

Inclusion Body Myositis Updated

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Disclosures

- **Financial disclosures: none**
- **Off-label use: everything described is off label**

History

- 51 yo man referred for myositis
- Insidious weakness – 5 years; PM diagnosed by EMG and muscle biopsy
- Prednisone – improved; never off; min 7 mg/d
- Methotrexate – improved – energy better; stopped due to transaminase elevation
- Azathioprine 10 months; etanercept 6 weeks
- Ongoing muscle weakness; clumsy walking; difficulty upstairs, out of chair, lifting
- Sicca symptoms; Raynaud's

History, 2

PMH

- Steroid-induced DM
- Hypertension
- Nephrolithiasis
- GERD
- Hypogonadism

Social history

- Truck driver - difficulty into truck
- Little EtOH

Family history

- Sister with SLE
- Mother with RA

Meds

- Etanercept 50 mg/wk
- Azathioprine 100 mg BID
- Prednisone 20 mg/d
- Hyzaar 50/12.5 mg/d
- Protonix 40 mg/d
- Avandamet 4/1000 mg/d
- Folic acid 1 mg/d
- Vitamin K 100 mcg/d
- MVI
- Calcium 2000 mg/d
- Fosamax 70 mg/wk

Studies

Laboratory tests

- CBC normal
- ESR and CRP normal
- Chem: Creat 0.7, others normal
- CK 628, aldolase 11.4, LDH 236
- AST 56, ALT 121
- ANA (+), SSA/Ro (+), SSB/La (+), Jo-1 (-)

CXR: Shallow inspiration, okay otherwise

EMG: Not done, per patient request

Muscle Biopsies

Outside biopsy

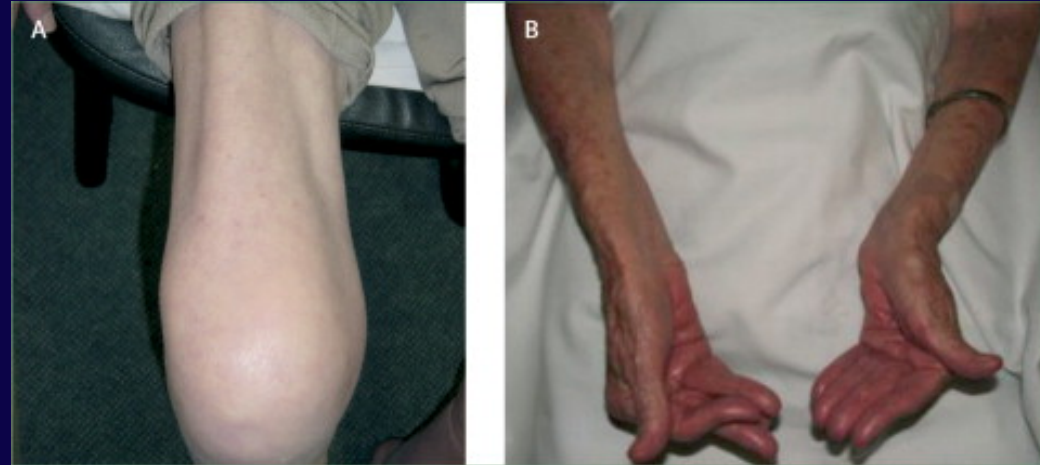
- Inflammatory myopathy. Autoaggressive inflammatory infiltrate. Vacuolated fibers, small groups of atrophic fibers. Likely IBM but without Congo red stained slides, cannot make the diagnosis.

Mayo biopsy

- Advanced myopathy making interpretation difficult
- Congo red staining (+)

Clinical Features of IBM

- Insidious onset
- ~6 years – symptoms to diagnosis
- Weakness generalized or localized to limbs; may be asymmetric
- DTRs normal initially, eventually diminished in 40%
- Dysphagia in 2/3 – late
- Myalgia uncommon but aching in thighs and knees in some



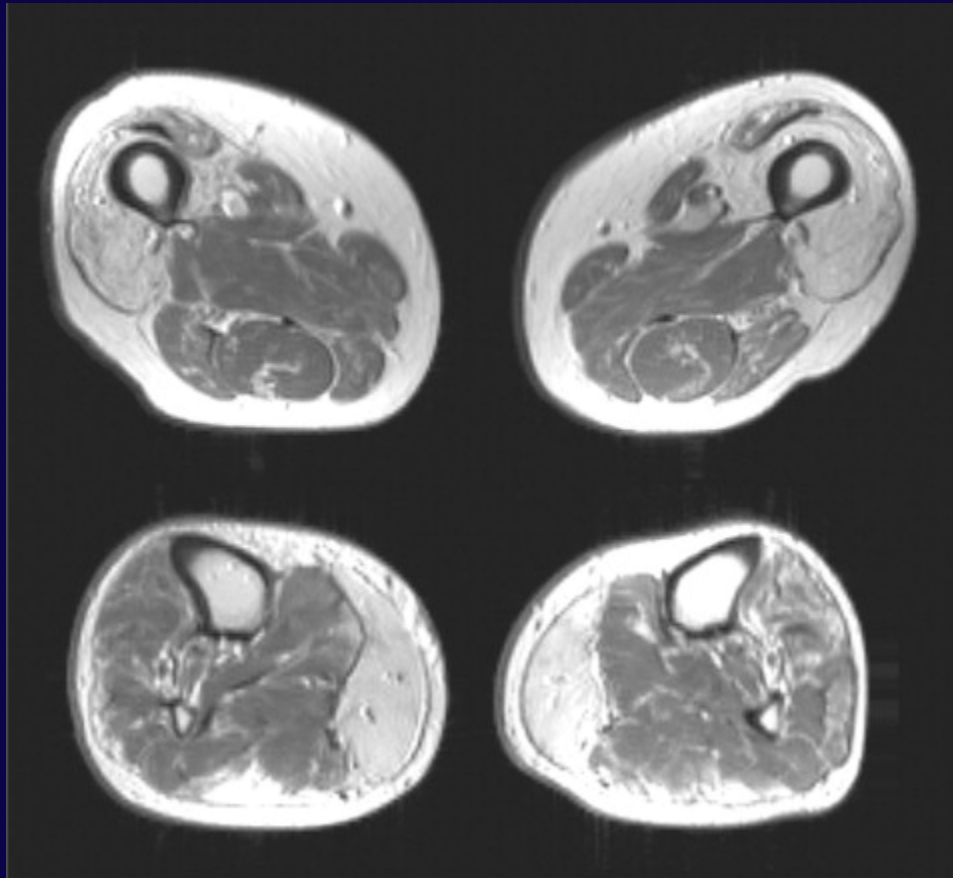
Typical involvement:

- Finger flexors
- Wrist flexors
- Knee extensors
- Ankle dorsiflexors



MRI in IBM

**Proton-density MRI:
involvement of
quadriceps femoris (top)
and medial
gastrocnemius (bottom)**



Epidemiology of IBM

- Represents ~16-30% of most series
- Commonest form of myositis after age 50
- Male:female ratio = 3:1
- Prevalence
 - 4.9/million – Netherlands
 - 9.3/million – Western Australia
 - Age adjusted, over 50 yo: 35/million

Epidemiology of IBM and PM Olmsted County, 1981-2000*

	IBM	PM
Incidence	0.79 (0.24-1.35)	0.41 (0.08-0.73)
Prevalence	7.06 (0.87-13.24)	3.45 (0.00-7.35)

**Age- and sex-adjusted rates per 100,000 population; (95% CI)*

Proposed Classification Criteria for IBM

Muscle biopsy

1. Inflammatory myopathy - MNC invasion of muscle fibers
2. Vacuolated muscle fibers
3. Either:
 - a) Intracellular amyloid deposits
 - b) EM - 15-18 nm tubulofilaments

Laboratory features

1. Serum CK < 12 X ULN
2. EMG consistent with IIM

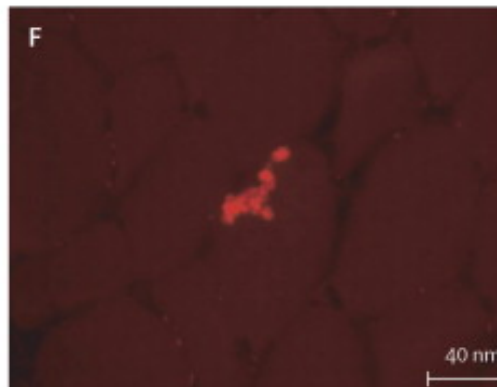
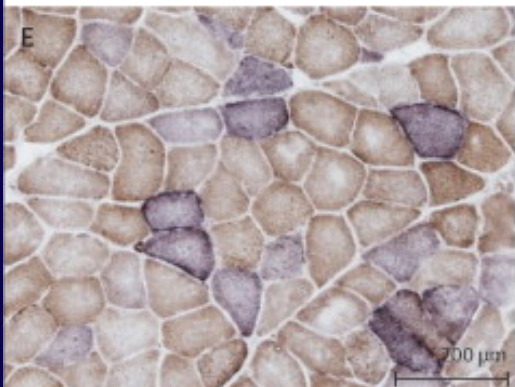
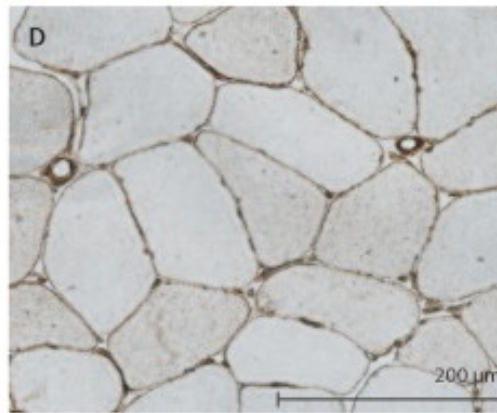
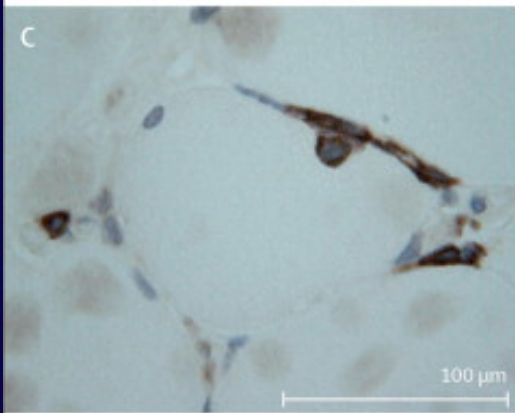
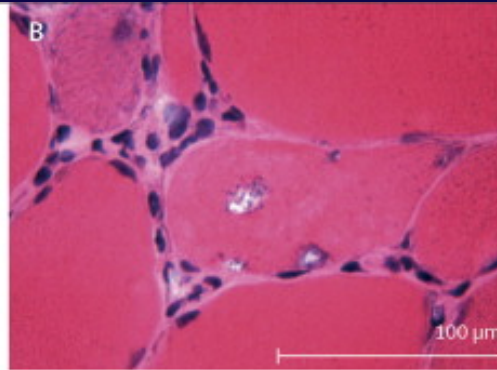
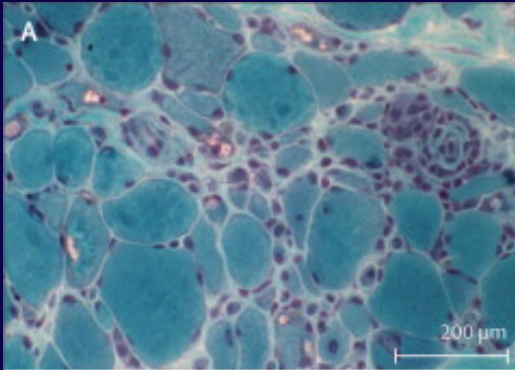
Clinical criteria

1. Disease duration > 6mos
2. Age of onset > 30 yrs
3. Muscle weakness:
 - a) Proximal and distal involvement of arms and legs
 - b) At least one of the following:
 - Finger flexor weakness
 - Wrist flexor > extensor weakness
 - Quadriceps weakness

Definite: Biopsy 1, 2, and 3a or 3b

Possible: Biopsy 1 + Clinical 1, 2, 3a and 3b + Lab 1 and 2

Histologic Findings in IBM



- A. Rimmed vacuoles in atrophic fibers; perivascular and endomysial infiltrates
- B. Rimmed vacuoles; interstitial inflammation on H&E
- C. Autoaggressive CD8+ T-cells
- D. MHC-1 staining
- E. COX deficient fibers
- F. Amyloid deposits on Congo red staining

Needham & Mastaglia, Lancet Neurol 6: 620-31, 2007

Pathologic Findings in IBM

- **Inflammation – invasion of muscle fibers expressing MHC-I by CD8+ T-cells**
- **Cytoplasmic and intranuclear inclusions containing amyloid β and other Alzheimer-type proteins**
- **Loss of COX activity in muscle fibers, associated with mtDNA mutations**

Pathogenesis of IBM

- **Degenerative process**
 - **Accumulation of Alzheimer's-associated proteins**
 - **Nuclear degeneration**
- **Autoimmune features**

Proteins in IBM Vacuoles

- Amyloid- β
- Amyloid- β precursor protein (A β PP)
- Prion protein
- Apolipoprotein E
- Ubiquitin
- Phosphorylated tau
- α -1-antichymotrypsin
- Presenilin-1

Myositis Associated Autoantibodies (%)

Autoantibody	PM <i>n</i> =58	DM <i>n</i> =79	IBM <i>n</i> =26	Total <i>n</i> =212
ANA	40	62	23	52
DNA	3	3	4	5
Ro/SS-A	12	11	12	12
La/SS-B	5	6	8	8
U1RNP	7	13	0	11
PM/ScI	0	4	0	2
Any	57	77	36	66

Myositis Specific Autoantibodies (%)

Autoantibody	PM <i>n</i> =58	DM <i>n</i> =79	IBM <i>n</i> =26	Total <i>n</i> =212
Anti-synthetase	33	33	0	23
Anti-SRP	12	0	0	3
Anti-Mi-2	0	13	0	5

Myositis Associated Autoantibodies (%)

Autoantibody	PM <i>n</i> =198	DM <i>n</i> =181	IBM <i>n</i> =38	Total <i>n</i> =417
Anti-PM/ScI-100	7	6	0	6
Anti-PM/ScI-75	3	3	0	3
Anti-Ro60/SS-A	3	4	11	4
Anti-Ro52	27	24	21	25
Anti-La/SS-B	6	3	8	5
Anti-U1RNP	9	4	3	6

Immune-related Conditions in Patients with IBM*

Autoimmune Disorders

Pernicious anemia	3
Dermatitis herpetiformis	2
Psoriasis	2
CVID	2
Cutaneous lupus	1
ITP	1
Hashimoto's thyroiditis	1
Transverse myelitis	1
Dermatomyositis	1
Gluten sensitive enteropathy	1

Autoantibodies

ANA	20
SSA/Ro	11
SSB/La	2
RNP	1
Smith	2
Jo-1	3
Cardiolipin	10
RF	13

**99 patients seen in Neuromuscular Diseases section of NIH; retrospective chart review*

Primary Sjögren's Syndrome Associated with IBM

- 518 patients with primary SS
 - Seen 1985-2000
 - Diagnosis on histology
- 3 with IBM (0.6%)
- 3 previous case reports
- Clinical features:
 - 5/6 women
 - Timing - 4/6 SS years before IBM
 - 4/6 - extraglandular disease

Therapy Overview

- **Most patients do not respond to anti-inflammatory, immunosuppressive therapy**
- **A small proportion do respond, at least initially; can't identify who will respond**
- **Treatment is empirical and varies by center**
- **Patients with autoimmune disease are most likely to respond**
- **IVIg might help severe dysphagia**

Response to Therapy

	PM (27)	IBM (64)	PM/IBM (16)
Treated	27	32	14
Improved	22	2	1
Stabilized	2	1	4
Worsened	0	28	9
No info	3	1	0
Untreated	0	32	2
Improved	0	0	0
Stabilized	0	4	0
Worsened	0	26	1
No info	0	2	1

**Biopsies at Mayo 1998-2003; PM/IBM – PM bx but IBM clinically*

Steroids for IBM

- 8 patients, biopsy-proven IBM
- Prednisone 100 mg/d – 4 weeks then 100 mg every other day for ≥ 6 mos
- Repeat biopsy

	Pre	Post
Muscle score	7.3	6.4
CK	819	197
	Change	
Cell infiltration	-2.53	
Vacuolated fibers	+4.41	
Amyloid-positive fibers	+1.63	

Methotrexate and IBM

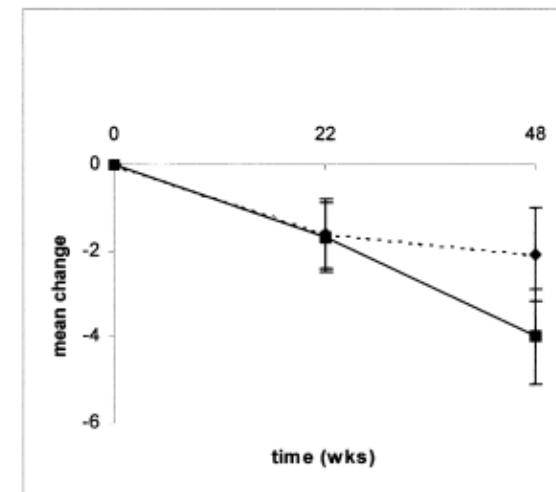
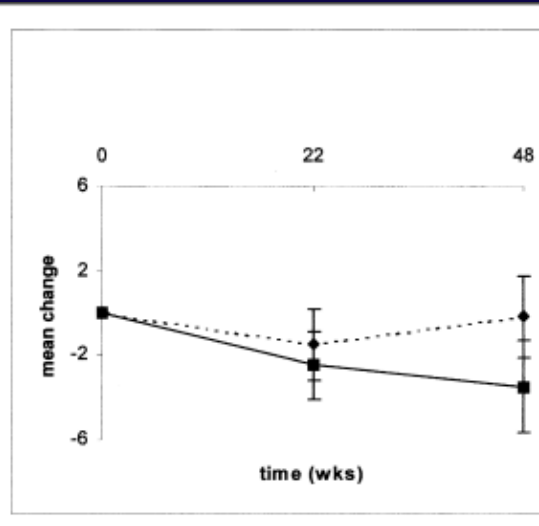
- RCT, MTX vs. placebo
- Methotrexate 5-20 mg/wk
- n=44

Quantitative
muscle test

Manual
muscle testing

Percent change

	MTX	Placebo
QMT	-0.2	-3.4%
MMT	-0.5	-2.0%

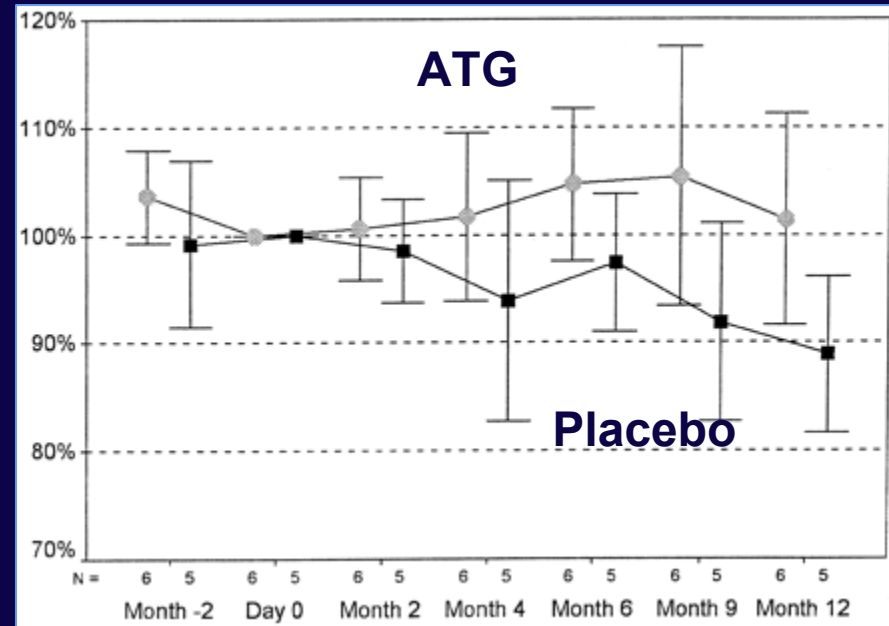


IVIg in IBM

- **19 pts, disease duration 7.4 yrs, DB, RCT, cross-over, 3 mos each IVIg and placebo**
 - **Slight gain of strength with IVIg and loss with placebo, not significant**
 - **Swallowing function improved statistically**
Dalakas, et al., Neurology 48: 712-6, 1997
- **22 pts, disease duration 5.2 yrs DB, RCT, cross-over, 6 mos each IVIg and placebo**
 - **No progression of disease in 90% of pts**
 - **Groups mismatched for disease duration**
 - **Mild, significant improvement in Neuromuscular Symptom Score only**
Walter, et al., J Neurol 247: 22-8, 2000

Anti-thymocyte Globulin in IBM

- Randomized, n = 11 – 6 ATG, 5 placebo
- All received MTX, 7.5 mg/wk
- ATG before MTX:
5 mg/kg day 1
4 mg/kg day 2
then adjusted to CD3 #
total 7 days
- Prednisone 10 – 30 mg qod in 5 on ATG and 4 on placebo

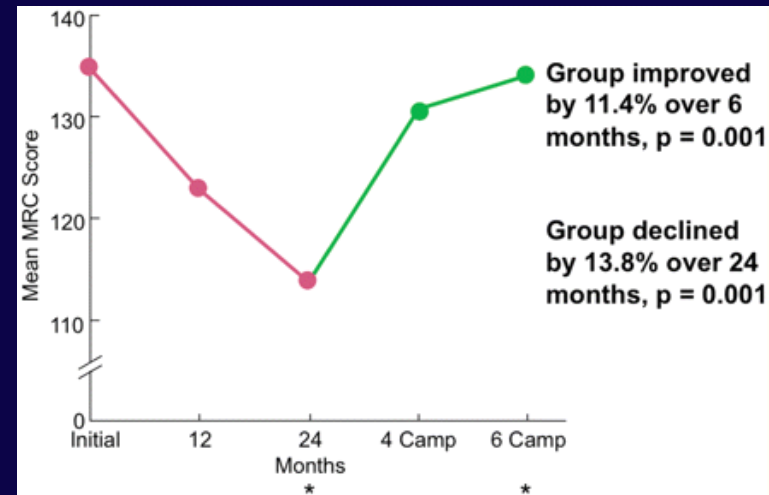
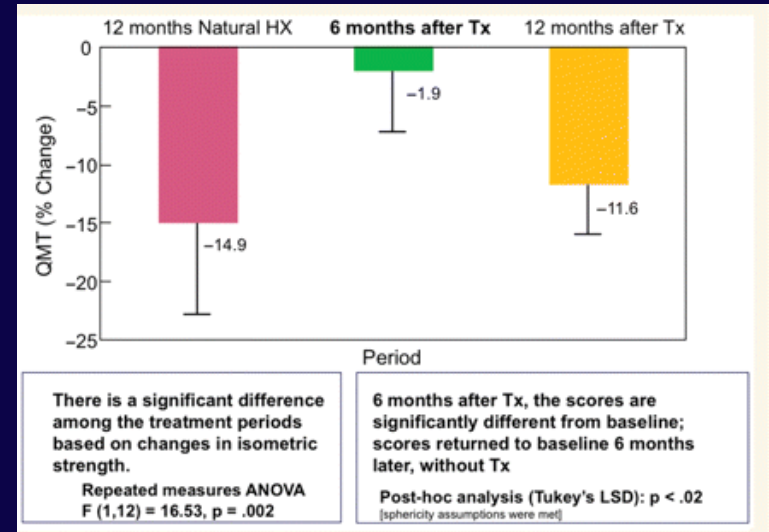


Strength

ATG	+1.4%	
Placebo	-11.1%	$p = 0.021$

Alemtuzumab in IBM

- Open label
- Alemtuzumab 0.3 mg/kg/day x 4 days
- Repeat muscle biopsies showed reduction of CD3 cells by 50%; depletion correlated with improvement
- “Well tolerated” – no infections, thyroiditis, or ITP up to 2 yrs after treatment



Biologic Agents in IBM

- **β IFN-1 α – ineffective at 30 and 60 μ g/wk**

The Muscle Study Group, Neurology 63: 718-20, 2004

The Muscle Study Group, Neurology 57: 1566-70, 2001

- **Etanercept – ineffective**

Barohn, et al., Neurology 66 (Suppl 1): S123-4, 2006

Other Therapies in IBM

- Oxandrolone – borderline significant effect on isometric muscle strength in 8 month DB, cross-over trial

Rutkove, Neurology 58: 1081-7, 2002

- Coenzyme Q10
- Carnitine
- Antioxidants
- Clenbuterol (beta agonist with anabolic effects)

Other Therapeutic Considerations

- **Dysphagia**
 - **IVIG**
 - **Dilation**
 - **Cricopharyngeal myotomy**
 - **Botulinum toxin injection**
- **Exercise**
- **Orthotics**
- **Tendon transfer**

Summary

- **IBM is the most common form of inflammatory myositis in patients > 50 years**
- **Diagnosis of IBM is problematic; muscle biopsy is essential but may not reveal essential findings; a high degree of suspicion is needed**
- **The pathogenetic mechanisms causing IBM are not clearly understood**
- **IBM can be associated with autoantibodies and autoimmune disease**
- **Optimal therapy for IBM has yet to be established**