstitial lymphocytic infiltration and partial invasion

From the collection of Nizar Souayah, New Jersey Medical School, Newark, NJ; used with permission
Figure 3: Polymyositis with endomysial inflammation associated with fibre necrosis

From the collection of Nizar Souayah, New Jersey Medical School, Newark, NJ; used with permission
Figure 4: Childhood dermatomyositis with prominent perifascicular atrophy

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