# Multiple Sclerosis Update

## Providing care for our patients in a way that is consistent with their Overall Health Care Strategy

**Neurology for The Non-Neurologist 2023**
**Hershey, PA 17033**

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# Disclosures

- I have no financial disclosures or conflicts related to this topic
- I run a large MS Program at an Academic Center
- I have a passion for giving my MS patients excellent care
- I have three daughters who need my attention



Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

# Objectives

- Review the basics of the Multiple Sclerosis
- To define MS evidence based lifestyle recommendations
- To link each lifestyle recommendations to their overall health

# Agenda

- Multiple Sclerosis review
- Multiple Sclerosis Diagnosis
- Multiple Sclerosis Treatment
- Multiple Sclerosis Lifestyle Regimen



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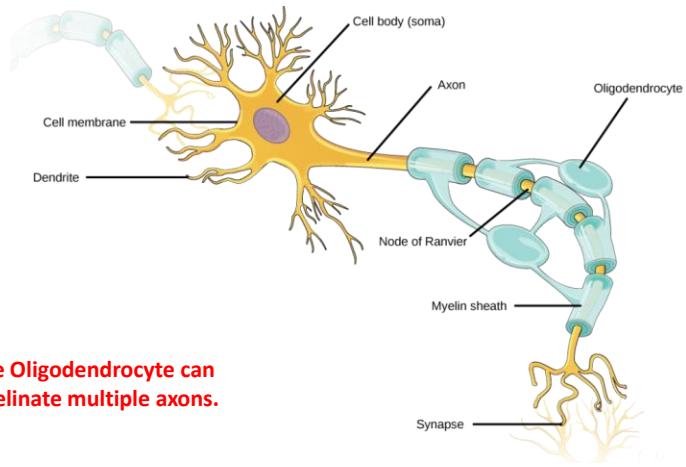
# MS is an Autoimmune Condition

- Evidence of inflammatory cytokines, activated astrocytes and macrophages
- Biomarkers include CSF Oligoclonal bands (antibodies) and IgG (index, syn rate)
- Immunosuppressants and Immunomodulators impact disease progression
- Target is oligodendrocytes (myelin) with secondary axonal damage
- Only CNS myelin appears to be involved.
- Inflammatory lesions follow the pattern of vascular supply
- More common in women 3:1

# CNS Neuron and Myelin Review




**One Oligodendrocyte can myelinate multiple axons.**



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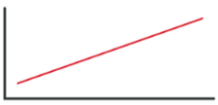
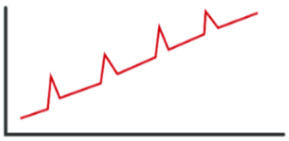
## Relapsing-remitting forms of MS most common, represent balance of inflammation and autoregulation.

Primary progressive: 10%



Secondary progressive
10 years = 50% of RR5 years = 90% of RR

Progressive-relapsing (obsolete)



Relapsing-remitting: 85%

(Jacobs *et al.*, 2016)

## 85% have Relapsing Remitting MS

- What does a relapse look like?
  - Gradual in onset (hours to days)
  - Focal neurological symptom
  - Usually a new neurological symptom
  - Not explained by heat (Uhtoff's Phen)
  - Not explained by any other cause

*"New focal neuro deficit in a 75 year old male is a stroke until you prove otherwise 25 year old MS patient is an exacerbation until you prove otherwise"*

**Numbness Weakness**
**Blurry vision Incoordination**
**Double vision Tremor**
**Incontinence Pain**



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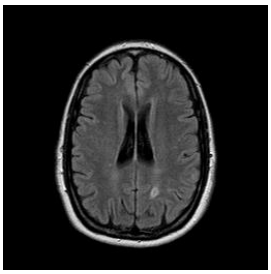
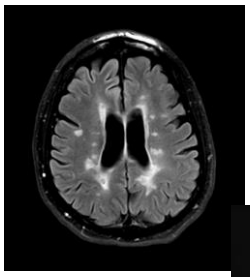
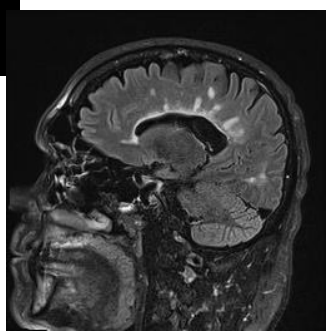
# MS MRI







**Periventricular**
**Perpendicular to the ventricle**
**Round or oval**
**White matter tracts**
**Corpus Callosum**

***The McDonald Criteria Relies heavily on MRI to make a speedy diagnosis***

# MS and EBV is complicated

**Conclusion: Infectious Mononucleosis (IM) in early adulthood associated with a higher risk of MS later in life (HR 1.89, CI 1.18-3.05):**

- **Large data base evaluated (approx. 2.5 M Sweds 1958-2018)**
- **EBV can have variants (EBV A & B, type 2,3,4, 6)**
- **Childhood EBV usually asymptomatic reduces risk of IM**
- **"mononeucleosis" caused by EBV, CMV, other viruses**
- **Antibody testing is not reliable indicator of previous infection**
- **EBV proteins share epitopes with Myelin Basic Proteins**
  - **BRRF-2, EBINA-1, BFRF3**

Bhargava, Pavan et al. High-doses vitamin D supplementation reduces IL-17 producing CD4+ T-cells in multiple Sclerosis Patients. Neurology. April 8, 2015



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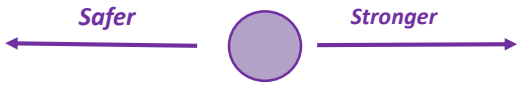
# More MS Drugs Options

| **Self Injections**: | **Pills**: | **Infusions**: |
|---|---|---|
| Glatiramir | Teriflunomide | Natalizumab |
| Interferons | Fumerates | Ocrelizumab |
| Ofatumumab | S1P modulators | Mitoxantrone |
| | Cladribine | Lemtrada |




***We need to know patients risk tolerance and have a strategy for monitoring disease progression vs stability.***

# Bruton's Tyrosine Kinase Inhibitors

- Currently used for Cancer Treatment
  - Plays a role in modulating growth factor signaling
  - Unique TK proteins seen in AML, CLL, Breast, Lung CA
  - Targeting akin to MABs but smaller, oral molecules ?
- Masitinib, Phase 3 Clinical Trial (PRDBPlaceboC)
  - 611 patients randomized, PPMS, SPMS
  - Reduced EDSS progression over 96 weeks, p value 0.0256
  - Secondary endpoints: 25 ft walk, 9 hole PEG, QoL
  - AE: diarrhea, nausea, rash, hematologic events
  - Targets Mast Cells and Microglia (Envobrutinib targets B-cells)
  - Neuroprotective in ALS or Alzheimers?

1. Arora, Amit et al. Role of Tyrosine Kinase Inhibitors in Cancer Therapy. The Journal of Pharmacology and Exprimental Therapies. 315:971-979. October 12, 2018.
2. Vermersch, Patrick et al. Efficacy and Safety of Mastinib in Progressive Forms of Multiple Sclerosis. Randomized, Phase 3, Clinical Trial. Neurology: Neuroimmunology & Neuroinflammation. Volume 9, Number 3. May 2022



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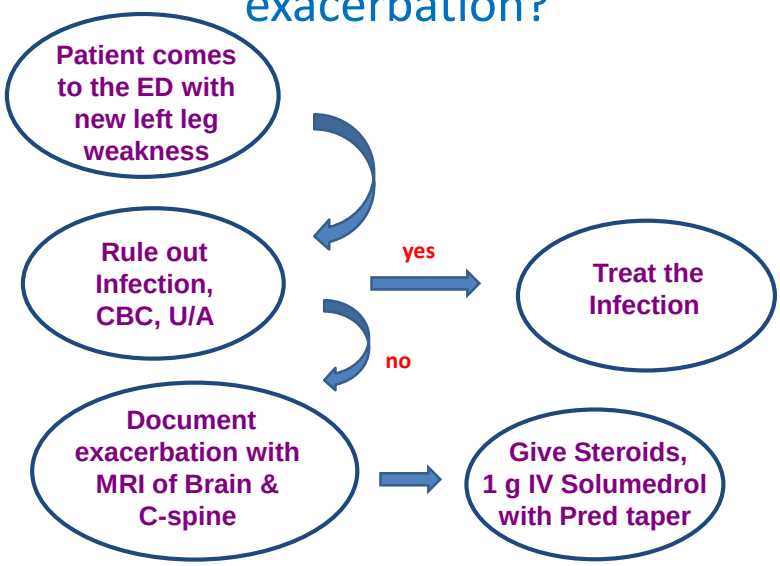
# HSCT in MS

- 210 patients with RRMS, mean EDSS of 6, active disease
- Followed for 6+ years (1997 to 2019)
- Durable suppression of MS?
- Not randomized, no placebo, not blinded

| | RRMS | PMS |
|---|---|---|
| 5 year NEDA-3 | 62.2% | N/A |
| 10 year NEDA-3 | 40.5% | N/A |
| 5 year disability free | 85.5% | 71.3% |
| 10 year disability free | 71.0% | 57.2% |

1. Boffa, Giacomo et al. Long-term Clinical Outcomes of Hematopoietic Stem Cell Transplant in Multiple Sclerosis. Neurology. Feb 23, 2021. Vol 96. #8. pp 1215-1226

# How do we evaluate a potential exacerbation?



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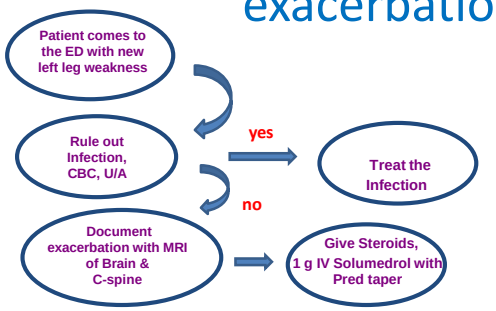
# How do we evaluate a potential exacerbation?




**The MS world has changed!**

1. **More MS Drug options (tolerate exacerbations less)**
2. **Many MS drugs suppress the immune system (more kinds of infections!)**
3. **Steroids carry risk too**
4. **Lab testing can help us manage patient**

# MS Lifestyle Regimen



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## More than 20 Vitamin D MS studies

- Vitamin D slows progression
- Vitamin D + Glatiramir or + Interferon
- Fewer attacks when Vitamin D is normal
- Vitamin D and pregnancy
- Vitamin D levels and MRI findings
- Vitamin D twin studies
- Vitamin D supplementation reduces IL17 levels

***Consistent with other vitamin D study results related other autoimmune disorders including Lupus and RA and Myasthenia Gravis and Celiac Disease.***

Bhargava, Pavan et al. High-doses vitamin D supplementation reduces IL-17 producing CD4+ T-cells in multiple Sclerosis Patients. Neurology. April 8, 2015

## Vitamin D2 + Vitamin K2?

- a growing body of evidence suggests a synergistic effect of vitamin K combined with vitamin D for
  - Better bone density, fewer fractures (M & W)
  - Better cardiovascular health (less vessel calcification? Better insulin metabolism?)
- Studies used vitamin K2 45 mg/day + Ca + D3
- Supplements or food sources?
- **Small study suggest MS patients have lower K2 levels compared to age matched controls**

Adriana J. van Ballegooijen, et al. "The Synergistic Interplay between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review." International Journal of Endocrinology Volume 2017, Article ID 7454376, 12 pages
Lasemi, Reza et al. "jVitamin K in Multiple Sclerosis Patients" Wien Klin Wochenschr : Central European Journal of Medicine. (2018) 130:307–313



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## Vitamin D & K2 foods


## Exercise in MS

- **Hundreds of studies on Exercise and MS**
  - **Walking, running, weight training, yoga, pilates, PT/OT, swimming**
  - **Every study showed a benefit (fewer attacks, better balance, fewer falls, better energy, less disease progression, better memory)**
  - **Some function can improve or can be regained.**
- **Exercise and vitamin D supplementation may work synergistically to improve vitamin D levels.**
- **IL17 and TNF-a levels reduced in patients who exercised** **New**

1. Backus, D "Increasing Physical Activity and Participation in patients with Multiple Sclerosis: A Review" Archives of Physical Medicine & Rehabilitation. 97(9 Suppl):S210-7, 2016 Sep.
2. Wong, Vicki et al. A Systematic review of aerobic and resistance exercise and inflammatory markers in people with multiple sclerosis. Behavioral Pharmacology 2019 30:pp 652-659



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# BMI and MS

- High BMI increases risk to develop MS
  - BMI > 30 at age 18, 2.25x increase risk of developing MS (NHS)
  - BMI > 30 in 20s, 2,15x incr risk even controlling for genetis (Kaiser)
  - Obesity as a chronic, low-grade inflammatory response?
- Higher BMI, triglycerides, non-HDL lipds associated with more frequent relapses and more significant disability progression.
- Norweigan population (643K people) based study 1963-75: Higher BMI age 14-24 associated with higher risk of MS (1.4x men, 1.59x women)
- Obesity/metabolic syndrome linked to accelerated rates of brain atrophy in people with MS.

1. Gianfrancesco, Milena et al. Obesity and Multiple Sclerosis Suseptibility: a Review. Journal of Neurology Neuromedicine 2012 (197) pp1-5
2. Tetty, Prudence et al. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event. Journal of Neurology, Neurosurgery and Psychiatry. March 20,2017. vol 88. pp 395-401
3. Fitzgerald KC, Salter A, Tyry T, et al. Measures of general and abdominal obesity and disability severity in a large population of people with multiple sclerosis. *Mult Scler*. Epub ahead of print 13 May 2019. DOI:
4. Filippatou A, Lambe J, Sotirchos E, et al. Association of body mass index with longitudinal rates of retinal atrophy in multiple sclerosis. *Mult Scler* 2020; 26(7): 843–854.
5. Hoglund, Rue et al. Association of Body Mass Index in Adolescense and Young Adulthood and Long-term Risk of Multiple Sclerosis. Neurology 2021. vol 97.#23. Dec 7, 2021

# Benefits of Exercise (CDC)

- **Improve your brain health**
- **Help manage weight**
- **Reduce the risk of disease (DM)**
- **Improve cardiovascular health**
- **Reduces Stress/Anxiety**
- **Strengthen bones and muscles**
- **Improve your ability to do everyday activities**

https://www.cdc.gov/physicalactivity/basics/pa-health



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# Lactobacillus bacteria

- **Maassen, Catharina B M; Claassen, Eric. "Strain-dependent effects of probiotic lactobacilli on EAE autoimmunity" Vaccine. 26(17):2056-7, 2008 Apr 16.**
- **Drs. Sushrut Jangi Howard L. Weiner, and colleagues from Harvard's Brigham & Women's Hospital in Boston studying gut biome. MS patients have different bacteria!**
- **Kouchaki E, Tamtaji OR, Salami M, et al. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. *Clin Nutr.* 2016.**
- **22 Preclinical (Animal) Trials Support improvement (Jinchi, Jiang et al. Efficacy of probiotics in Multiple Sclerosis: a systematic review of preclinical trials and meta-analysis of randomized control trials. Food Function. March 21, 2021. pp2354-2377**

# Benefits of Probiotic

- Reduces inflammation
- Improve brain health (young and older)
- Improve stroke recovery
- Improve RA disease course
- Reduces the frequency of Migraine h/a

1. Elham Bidabadi MD, et al. "The Effect of Probiotics on Headaches in Children with Migraine Treated with Sodium Valproate: A Randomized Controlled Clinical Trial" Iran Journal of Child Neurology. 2023 Spring; 17(2): 119–126.
2. Simona Gabriela Bungau et al. "Targeting Probiotics in Rheumatoid Arthritis." Nutrients. 2021, 13, 3376, 18 pages
3. Chatuthanai Savigamin et al. "Probiotic as a Potential Gut Microbiome Modifier for Stroke Treatment: A Systematic Scoping Review of In Vitro and In Vivo Studies." Nutrients 2022, 14, 3661, 13 pages



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# Coffee

- **Hedstrom AK; Mowry EM et al. " High consumption of coffee is associated with decreased multiple sclerosis risk; results from two independent studies." Journal of Neurology, Neurosurgery & Psychiatry. 87(5):454-60, 2016 May.**

- **MS patient who are Coffee drinkers do better (cause/effect?)**
- **Caffeine improved EAE mouse model disease**
- **Coffee drinkers may have a lower risk of Alzheimers and Parkinsons**
- **Coffee drinkers may live longer.**

**Verdict: Coffee is likely good for MS and all of us!**

# USA Coffee Consumption

- **68% of Americans drink coffee daily**
- **Top Brands (USAToday 2020, Harris Poll)**
  1. **Dunkin**
  2. **Starbucks**
  3. **Café Bustelo**
  4. **Green Mountain**
  5. **Folgers**
  6. **Community**
  7. **Peet's**
  8. **McCafe/McDonalds**



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# Coffee Benefits?

**Heals Liver Damage from:**

- **Hep B, C**
- **fatty liver/NASH**
- **Alcohol cirrhosis**

**Extend lifespan**

**"The exact mechanism of beneficial effects of coffee is not clear. Coffee contains more than 1000 substances, including caffeine, diterphenoic alcohols, potassium, niacin, magnesium, and the antioxidants like chlorogenic acid (CGA), and tocopherols."**

Wadhavan, Manav et al. "Coffee and Liver Disease." Journal of Clinical Experimental Hepatology. 2016 Mar; 6(1): 40–46.Published online 2016 Feb 27.

# Coffee and Life Expectancy

**All types of coffee were linked with a reduction in death from any cause. The greatest risk reduction seen with two to three cups per day, which compared to no coffee drinking was associated with a 14%, 27% and 11% lower likelihood of death for decaffeinated, ground, and instant preparations, respectively.**

Chieng D, Canovas R, Segan L, *et al*. The impact of coffee subtypes on incident cardiovascular disease, arrhythmias, and mortality: long-term outcomes from the UK Biobank. *Eur J Prev Cardiol*. 2022. doi:10.1093/eurjpc/zwac189.



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# Tobacco and MS


- More than 100 studies on MS and smoking.
- Weston, Mikail; Constantinescu, Cris S. et al. "Tobacco smoking and excess mortality in multiple sclerosis: a chort study. Journal of Neurology, Neurosurgery & Psychiatry. 85(10):1091-5, 2014 Oct.
- Every study consistently shows that smoking tobacco products can:
  - Increase your risk of developing MS
  - Increase your baby's future risk of MS if you smoke while pregnant
  - Worsen your disease progression if you have MS
  - **Reduce your "all cause of death" life expectancy.**
  - **Increase risk of lung disease**
  - **Increase heart disease, diabetes, rheumatoid arthritis**
  - **Increase risk of cancer**
  - **Slow bone healing after fractures**

# Other Neuroprotective Options

- Taurine (anti-oxidant?)
- Berries slowed cognitive decline in elderly (correlation only)
- Omega-3
  - Improves memory testing
  - Less Brain atrophy
- Dark Chocolate
  - Acute memory (caffeine v cerebral blood flow)
  - Improves mood (gut biome/prebiotic link?)

- Black Tea
  - Improves brain organization, cognition
  - Improves BMD, reduces risk of fractures
- Green Tea
  - Improves memory, cognition and fMRI

**Polyphenols? Flavonoids? Other antioxidants? Caffiene?**



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# Additional References

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Dighriri et al. "Effects of Omega-3 Polyunsaturated Fatty Acids on Brain Functions: A Systematic Review. " Cureus 14(10): e30091, 2022

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Sun, Kang et al. "Association between tea consumption and osteoporosis A meta-analysis" Medicine (2017) 96:49(e9034), 9 pages.

Rahimlou, Mehran et al. "Probiotic supplementation and systemic inflammation in relapsing-remitting multiple sclerosis: A randomized, double-blind, placebo-controlled trial" Frontiers in Neuroscience., 20 September 2022 Sec. Gut-Brain Axis. Volume 16 - 2022 |

The New York Times

***Harvard Scholar Who Studies Honesty Is Accused of Fabricating Findings***

**By Noam Scheiber**

Published June 24, 2023Updated June 25, 2023

Over the past two decades, dozens of behavioral scientists have risen to prominence pointing out the power of small interventions to improve well-being.
The scientists said they had found that automatically enrolling people in organ donor programs would lead to higher rates of donation, and that moving healthy foods like fruit closer to the front of a buffet line would result in healthier eating.

Many of these findings have attracted skepticism as other scholars showed that their effects were smaller than initially claimed, or that they had little impact at all. But in recent days, the field may have sustained its most serious blow yet: accusations that a prominent behavioral scientist fabricated results in multiple studies, including at least one purporting to show how to elicit honest behavior.

The scholar, Francesca Gino of Harvard Business School, has been a co-author of dozens of papers in peer-reviewed journals on such topics as how rituals like silently counting to 10 before deciding what to eat can increase the likelihood of choosing healthier food, and how networking can make professionals feel dirty.



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## Thank You & Questions


"I give neurons good hugs"

-Ollie Gogh Dendrocyte

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