



# Evolving Applications of IVIG in myositis

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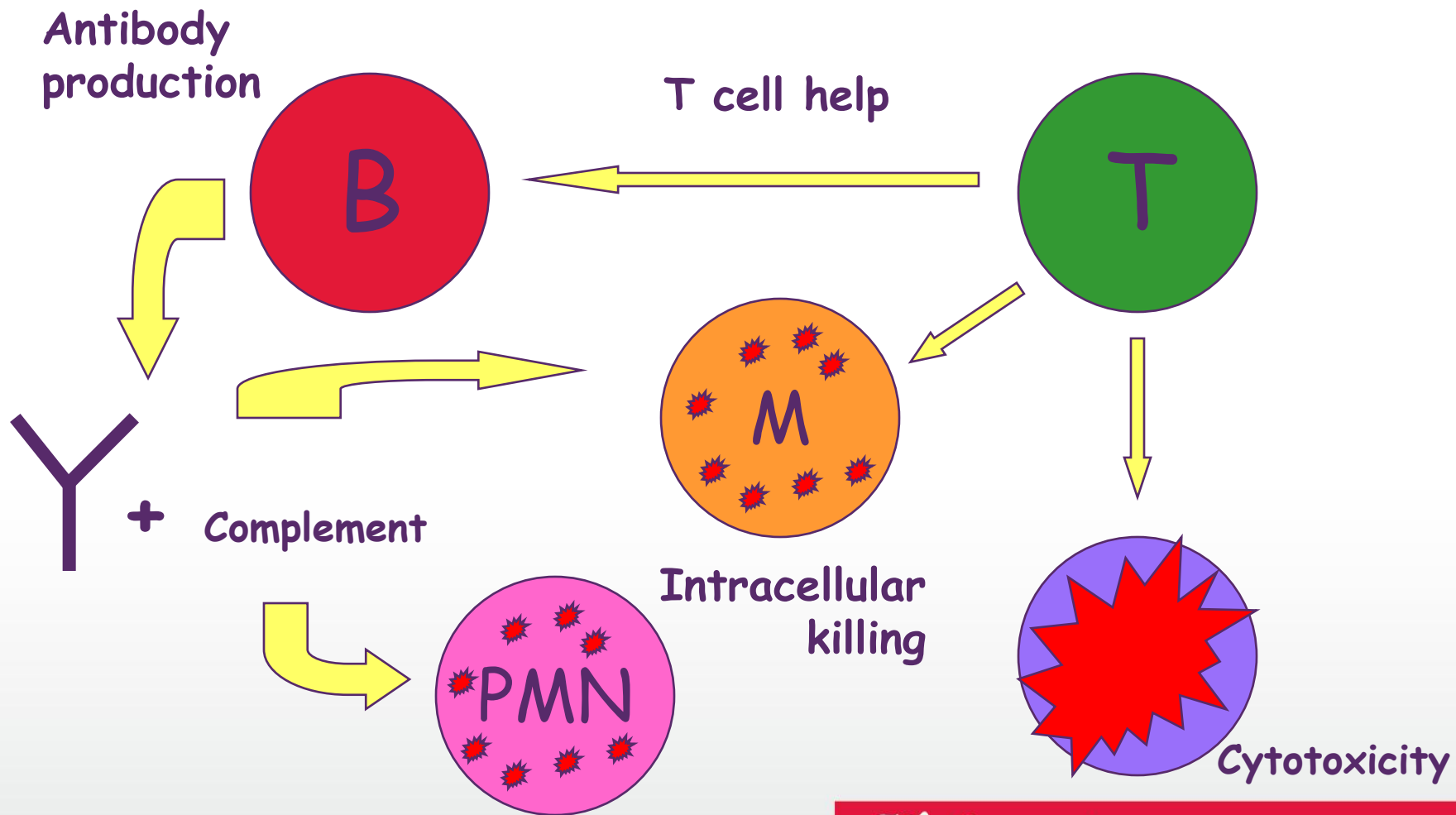
# Disclosure

- I have no affiliation with pharmaceutical companies

# Immune Function

- **Protects against invading pathogens**
  - Clears extracellular pathogens and their toxins
  - Kills intracellular pathogens
  - Kills virally infected cells
- **Surveillance for and killing of malignant cells**
- **Can result in allergic or autoimmune disease**

# Basics of immune mechanisms



# Innate Immunity

- **Phagocytes**

- Monocytes/Macrophages - antigen-presenting cells
- Neutrophils

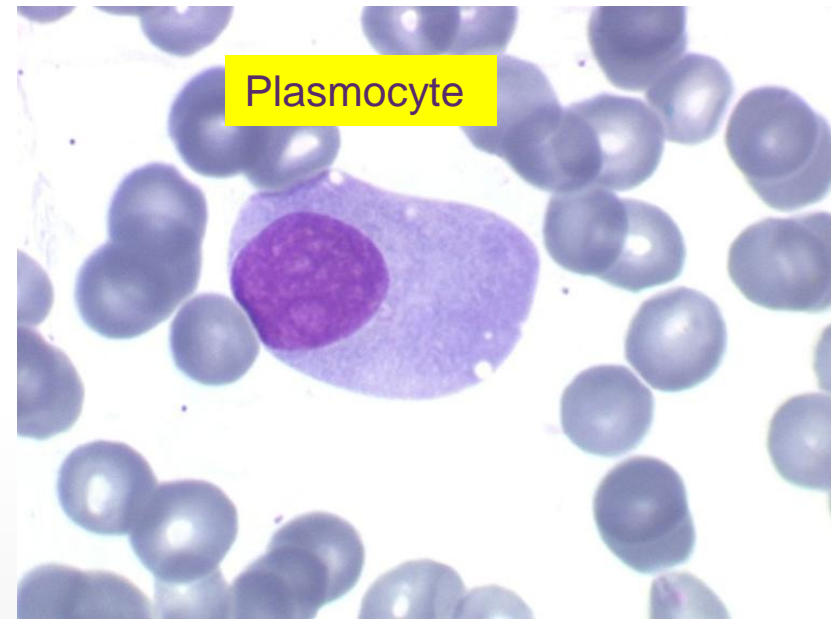
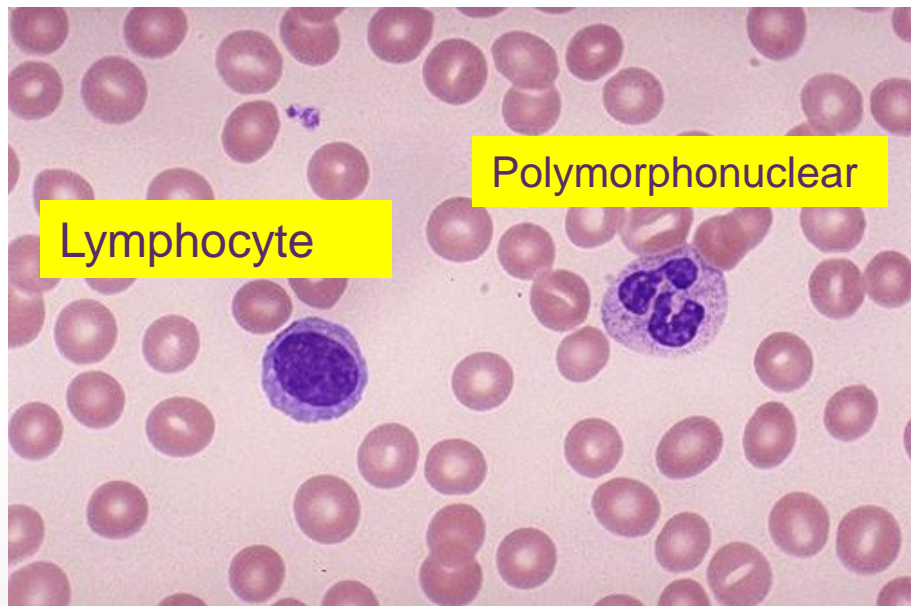
- **Pattern recognition receptors**

- Recognize class of pathogens without memory
- Necessary for adaptive immune response

- **Serum proteins**

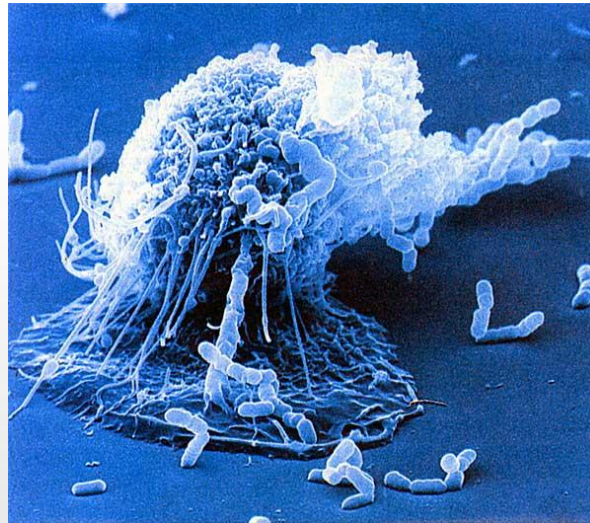
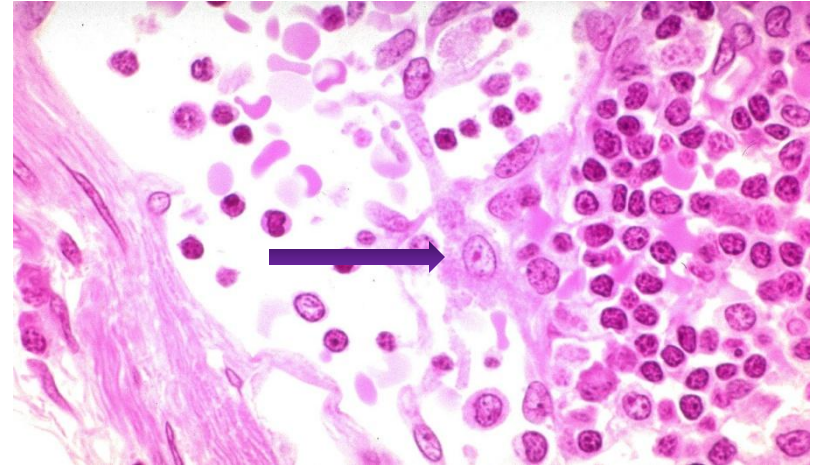
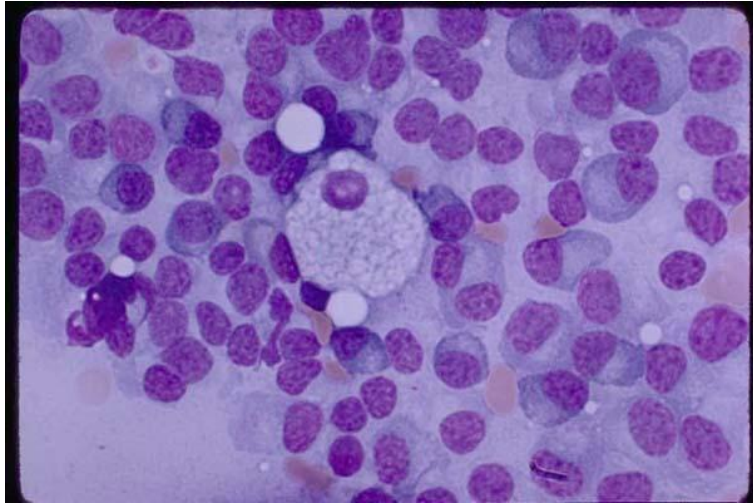
- Complement proteins (alternative pathways)
- Other active phase reactants
- Kill invading pathogens or facilitate uptake of pathogens by phagocytic cells

# White blood cells





# Macrophages



# Adaptive Immunity

- Specific recognition of antigens
- Delay of 5-7 days (for clonal expansion)
- Memory response
- Antibodies made by B cells
  - clear extracellular pathogens and their toxins
- T cells
  - help monocytes clear intracellular pathogens
  - kill virus infected cells and malignant cells
  - help B cells make antibodies



# Immune states

- Autoimmunity
- Loss of Immunological Tolerance
- Immunologic tolerance
- Keeping the immune system from attacking self

# How is self-tolerance broken

- Auto-immunity results from the loss of tolerance
- Genetic predisposition and environmental factors triggers the development of auto-immune diseases
  - Viral or bacterial infection
  - Molecular mimicry
  - Endogenous antigens in the presence of inflammatory cytokines from the infection
  - Genetic susceptibility

# IVIG for 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 autoimmune myopathy
- Other (sarcoidosis, eosinophilic, focal nodular)

- Infectious

- Viral – HIV, influenza
- Parasites – trichinella, toxoplasma, cysticercosis
- Bacterial
- Fungal

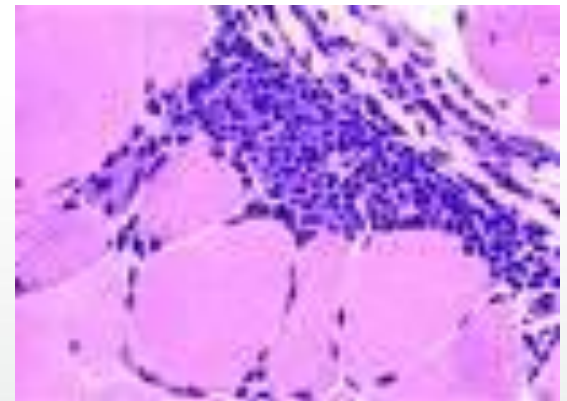
# Polymyositis

- 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

- Elevated muscle enzymes, myoglobinuria
- Associated Ab - anti-Jo, PM-1, Mi-2
- EMG - myopathic pattern, fibrillations/ + waves
- Biopsy - necrosis, endomysial inflammatory infiltrates



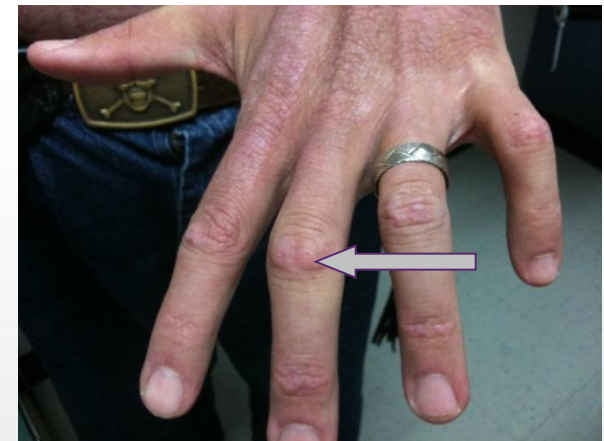
# Dermatomyositis

- Humoral mediated immune disease
- Females > Males
- Children and adults affected
- Malignancy in ~15%
- Limb-girdle weakness
- Associated w. retinopathy, uveitis, angina, arrhythmia, interstitial lung disease, esophagitis

Heliotrope rash

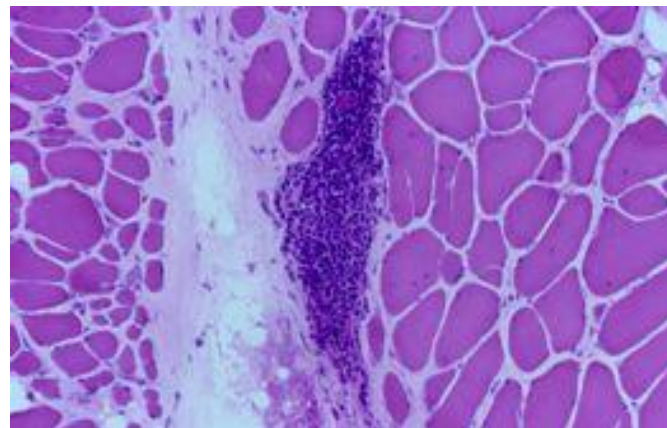


Gottron papules



# Dermatomyositis Diagnosis

- CK and aldolase are elevated but do not correlate with severity
- EMG/NCS - similar to polymyositis
- Biopsy - perifascicular atrophy, perimysial inflammation
- ANA, IgG, IgA



# 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

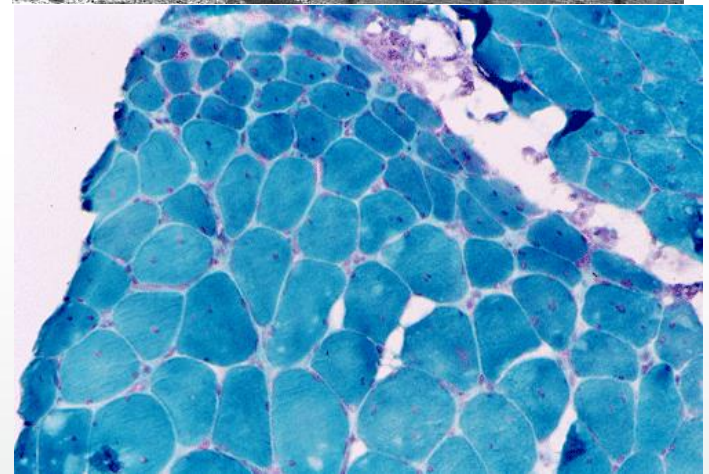
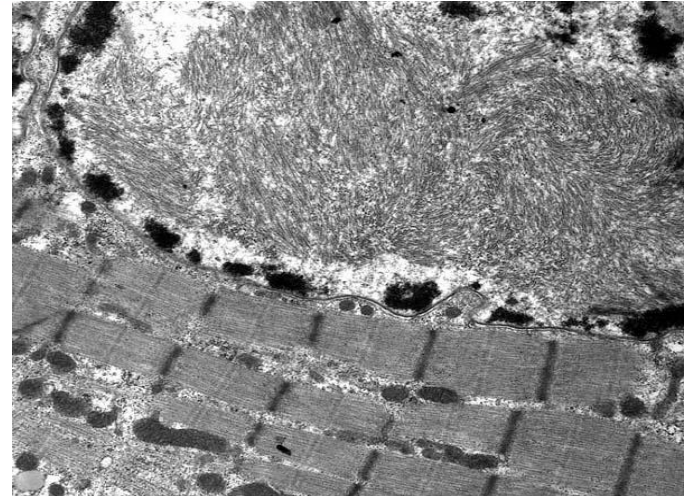
- Onset ->80% above age of 50
- Males > Females
- Slow progression - 5-20 yrs
- Distal arm + proximal leg weakness
- Predilection - finger flexors and quadriceps, face spared
- Polyneuropathy
- Early loss of patellar reflex
- Painless
- Swallowing problems - ~ 30%





# Inclusion body myositis

- No association with cancer or systemic diseases
- CK normal or slightly increased
- EMG/NCS - SNAPs may be abnormal, myopathic +/- neurogenic EMG
- Biopsy - filamentous inclusions, rimmed vacuoles, inflammation, amyloid depositions, mitochondrial pathology variants
- Poor response to Rx (IVIg, immune suppression)

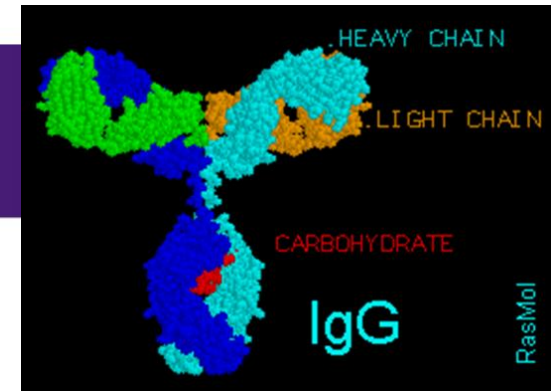




# Inflammatory Myopathy Treatment

- **Corticosteroids – considered first line**
  - Caution – steroid myopathy
- **Azathioprine (Imuran)**
- **Methotrexate**
- **Tacrolimus (Prograf)**
- **Cyclosporine**
- **Mycophenolate (Cellcept)**
- **Cyclophosphamide (Cytoxan)**
- **Rituximab (Rituxan) , infliximab (Remicade), etanercept (Enbrel)**
- **ACTH**

# 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 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 (Europe)



# 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

# Proposed IVIG mechanisms of action 1

- **B-cells function background** - produce immune globulins against antigens/autoantigens produced by plasma cells are responsible for the humoral immune response and clinical features in autoimmune diseases
- **Effect on the B-cells**
  - Contains auto-idiotypic antibodies that ameliorate symptoms (suppression of the autoantibodies)
  - Suppresses auto-antibody production
  - Inhibits B-cell differentiation (into plasma cells)
  - Inhibits Interleukin-6 and tumor necrosis factor alpha (TNF)
  - Accelerates breakdown of endogenous IgG
  - Promotes B-cell apoptosis (programmed cell death)
  - Suppresses auto-reactive B-cells
  - Modulates the migration of the B-cells from the bone marrow to the lymphoid organs

# Proposed IVIG mechanisms of action 2

- **Effect of IVIG on T- cells**

- T-cell function background

- Cell-mediated immunity
    - Handle pathogens inside the cells - IL-2, IFN- $\gamma$
    - Regulate B-cell function- IL4, IL-5, IL-6, IL-10

- IVIG Decreases production of interleukins and interferon gamma; Restores balance between T cell subpopulations

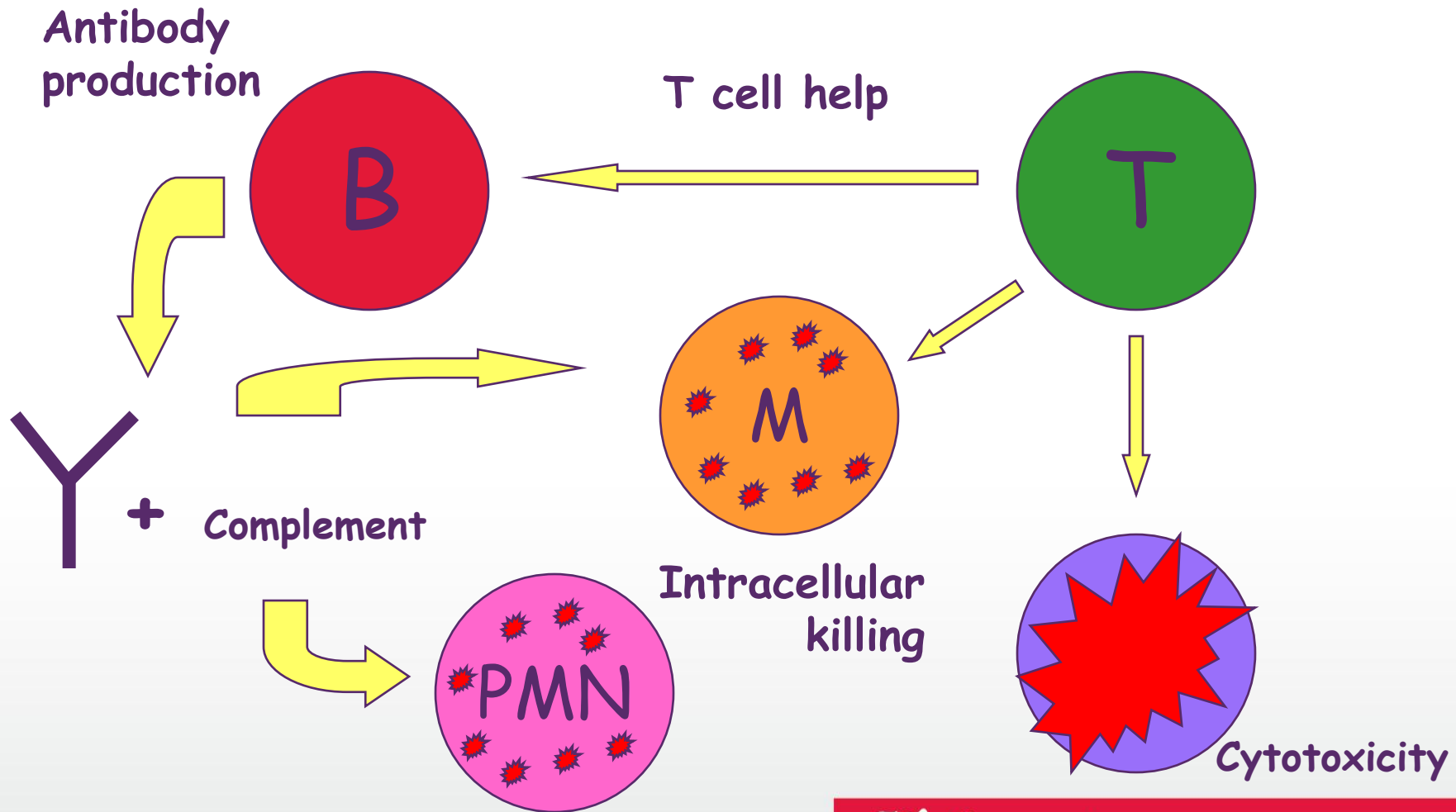
- **Effect of IVIG on complement system**

- Background - system of proteins that kills bacteria
  - Antibody-antigen complexes activate the complement cascade - results in production of membrane attack complexes (MAC) cause tissue/cell membrane damage
  - IVIG decreases MAC production and tissue damage and increases degradation of complement components

# Proposed IVIG mechanisms of action 3

- Effect of IVIG on macrophages - inhibits macrophage - mediated tissue damage
- Effect of IVIG on cell migration
  - White blood cells migrate across barriers in normal or exaggerated immune response
  - IVIG modulates the degree of migration by changing the function of the blood vessel wall and secretion of molecules that promote the migration cells normal
- Other effects of IVIG - induces anti-inflammation reaction

# Basics of immune 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 I., 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

# IVIg side effects 1

- 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 2

- **Serious - rare**

- Aseptic meningitis
- Deep venous thrombosis
- Pulmonary embolism
- Myocardial infarction
- Stroke
- Caution in hypercoagulable states and severe cardiovascular disease

# IVIg side effects 3

- 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.



# Conclusions

- Inflammatory myopathies are a group of common muscle disorder
- Various immune suppressants exist
- IVIG is relatively safe, widely used for neurological and non-neurological disorders, including inflammatory myopathies alone or in conjunction with other medications
- IVIG can be given at home, infusion center and hospital by TRAINED personnel



Thank you!



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