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Introduction to Multiple Sclerosis

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2/24/22

Pathophysiology

Multiple Sclerosis is an autoimmune disorder of the central nervous system (brain and spinal cord)

There are characteristic lesions of focal inflammation within the white matter that can be seen on Magnetic Resonance Imaging (MRI), and grey matter and cortical less that may not be reliably seen on imaging but has been visualized on pathologic tissue

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Epidemiology

- Most commonly presents in young adults, mean onset of age 20-30
- Prevalence ranges from 5-300 per 100,000, higher rates at higher latitudes
- The development of MS has been associated with:
  - Higher latitude, less sun exposure, and lower vitamin D level
  - Certain genetic factors (HLA-DR1*15:01 allele. Carriers have an increased risk of developing MS)
  - Childhood obesity
  - Smoking
  - Epstein-Barr Virus

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Clinical Presentations of Multiple Sclerosis

Relapsing Remitting Multiple Sclerosis

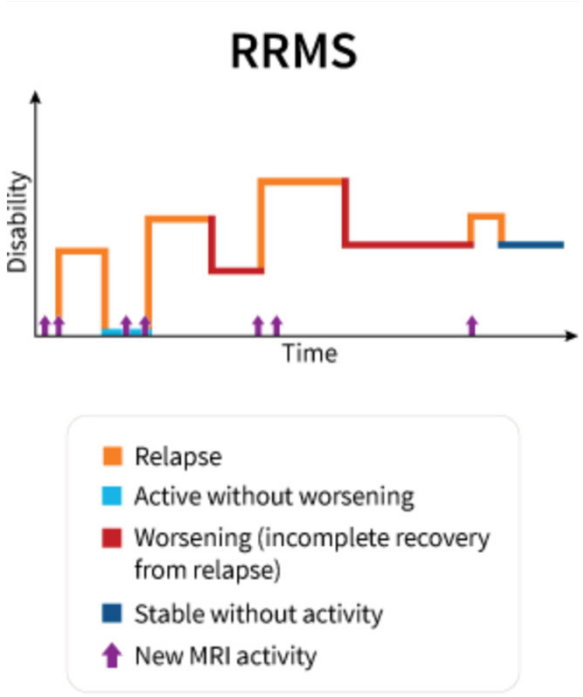
- Characterized by recurrent neurologic symptoms that can last weeks to months that usually improve or partially improve

Primary Progressive Multiple Sclerosis

- Characterized by progressive neurologic symptoms that do no improve

Secondary Progressive Multiple Sclerosis

- Characterized by the transition from relapsing disease to more progressive disease



Source: Lublin et al., 2014.

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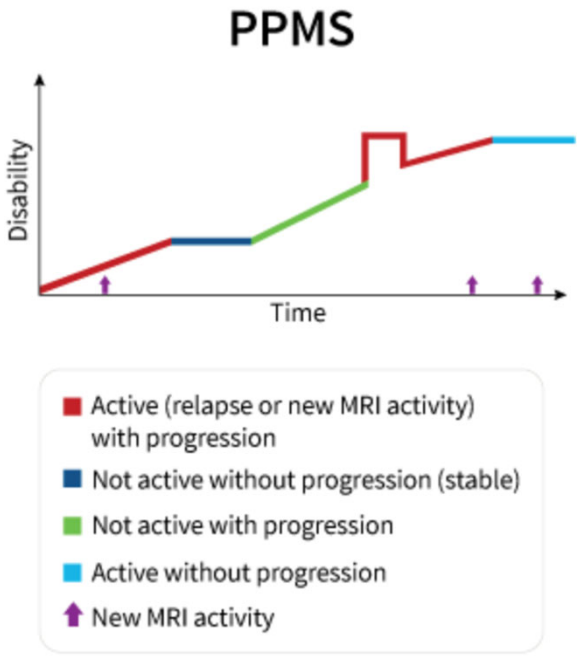

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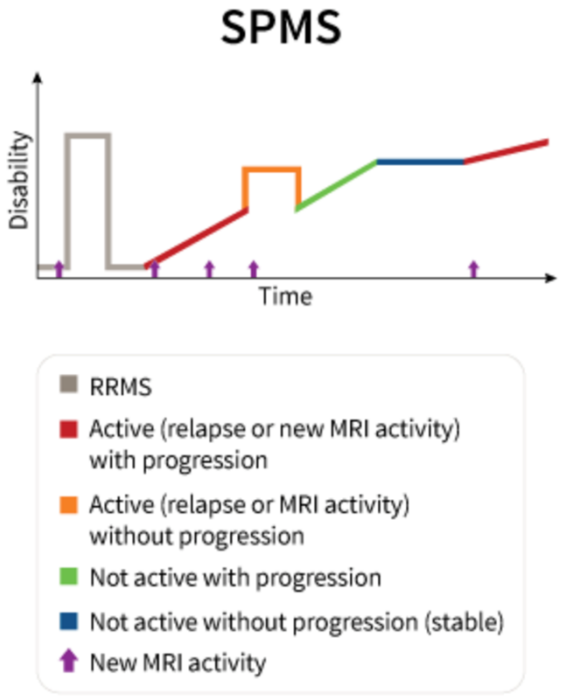

Source: Lublin et al., 2014.

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Diagnosis: 2017 McDonald Criteria

Number of Clinical Attacks	Number of Lesions With Objective Clinical Evidence	Additional Data Needed for a Diagnosis of Multiple Sclerosis
≥2	≥2	None[c]
≥2	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomic location[d])	None[c]
≥2	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI *or* demonstration of CSF-specific oligoclonal bands[e]
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI *And* Dissemination in time demonstrated by an additional clinical attack or by MRI *or* demonstration of CSF-specific oligoclonal bands[e]

Solomon, Andrew J.
CONTINUUM: Lifelong Learning in Neurology25(3):611-635, June 2019.

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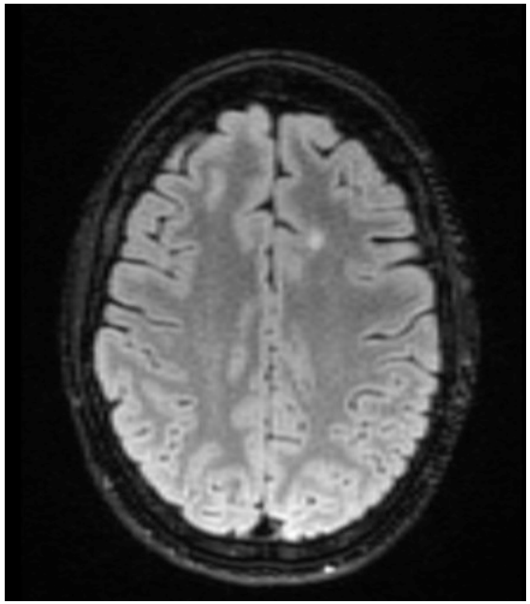
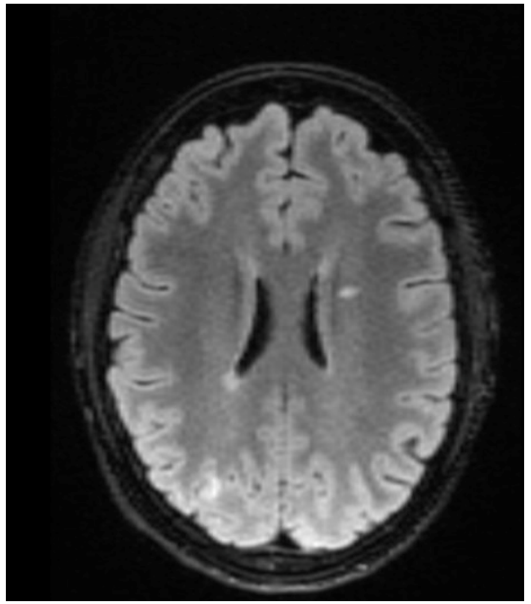
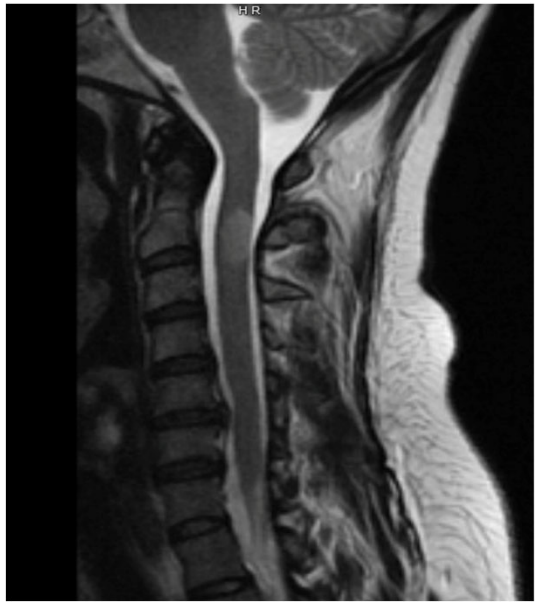
Characteristic MRI findings







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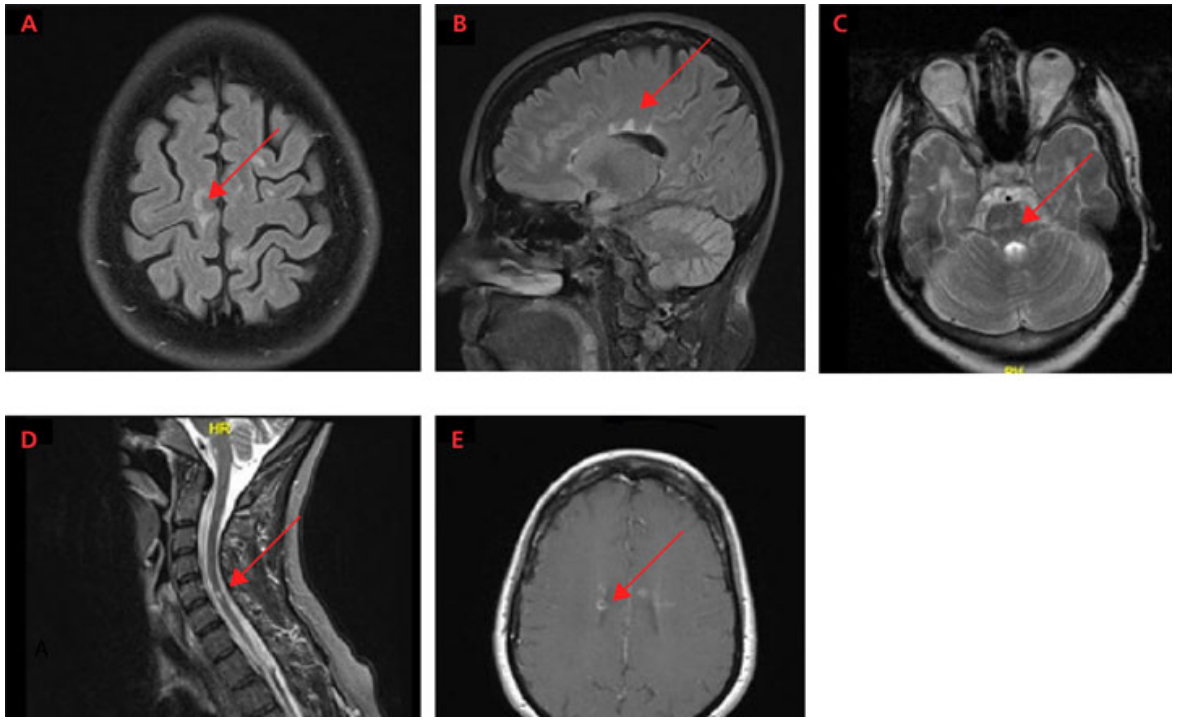
Characteristic MRI findings



Hersh CM, Fox RJ
Multiple Sclerosis Disease Management, 2018

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Natural History of Multiple Sclerosis

- About 80% of patients with Multiple Sclerosis (MS) have an initial clinical presentation of MS that consists of an acute neurological deficit (relapse) followed by recovery (aka relapsing remitting multiple sclerosis)

- Observational studies suggest that 58% of RRMS have converted to SPMS after 11-15 years and 66% after 16-25 years

B. Weinstock-Guttman, E. Grazioli, C. Kolb. Chapter 5 - Multiple Sclerosis Subtypes: How the Natural History of Multiple Sclerosis Was Challenged due to Treatment. Ruth Arnon, Ariel Miller. Translational Neuroimmunology in Multiple Sclerosis, Academic Press, 2016, Pages 55-65.

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Natural History of Multiple Sclerosis

A natural history study of 1215 patients with MS in Lyon, France found the following:

- Median time to second episode was 1.9 years
- There was no difference in the predictive value of unifocal or multifocal presentation, but time to second episode with optic neuritis initial presentation was longer than with brainstem or spinal cord presentations
- Slower progression related to:
  - Optic neuritis as initial episode
  - Good recovery from initial clinical event
  - Long period before second relapse
  - Fewer relapses in the first 5 years

11 C Confavreux, S Vukusic, P Adeleine. **Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process.** Brain, 126 (2003), pp. 770-782

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Acute Management of MS Relapse

Optic Neuritis Treatment Trial (Beck et al, 1992)

- 457 patients recruited from 1988-1991, mean age 32, 77% female
- Each patient was randomly assigned one of three regimens:
  - 1 mg/kg/day x 14 days oral prednisone
  - IV methylprednisolone 250 mg every 6 hours x 3 days followed by 1 mg/kg day oral prednisone x 11 days
  - Placebo group
- Conclusion: high dose IV methylprednisolone accelerated visual **recovery but did not improve 6 month or 1 year visual outcome compared with placebo**

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Acute Management of MS Relapse

Effect of Treating Acute Optic Neuritis with Bioequivalent Oral versus IV corticosteroids (Morrow et al, 2018)

- 45 randomized participants
  - 1:1 randomization of IV methylprednisolone 1000 mg or oral prednisone 1250 mg
- Results:
  - At 6 months, the mean P100 latency improvement was 62.9 ms in the IV group and 67.2 ms in the oral group (not statistically different)
  - Visual acuity was not statistically different between the two groups
  - Low contrast visual acuity was not statistically different between the two groups
- Conclusion: Use of an oral high dose corticosteroid is as effective as the IV equivalent in the treatment of optic neuritis

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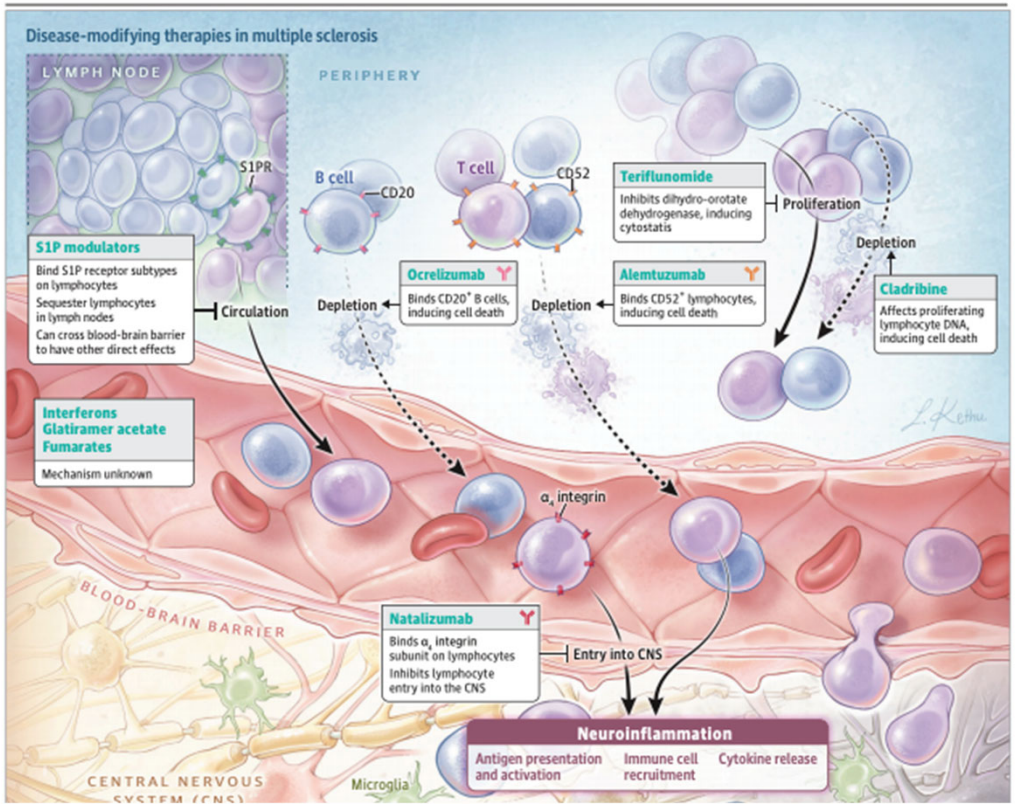
Disease Modifying Therapy:

Prescribed to reduce risk of relapse and progression



14 McGinley MP, Goldschmidt CH, Rae-Grant AD. **Diagnosis and Treatment of Multiple Sclerosis: A Review.** JAMA. 2021 pp. 765-779

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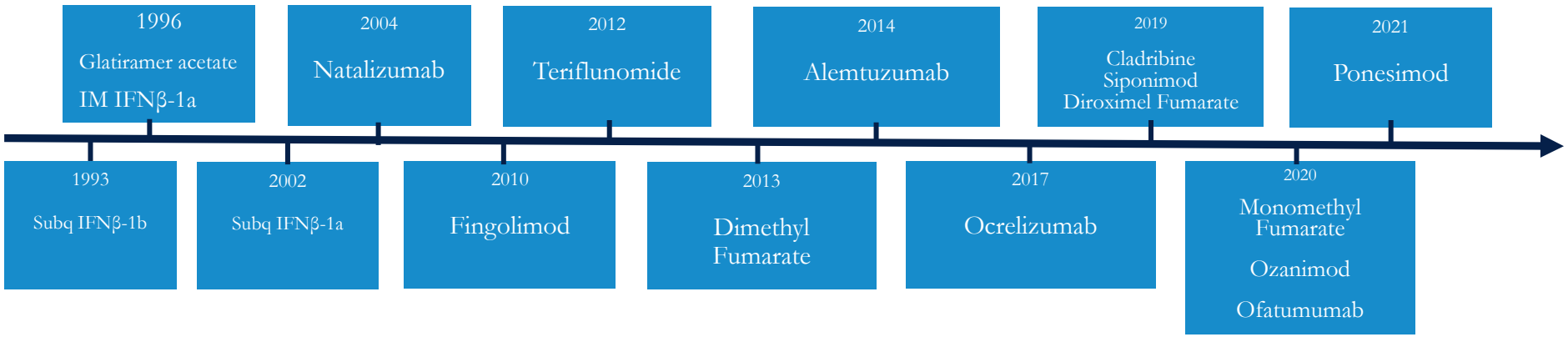
Timeline of Therapeutics for Multiple Sclerosis



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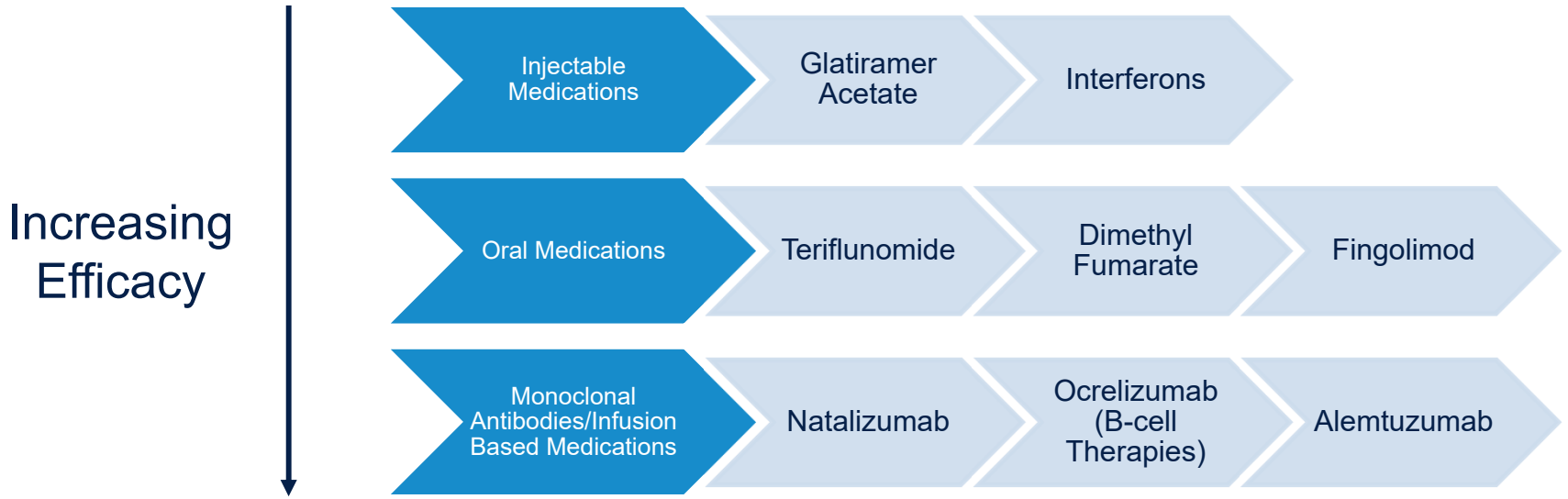
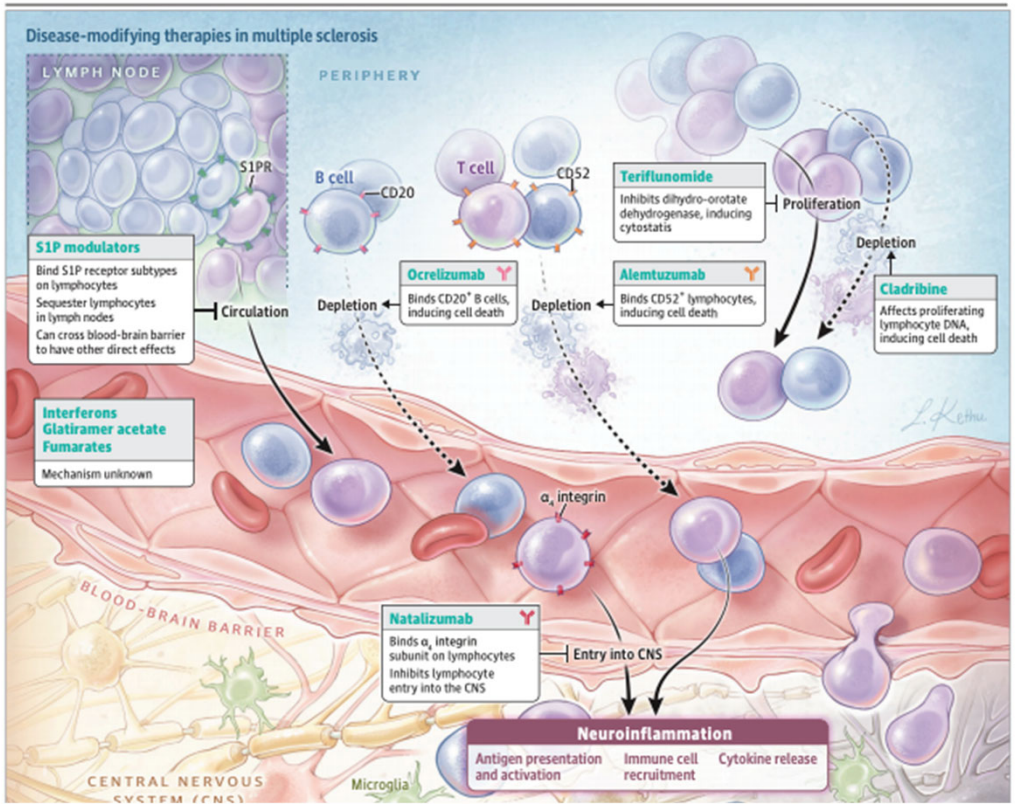
Efficacies of Immunotherapies



Mechanisms of Action of Immunotherapies



17 McGinley MP, Goldschmidt CH, Rae-Grant AD. **Diagnosis and Treatment of Multiple Sclerosis: A Review.** JAMA. 2021 pp. 765-779

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How to Decide on Immunotherapy

- Shared Decision Making Process between physician and patient

- Factors to Consider
  - Patient age and other medical conditions
  - Type of multiple sclerosis
  - Level of disease activity and other characteristics of the disease
  - Family planning/pregnancy planning

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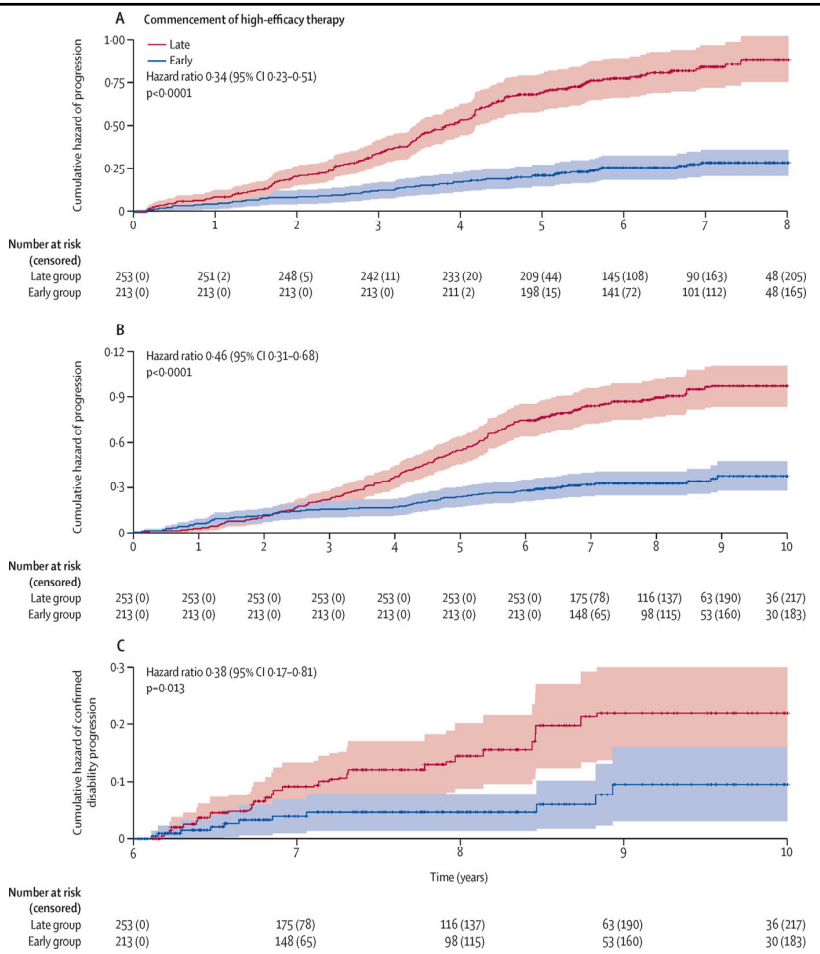
Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study

Anna He, et al performed a retrospective international observation study to evaluate timing of high efficacy therapy and multiple sclerosis outcome. The study compared high started high-efficacy therapy (rituximab, ocrelizumab, mitoxantrone, alemtuzumab, or natalizumab) early (within zero to 2 years of onset) versus late (4-6 year of onset).



The Lancet Neurology 2020 19307-316DOI: (10.1016/S1474-4422(20)30067-3)

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Emerging Therapeutics

- Bruton Tyrosine Kinase (BTK) Inhibitors
  - BTK is a critical molecule in intracellular signaling from B-cell and myeloid receptors
  - In EAE models, B-cell-T-cell interactions are affected by BTKi, which leads to reduction the ability to activate naïve T-cells that promote encephalitogen T-cells and leads to reduction in pro-inflammatory cytokine secretion (Torke et al, Acta Neuropathol, 2020)

García-Merino A. Bruton's Tyrosine Kinase Inhibitors: A New Generation of Promising Agents for Multiple Sclerosis Therapy. *Cells*. 2021;10(10):2560. Published 2021 Sep 27. doi:10.3390/cells10102560

Bruton Tyrosine Kinase Inhibitors under investigation for Multiple Sclerosis

- BTKi are small-molecule agents
  - Advantages:
    - Oral dosing
    - Intracellular targeting
    - Lower manufacturing costs
    - Ability to cross the blood brain barrier
      - If these medications can control persistent CNS inflammation, this may better target progressive multiple sclerosis

Zheng J., Wu J., Ding X., Shen H.C., Zou G. Small Molecule Approaches to Treat Autoimmune and Inflammatory Diseases (Part I): Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* 2021;38:127862. doi: 10.1016/j.bmcl.2021.127862

Treatment Duration

- At this time, generally patients are on treatment indefinitely unless there are serious adverse effects or based on individualized decisions among patients and their physicians

- There is currently an ongoing study DISCOMS Study
  - Evaluating the discontinuation of disease modifying therapy in Multiple Sclerosis

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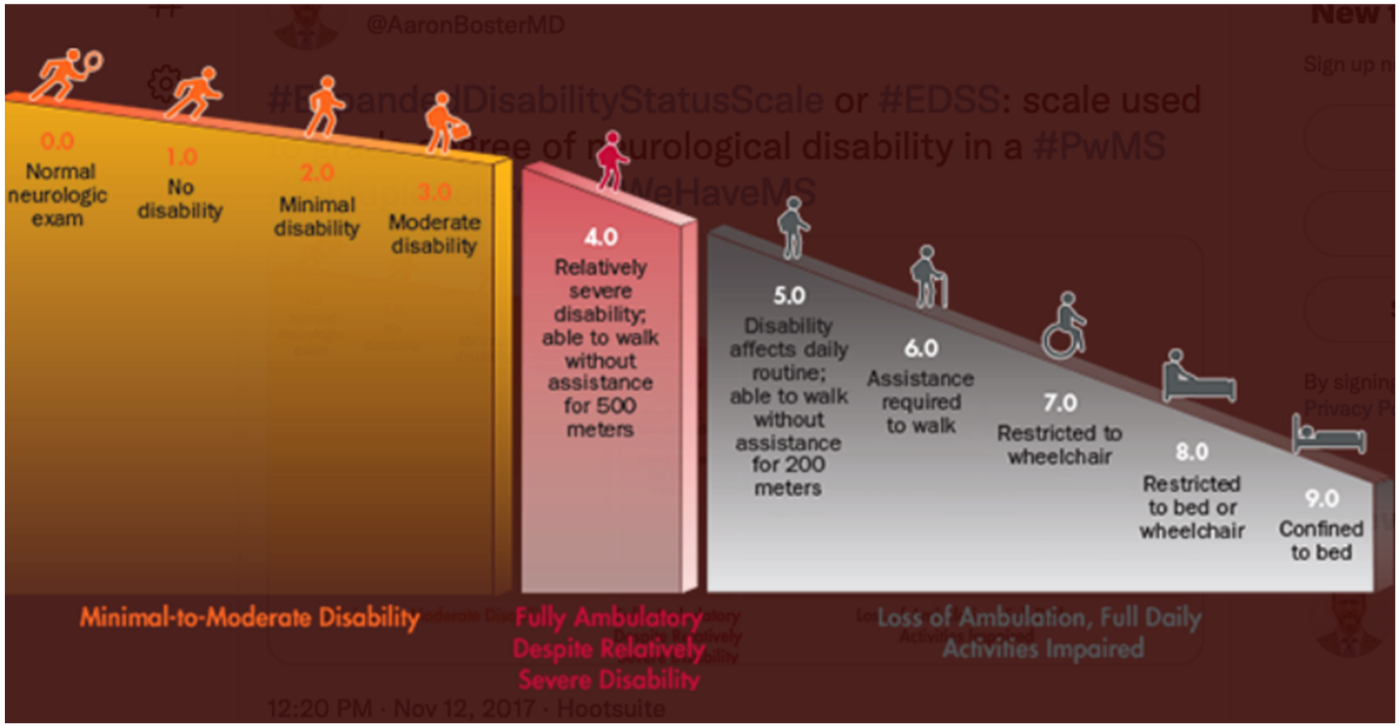
How do we monitor disease outcomes?

- Number of relapses
- MRI activity
  - New T2 lesions, enlarging T2 lesions, enhancing lesions
  - Brain atrophy
- Disability Progression
  - Extended Disability Status Scale
  - Multiple Sclerosis Functional Composite
    - Timed 25 foot walk
    - 9 hole peg test
    - Low contrast visual acuity
    - Symbol digit modalities test

How do we monitor disease outcomes?



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Depression/Anxiety

- Depression and anxiety affects 20-50% of people living with multiple sclerosis
- Suicide rates are 2x higher in people living with multiple sclerosis compared to the general population
- Suicidal ideation associated with:
  - Age > 65
  - Bowel/bladder dysfunction
  - Swallowing Dysfunction
  - Speech involvement

25 Thomas P. Leist "Depression and Multiple Sclerosis". Practical Neurology. March/April 2018.

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Fatigue

- Fatigue is reported in at least 75% of people living with multiple sclerosis, and it leads to socioeconomic consequences– loss of work hours and unemployment

- Fatigue is likely multifactorial in multiple sclerosis related to:
  - CNS damage, medication side effects, immunologic abnormalities, sleep disorders related to disease, disability status

- Treatment:
  - Energy conservation, cognitive behavioral therapy, pharmacologic

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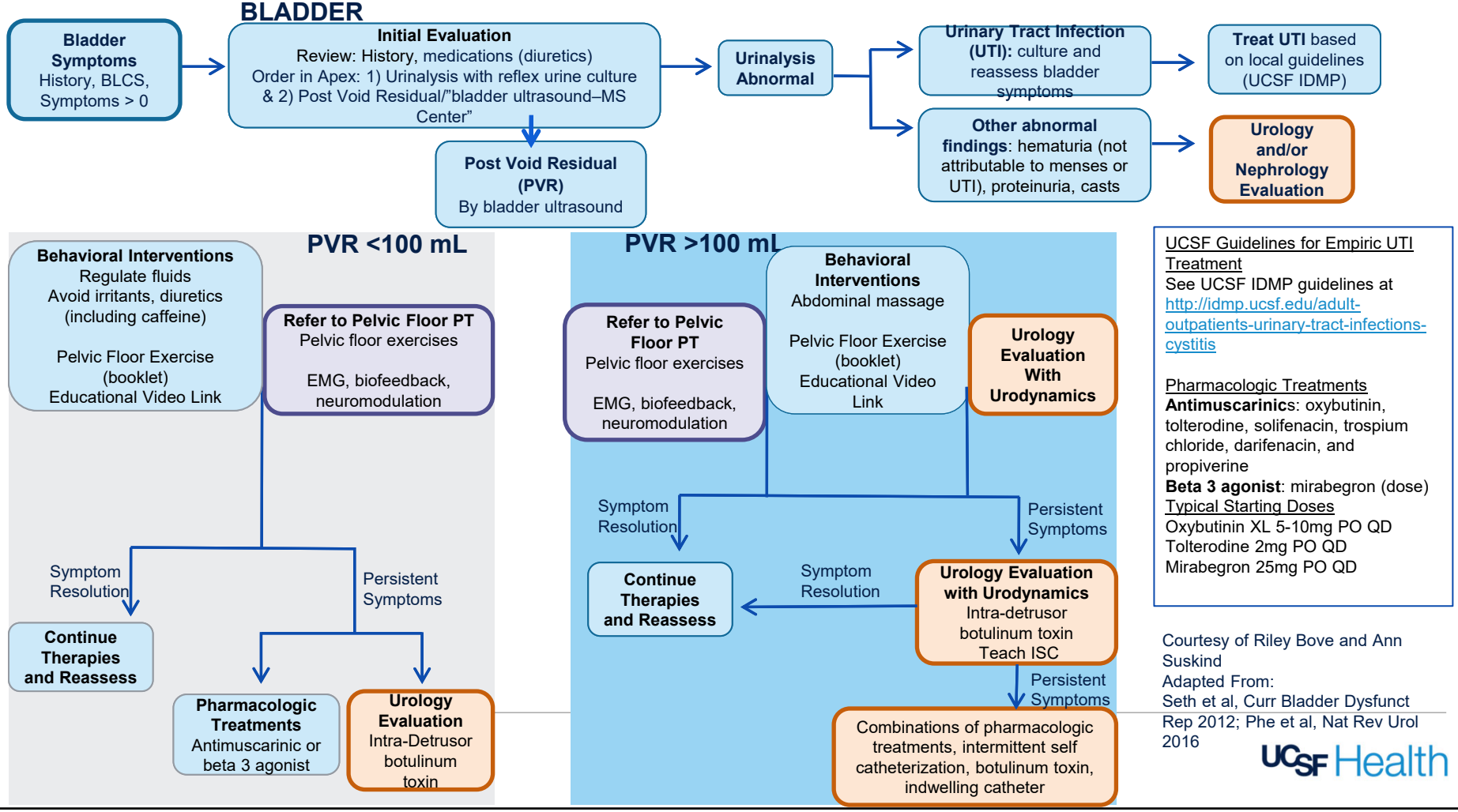
UCSF MS AND NEUROINFLAMMATION CLINIC APPROACH TO NEUROGENIC BLADDER



UCSF Guidelines for Empiric UTI Treatment
See UCSF IDMP guidelines at http://idmp.ucsf.edu/adult-outpatients-urinary-tract-infections-cystitis

Pharmacologic Treatments
Antimuscarinics: oxybutinin, tolterodine, solifenacin, trospium chloride, darifenacin, and propiverine
Beta 3 agonist: mirabegron (dose)
Typical Starting Doses
Oxybutinin XL 5-10mg PO QD
Tolterodine 2mg PO QD
Mirabegron 25mg PO QD

Courtesy of Riley Bove and Ann Suskind
Adapted From:
Seth et al, Curr Bladder Dysfunct Rep 2012; Phe et al, Nat Rev Urol 2016

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Gait Impairment and Falls

- Gait impairment is related to both strength and endurance (fatigability with prolonged activity often a feature of progressive MS)
- People living with MS also tend to have impaired gait biomechanics with decreased motion at the hip and ankle with with hyperextension of the knee– foot drop is very common
- Recommend early physical therapy evaluation and assistive device use to reduce risk of falls
- Devices like motorized scooter can assist with energy conservation and also reduce

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Other Common Symptoms

Symptom	Prevalence	Management
Spasticity	~84%	Baclofen, tizanidine, benzos, botulinum toxin, intrathecal baclofen pump
Neuropathic Pain	~40%	Gabapentin, TCA, carbamazepine
Cognitive Impairment	~40-50%	CBT, exercise, stimulants
Sexual Dysfunction	~70%	Silenafil, lubricants, couples therapy

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