

University of Pittsburgh  
**Immune Mediated Necrotizing Myopathy**  
 Northwest Rheumatism Society  
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### Idiopathic Inflammatory Myopathies (Myositis)

Heterogeneous, systemic autoimmune disease with primary target of muscle and/or skin

**Clinical subsets**

- Adult Polymyositis (PM)
  - Necrotizing Myopathy (NM)
  - Anti-synthetase Syndrome (ASSD)
- Adult Dermatomyositis (DM)
  - Cancer-associated Dermatomyositis (CADM)
- Juvenile myositis (JM >> PM)
- Cancer-associated myositis (CAM)
- Connective tissue disease-associated myositis
- Inclusion body myositis (IBM)

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### Bohan & Peter Classification Criteria for PM/DM

- Symmetric proximal muscle weakness
- Elevation of muscle enzymes: CK, Aldolase, AST, ALT, LDH
- EMG/NCS: Myopathic (Short duration & low amplitude polyphasic motor units)
- Characteristic muscle pathology: Myofiber degeneration/regeneration, mononuclear infiltrates, perifascicular atrophy
- Skin rash of DM: Gottron's papules or sign, heliotrope rash

	Definite	Probable
Dermatomyositis	4 (including rash)	3 (including rash)
Polymyositis	4 (without rash)	3 (without rash)

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### Mimics of Polymyositis?

- Inclusion body myositis
- Muscle dystrophies
- Metabolic Myopathies
- Drugs - steroids
- Thyroid disease
- Neuromuscular disease
- Malignancy

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### No Myositis Autoantibodies in Bohan & Peter

1975 Bohan & Peter

1976 M-2

1980 Jo-1

1980-2000 Anti-Synthetase

1986 SRP

1997 MJ

2005 MDA5

2006 TIF-1

2007 SAE

2010 HMGR

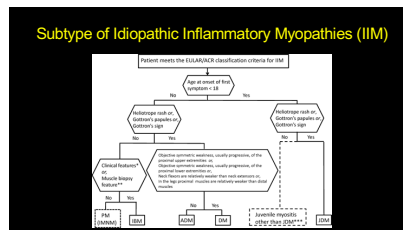
2017 New Myositis Classification

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### 2017 EULAR-ACR Classification Criteria for Myositis

	Risk Score (with 8x)	Risk Score (No 8x)
Age of Onset	15-40 years: 1.5	> 40 years: 1.3
Objective asymmetric proximal weakness	Upper Extremity: 2.2	Lower Extremity: 2.1
DM rash	Heliotrope: 3.2	Gottron-Papules: 2.7
Gottron-Papules	3.7	3.3
Myofascia	1.0	0.6
Serum CK	Elevated: 1.2	1.4
Anti-Jo-1	+	3.8
Muscle Biopsy	Endomyosial infiltration of lymphocytes: 1.7	Perifascial and/or perivascular infiltration: 1.2
Perifascicular atrophy	1.9	

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### Performance of EULAR-ACR Classification

	EULAR-ACR Criteria (No 8x)	EULAR-ACR Criteria (With 8x)	Bohan & Peter	Targoff	Dalakas & Hohlfeld	ENMC Hoogendoorn
Sensitivity	87	93	98	96	6	52
Specificity	82	88	55	31	99	97

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### Immune Mediated Necrotizing Myopathy

- Immune Mediated Necrotizing Myopathy (IMNM)
- Necrotizing Autoimmune Myopathy (NAM)
- Autoimmune Necrotizing Myopathy
- Necrotizing Myopathy

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### A Case

- 64 y/o Caucasian female with h/o HTN, DM and Hypercholesterolemia
- March 2009: Started on Statin
- May 2010: Myalgias and weakness (lower extremity)
- June 2010: CK 5420; Creatinine normal
  - Stopped Statins “You will get better in few weeks”
- July 2010: Worsening of weakness, arm weak, CK: 12300
- Sept 2010: Requiring assistance to ambulate, CK: 11400
- Oct 2010: Dysphagia and hoarseness

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Typical Case of Immune Mediated Statin Myopathy

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### Muscle biopsy: Necrotizing Myopathy

Necrosis Myophagocytosis

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### Muscle biopsy: Necrotizing Myopathy

Myophagocytosis

Esterase stain macrophages

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### Muscle biopsy: Necrotizing Myopathy

Necrosis Myophagocytosis

No or scant inflammation

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### Polymyositis - Histopathology

- cellular infiltrate predominantly within the fascicle with inflammatory cells invading individual muscle fibers
- inflammatory cells - cytotoxic CD8+ T cells (cell-mediated)

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### MHC1 upregulation : suggest autoimmunity

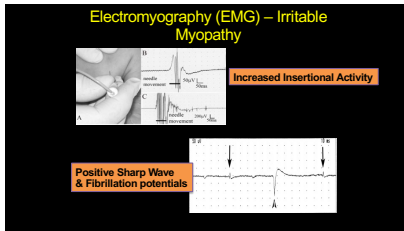
Normal staining of MHC-1 in capillaries Abnormal staining of MHC-1 in sarcolemma and sarcolemma membrane

Chomayni-Stevenson 2010

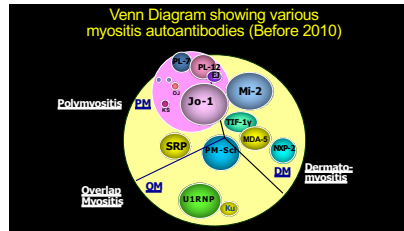
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### Muscle MRI: Edema on MRI

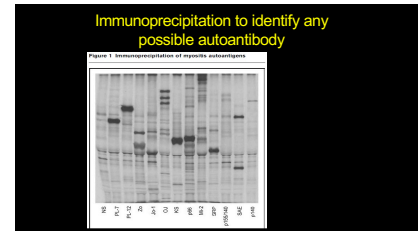
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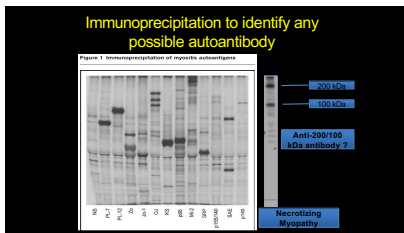
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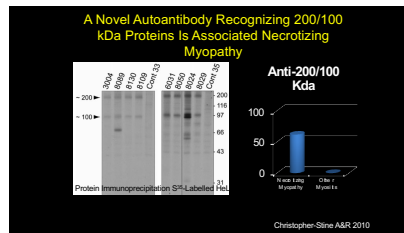
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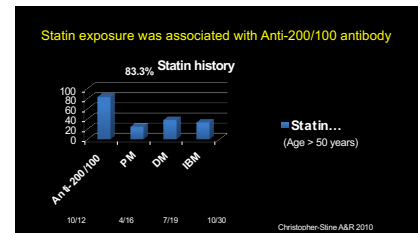
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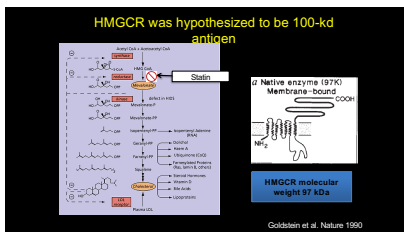
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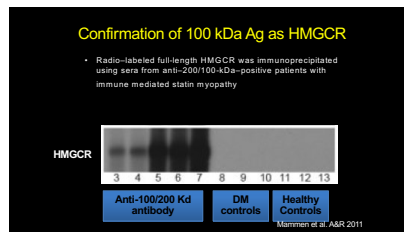
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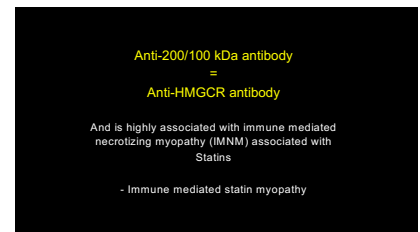
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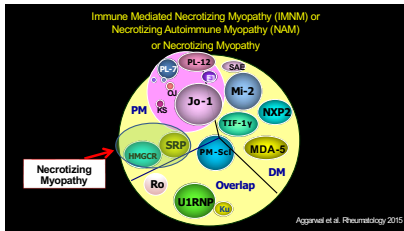
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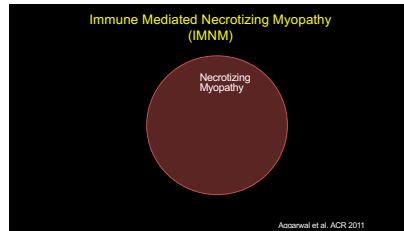
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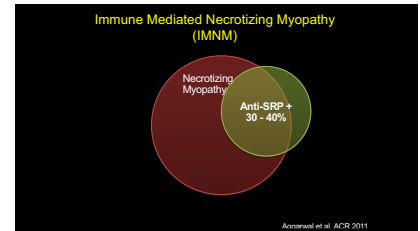
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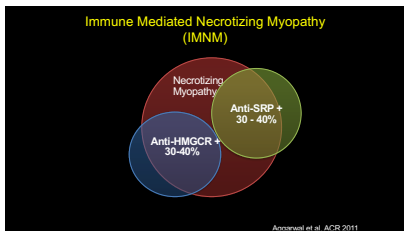
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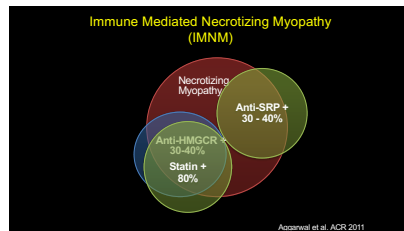
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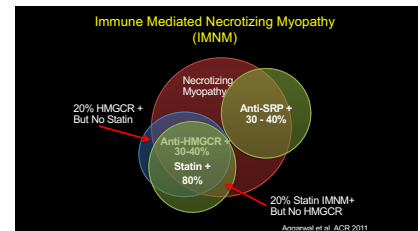
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Should we routinely check anti-HMGCR antibody ?

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**Anti-HMGCR antibody ELISA**

Table 3. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase ELISA versus IP\*

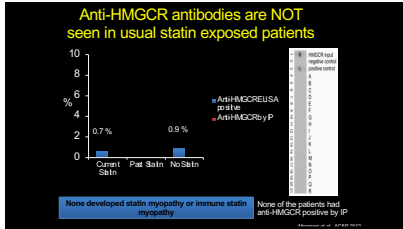
	IP positive	IP negative
ELISA positive	17	2
ELISA negative	1	287

- Sensitivity: 94.4%
- Specificity: 99.3%
- False Positive: 10.5%
- False negative: 0.3%

Too many patients are on Statin : 18% will be false positivity  
Too few patients have immune mediated : 2 per million per year

Mammen et al. ACR 2012

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### Anti-HMGR antibody in Statin Myopathy (self limiting)

- 51 statin myopathy was compared with 47 controls

Muscular weakness	
Low	8 (15.7)
Moderate	9 (17.6)
Myalgia	
Low	6 (11.4)
Moderate	19 (37.1)
Severe	6 (11.4)
Creatine kinase >300 units/liter	3 (6.0)
Myoglobinuria	6 (12.0)
Rhabdomyolysis	1 (2.0)

Statin Myopathy with + HMGR antibody : 0%  
Controls with + HMGR antibody : 0%

Mammen et al. *ACER* 2012

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Anti-HMGR antibody is highly specific for immune mediated necrotizing myopathy (80-90% statin history)

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### Do not check Anti-HMGR antibody

- We do NOT recommend to check Anti-HMGR antibody
  - Before starting statins
  - Statin exposed patients without muscular symptoms
- Self limiting typical statin myopathy

Check anti-HMGR antibody if suspected immune mediated necrotizing myopathy (esp. if history of statin exposure)

Loaneathan & Aggarwal et al. *Curr Opin Clin Invest* 2016

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### Key clinical features of Immune Mediated Necrotizing Myopathy (Statin/HMGR+)

- Strong Statin Association (on statin or h/o of statin exposure)
  - 20% No statin history
  - Age > 50 (higher association with statin, > 90%)
  - Age: Middle age to Elderly; M = F
  - Subacute to insidious onset
  - Progressive despite stopping statins
  - Severe muscle weakness (100% proximal weakness); Myalgia, arthralgia, dysphagia
  - No Rash, ILD, Sicca, Raynaud's, Arthritis, Cancer
  - Very High CK (mean : 10,000; range : 3-24 K)
  - Statin duration (0-83 months): 31.3 +/- 27.4 months
  - Statin: no particular agent
  - Require immunosuppressive therapy (long term)

Loaneathan & Aggarwal et al. *Curr Opin Clin Invest* 2016

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### Do not rechallenge with Statin

- Relapse can occur with re-exposure to a statin
- All reported cases of rechallenge led to relapse sooner or later
- If high cardiovascular risk
  - Non-statins
  - Fibrates
  - Ezetimibe
  - PCSK-9 inhibitors

Loaneathan & Aggarwal et al. *Curr Opin Clin Invest* 2016

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### Anti-SRP Subset

- Younger patients
- Acute onset of severe weakness with myalgias
- Very high CPK, early atrophy
- Severe refractory dysphagia
- No other organ
- Poor prognosis and refractory to treatment

Bx shows: Necrosis (arrow) Myophagocytosis (arrowhead) But no inflammation

Gable Epstein, *Muscle & Nerve*, 2010

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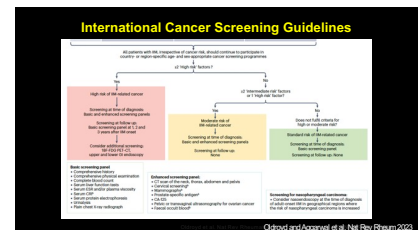
### International Cancer Screening Guidelines

IM diagnosis (either a score of function normal)

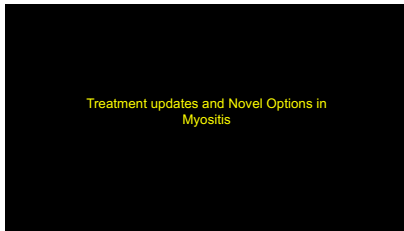
IM subtype	High-risk features	Intermediate-risk features	Low-risk features
IM subtype	Demographics	Demographics	Demographics
MSK and MSK	Anti-SRP antibodies, Anti-HMGR antibodies	Anti-SRP antibodies, Anti-HMGR antibodies, Anti-MG antibodies, Anti-HMGCR antibodies	Anti-SRP antibodies, Anti-HMGR antibodies, Anti-MG antibodies, Anti-HMGCR antibodies
Clinical features	Age < 40 years at IM onset, Proximal high-grease weakness, Rapid fatigue, Dysphagia (moderate to severe), Colocalized necrosis	Male sex	Proximal phenotype, Inflammatory etiology, Intestinal Lung Disease
Total			

Oktay and Aggarwal et al. *Int Rev Rheum* 2023

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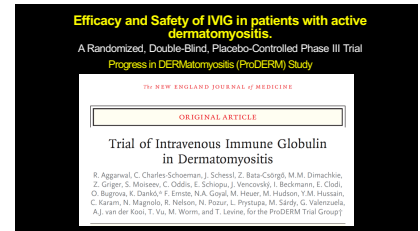
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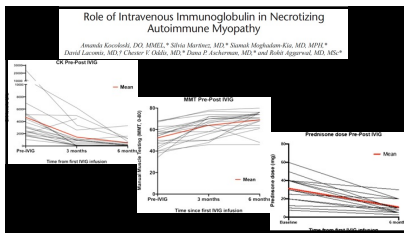
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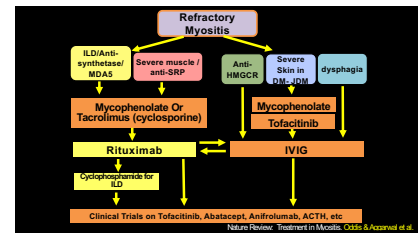
Treatment Considerations

- Stop Statins in anti-HMGCR antibody positive
- Steroid Therapy – modest response
  - Prednisone 1 mg/kg po bid a fast taper over 3 months
- Long term immunosuppressive therapy
  - Methotrexate
  - Azathioprine
  - Mycophenolate
  - Tacrolimus
- Refractory: >80% require 2+ immunosuppressive agents
  - IVIG (Monotherapy or Combination) or Rituximab

Treat Long Term (1-2 years);

Loonathan & Azevoul et al. Expert Rev Clin Immunol. 2016

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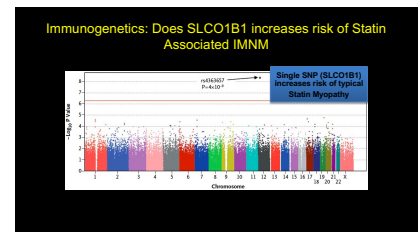
Join our efforts for clinical research or trials in Myositis through Myositis Clinical Trial Consortium (MCTC)

MCTC

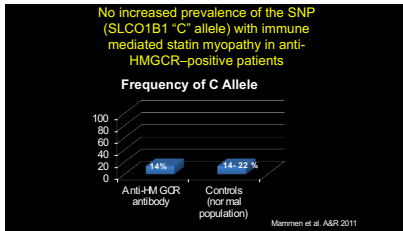
https://myositisclinicaltrialsconsortium.org

Email me if interested in myositis : Aggarwalr@UPMC.edu

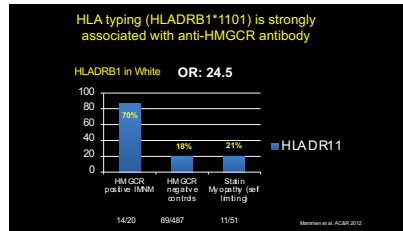
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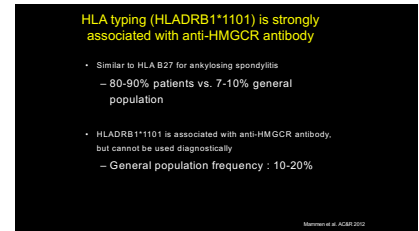
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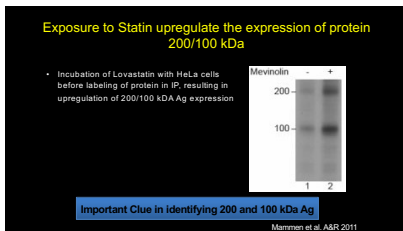
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