Myositis 101: Clinical Features, Diagnosis and Management

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TMA San Diego
September 7, 2017
Overview of Myositis

• Clinical features of Inflammatory myopathies

• Diagnosis
  • Muscle biopsy features
  • New antibodies & Muscle imaging
    • May improve diagnostic challenges

• Management: Immunotherapy or not?
Inflammatory Myopathies:

Autoimmune Myopathies

• Polymyositis (PM)
• Dermatomyositis (DM)
• Immune-mediated necrotizing myopathy (IMNM)

• Inclusion body myositis (sIBM)
  • A degenerative disease of muscle?
  Abnormal cytoplasmic aggregates (e.g., TDP-43)
  • Partially autoimmune?
Clinical Features
Clinical Features of PM, DM, IMNM

• Weakness of Proximal muscles
  • Symmetric
  • Shoulder girdle and hip girdle muscles
  • Difficulty with “Chairs, Stairs, Hair”

• Females > Males

• Onset: Subacute

• Responsive to immunotherapy
Dermatomyositis

- Distinct Skin rash (hallmark) may precede weakness by weeks to months
- Some may never develop weakness (amyopathic DM)
- Associated with Extramuscular manifestations: pulmonary, cardiac, gastrointestinal, & joints
Dermatomyositis: Skin manifestations

- **Heliotrope rash**
  - Rash over face, neck, anterior chest (V-sign) and upper back (shawl sign), extensor surfaces

- **Gottron papules**

- **Subcutaneous calcifications**

- **Nail beds with capillary telangiectasias, mechanic hands**
Clinical Features of:

Sporadic Inclusion Body Myositis (sIBM)

- Most common acquired myopathy > age of 50 years

- Slow progressive muscle disease

- Atrophy and asymmetric, predominantly affecting finger flexors, hip flexors, and knee extensors

- Males > Females
Leg Weakness: Slow progressive in IBM

- Falls
- Gait difficulty
- Arising from low seated position
- Difficulty climbing stairs
- Foot drop (dorsiflexion weakness)
- Knee buckling (quadriceps)
Grip weakness in IBM

- Grip difficulty
- Opening jars
- Manipulating keys
- Writing
- Carrying objects
- Upper arm weakness over time
Swallowing difficulty in IBM

- Frequent, embarrassing and potentially dangerous
- Initially, describe a “stuck” sensation when swallowing
- Unintended weight loss
- Higher incidence of Aspiration pneumonia
- Prevalence ranging from 40-80%
Evaluation
Diagnostic studies

• Muscle Enzymes (Creatine Kinase)
• Nerve conduction/Needle EMG studies
• Muscle biopsy
• Antibodies
• Muscle MRI
Histological differences

Pathologic hallmarks

• Dermatomyositis: Perifascicular atrophy

• Polymyositis: Primary inflammation, Nonnecrotic muscle fiber, surrounded and invaded by CD8+ T cells

• Immune-mediated necrotizing myopathy: Degeneration and regeneration, necrotic fibers, with a paucity of inflammation

• Inclusion body myositis: Rimmed vacuoles, inflammation
Muscle biopsy: Key features

Treatable conditions:

No response to immunotherapy: IBM or Dystrophies- don’t respond to immunotherapy

Rimmed vacuoles seen in INCLUSION BODY MYOSITIS

Perifascicular atrophy seen in DERMATOMYOSITIS

Endomysial inflammation seen in POLYMYOSITIS

Necrosis seen in NECROTIZING Myopathy

Dystrophic changes in muscular dystrophy
Muscle Histopathology in Dermatomyositis

- Perivascular, perimysial inflammation
- Perifascicular atrophy
- MAC deposition on blood vessels
- Reduced capillary density (immune mediated microangiopathy)
- Tubuloreticular inclusions on endothelial walls on EM
Muscle biopsy in **Necrotizing Myopathy**: Paucity or lack of inflammation, yet **necrotic fibers**
Muscle Histopathology in IBM

Karpati made most definitive description:
Neurology 1978 28(1): 8-17

**Endomysial inflammation**, inflammatory cells surrounding myofibers, invasion of non-necrotic muscle fibers

**Variation** in fiber size, angular fibers (neurogenic atrophy), fibrosis (chronicity)

**Rimmed vacuoles** in some fibers- commonly visible on Gomori trichrome- vacuoles contain degraded nuclei and membranous material

**Tubulofilamentous inclusions** on EM- within nuclei or in clumps in sarcoplasm suggestive of former nuclei devoid of nuclear membrane
Myositis Specific Autoantibodies
## Myositis Specific Antibodies In PM and DM

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Immune target</th>
<th>Function of autoantigen</th>
<th>Clinical associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)</td>
<td>tRNA synthetases</td>
<td>Aminoacylation of tRNAs</td>
<td>PM</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>NuRD subunit</td>
<td>Gene transcription</td>
<td>Anti-synthetase syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nucleosome remodeling</td>
<td>“Classic DM”</td>
</tr>
<tr>
<td>Anti-TIF1-γ</td>
<td>Transcriptional intermediary factor 1γ</td>
<td>Ubiquitination</td>
<td>Mild disease</td>
</tr>
<tr>
<td>Anti-NXP-2</td>
<td>Nuclear matrix protein 2</td>
<td>Gene transcription</td>
<td>Severe DM</td>
</tr>
<tr>
<td>Anti-MDA5</td>
<td>Melanoma differentiation-associated protein 5</td>
<td>Innate antiviral response</td>
<td>Cancer-associated DM</td>
</tr>
<tr>
<td>Anti- SAE</td>
<td>SUMO-1 activating enzyme</td>
<td>Protein sumoylation</td>
<td>Amyopathic DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gene transcription</td>
<td>ILD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor prognosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initially amyopathic DM</td>
</tr>
</tbody>
</table>
Dermatomyositis Autoantibodies may help diagnostic yield and predict prognosis
Table 2 Myositis-specific antibodies: target antigens and clinical associations in adult myositis patients

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Severe DM
Cancer-associated DM

ILD
Poor prognosis

DM
Initially amyopathic DM
Increased Cancer Risk in DM, but not PM or IBM

Greatest risks for:

- Ovarian
- Lung
- Gastric
- Colorectal
- Pancreatic
- Lymphomas

Hill et al., Lancet 2001
Recommend extensive cancer screening in high risk DM patients
Cancer Screening Recommendations?

- A single PET/CT may be as good as intensive screening

Conventional Cancer Screening versus PET/CT in Dermatomyositis/Polymyositis

Albert Selva-O’Callaghan, MD, PhD,* Josep M. Grau, MD, PhD,⁎ Cristina Gámez-Cenzano, MD, PhD, ⁎ Antonio Vidal-Pascual, MD, PhD, Xavier Martínez-Gómez, MD, Ernesto Trallero-Araguás, MD, Eduard Andía-Navarro, MD, Miquel Vilardell-Tarrés, MD, PhD

Am J. Med 2010

- Conventional screen: physical exam + labs + chest/abdomen CT + mammography + gyn exam (including U/S), tumor markers (CA125, CA 19-9, CEA, PSA)
  - PPV= 78%, NPV = 96%

- Whole-body FDG-PET/CT
  - PPV= 86%, NPV = 94%
Immune-Mediated Necrotizing Myopathy
Myositis Antibodies Associated with Necrotizing myopathies

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<tr>
<td>Anti-SRP</td>
<td>Signal recognition particle</td>
<td>Protein translocation across the ER</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>3-Hydroxy-3-methylglutaryl-CoA reductase</td>
<td>Cholesterol biosynthesis</td>
<td>Necrotizing myopathy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><em>Prior statin use</em></td>
</tr>
</tbody>
</table>
NT5C1A Antibody in IBM

- In 2013, Cytosolic 5’-Nucleotidase 1A (NT5C1A) Antibody
- May be involved in DNA repair metabolism
- NT5C1A in sporadic Inclusion Body Myositis patients
  - 60-70% Sensitivity
  - 83-92% Specific

NT5C1A Antibody in IBM vs. Autoimmune diseases

- Detected in 61% of 117 patients with IBM
- 5% with PM
- In Sjogrens (23%) & SLE (14%) - but no muscle weakness
- NT5C1A Ab may be helpful in differentiating IBM from PM
Seropositivity for NT5c1A antibody in sporadic inclusion body myositis predicts more severe motor, bulbar and respiratory involvement

N A Goyal, 1 T M Cash, 1 U Alam, 1 S Enam, 1 P Tierney, 1 N Araujo, 1 F H Mozaffar, 1 A Pestronk, 2,3 T Mozaffar1,4

J Neurol Neurosurg Psychiatry 2015;0:1–6. doi:10.1136/jnnp-2014-310008

- 25 sIBM patients enrolled in the study
- NT5C1A antibodies detected in 18/25 subjects (72%)
- May predict more severe phenotype
  - Greater motor deficits (assistive devices)
  - Dysphagia
  - Respiratory insufficiency
Muscle Imaging
Muscle Imaging (MRI)

- Easy technique to visualize affected muscles and pattern of muscle involvement
- Detect subclinical changes (prior to detectable weakness on exam)
- May help measure disease progression/activity
Muscle Imaging (MRI)

- Edema
- Atrophy
- Fatty replacement
- Fascial edema

**Figure 1** Examples of T1-weighted (T1W) turbo spin echo (TSE) and short-tau inversion recovery (STIR) sequences showing oedema (red arrows), atrophy (red arrow heads), fatty replacement (blue arrows) and fascial oedema (blue arrow heads) in patients with immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM) and dermatomyositis (DM).

Pinal-Fernandez et al., Ann Rheum Dis 2016
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox¹, Monique Reijnierse², Carla S. P. van Rijswijk², Axel R. Wintzen¹, Jan J. Verschuuren¹ and Umesh A. Badrising¹

MRI forearm:
Severe fatty infiltration of Flexor digitorum profundus (FDP)

MRI Upper thigh:
Severe fatty infiltration of Vastus lateralis, relative sparing of rectus femoris and hamstrings
Muscle Imaging MRI- in sIBM especially helpful if mild finger flexor weakness and want to confirm muscle involvement

“Increased T2 signal in medial forearm flexor compartment muscles”
Treatment/Management in DM, PM and Necrotizing myopathy
Treatment: in DM and PM

- Generally good response to therapy
- Understanding of therapeutics: based on small clinical trials, expert experience, and retrospective case series
- Currently, no single correct treatment approach
- Most experts agree that first-line therapy is corticosteroids
- Equipoise on when to begin other therapies
Treatment: DM and PM

- 1\textsuperscript{st} line agent: steroids
- 2\textsuperscript{nd} line agents: Methotrexate, Azathioprine, other immunosuppressive agents (mycophenolate mofetil)
- IVIg shown to be quite effective
- Rituximab for refractory disease
- 3\textsuperscript{rd} line agents (options, less evidence): cyclosporine, tacrolimus, cyclophosphamide
Corticosteroids: Starting treatment

- Considered first-line therapy in DM and PM
- Generally initiated with prednisone at a dose of 0.75-1mg/kg/day, not exceeding 60-80mg daily
- In severe weakness or multisystem involvement (severe rash, dysphagia, interstitial lung disease), short course of IV methylprednisone (1g/d x 3-5 days), followed by high dose oral prednisone
- High dose steroids should be maintained until strength normalizes or improvement plateaus
- Maintained on high dose *2-4 months
Corticosteroids: Tapering

• After improvement in strength (may be 2-4 months)

• Taper methods vary:
  • When high dose, (taper by 20%) or by 10mg/day *every 4 weeks
  • When at 20mg/day, taper by 5mg *every 4 weeks
  • When at 10mg/day, taper by 1-2.5mg/day *every 4 weeks or even every 6-12 months

• Goal: reduce dose to lowest effective dose (maintaining disease control and balancing with prednisone side effects)

• Rapid taper may result in “back-and-forth” of dose and exacerbations of disease
Concurrent Management: Side effects of Steroids

- Monitor: Glucose, potassium levels, blood pressure, eye exam
- Risk of osteoporosis with steroid use
- Baseline and annual DEXA (dual-energy Xray)
- Vitamin D (2000IU/d) and Calcium (1g/d)
- Bisphosphonates if higher risk of osteoporosis
- Dietician to prevent weight gain (low sodium, low carb, high protein diet)
When to Consider Starting a Second-line Agent?

Addition of another immunosuppressive drug:

- Moderate to Severe weakness (at onset)
- Refractory disease (persistent weakness)
- Repeated disease flares
- To allow reduction of dose and duration of glucocorticoid therapy and associated side effects
Treatment options:
Second-line Agents
Generally start with:
Methotrexate or Azathioprine
Methotrexate

- Binds to and inhibits dihydrofolate reductase, resulting in inhibition of DNA synthesis, repair and replication
- Oral or subcutaneous, titrated dose to 15-25mg/wk
- Several case series and expert consensus on efficacy
- Folate 1mg daily
- Monitor: Blood counts, liver and renal indices
- Risk of Pulmonary fibrosis: Avoid in ILD or Jo-1 Ab
Azathioprine

• Inhibits purine metabolism, interfering with cellular replication

• Started at 50mg twice daily, then increase by 50mg every 2-4 weeks, up to 2-2.5mg/kg/day

• Some studies show similar efficacy to MTX, but may take up to 6 months (rather than 2-3 months)

• 10% of patients reaction: fever, abdominal pain, nausea, vomiting, pancreatitis or rash - STOP drug

• Monitor: blood counts (bone marrow suppression), liver and kidney
Treatment options:
Second-line Agents
Other Options
Intravenous Immunoglobulin (IVIg)

- Immunomodulatory agent thought to suppress inflammatory/immune-mediated process
- Several studies show efficacy
- Used in: refractory to prednisone taper, flare on prednisone, refractory to other 2nd line agents
- *Or* in: Severe myositis, start IVIg with steroids and then add 2nd-line agent
- Dose: 2g/kg over 2-5 days, maintained at 1g/kg/month for a few months, then taper pending response
- Well tolerated, S/E: flu-like symptoms, headache
Rituximab

- Monoclonal Ab directed against CD20 antigen on B-lymphocytes
- Several small case reports note benefit in refractory DM and PM
- Use in patients refractory to prednisone and failed one second-line agent
- Dose: 750mg/m² (up to 1g) IV, repeated in 2 weeks (consider repeating every 6-18 months)
- Risk of acute of infusion reaction and long-term immunosuppression
Treatment Algorithm

Treatment of myositis

Mild disease

Oral glucocorticoids (GC) (prednisone: 1 mg/kg/d)

Clinical response after 4 weeks?

Yes

Taper prednisone by 20–25% of existing dose monthly to minimum effective dose and continue for 6–12 months

No

Moderate or severe disease

Oral GC therapy (1 mg/kg/d; no > 80 mg/d)

Plus

Methotrexate (begin 10–15 mg/week oral or SQ up to 25 mg/week) or Azathioprine (begin 50 mg/d; increase to 1.5 mg/kg/d within a month; maximum dose = 2.5 mg/kg/d)

Clinical response after 2 to 3 months?

Yes

Options for moderate disease:
1. Methotrexate/azathioprine combination
2. Mycophenolate mofetil (particularly in myositis-ILD or refractory cutaneous disease)
3. Cyclosporine or tacrolimus (particularly myositis-ILD)

Options for severe disease:
1. Rituximab (1 g 2 weeks apart)
2. IVIG (2 g/kg/month in 2 doses for 3 months)
3. Cyclophosphamide (for severe myositis and/or worsening ILD and/or systemic vasculitis)

Clinical response?

Yes

Options for moderate disease:
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2. Mycophenolate mofetil (particularly in myositis-ILD or refractory cutaneous disease)
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Clinical response?

No

Other immunosuppressive drug combinations
Investigational agents [e.g., ACTH gel, tocilizumab, anti-IFNα (sifalimumab) other biologic drugs]
Clinical trials
Polymyxin B hemoperfusion in rapidly progressive acute ILD
BiPAP for the treatment of ventilatory failure due to diaphragmatic weakness
Botulinum toxin administration in severe dysphagia due to cricopharyngeal dysphagia

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Treatment of inflammatory myopathy: emerging therapies and therapeutic targets
Siamak Moghadam-Kia, Rohit Aggarwal, and Chester V Oddis

Treatment of anti-HMGR Ab Immune-Mediated Necrotizing Myopathy

• Reports suggest multiple immunosuppressive agents to treat effectively

• Over half published cases = Steroids + 2 agents

• IVIg was often 3rd agent added to achieve remission

• Also screen for supplements or foods hiding statins (mushrooms, red rice yeast)!

Mammen and Tiniakou, NEJM, 2015
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Mammen and Tiniakou, NEJM, 2015
Treatment/Management in Inclusion body Myositis
Pathogenesis in IBM? – still Unclear

Unclear if primary inflammatory myopathy or primary degenerative myopathy with secondary inflammatory response

- Immune injury of IBM myofibers due to cytotoxic T cells? – but no response to immunotherapy
- Degenerative disorder with abnormal depositions of amyloid, ubiquitin, tau?
- Rimmed vacuoles lined with nuclear membrane proteins, suggesting derived from myonuclear breakdown
- Discovery of TDP-43 nucleic acid binding protein nonnuclear sarcoplasmic accumulation – toxic to cells

Normal muscle

SARCOPLASMIC REDISTRIBUTION OF NUCLEAR TDP-43 IN INCLUSION BODY MYOSITIS
Immunosuppression in sIBM

Literature and anecdotal reports

Refractory to immunosuppressive treatment:

• Steroids (uncontrolled trials – stabilization or temporary improvement, prospective trial up to 12 months showed fall in CK level yet deterioration in muscle strength)

• Methotrexate (some trials with apparent stabilization over short period, largest trial of 12 months in 44 patients- MTX did not slow progression of disease)

• Azathioprine

• Cyclophosphamide
IVIg in sIBM

Retrospective study in 16 IBM patients suggested short term benefit in leg muscle strength and dysphagia (benefit was only temporary and limited to a small proportion of patients) Clin Exp Rheumatol 2012; 30:838-842

Case series or Controlled studies

• None which show complete responses or major benefit
• 3 double blind studies with IVIG – “no statistically significant improvement in muscle strength”
Does Treatment with Immunotherapy make sIBM worse in the long run?

**Table 5** Comparison of treated and untreated patients with sporadic IBM

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Untreated (n = 65)</th>
<th>Treated (n = 71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (n = 136)</td>
<td>40 (61.5)</td>
<td>38 (53.5)</td>
<td>0.39</td>
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<tr>
<td>Age at first symptoms, years (n = 136)</td>
<td>63 (57–72)</td>
<td>60 (53–65)</td>
<td>0.02</td>
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<tr>
<td>First symptoms (n = 136)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Muscle weakness and swallowing difficulties</td>
<td>4 (6.1)</td>
<td>7 (10.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Muscle weakness only</td>
<td>59 (90.8)</td>
<td>60 (84.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Swallowing troubles only</td>
<td>2 (3.1)</td>
<td>4 (5.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Previous diagnosis (n = 136)</td>
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<tr>
<td>None</td>
<td>53 (81.5)</td>
<td>41 (57.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>4 (6.1)</td>
<td>19 (26.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>8 (12.3)</td>
<td>11 (15.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Delay between first symptoms and sporadic IBM diagnosis, months (n = 136)</td>
<td>59 (33–86)</td>
<td>58 (25–98)</td>
<td>0.71</td>
</tr>
<tr>
<td>Status at the last visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since sporadic IBM diagnosis, months (n = 136)</td>
<td>18 (3–46)</td>
<td>50 (13–87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, years (n = 136)</td>
<td>73 (66–79)</td>
<td>71 (65–76)</td>
<td>0.21</td>
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<tr>
<td>Muscle weakness (n = 136)</td>
<td>65 (100)</td>
<td>71 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe proximal weakness (n = 136)</td>
<td>28 (43.1)</td>
<td>36 (52.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Severe distal weakness (n = 136)</td>
<td>25 (38.5)</td>
<td>28 (39.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Swallowing troubles (n = 136)</td>
<td>29 (44.6)</td>
<td>33 (46.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Creatine kinase, IU/l (n = 87)</td>
<td>367 (219–649)</td>
<td>209 (117–559)</td>
<td>0.11</td>
</tr>
<tr>
<td>Grip strength kgN (n = 76)</td>
<td>13.4 (11.0–17.2)</td>
<td>13.5 (9.0–18.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Walton (n = 113)</td>
<td>4 (3–6)</td>
<td>6 (3–6)</td>
<td>0.007</td>
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<tr>
<td>RMI (n = 88)</td>
<td>11 (9–13)</td>
<td>10 (4–11)</td>
<td>0.004</td>
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<tr>
<td>IWCI (n = 71)</td>
<td>50 (30–65)</td>
<td>40 (25–50)</td>
<td>0.04</td>
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<tr>
<td>Current handicap for walking (n = 136)</td>
<td></td>
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<tr>
<td>None</td>
<td>20 (30.8)</td>
<td>13 (18.3)</td>
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<tr>
<td>One or two canes</td>
<td>26 (40.0)</td>
<td>26 (36.6)</td>
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<tr>
<td>Wheelchair</td>
<td>19 (29.2)</td>
<td>32 (45.1)</td>
<td></td>
</tr>
</tbody>
</table>

**Treated group:**
Less independent mobility, Increased use of wheelchair
Therapeutic Agents Investigated in sIBM

- **Arimoclomol**
  - May upregulate the cytoprotective heat shock response (HSR) by amplifying heat shock protein expression and potentially dampen the detrimental aspects of inflammation and degeneration
  - Placebo controlled trial (16 active, 8 placebo) – well tolerated, demonstrated proof of concept and supporting further research
    - *Ann Rheum Dis* 2013

- **Etanercept** (Tumor necrosis factor antagonist)
  - Pilot trial (*Neurology* 2006) no significant benefit in hand grip at 6 months, but improvement in hand grip at 12 months
  - Placebo-controlled 30 patient study completed

- **Alemtuzumab** (CAMPATH)
  - Monoclonal Ab, causes depletion of blood lymphocytes
  - Proof of principle study in 13 patients (*Brain* 2009) reported slowing of disease progression up to 6 months, improvement in strength in some, and reduced endomysial inflammation
Newer Agents: Myostatin Antagonists in sIBM

- Myostatin negatively regulates skeletal muscle growth
- Inhibition of myostatin results in hypertrophy of skeletal muscles (increased muscle mass and strength)
- Myostatin pathway under investigation using 2 agents
  - Follistatin gene transfer (antagonist of myostatin)
  - BYM338 (monoclonal Ab that binds competitively to activin receptor type IIb with greater affinity than myostatin)
- BYM338 given to two atrophy mouse models - steroid myopathy and disuse – recovery of muscle loss
14 sIBM patients (11 active, 3 placebo):
- Increased thigh muscle volume in treated patients 8 weeks after dosing
- Improved 6 minute walk distance in treated patients 16 weeks after dosing
Management: Multidisciplinary Care

- **Mobility**
  - Assistive devices (AFOs, cane, braces, walker, wheelchair)
  - Risk of falls

- **Dysphagia**
  - Diet modification
  - Dilation, botulinum toxin, cricopharyngectomy
  - Gastrostomy tube
  - Risk of aspiration pneumonia

- **Respiratory insufficiency:** Noninvasive ventilation (BiPAP)

- **Adaptive Equipment**
  - Shower chair, stair lift, safety rails, hospital bed
  - Home safety evaluations and bathroom modifications

- **Role of Exercise:** May slow progression
Take Home Points

• Myositis cases diagnostically challenging

• Careful attention to clinical exam for clues to correct diagnosis

• Diagnostic process (in addition to muscle biopsy):
  • Antibodies (Myositis Panel, HMGCR, NT5C1A Ab): quite helpful for establishing diagnosis and predicting treatment response

• Muscle imaging:
  • Detecting subclinical muscle involvement
  • Pattern of muscle involvement
  • Disease activity

• Establishing diagnosis, before embarking on immunosuppression

DM, PM, IMNM- treatable! Immunotherapy options!
Thank you
### Myositis Specific Antibodies

**TIF1-γ Positive**

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Immune target</th>
<th>Function of autoantigen</th>
<th>Clinical associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)</td>
<td>tRNA synthetases</td>
<td>Aminoacylation of tRNAs</td>
<td>PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-synthetase syndrome</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>NuRD subunit</td>
<td>Gene transcription</td>
<td>“Classic DM”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nucleosome remodeling</td>
<td>Mild disease</td>
</tr>
<tr>
<td><strong>Anti-TIF1-γ</strong></td>
<td>Transcriptional intermediary factor 1γ</td>
<td>Ubiquitination</td>
<td>Severe DM Cancer-associated DM</td>
</tr>
<tr>
<td>Anti-NXP-2</td>
<td>Nuclear matrix protein 2</td>
<td>Gene transcription</td>
<td>Severe DM Cancer-associated DM</td>
</tr>
<tr>
<td>Anti-MDA5</td>
<td>Melanoma differentiation-associated protein 5</td>
<td>Innate antiviral response</td>
<td>Amyopathic DM ILD Poor prognosis</td>
</tr>
<tr>
<td>Anti-SAE</td>
<td>SUMO-1 activating enzyme</td>
<td>Protein sumoylation</td>
<td>DM Initially amyopathic DM</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Signal recognition particle</td>
<td>Protein translocation across the ER</td>
<td>Necrotizing myopathy</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>3-Hydroxy-3-methylglutaryl-CoA reductase</td>
<td>Cholesterol biosynthesis</td>
<td>Necrotizing myopathy Prior statin use</td>
</tr>
</tbody>
</table>
Differential Diagnosis: Pathological

- **Endomysial inflammation:**
  - Polymyositis
  - Muscular dystrophies

- **Vacuoles +/- Rims or Aggregates**
  - Oculopharyngeal muscular dystrophy
  - Distal myopathies
    (Welander, Finishing-Markesbery, Distal dystrophy, Oculopharyngeal distal)
  - Toxic drug induced: chloroquine or colchicine myopathy
  - Hereditary Inclusion body myopathies
    - HIBM (GNE/Nonaka)
    - Myopathy + Paget’s and Frontotemporal Dementia (IBMPFD)
  - LGMD 1A, 1D, 1G, 2G
  - Glycogen storage
  - Myofibrillar myopathy
  - Periodic paralysis
Differences in classifications and approaches

With antibodies and muscle imaging, those differences have been narrowing!
Unicorns, dragons, polymyositis, and other mythological beasts

Anthony A. Amato, MD; and Robert C. Griggs, MD
Unicorns, Dragons, Polymyositis, and other Mythological Beasts:
The truth about polymyositis

So how rare is polymyositis?

Are there pathological differentiators?

What about other antibodies?

So is PM nothing more than sIBM or necrotizing immune myopathy (NAM)?
Polymyositis, a very uncommon isolated disease: clinical and histological re-evaluation after long-term follow-up

Veronica Silva Vilela · Sergio Prieto-González · José C. Milisenda · Albert Selva-O’Callaghan · Josep M. Grau

Table 1 Clinical, laboratorial and pathologic features, evolution and final diagnosis of the ten patients initially diagnosed as isolated PM

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial clinical features (y)</th>
<th>CK (mg/dl)</th>
<th>Biopsy findings (first evaluation)</th>
<th>Clinical follow-up</th>
<th>Biopsy findings (re-evaluation)</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 73 Proximal weakness</td>
<td>390</td>
<td>PM</td>
<td>Disabled</td>
<td>Red ragged cell</td>
<td>Definite IBM</td>
</tr>
<tr>
<td>2</td>
<td>F, 39 Myalgia and mild weakness</td>
<td>460</td>
<td>PM</td>
<td>RA after 8 years of follow-up</td>
<td>No changes</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>3</td>
<td>F, 59 Proximal weakness</td>
<td>3,000</td>
<td>PM</td>
<td>Remission with GC</td>
<td>No changes</td>
<td>Isolated PM</td>
</tr>
<tr>
<td>4</td>
<td>F, 56 Proximal weakness</td>
<td>7,160</td>
<td>PM</td>
<td>Partial improvement with ciclosporine</td>
<td>Severe necrosis.</td>
<td>NAM</td>
</tr>
<tr>
<td>5</td>
<td>F, 51 Proximal with neck weakness</td>
<td>273</td>
<td>PM</td>
<td>Died</td>
<td>Vacuoles</td>
<td>Definite IBM</td>
</tr>
<tr>
<td>6</td>
<td>F, 48 Proximal weakness</td>
<td>13,000</td>
<td>PM</td>
<td>Stable with GC and IVIG</td>
<td>Mitochondrial changes</td>
<td>Probable IBM</td>
</tr>
<tr>
<td>7</td>
<td>M, 77 Proximal with neck weakness</td>
<td>2,537</td>
<td>PM</td>
<td>Disabled</td>
<td>Ragged red cell</td>
<td>Probable IBM</td>
</tr>
<tr>
<td>8</td>
<td>M, 56 Proximal weakness</td>
<td>3,000</td>
<td>PM</td>
<td>Improvement with GC SSc after 10 of follow-up</td>
<td>No changes</td>
<td>SSc</td>
</tr>
<tr>
<td>9</td>
<td>F, 29 Asymptomatic (CK rising)</td>
<td>Not available</td>
<td>PM</td>
<td>Improvement with levothyroxine</td>
<td>No changes</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>10</td>
<td>M, 39 Severe proximal weakness</td>
<td>CK 2,600</td>
<td>PM</td>
<td>Anti-SRP Improvement with GC and IVIG</td>
<td>Severe necrosis</td>
<td>NAM</td>
</tr>
</tbody>
</table>

F female, M male, y years, CK creatine kinase, Anti-SRP Ab anti-signal recognition particle antibody, GC glucocorticoids, IVIG intravenous immunoglobulin, PM polymyositis, and SSc systemic sclerosis
Muscle biopsy

Treatable conditions:

Endomysial inflammation seen in **POLYMYOSITIS**

No response to immunotherapy: IBM or Dystrophies- don’t respond to immunotherapy

Rimmed vacuoles seen in **INCLUSION BODY MYOSITIS**

Perifascicular atrophy seen in **DERMATOMYOSITIS**

Dystrophic changes in muscular dystrophy
Patient’s Muscle Biopsy & Diagnosis: Dermatomyositis

Inflammation surrounding a non necrotic fiber, just about to “invade”

Perifascicular atrophy seen in DERMATOMYOSITIS
DM Antibodies associated with unique dermatologic features

Mi-2: Severe Shawl sign

NXP2: Calciosis

MDA5: Palmar papules, ulcerations

http://neuromuscular.wustl.edu
## Presence of Histopathologic Features versus Antibodies in DM

### Table 2. Muscle biopsy features, treatments, and duration of disease at biopsy according to autoantibody subsets in patients with dermatomyositis (DM).

<table>
<thead>
<tr>
<th>Feature</th>
<th>All DM, n = 91</th>
<th>All Jo1, n = 13</th>
<th>Jo1 with Ro52, n = 9</th>
<th>Jo1 without Ro52, n = 4</th>
<th>Anti-TIF1-γ, n = 25</th>
<th>NXP2, n = 17</th>
<th>Mi-2, n = 12</th>
<th>MDA5, n = 5</th>
<th>PM-Scl, n = 9</th>
<th>Ro52, n = 22</th>
<th>No Antibody, n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perivascular inflammation</td>
<td>56 (62%)</td>
<td>9 (69%)</td>
<td>8 (89%)</td>
<td>1 (25%)</td>
<td>16 (64%)</td>
<td>11 (65%)</td>
<td>10 (83%)</td>
<td>1 (20%)</td>
<td>7 (78%)</td>
<td>15 (68%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Perifascicular atrophy</td>
<td>46 (51%)</td>
<td>8 (62%)</td>
<td>7 (78%)</td>
<td>1 (25%)</td>
<td>16 (64%)</td>
<td>9 (53%)</td>
<td>8 (67%)</td>
<td>2 (40%)</td>
<td>3 (33%)</td>
<td>12 (55%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Primary inflammation</td>
<td>21 (23%)</td>
<td>4 (31%)</td>
<td>4 (44%)</td>
<td>0 (0%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td>6 (50%)</td>
<td>0 (0%)</td>
<td>6 (67%)</td>
<td>6 (27%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Mitochondrial dysfunction*</td>
<td>14 (28%)</td>
<td>2 (25%)</td>
<td>2 (29%)</td>
<td>0 (0%)</td>
<td>7 (47%)</td>
<td>2 (25%)</td>
<td>2 (29%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>4 (29%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Necrotizing myopathy</td>
<td>15 (16%)</td>
<td>2 (15%)</td>
<td>0 (0%)</td>
<td>2 (50%)</td>
<td>2 (8%)</td>
<td>3 (18%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
<td>2 (22%)</td>
<td>4 (18%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Immunosuppressant prior to biopsy**</td>
<td>55 (61%)</td>
<td>8 (62%)</td>
<td>6 (67%)</td>
<td>2 (50%)</td>
<td>17 (71%)</td>
<td>7 (44%)</td>
<td>7 (58%)</td>
<td>5 (100%)</td>
<td>5 (56%)</td>
<td>15 (68%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Taking immunosuppressant during biopsy†</td>
<td>49 (56%)</td>
<td>6 (55%)</td>
<td>5 (63%)</td>
<td>1 (33%)</td>
<td>16 (67%)</td>
<td>7 (44%)</td>
<td>6 (50%)</td>
<td>4 (100%)</td>
<td>4 (44%)</td>
<td>17 (81%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Corticosteroids during biopsy**</td>
<td>42 (47%)</td>
<td>4 (31%)</td>
<td>3 (33%)</td>
<td>1 (25%)</td>
<td>14 (58%)</td>
<td>6 (38%)</td>
<td>6 (50%)</td>
<td>4 (80%)</td>
<td>3 (33%)</td>
<td>14 (64%)</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>

- **Perivascular Inflammation (62%)**
- **Perifascicular atrophy (51%)**
  vs. **Presence of Ab 84%**
- **Primary inflammation (23%)**
Statin Associated Immune-Mediated Necrotizing Myopathy

And anti-HMGCR Antibodies

A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy

Lisa Christopher-Stine, Livia A. Casciola-Rosen, Grace Hong, Tae Chung, Andrea M. Corse, Andrew L. Mammen

Autoantibodies against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCR) in Patients with Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, MD, PhD, Tae Chung, MD, Lisa Christopher-Stine, MD, MPH, Paul Rosen, Antony Rosen, MD, and Livia A. Casciola-Rosen, PhD
Johns Hopkins University School of Medicine, Baltimore, MD
Anti-HMGCR Ab specific to autoimmune myopathy patients

- Not present in 1966 subjects *without* myopathy
  - 763 current statin users
  - 322 former statin users
  - 881 statin naïve subjects

- Not present in 51 patients with *self-limited* statin intolerance

Mammen et al., 2012
Inclusion Body Myositis
60-year-old with > 10 years of “Refractory Polymyositis”

On exam:
• Facial weakness with eye closure

• Prominent atrophy in forearm muscle compartment (right > left) and both quadriceps (left > right)

• Asymmetric, diffuse limb weakness, worse in:
  deep finger flexors > deltoids
  quadriceps > hip flexors
Why is sIIBM Commonly Misdiagnosed?

Leading to a delay in diagnosis
Differential: Clinical mimickers

- Polymyositis (Most common)
- Neuropathy (CIDP)
- Muscular dystrophies:
  - Myotonic dystrophy
  - Facioscapulohumeral muscular dystrophy
- Amyotrophic lateral sclerosis (ALS)
- Hereditary inclusion body myopathy
- Distal myopathies
- Weakness attributed to aging?
Evaluation can be misleading at times
Electrodiagnostic studies

- Irritable myopathy
- Confusion: myopathic and neuropathic motor unit action potentials seen
- Up to 1/3 of patients: mild distal sensory axonal peripheral neuropathy
Creatine Kinase levels

- Normal to Moderate Elevation in many
- If Normal
  - May not think of a myopathic process
- Markedly elevated in some (>1000 U/L)
  - May think of polymyositis or a muscular dystrophy

Table 7: Retrospective studies on the natural history of sporadic IBM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Male (%)</th>
<th>Age at onset (years)</th>
<th>Age at diagnosis (years)</th>
<th>Creatine kinase level (IU/L)</th>
<th>Patients receiving immunosuppressors (%)</th>
<th>Progression despite therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringel et al., 1987</td>
<td>19</td>
<td>79</td>
<td>57.8</td>
<td>62.9</td>
<td>197</td>
<td>22.5</td>
<td>80.2</td>
</tr>
<tr>
<td>Lotz et al., 1989</td>
<td>40</td>
<td>72.5</td>
<td>56.1</td>
<td>62.4</td>
<td>1145</td>
<td>87.5</td>
<td>46.4</td>
</tr>
<tr>
<td>Sayers et al., 1992</td>
<td>32</td>
<td>62.5</td>
<td>58</td>
<td>61</td>
<td>279</td>
<td>44.4</td>
<td>93.75</td>
</tr>
<tr>
<td>Beyenburg et al., 1993</td>
<td>36</td>
<td>58.3</td>
<td>47</td>
<td>53.1</td>
<td>698</td>
<td>73.3</td>
<td>75</td>
</tr>
<tr>
<td>Lindberg et al., 1994</td>
<td>18</td>
<td>55.5</td>
<td>60.4</td>
<td>62.7</td>
<td>444</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>Amato et al., 1996</td>
<td>15</td>
<td>86.6</td>
<td>58</td>
<td>64</td>
<td>417</td>
<td>35.9</td>
<td>100</td>
</tr>
<tr>
<td>Peng et al., 2000</td>
<td>78</td>
<td>78.2</td>
<td>56.5</td>
<td></td>
<td>267</td>
<td>52.2</td>
<td></td>
</tr>
<tr>
<td>Felice and North, 2001</td>
<td>35</td>
<td>65.7</td>
<td>64.3</td>
<td>70</td>
<td>417</td>
<td>35.9</td>
<td>100</td>
</tr>
<tr>
<td>Badrising et al., 2005</td>
<td>64</td>
<td>67.2</td>
<td>57.6</td>
<td></td>
<td>267</td>
<td>52.2</td>
<td></td>
</tr>
<tr>
<td>Present study 2011</td>
<td>136</td>
<td>57.3</td>
<td>61</td>
<td>66</td>
<td>417</td>
<td>35.9</td>
<td>100</td>
</tr>
</tbody>
</table>
Myositis with endomysial cell invasion indicates inclusion body myositis even if other criteria are not fulfilled

J. van de Vlekkert a,*, 1, J.E. Hoogendijk b, M. de Visser a

a Department of Neurology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands
b Rudolf Magnus Institute for Neuroscience, Department of Neurology, University Medical Center Utrecht, Heidelberlaan 100, 3584 CX Utrecht, The Netherlands

Investigated the disease course in patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic fibers

**Hypothesis**: disease course in these patients will be in keeping with IBM and not PM, even if they did not fulfill histopathological or clinical criteria for IBM at onset

Table 1
Classification at baseline and at follow up in 81 patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic muscle fibers.

<table>
<thead>
<tr>
<th></th>
<th>RVs present</th>
<th>Clinical IBM</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation N (%)</td>
<td>49 (60.5)</td>
<td>14 (17.3)</td>
<td>18 (22.2)</td>
</tr>
<tr>
<td>At follow up N (%)</td>
<td>ND</td>
<td>29 (36)</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

RV: rimmed vacuoles; clinical IBM: rimmed vacuoles absent, but fulfilling clinical criteria for IBM; unclassified: fulfilling neither pathological nor clinical criteria for IBM; ND: not determined.
Why Misdiagnosed as Polymyositis?

- CK level: markedly elevated, misleading?

- Muscle biopsy:
  - Report “Inflammation consistent with polymyositis”
  - Comment on “few rimmed vacuoles and differential includes sIBM” overlooked

- Detailed clinical exam missed finger flexor involvement

- Other factors that should have raised suspicion for sIBM
  - Age of 50 years
  - Lack of response to immunosuppression
sIBM pattern helps differentiate from other myopathies:
- Marked FDP involvement
- Fatty infiltration up to 87%
- Sparing of rectus femoris and adductor muscles
- Asymmetry
How to Monitor Disease Control?

• Regardless of choice of initial therapy, early treatment associated with less muscle damage

Indicators of treatment response:

• Objective changes in muscle strength on clinical exam (Mainstay for determining dose adjustment of immunotherapy)

• CK muscle enzyme levels (not as reliable), but rises in levels associated with weakness suggest relapse

• Muscle MRI: new marker to assess disease activity
Corticosteroids: Incomplete response?

• In up to 50%, response may be incomplete on steroids alone, patients may require small dose of prednisone or other second-line agents for long-term control (Troyanov et al 2005)

• If High-dose steroids ineffective, clinicians should reconsider the diagnosis (Mimickers!)
  • IBM
  • Muscular dystrophy or Hereditary myopathy
  • Or Underlying malignancy
Life Expectancy in sIBM: Normal

Survival seems to be similar to the general population

During a 12 year follow up study:
46 of 64 patients died during follow up period
Median age at death = 81 years
In Netherlands, life expectancy 79 years

Figure 3 Kaplan-Meier curve showing a comparable survival between sIBM patients and an age- and sex-matched Dutch general population. The curve for the general Dutch population is adjusted for life expectancy for each individual sIBM patient based on the age of onset and gender.

Cox et al. Brain 2011
Morbidity & Mortality in sIBM

Late Stage disease can cause very significant morbidity

Leading causes of Death:

- Respiratory (pneumonia)
- Cachexia (severe wasting with loss of weight and muscle mass)

Table 2 Causes of death in the Dutch population in the age category 80-85 years and the sporadic IBM cohort

| Cause of Death                                           | Dutch population age category 80-84 years (%) | Patients with sporadic IBM (%) | P-value | Corrected P-value$^1$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases</td>
<td>1.4</td>
<td>2.2</td>
<td>0.66</td>
<td>NS</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>23.8</td>
<td>4.3</td>
<td>0.002</td>
<td>0.03*</td>
</tr>
<tr>
<td>Diseases of blood/blood-forming organs</td>
<td>0.4</td>
<td>0</td>
<td>0.67</td>
<td>NS</td>
</tr>
<tr>
<td>Endocrine/metabolic diseases</td>
<td>3.6</td>
<td>0</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Mental and behavioural disorders</td>
<td>5.6</td>
<td>0</td>
<td>0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>2.8</td>
<td>2.2</td>
<td>0.80</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the circulatory system (myocardial infarction)</td>
<td>37.7 (7.8)</td>
<td>19.6 (4.3)</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Diseases of the respiratory system (pneumonia)</td>
<td>11.5 (4.4)</td>
<td>41.3 (28.3)</td>
<td>0.0001*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>4.2</td>
<td>0</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the skin</td>
<td>0.3</td>
<td>0</td>
<td>0.71</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the bone/connective tissue</td>
<td>0.7</td>
<td>0</td>
<td>0.57</td>
<td>NS</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>2.8</td>
<td>0</td>
<td>0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Cachexia</td>
<td>0.1</td>
<td>6.5</td>
<td>0.0001*</td>
<td>0.001*</td>
</tr>
<tr>
<td>External causes of injury and poisoning</td>
<td>2.1</td>
<td>6.5</td>
<td>0.04</td>
<td>0.51</td>
</tr>
<tr>
<td>Other/uncertain</td>
<td>3.0</td>
<td>17.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Corrected P-value is calculated with a Bonferroni correction of 14. *Significant value.