Evolving Uses of IVIG in myositis

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Immune Function

- **In Normal State:**
  - Protects against pathogens
  - Provides surveillance for killing of malignant cells

- **In Disease State - the 2 ends of the spectrum:**
  - Too much reaction – Autoimmune diseases
    - The body attacks self
  - Too little or no reaction – primary or secondary Immune Deficiency
    - Susceptibility to recurrent infections and malignancy

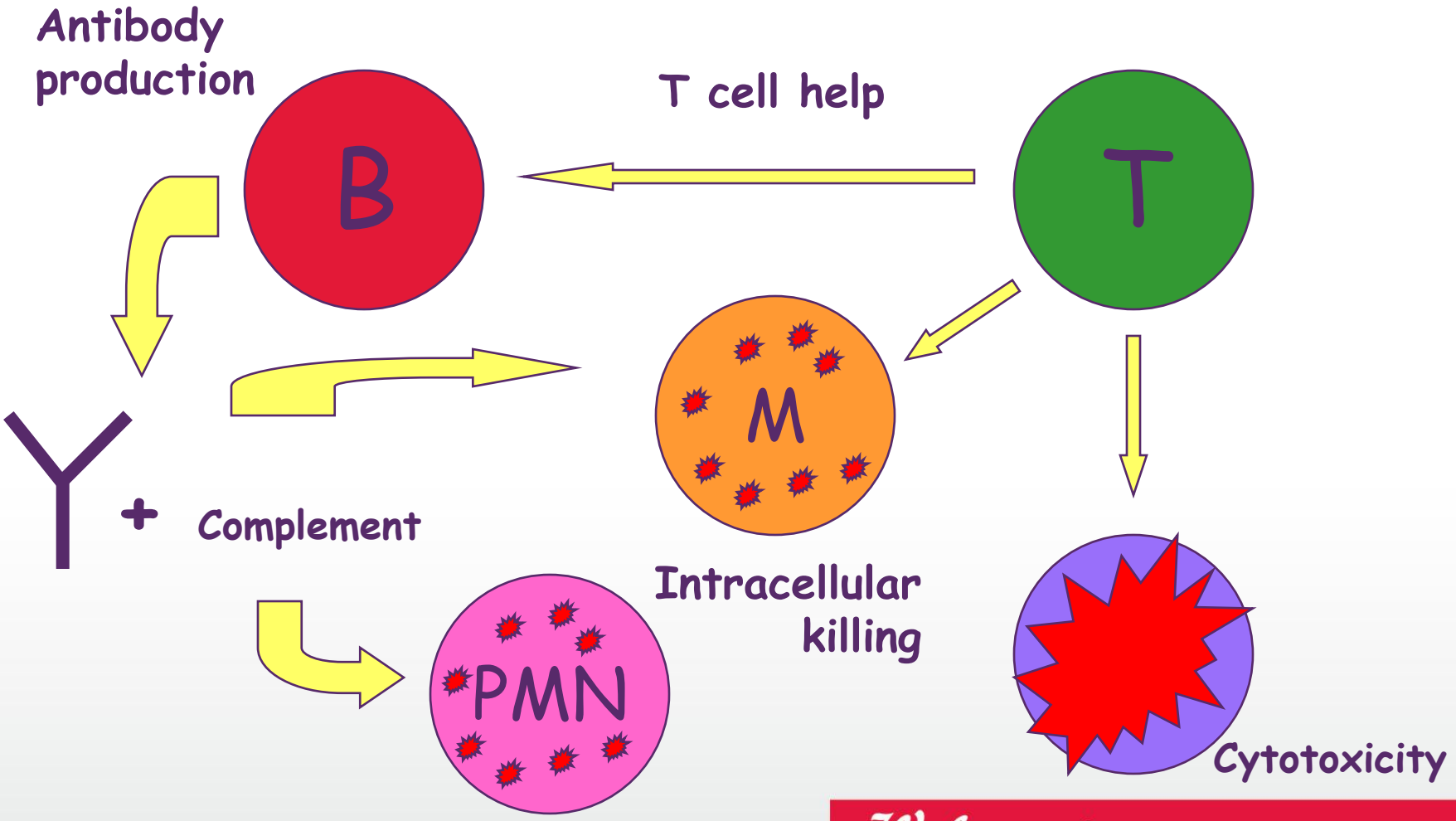
Immune states

- **Immune Deficiency – primary or secondary**
  - Susceptibility to recurrent infections and malignancy

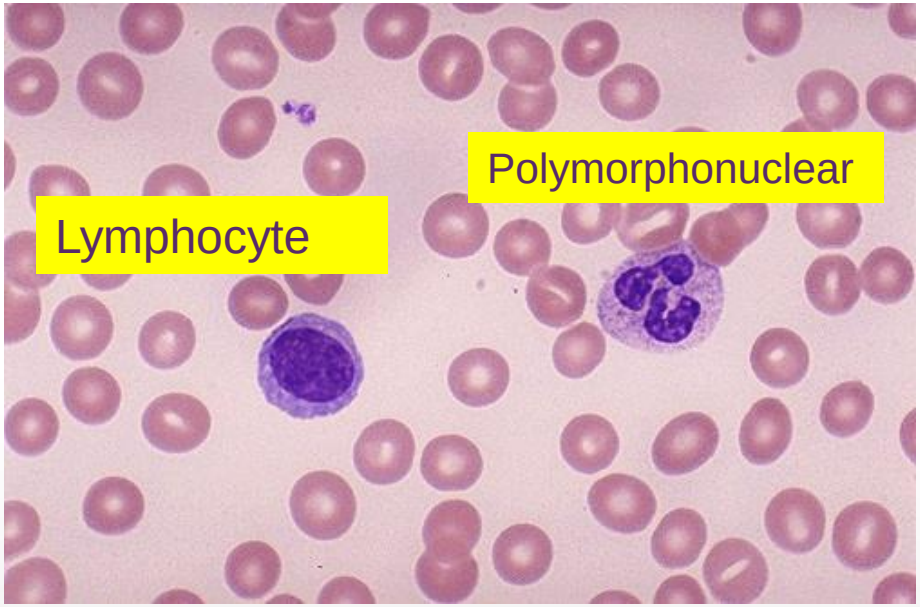
- **Autoimmunity**
  - Loss of Immunological Tolerance
  - Viral or bacterial infections
  - Molecular mimicry
  - Genetic susceptibility

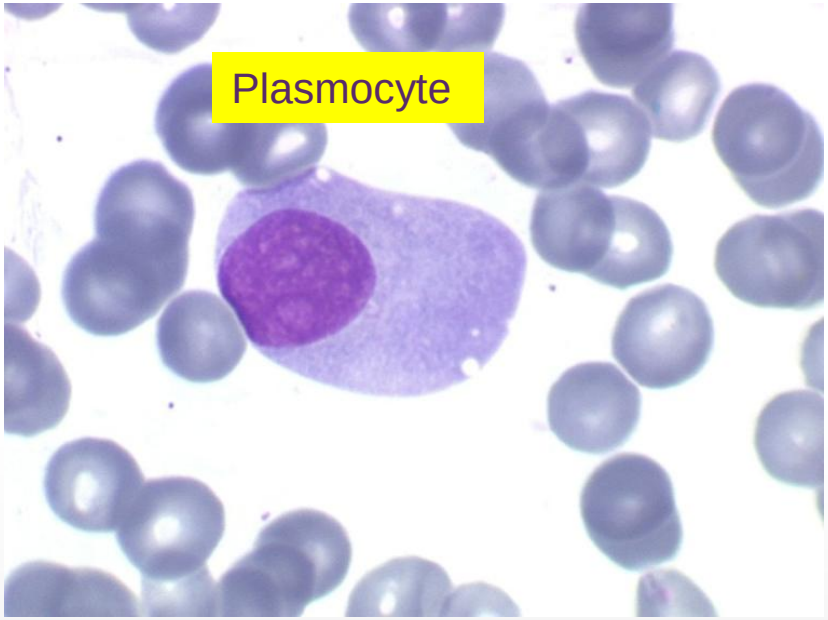
- **Immunologic tolerance**
  - Keeping the immune system from attacking self

Basics of immune mechanisms

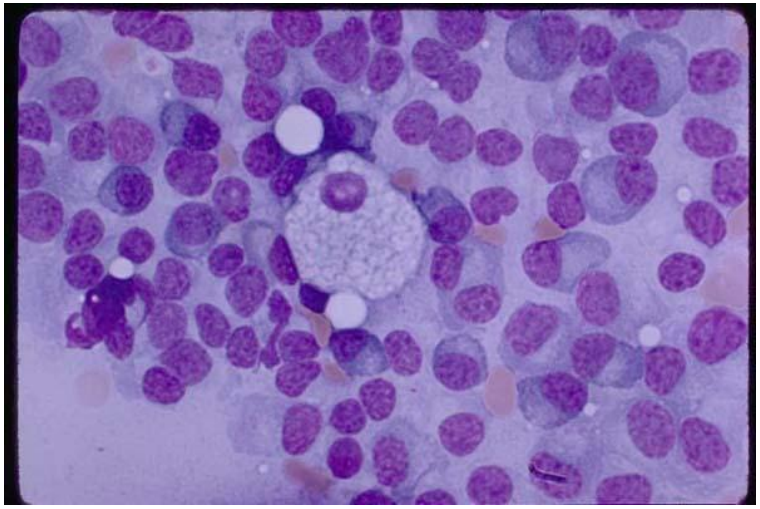


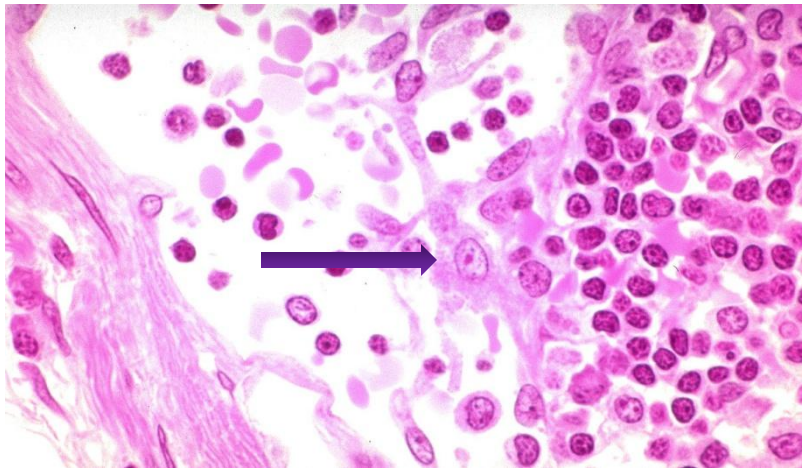
White blood cells

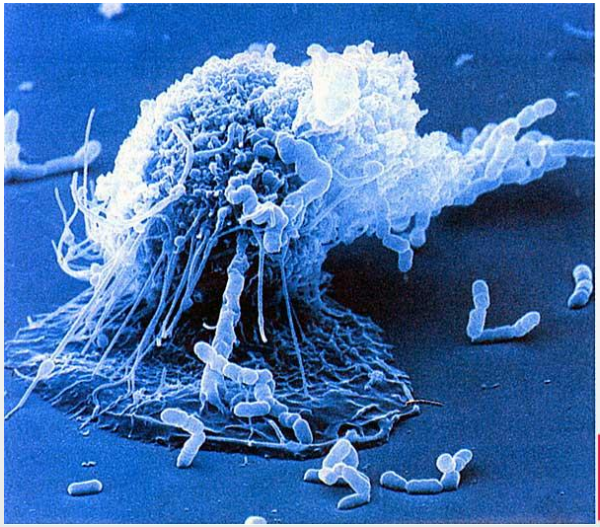




Macrophages







Neurologic disorders with immune mechanism

- Guillain-Barre syndrome
- CIDP
- Myasthenia gravis exacerbation/crisis
- Multiple sclerosis
- Inflammatory myopathies
- Multifocal motor neuropathy
- Stiff person syndrome
- Autoimmune encephalitis

Inflammatory myopathy

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Inflammatory myopathies

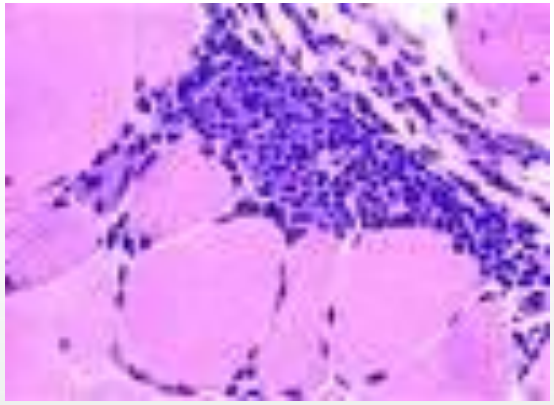
- **Idiopathic**
  - Dermatomyositis
  - Polymyositis
  - Inclusion body myositis
  - Necrotizing
  - Other(sarcoidosis, eosinophilic, focal nodular
- **Infectious**
  - Viral – HIV, influenza
  - Parasites – trichinella, toxoplasma, cysticercosis
  - Bacterial
  - Fungal

Polymyositis

- Most common acquired myopathy
- Cell mediated autoimmune disease
- Subacute or chronic
- Females > Males, 30-60 year-old or older
- Proximal, neck, pharyngeal muscle weakness
- <30% have pain
- Associated with interstitial lung disease, cardiomyopathy, arrhythmia, esophageal paresis
- Associate cancer in <9%

Polymyositis Diagnosis

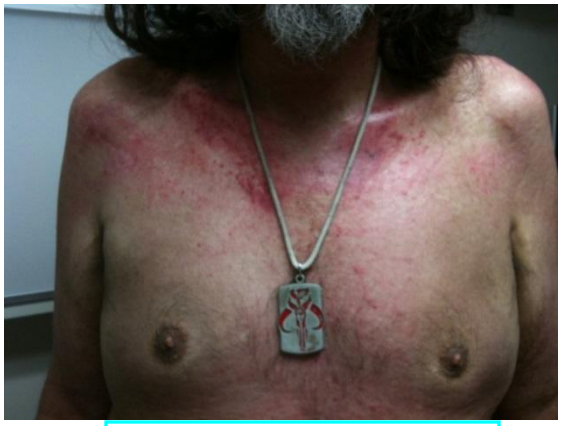
- Muscle breakdown
  - Elevated muscle enzymes in blood
  - Myoglobin in urine
- Associatd Antibodies – anti-Jo, PM-1, Mi-2
- EMG - myopathic pattern, fibrilations/positive waves
- Biopsy – necrosis, endomysial inflammatory infiltrates
- Coexists with other autoimmune conditions



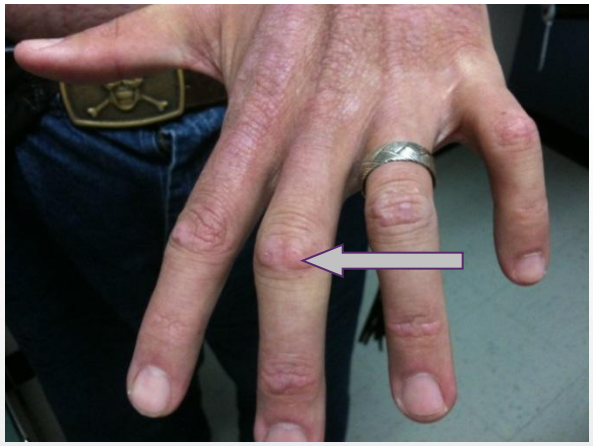
Dermatomyositis

- Humoral mediated immune disease
- Females > Males
- Children and adults affected
- Malignancy in ~15%
- Limb-girdle weakness
- Associated w. retinopathy, uveitis, cardiac (angina, arhythmia), interstitial lung disease, esophagitis, vasculitis, skin changes

Heliotrope rash

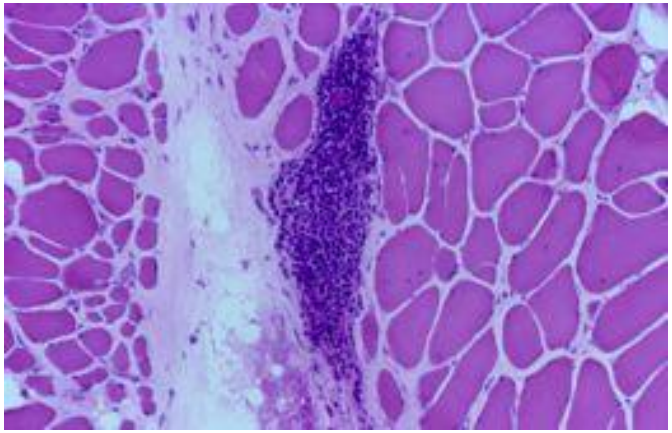


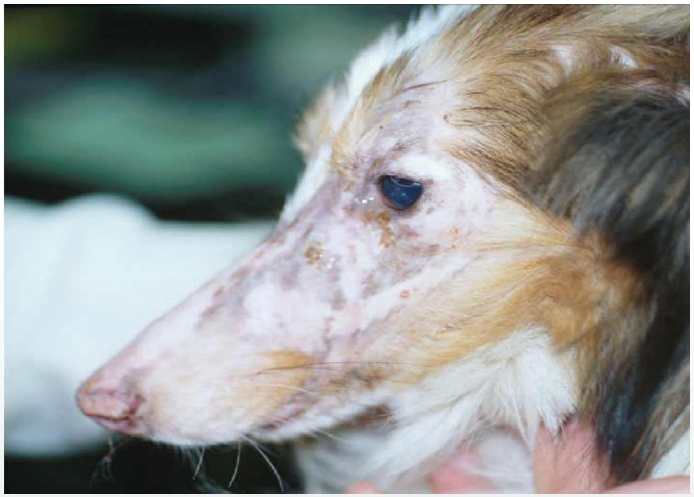
Gotron papules



Dermatomyositis Diagnosis

- Muscle breakdown
  - Elevated muscle enzymes in blood
  - Myoglobin in urine
  - No correlation with severity
- EMG/NCS – similar to polymyositis
- Biopsy – perifascicular atrophy, perimysial inflammation
- Coexists with other autoimmune conditions





Dermatomyositis Diagnosis Prognosis

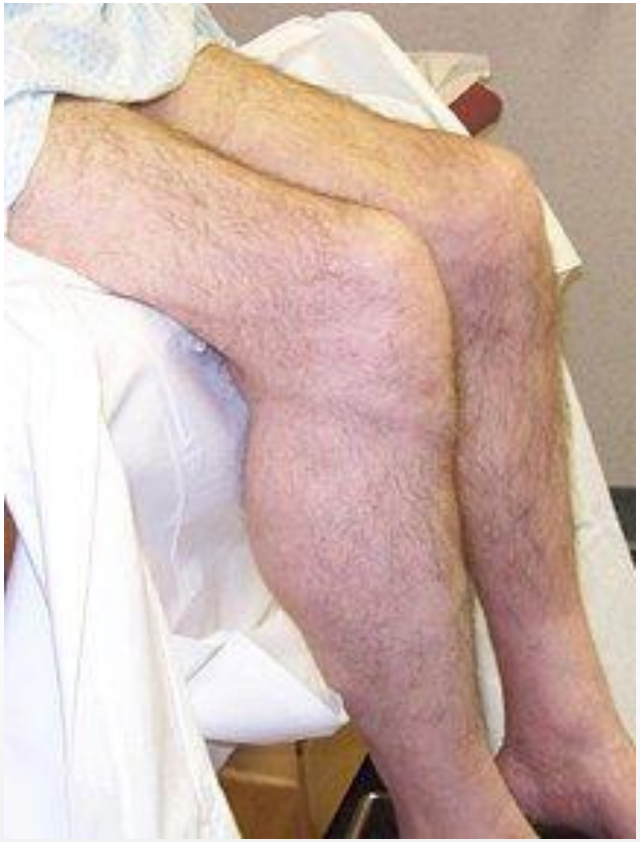
- Mortality: 2% to 7%
- Incomplete recovery: Common
- Relapses (polycyclic): Common
- Chronic course requiring medication > 3 years: 30% to 60%
- Long term remission (Monophasic) ~ 37%
- Worse with
  - Cardiac /lung involvement
  - Inadequate treatment
  - Gottron's papules & nailfold pathology persisting after initial treatment

Dermatomyositis + malignancy

- **Females > Males**
- **Adults in any age**
  - Related neoplasms
    - Adenocarcinoma
      - Ovarian
      - Lung
      - Nasopharyngeal
      - Breast
    - Hematological
      - Lymphoma
      - Leukemia
- **5-year survival – 38% due to cancer**
- **Antibody: p155**

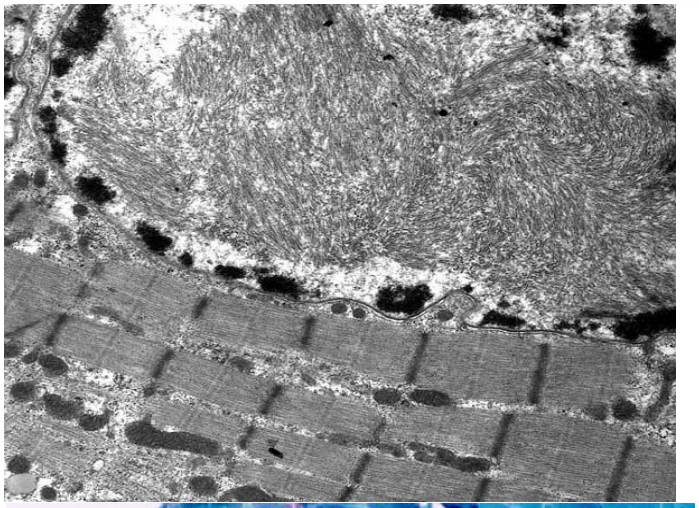
Inclusion body myositis

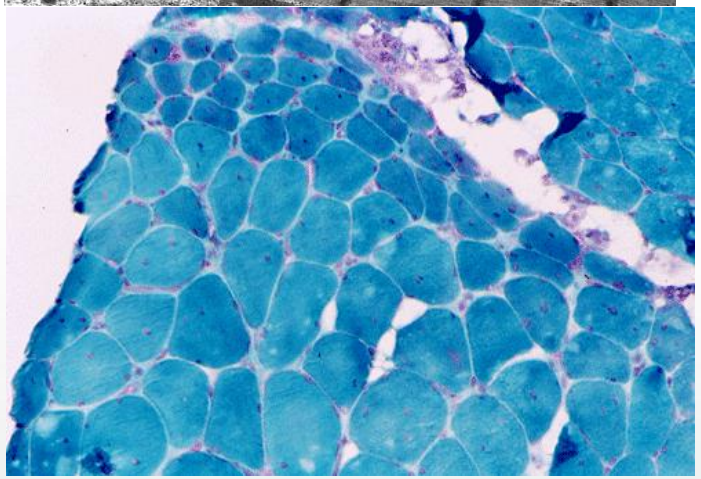
- Most common inflammatory myopathy above age of 50
- Onset ->80% above age of 50
- Males > Females
- Slow progression – 5-20 yrs
- Distal arm + proximal leg weakness
- Predilection – finger flexors and quadriceps, face spared
- Polyneuropathy
- Early loss of patellar reflex
- Painless
- Swallowing problems - ~ 30%



Inclusion body myositis

- No association with cancer or systemic diseases
- CK normal or increased
- NCS – sensory nerve changes
- EMG-myopathic +/- neurogenic changes
- Biopsy – inflammation, muscle fiber necrosis + degeneration (rimmed vacuoles + amyloid deposits)
- Oxidative stress–nitric oxide
- Mitochondrial pathology in some variants
- Poor response to Rx (IVIG, immune therapies) – short lived ~ 30%





Inflammatory Myopathy Treatment

- **Corticosteroids – considered first line**
  - IV pulse or daily
  - Caution! – steroid myopathy
- **IVIG – second line**
- **Azathioprine (Imuran)**
- **Methotrexate**
- **Tacrolimus (Prograf)**
- **Cyclosporine**
- **Mycophenolate (Cellcept)**
- **ACTH**
- **Rituximab (Rituxan) , infliximab (Remicade), etanercept (Enbrel) and others**
- **Cyclophosphamide (Cytoxan)**

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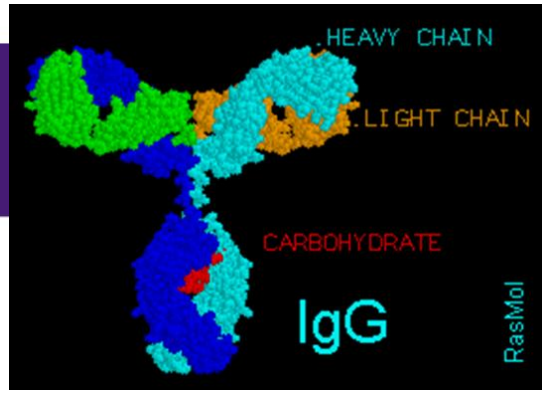
IVIG



- Different brand names- for IV, SC
- Biological product -pooled from multiple healthy human donors - Religious considerations
- Typical dose – 2 grams/kg over 2-5 days
- Half life – ~ 4 weeks. Treatments q 8-12 weeks
- Slight risk for transmission of infections, despite extensive testing
- Contraindications – severe or anaphylactic reaction to blood products, IgA deficiency with antibodies to IgA

Advantages of IVIG

- Easy to administer – peripheral line
- Does not require special equipment
- Does not require trained personnel
- Shorter duration of treatment
- No need for central line – no related complications
- Relatively similar to plasma exchange cost per treatment
- IVIG less expensive based on # hospital days
- Can be done as outpatient – home or center

Use in inflammatory myopathies 1

- Evidence - based guideline (Patwa et al, Neurology, 2012 Mar 27;78(13):1009-15)
- IVIG is possibly effective and may be considered in non-responsive DM (level C)
- Insufficient evidence **to support or refute** use of IVIG in IBM and PM (level U)
- More studies are needed

Use in inflammatory myopathies 2

- Efficacy in steroid resistant patients
- Severe, rapidly progressive DM/PM
- Studies have shown effect in PM, DM, JDM, NAM
- Mild, short term benefit in small number of IBM patients – strength, CK, dysphagia
- Usually considered as a second line
- Steroid-sparing agent, in combination with other immune suppressants

Use in inflammatory myopathies 3

- Relapses
- When immune suppression is contraindicated
- Refractory calcinosis, skin lesions in DM
- Interstitial lung disease in PM/DM (suggested first line)
- Esophageal complications in PM/DM – (suggested first line, +/- steroids)
- SC IVIG in active and refractory PM/DM
- Dose 2g/kg over 2-5 days every 4-6 weeks

Use in inflammatory myopathies 4

- **The Cochrane Collaboration review – 2012/ 9, Gordon et al.**
- 10 studies reviewed, total 258 patients
- 1 study with IVIG showed significant improvement in muscle strength in IVIG group over 3 months
- 1 study on etanercept (Enbrel) showed longer median time to relapse
- 4 negative studies on PLEX, leukopheresis, infliximab (Remicade) and eculizumab (Soliris)
- 3 studies comparing azathioprine with methotrexate, cyclosporine with methotrexate, IM MTX with PO MTX + azathioprine – no significant difference.
- 1 study – pulsed oral dexamethasone with daily oral prednisone showed shorter median time to relapse but fewer side effects.
- Most studies were small
- More studies are needed

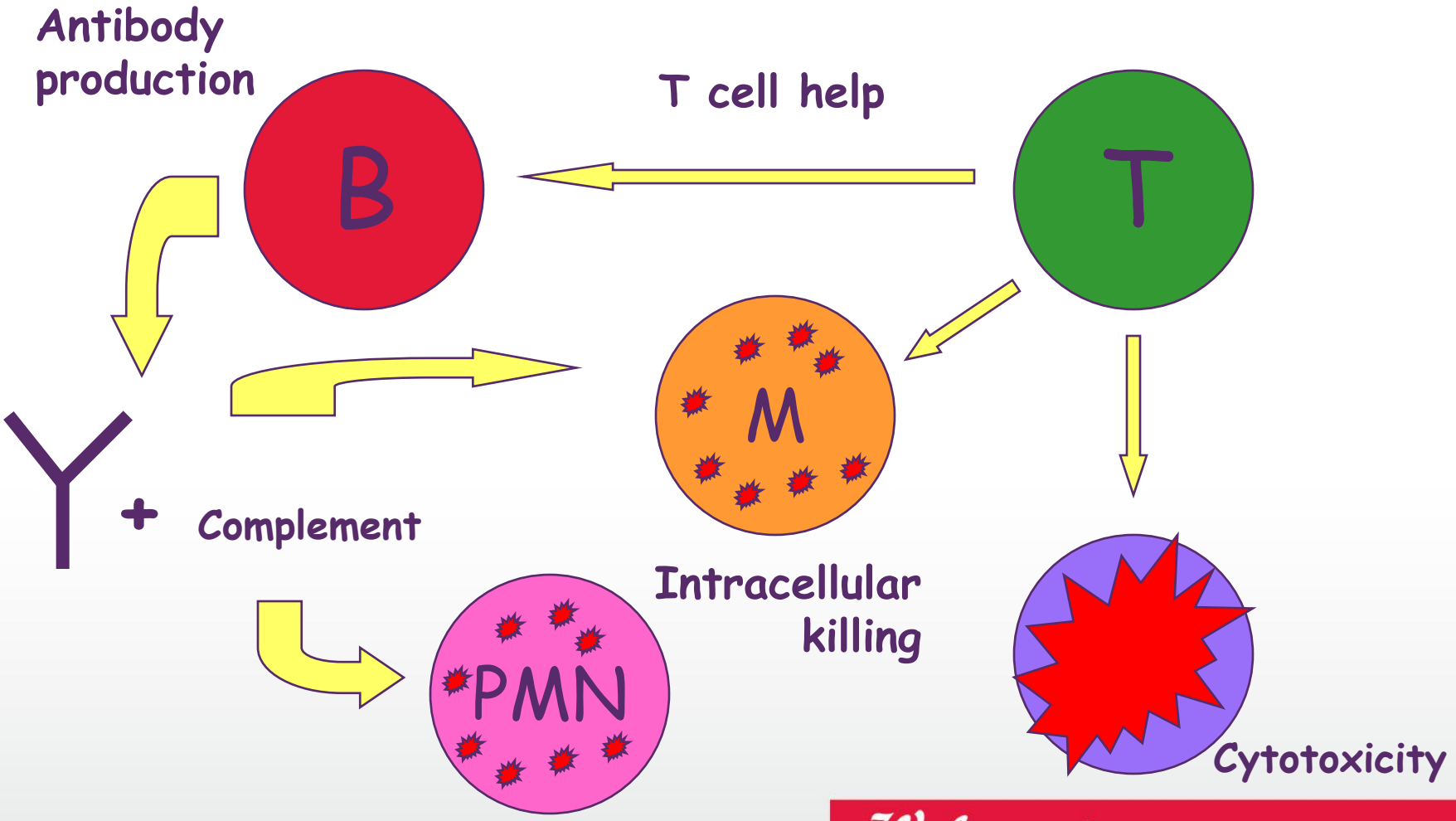
IVIG products differ in:

- IgA content – low Gammaplex, Gamunex, Privigen
- Osmolality – low Gamunex, Gammagard, Gammaked
- Sugar content – glycine Gamunex and Gammagard, sorbitol Flebogamma, sucrose Carimune, maltose Octagam
- Sodium content – none Gammagard liquid, trace Gamunex, Privigen, Flebogamma
- pH
- Half-life – long Octagam, Gamunex, Gammaked, (> or =35d)
- Concentration – 5%, 10%, 20% (Hizentra s.c.)
- Shelf life – 24 mo – 36 mo

IVIG mechanisms of action

- Competes with auto-antibodies
- Inhibits the complement activation
- Interferes with binding of the Fc receptor on the macrophages
- Suppresses cytokines
- Interferes with the T and B cell functions involved in the autoimmune processes
- Modulates cell migration
- Induces anti-inflammation reaction

Immune effector mechanisms



Selecting the right brand 1

- **For patients with congestive heart failure or compromised renal function - prefer IVIg product with:**
  - Low osmolality
  - Low salt
  - Higher concentration (low volume) – 10% products - Gammunex, Gammagard l., Privigen, Gammagard, Gammaked, Bivigam,
- **For patients with diabetes mellitus prefer an IVIG product with:**
  - Low osmolality
  - Low sugar content

Selecting the right brand 2

- Patients receiving IVIg containing sucrose may be at a higher risk for renal failure - Carimune

- Patients with Myositis and high myoglobin levels are at higher risk of developing renal failure while on IVIg containing sucrose - Carimune

Selecting the right brand 3

- **Patients with IgA deficiency may develop anaphylactic reactions. Prefer products with the lowest amount of IgA**
- **Avoid low pH preparations for:**
  - Patients with small peripheral vascular access
  - Predisposition for phlebitis
  - Examples
    - Gamunex – pH 4-4.5
    - Gammagard liquid - pH 4.6-5.1
    - Privigen – pH 4.6-5
    - Flebogamma – pH 5-6
- **pH does not matter with central lines**

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IVIg side effects

- **Common - immediately after infusions**
  - **Nervous system**
    - Headache
  - **Systemic**
    - Chills, sweating, flushing
    - Dizziness
    - Fatigue
    - Nausea
    - Hypotension
    - Tachycardia
  - **Musculoskeletal**
    - Pain and tenderness at the injection site
    - Muscle pain, lower back pain

IVIg side effects

- **Serious – rare**
  - Aseptic meningitis
  - Deep venous thrombosis
  - Pulmonary embolism
  - Pulmonary edema
  - Acute allergic pneumonitis
  - Myocardial infarction
  - Stroke
  - Caution in hypercoagulable states and severe cardiovascular disease

IVIg side effects

- **Anaphylaxis**
  - In patients with IgA deficiency
  - Rapid, allergic reaction
  - Typically occurs immediately after treatment
  - Associated with sensitization to IgA
  - Mild to severe
  - Life threatening – hypotension, SOB, shock, and loss of consciousness
  - Frequency 1:500 to 1:1000
  - Frequency of IgA deficiency ~ 1:500

How to minimize side effects

- **Pre-hydrate with:**
  - IV 0.9% saline
  - PO fluid intake before, during and after infusion
- **Pre-medicate with:**
  - Tylenol
  - NSAIDs
  - Antihistamines – Benadryl
  - Steroids
  - Aspirin
  - Anticoagulation ?
- **Slow the rate of infusion, use a lower dose**

"The Safety Profile of Home Infusion of Intravenous Immunoglobulin in Patients With Neuroimmunologic Disorders"

- ***Objectives:*** To assess the overall safety of high-dose intravenous immunoglobulin (IVIG) products used to treat patients with neuroimmunological disorders in a supervised home-based setting.
- ***Methods:*** The incidence of adverse reactions was assessed in a retrospective chart review of 420 patients who consecutively received 4076, home-based, individual, IVIG infusions between 01/09 and 12/09.
- ***Results:*** A total of 90 patients (21.4%) developed adverse reactions related to IVIG administration (2.6% per individual infusion). A total of 95.5% of adverse reactions were mild, and no serious side effects were observed. The incidence of adverse reactions was significantly lower in the subgroup of patients with neuroimmunological disorders who received premedication (18.2% compared with 29.3%, $P = 0.02$). There was no significant statistical difference in the incidence of side effects among the different brands of IVIG used in this study.
- ***Conclusions:*** The combination of premedication and well-defined clinical, IVIG infusion policies may reduce the incidence of high-dose IVIG adverse reactions administered in a home-based setting in patients with neuroimmunological disorders.

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Journal of Clinical Neuromuscular Disease: June 2011 - Volume 12 - Issue - pp S1-S10 ***Souayah et al.***

Conclusions

- Inflammatory myopathies are a group of common muscle disorder
- Various immune modulating therapies exist
- IVIG is relatively safe, widely used for inflammatory myopathies as well as many other neurological and non-neurological disorders
- IVIG does NOT suppress the immune response or increase the risk for cancers
- IVIG can be given at home, infusion center or hospital by TRAINED personnel
- The benefit of IVIG should be re-evaluated on regular basis

Thank you!

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