Myasthenia Gravis and Aging

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Disclosures:

- Served as a consultant for Advisory Board Meeting by Alexion, Amgen, Argenx, Johnson & Johnson, Kyverna, Vertex.

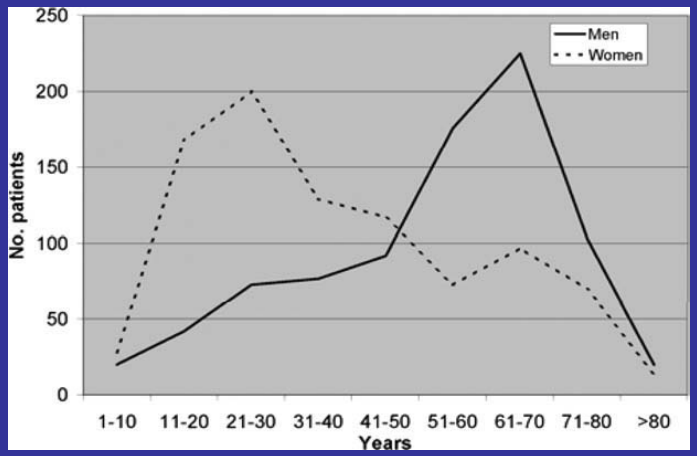
Who gets myasthenia gravis?

- All ethnic groups, both gender
- Prevalence of 100 to 200 cases per million and annual incidence of 2.5 to 20 per million
  - Approximately 2 to 3 times less common than multiple sclerosis (MS)
  - Approximately 8 to 10 times more common than amyotrophic lateral sclerosis (ALS, Lou Gehrig disease).

Epidemiology

- Onset Age: traditionally bimodal pattern
  - Early peak age: 2nd to 3rd decade: Female predominance
  - Late peak age: 6th to 7th decade: Male predominance

- Definition of early-onset MG: usually < 40 years of age
- Definition of late-onset MG: varies, probably >60-65 years of age
- Recent data from Duke university: more elderly, disease affecting young females and older populations (M>F still)



Guptill et al. Muscle Nerve 2011

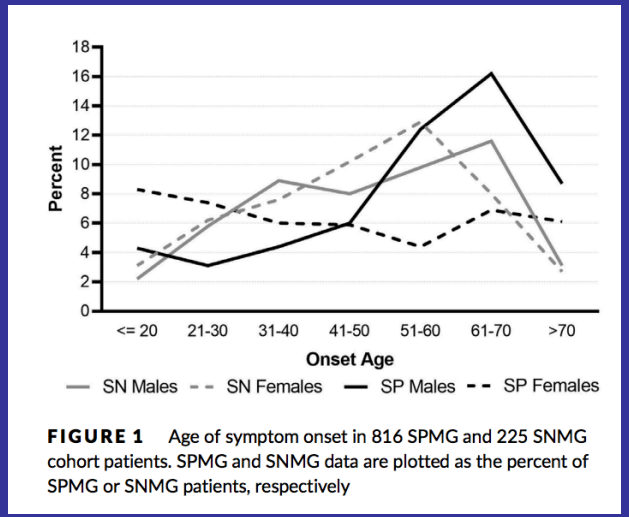


FIGURE 1 Age of symptom onset in 816 SPMG and 225 SNMG cohort patients. SPMG and SNMG data are plotted as the percent of SPMG or SNMG patients, respectively

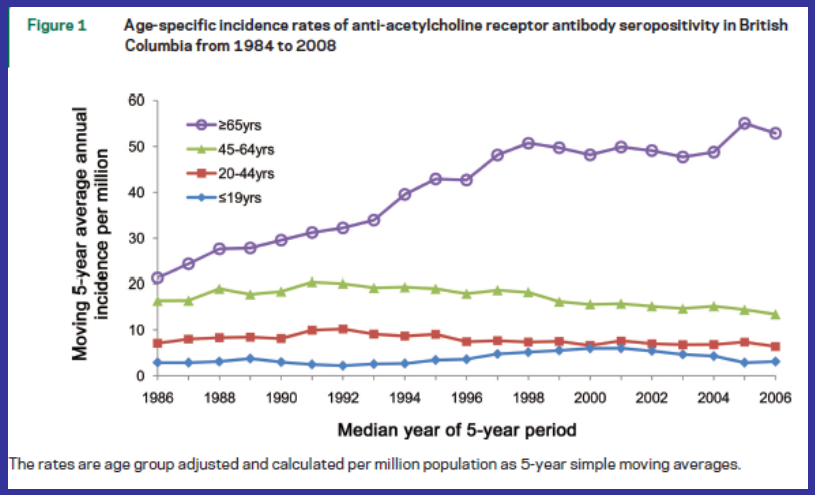
Sanders et al. Muscle Nerve. 2021

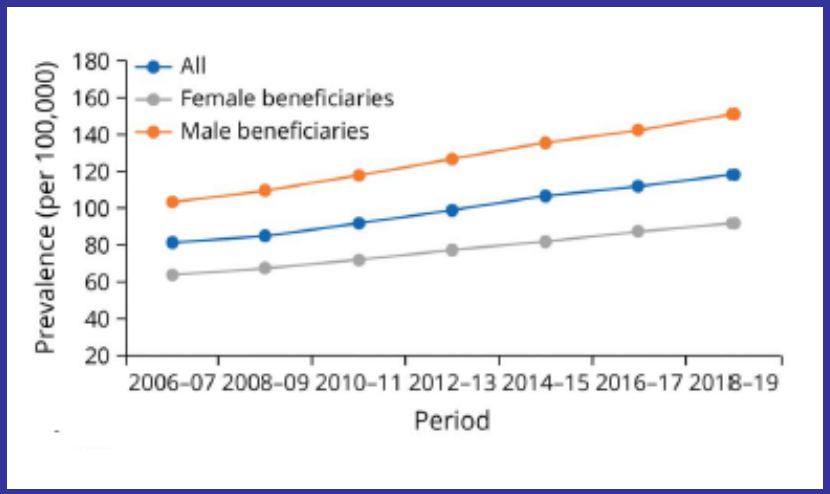
Epidemiology of MG in the elderly

- Unclear reason for male predominance in the elderly
- Lack of significant sexual predominance of other autoimmune diseases in the elderly
  - SLE: slight female predominance
  - Rheumatoid arthritis and Sjogren disease: equal in both sexes

Rising incidence of MG in the elderly

- Increase in the incidence of MG in the elderly
  - Casetta et al 2010: Italy
    - Late-onset MG increased > 3 fold from 1985-1990 to 1991-1996 and maintained thereafter
    - Equal increase in male/female
  - Matsui et al 2009: Japan
    - Increased 20 fold from 1981-1990 to 2001-2006
  - Pakzad et al 2011: Canada (Figure, 3 fold)
  - USA: Approximately 65% of MG patients is 65 years of age or older!





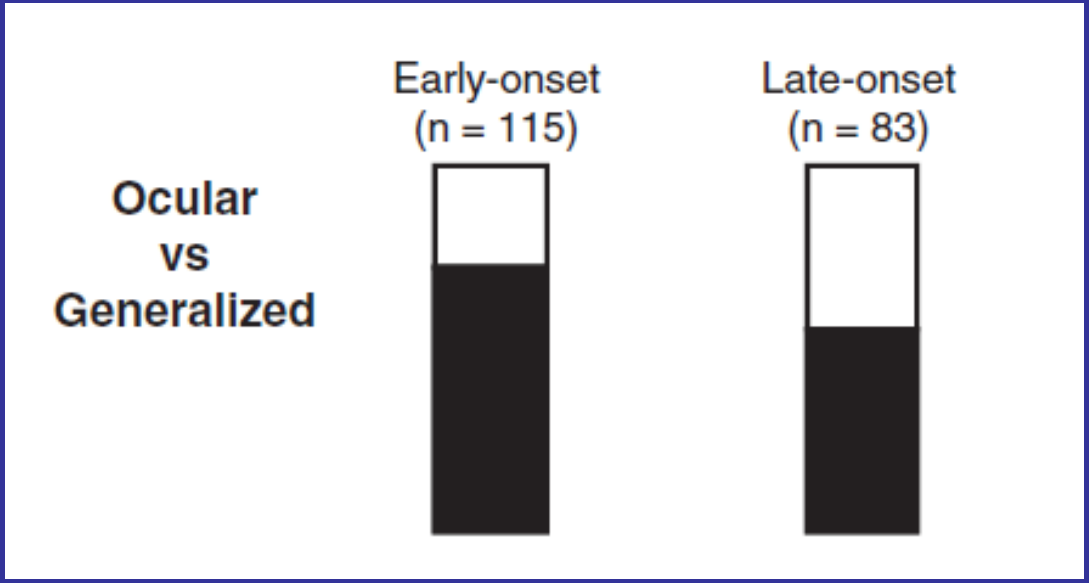
MG is still underdiagnosed in the elderly!

- Less physical and social activity in elderly may cover the deficits of muscle weakness.
- Other coexisting diseases may mask MG: e.g. cataract, COPD, arthritis, spine disease, heart disease
- Doctors tend to firstly think about normal aging or other diseases.
- Can be misdiagnosed as stroke, Parkinson or Lou-Gehrig disease.

Symptoms of MG in the elderly

- Matsui et al. 2009 (Japan): Ocular MG almost twice as common in older individuals than the younger group.
- Suzuki et al. 2011: 230: 148 (Japan, figure) more ocular MG in elderly
- Zivkovic et al 2012 (USA): ocular seen in 46% in LOMG (>65 yo) versus 18% in EOMG (<49 yo)

- Similar rates of MG crises between young and elderly MG patients, but crises may have more detrimental influence in the elderly.



Evolution of Ocular MG: recent trends

- Grob (1987): 1487 MG patients. Of all MG patients presented with ocular symptoms.
  - One third will remain ocular (14% of total MG patients).
  - Two thirds will generalize (78% within 1st year, 94% in first three years).
- More recent data:
  - Only 18% to 55% of OMG patients will evolve into Generalized MG (Peeler 2015; Nagia 2015; Mazzoli 2018; Hendricks 2019)

- Conclusions: Ocular MG accounts for a much larger portion nowadays.

Will MG symptoms get worse with age?

- MG tend to get better after the initial 2-3 years in the majority, with or without treatment.

- Unfortunately, exacerbation factors may increase with age:
  - Infection
  - Surgery
  - Use of medications
  - MG medication discontinuation (need, cost, unable to swallow)
  - Except pregnancy
- Capacity to cope with similar weakness worsens with age.

- When MG is worsening, it tends to worsen in days or weeks, rather than in months or years after a trigger.

Use of MG-ADL score to self-monitor progression

MG-ADL

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score:	

Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Neurology 1999;52(7):1487-9

How can I tell the difference between other conditions related to aging and MG?

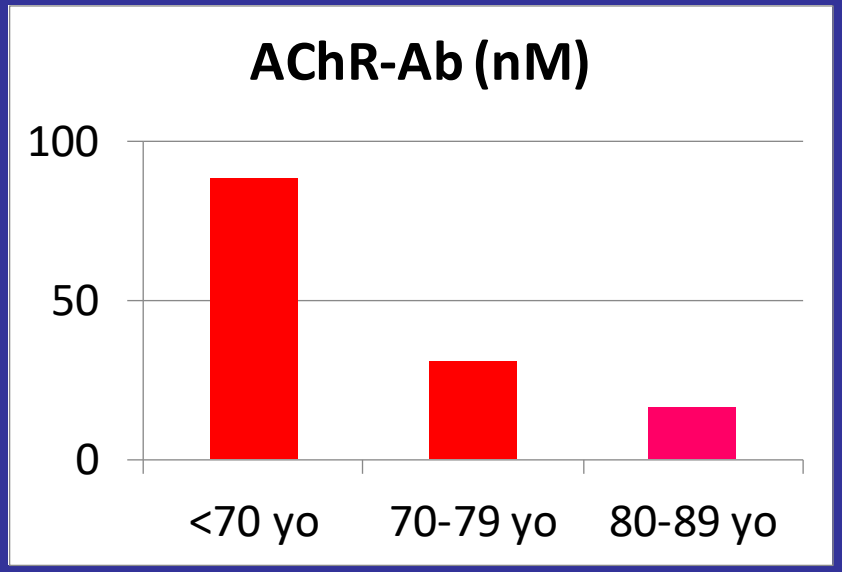
- MG symptoms are usually specific.
  - Eye symptoms: double vision, droopy eyelid, weakness in eye closure
    - Not just blurred vision. Not just seeing double with reading.
  - Bulbar symptoms: slurred speech, weak chewing, swallowing difficulty (choking, coughing, food coming out of nose)
    - Not just difficult to find words.
    - Not just food stuck in throat
  - Neck weakness: head drop and head lag
  - Arm/leg weakness: combing hairs/getting up from chairs
    - Not just a simple feeling of fatigue
  - Respiratory difficult: Rarely occur in isolation and almost never suddenly. Difficulty in laying flat.
    - Not just breathing difficulty walking upstairs.

Myasthenia gravis tend NOT to produce the following signs

- No loss of vision completely, one or both eyes, permanent or transient
- Cognition and mentation normal. Memory deficits and confusion are usually secondary and not prominent.
- No seizure, fainting episodes
- No jerky movement of limbs although muscle cramps can be present.
- Muscle stiffness is rare.
- Muscle wasting (shrinking) is uncommon except when myasthenia gravis is chronic and untreated.
- Usually no numbness or tingling. Secondary pain may be present but generally not prominent.
- Bladder and bowel function are usually normal although urgency may occur.

MG in the elderly: Lab testing

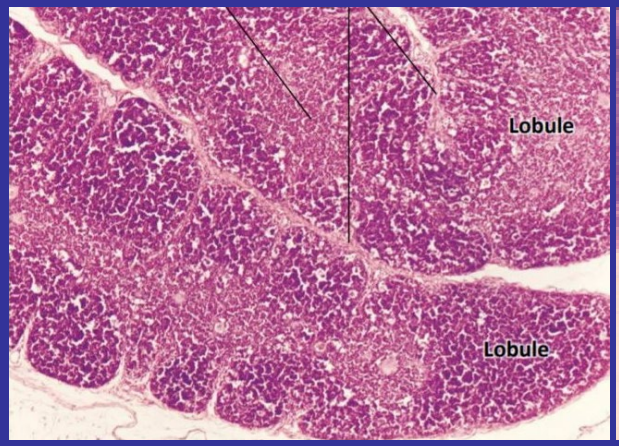
- AChR antibody is usually positive but its titer is lower in the elder MG patients.
  - Antibody more likely to be anormal in elderly MG:
    - Murai et al 2011 (Japan): positive in only 50% of infantile-onset, but nearly 90% of elderly-onset patients.
    - Zivkovic et al 2012 (USA): positive in 88% Late onset MG and in 65% early onset MG
  - Lower antibody titer in elderly:
    - Limburg et al. 1983 (Dutch)
    - Mantegazza et al. 1988 (Italy)
    - Kapinas et al. 1999 (Greece)
    - Matsui et al. 2009 (Japan)
    - Hellmann et al. 2013 (Israel, figure)
- MuSK antibody can be positive.



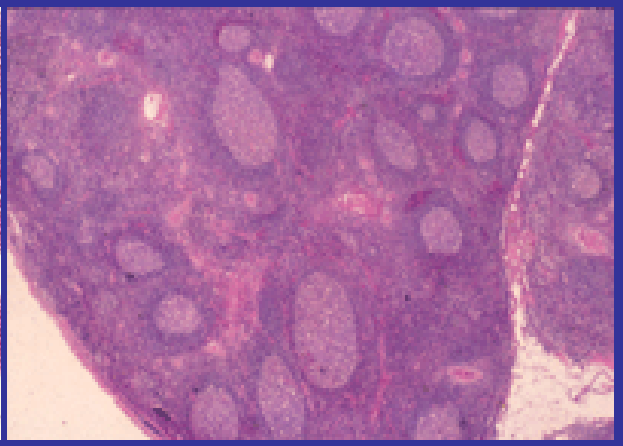
MG in the elderly: thymus gland

- Thymic hyperplasia is frequently seen in young MG patients.
- In eldely: Thymic atrophy and calcification are common, and thymic hyperplasia is less common (Mineo 2015).
- Thymectomy in elderly is limited by
  - Less active role of thymus gland
  - Less efficacy
  - Higher surgical risk
  - Influence of comorbidities

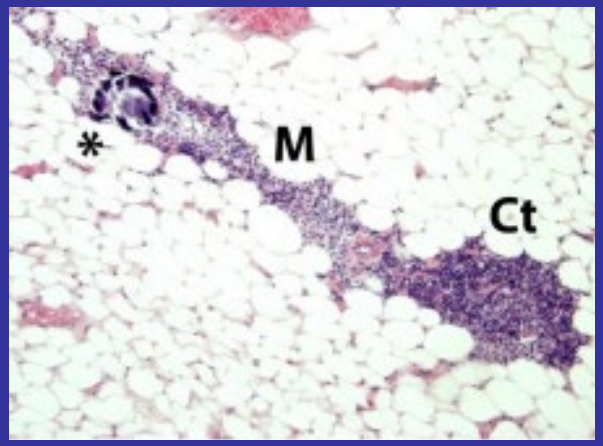
Healthy subject



Young MG patient

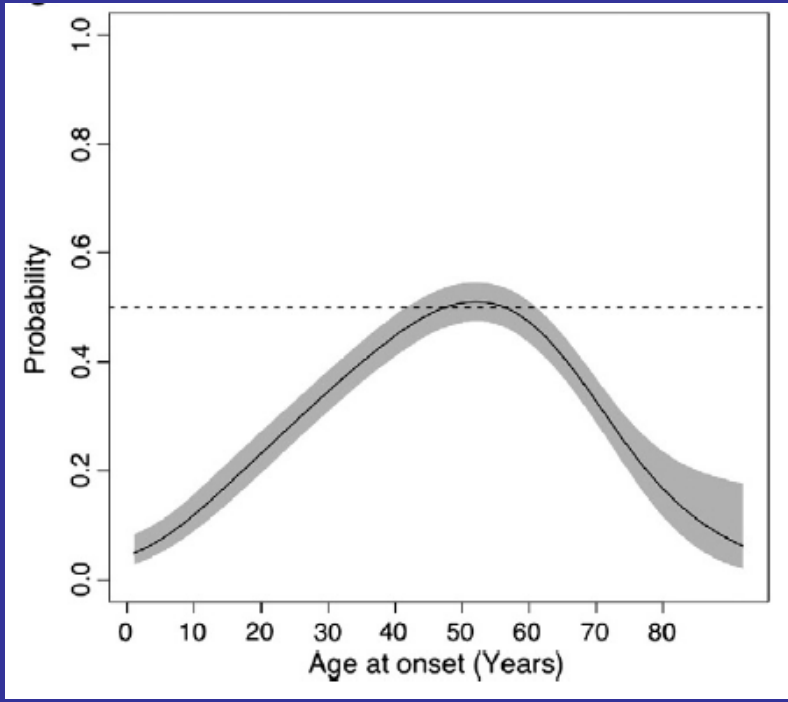


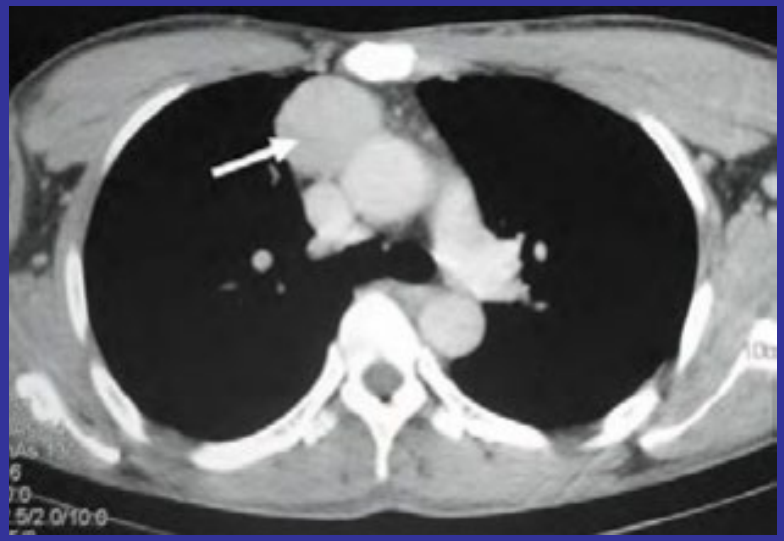
Elder MG patient



Thymoma and MG in the elderly

- Evoli et al 2000: Thymoma is more common in the elderly (21.5%).
- Murai et al 2011: Incidence of thymoma across age with a peak incidence around 50-60 years of age (figure)
- Thymoma is typically shown on CT chest. Every MG patient needs one.
- Typical treatment include tumor removal and possibly radiation/chemo.





Mittal et al. Afr J Rad 2013;17(3):108

Use of MG medications in the elderly

- Acetylcholine esterase inhibitors (pyridostigmine, mestinon)
  - Usually effective for droopy eyelid and speech difficulty.
  - Usually not more than 360 mg per day.
  - Side effects might be more common in the elderly.
  - Diarrhea can be more prominent in elderly due to pre-existing sphincter dysfunction
  - Increased oral secretion due to reduced pulmonary function and swallowing issues
  - Bradycardia could be more problematic and symptomatic.
  - More elder patients may not tolerate mestinon and steroids should be considered (Punga et al. 2008).

Use of corticosteroids in the elderly

- Corticosteroid seems to be more effective in the late-onset group than early onset (Pradas et al 1990; Cosi et al 1991).
- Pascuzzi et al. 1984 (figure). A higher percentage of satisfactory outcome is seen in older patients.
- In general, a lower dosage (20-40 mg prednisone daily) is used nowadays.

Table 6. Response to Prednisone as a Function of Age at Time of Treatment by 20-Year Age Groups[a]

Age Inst. Pred.[b]	No. of Patients	
	Total	MKD + REM (%)
FEMALES		
<19	12	9 (75)
20–39	25	17 (68)
40–59	22	16 (73)
>60	16	14 (88)
MALES		
<19	0	0 (0)
20–39	8	6 (75)
40–59	13	11 (85)
>60	20	20 (100)
SEXES COMBINED		
<19	12	9 (75)
20–39	33	23 (70)
40–59	35	27 (77)
>60	36	34 (94)

[a]Increasing age was associated with a satisfactory outcome ($p = 0.04$) with multivariate analysis.
[b]Age at institution of prednisone therapy (years).
MKD = marked improvement; REM = remission.

Use of corticosteroids in the elderly

- Side effects are more common in elderly.
- Side effect prevention for corticosteroid
  - Osteoporosis prevention, especially in elderly women
    - Take calcium 1 gram and vitamin D 1000 units daily.
    - Bone density scan yearly if daily prednisone is >25mg.
    - Biphosphonates should be used if there is evidence for osteoporosis.
  - Diabetes should be monitoring regularly if daily prednisone dosage is >10 mg per day.
  - Watch for shingle infection and skin breakdown
  - Watch for cataract and glaucoma
  - Watch for weight gain and leg edema

Other medications for MG in the elderly

- Azathioprine
  - Can take once daily unless feeling of stomach upset.
  - A minimally increased risk of malignancy especially skin cancer and lymphoma, usually in the elder male.
  - Interaction with allopurinol, warfarin and sometimes angiotension converting enzyme (ACE) inhibitors.

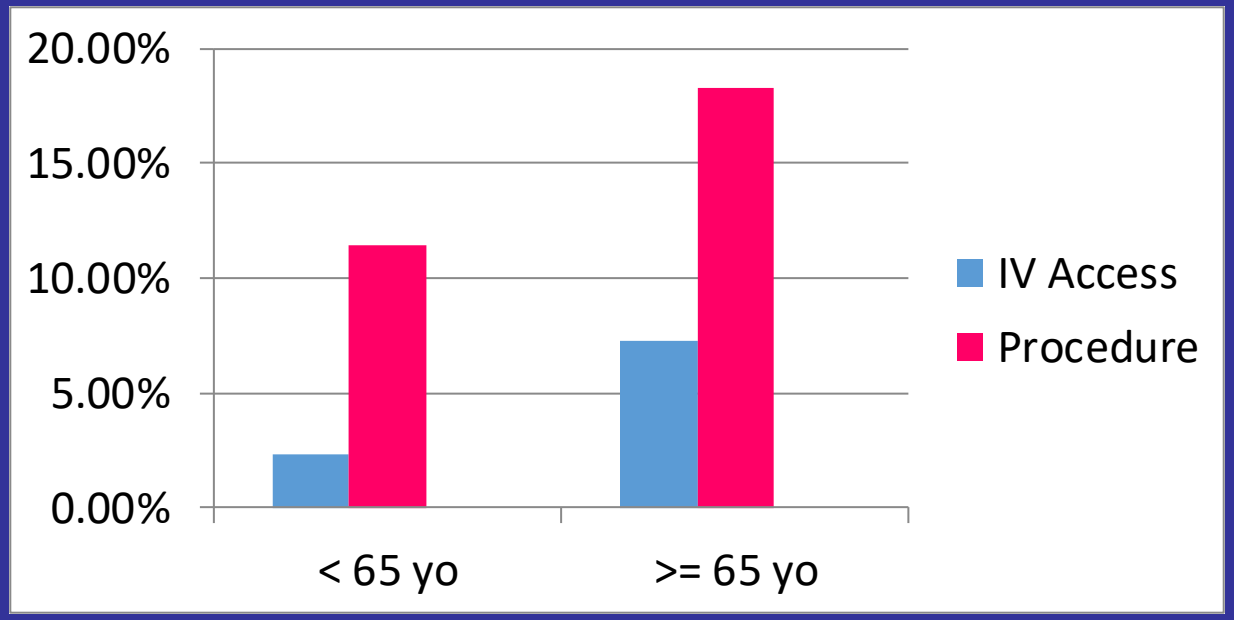
- Mycophenolate mofetil (cell cept)
  - Atypical infections (herpes, CMV etc.)
  - Take without food (2 hours before and 2 hours after meals)

- Tacrolimus
  - Similar to cyclosporine but less renal toxicity
  - May have rapid onset of action

Treatment Response of MG in the elderly

- IVIG/SCIG side effects:
  - No significant difference between young and elder (>60) patients with neuromuscular disorders (Lozeron et al 2016)
  - Rare reports of increased renal toxicity and thromboembolic complications seem to be higher in the elderly (Hefer et al 2004)

- Plasmapheresis-related side effects: More in elderly
  - Abdel-Rahman et al 2012: Plasmapheresis for neurological disorders.



A partial list of newer-generation immunotherapies

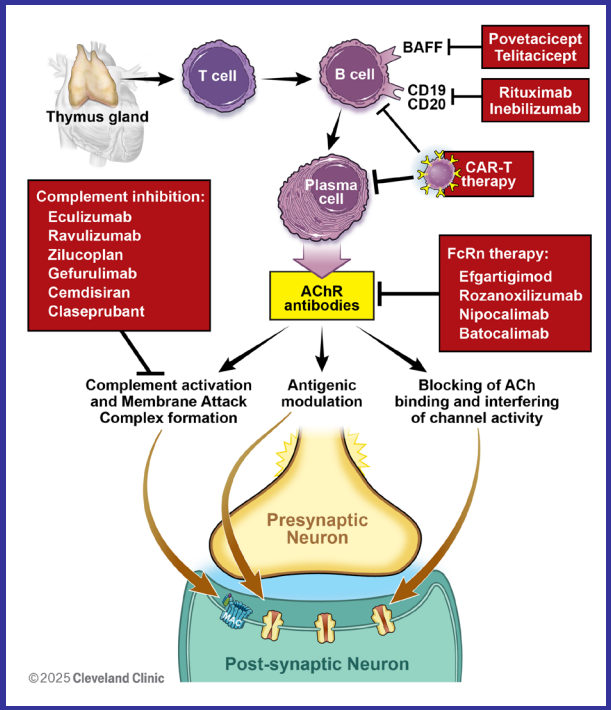
B cell depletion therapy:
- Inebilizumab
- Others: rituximab*, telitacicept*, povetacicept

Neonatal Fc receptor (FcRn) therapy
- Efgartigimod
- Rozanolixizumab
- Nipocalimab
- Others: Batoclimab*

Complement inhibition therapy
- Eculizumab
- Ravulizumab
- Zilucoplan
- Others: gefurulimab*, cemdisiran (+/- pozelimab)*, claseprubant

Cellular therapy:
- Stem cell and CAR-T/CAAR-T therapy

Others:
- Remibrutinib, satralizumab etc.



Green color denotes approved therapy; * Positive phase III trial results

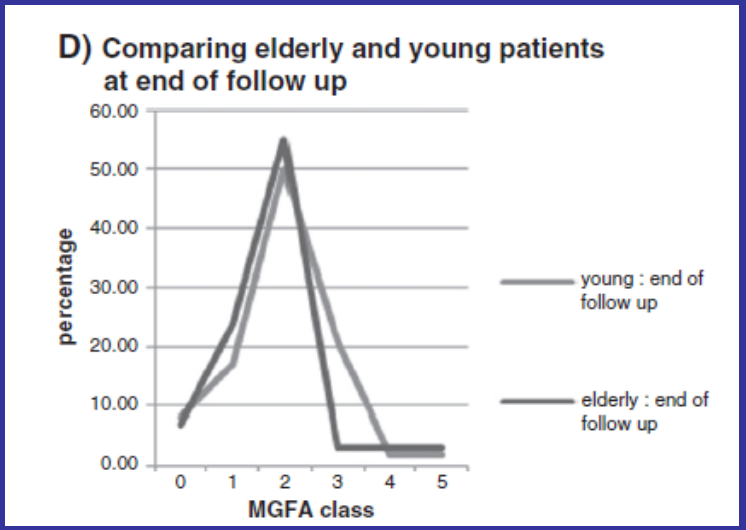
Comparison of Traditional and Newer Therapies in MG

Item	Traditional therapy	Newer therapy
Mechanism of action	Non specific, multiple (advantages and dis-advantages)	Specific, significant inhibition of one key step (advantages and dis-advantages)
Onset of action	Slow (except prednisone, cyclosporine, tacrolimus)	Fast (1-2 weeks) Inebilizumab: 2-3 months
Side effect	Many and various SEs, including cancer risk	Mostly infections and pain, some with serious infections in need of vaccinations
Route	Mostly oral	Mostly IV or SQ
PLEX interference	None	Mostly, except zilucoplan
Neutralizing Ab or anti-drug Ab	Not a concern	Likely concern for some, if not all, more concerns for FcRNs.
Complete stable remission (CSR)	Possible, as many acting on STOPPING ANTIBODY PRODUCTION	Unlikely, except inebilizumab
Cost	Mostly inexpensive	Mostly expensive

Prognosis of MG in the elderly

- Mixed results among different reports: favorable versus unfavorable
- More favorable in elderly.
  - Evoli et al (2000). With treatment, good outcome in 76% patients but remission in 6% only.
  - Hellmann et al (2013): outcome similar to young patients (figure)

- Why more favorable outcome in the elderly?
  - Less severe disease in some patients (more ocular)
  - Low titer of AChR antibodies
  - More responsive to steroid



Less Favorable Prognosis of MG in the elderly

- Less favorable outcome, especially for those MG patients requiring hospital admission (Mandawat et al. Ann Neurol 2010; 68: 797; Ashlekhlee et al. Neurology 2009; 72: 1548)
  - Older patients are more likely admitted, especially older men.
  - Older patients are more prone to have complications of MG.
  - In hospital mortality rate is significantly higher (> 9 times higher) in older population

Less Favorable Prognosis of MG in the elderly

- Why less favorable outcome in elderly (Kapinas et al 1999)?
  - Higher incidence of thymoma
  - Bulbar dysfunction may cause more symptoms (speaking, swallowing or breathing).
  - Less aggressive treatment approach by physicians due to concerns for age, side effects and comorbidities
  - Additional medical conditions may exacerbate MG symptoms.
  - Additional medical conditions may exacerbate side effects.
  - Reduced liver and/or kidney dysfunction may alter medication metabolism.
  - Higher infection risk due to reduced immunity.
  - Use of other medications may additionally impact neuromuscular transmission, or cause drug interactions.
  - Cost of treatment and less favorable insurance coverage

Exercise in MG, randomized trial

- Birnbaum et al; MGEX Study Group. Home-based exercise in autoimmune myasthenia gravis: A randomized controlled trial. Neuromuscul Disord. 2021;31(8):726-735.
  - A parallel-group, multi-center prospective RCT of patients with stabilized gMG with no contra-indication to exercise.
  - Participants received usual care alone (n=20) or usual care and exercise (n=23).
  - Exercise intervention consisted of 3-weekly 40 min sessions of an unsupervised, moderate-intensity home rowing program over 3 months.
  - MG-ADL and six-minute walking improved at month 6 (mean ADL score change of 1.9 points) but not maintained at month 9.
  - Well tolerated exercise. Two patients hospitalized for MG exacerbation were from the usual care group. None from the exercise group.

Exercise in MG, taken home message

- Anziska and Inan. Semin Neurol 2014; 34: 542-556
  - MG patients may benefit from exercise by reversing their baseline reconditioning.
  - Aerobic activity at mild–moderate exertion on a regular basis seems to improve MG functional status and quality of life.
  - Avoid long runs at extreme temperature.
  - Respiratory training seems to improve QoL, respiratory endurance, self-perception of physical fitness, and decreased fatigability.
- Recommendations
  - Regular exercise is beneficial.
  - Avoiding prolonged-endurance type exercises
  - Working out only after adequate rest.
  - Exercising during cooler times of the day

Immunization and Myasthenia Gravis

- Vaccine-related worsening of MG is rare.
- Vaccinations are mostly safe in patients with MG.
- Taking immunosuppressive medication fir MG, live, attenuated vaccines should be avoided.
  - Examples: old shingles vaccine (Zostavax), the nasal spray form of influenza vaccine, polio
  - The new shingles vaccine (Shringx) and the injective form of influenza vaccine should be safe.
  - COVID vaccination and COVID do not seem to alter MG much.

- Immunosuppressive drugs may decrease the response of immunizations and may put patients at risk of not achieving full immunity.