
Multiple Sclerosis: When to worry, when to refer and when to reassure

NEW BRUNSWICK INTERNAL MEDICINE UPDATE

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Conflict of Interest

- None

Learning Objectives

- Recognition of prevalence of MS
- Review of the “topography” of MS and potential symptoms
- Understand the pathology of MS and the influence on disease progression
- Review the currently available therapies and what can go wrong
- When to refer to Neurology OR Neurology may refer to you

Multiple Sclerosis – Demographics & Prevalence

Prevalence:

- estimated to be **290/100,000** in Canada (one of the highest in the world)
- Females 418/100,000 vs males 159/100,000
- Female/male 2.6/1

82% diagnosed at 20-49 years of age

Compared to other neurologic disorders

- Begins at an earlier age
- Impacts education & employment
- Long duration illness

Statistics Canada, Health Reports 2018, Vol 29, no. 1, 3-8

Multiple Sclerosis – Demographics & Prevalence

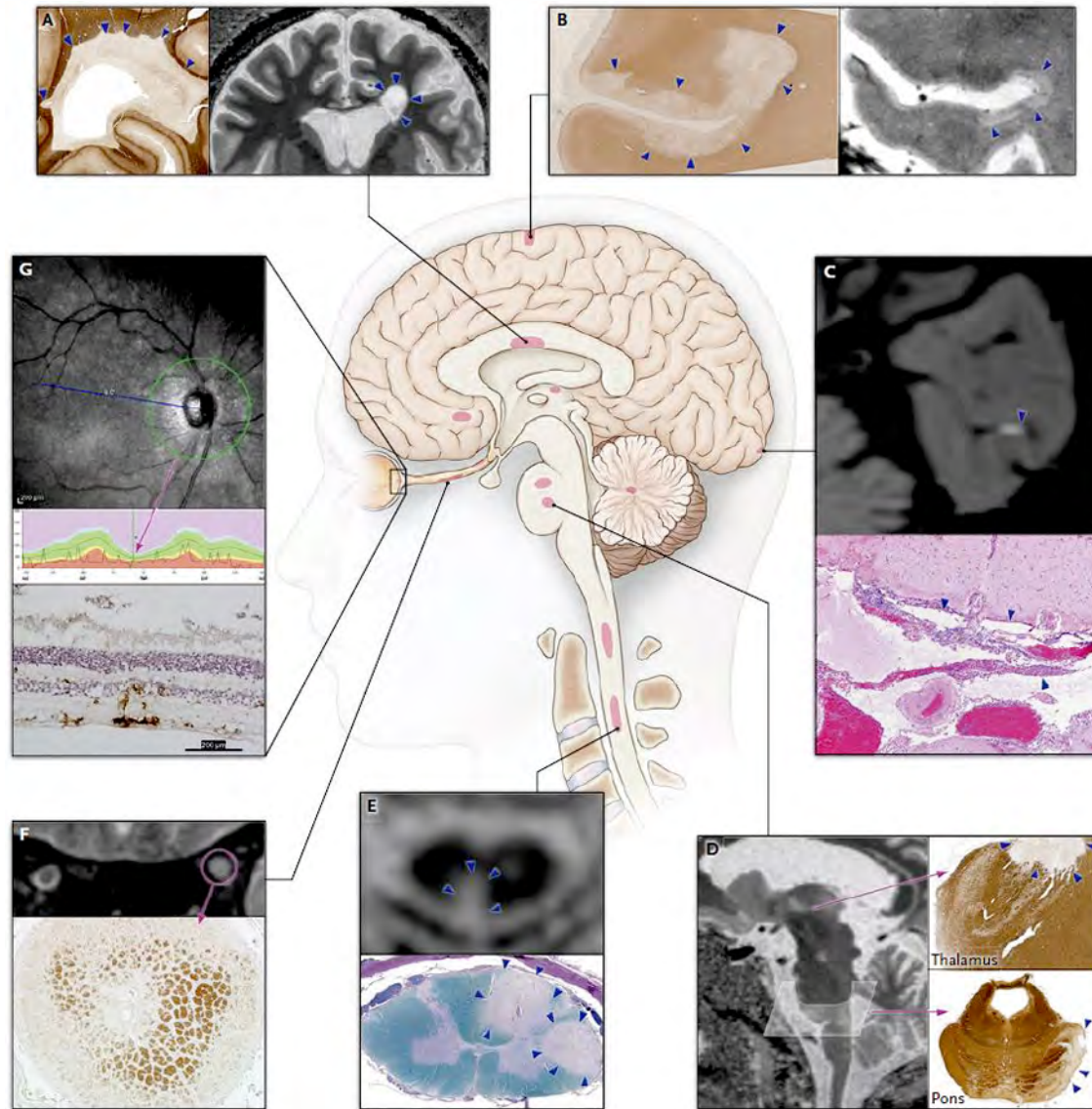
- Prevalence of MS patients receiving home care, residing in nursing homes or occupying hospital beds in Canada is **7-21 X higher** than for the general population
- MS patients in nursing homes:
 - Younger at admission
 - More physically disabled
 - Less cognitively impaired
 - Depression common

CJNS 2018; 45(2): 188-198

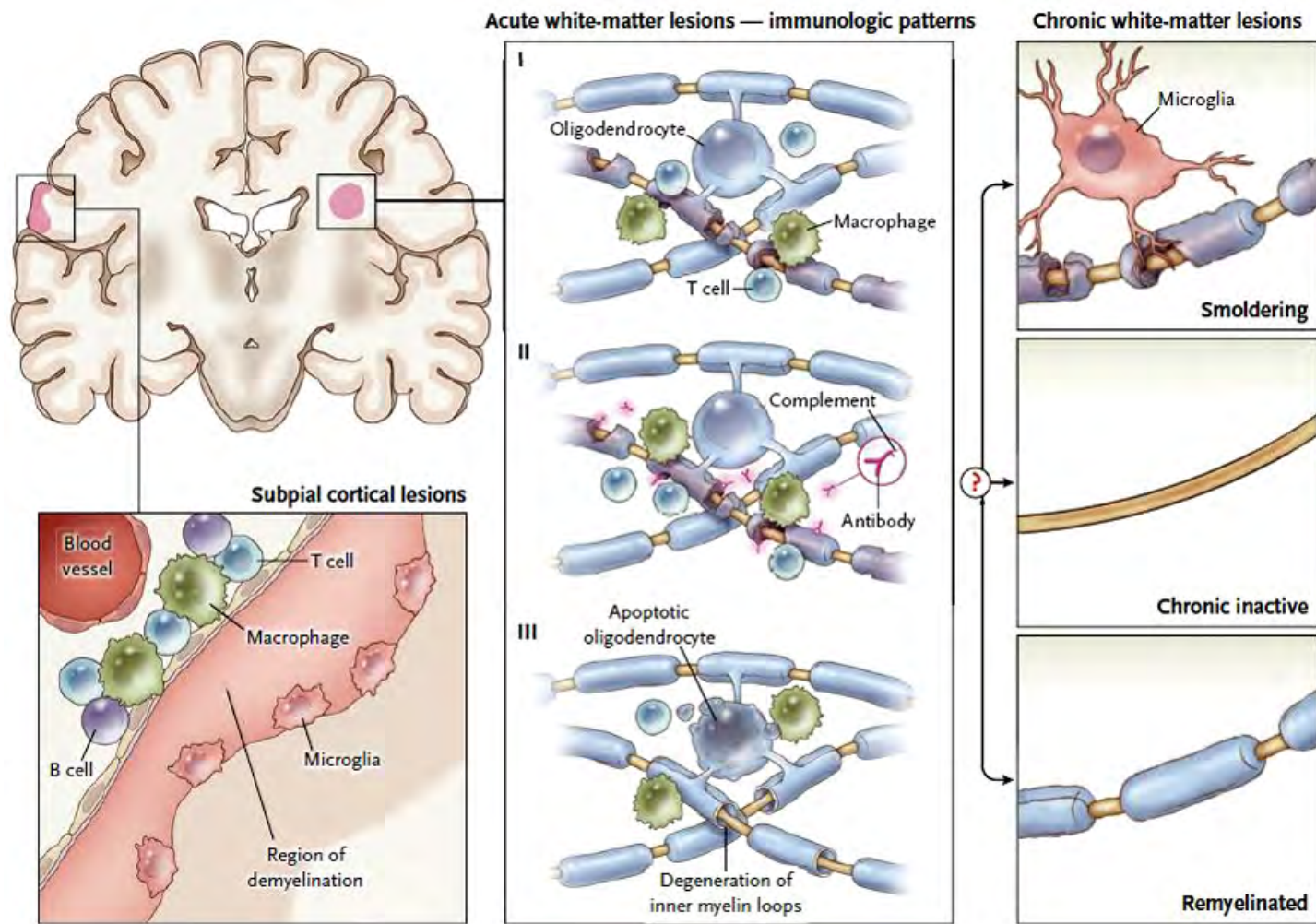
Etiology & Pathogenesis

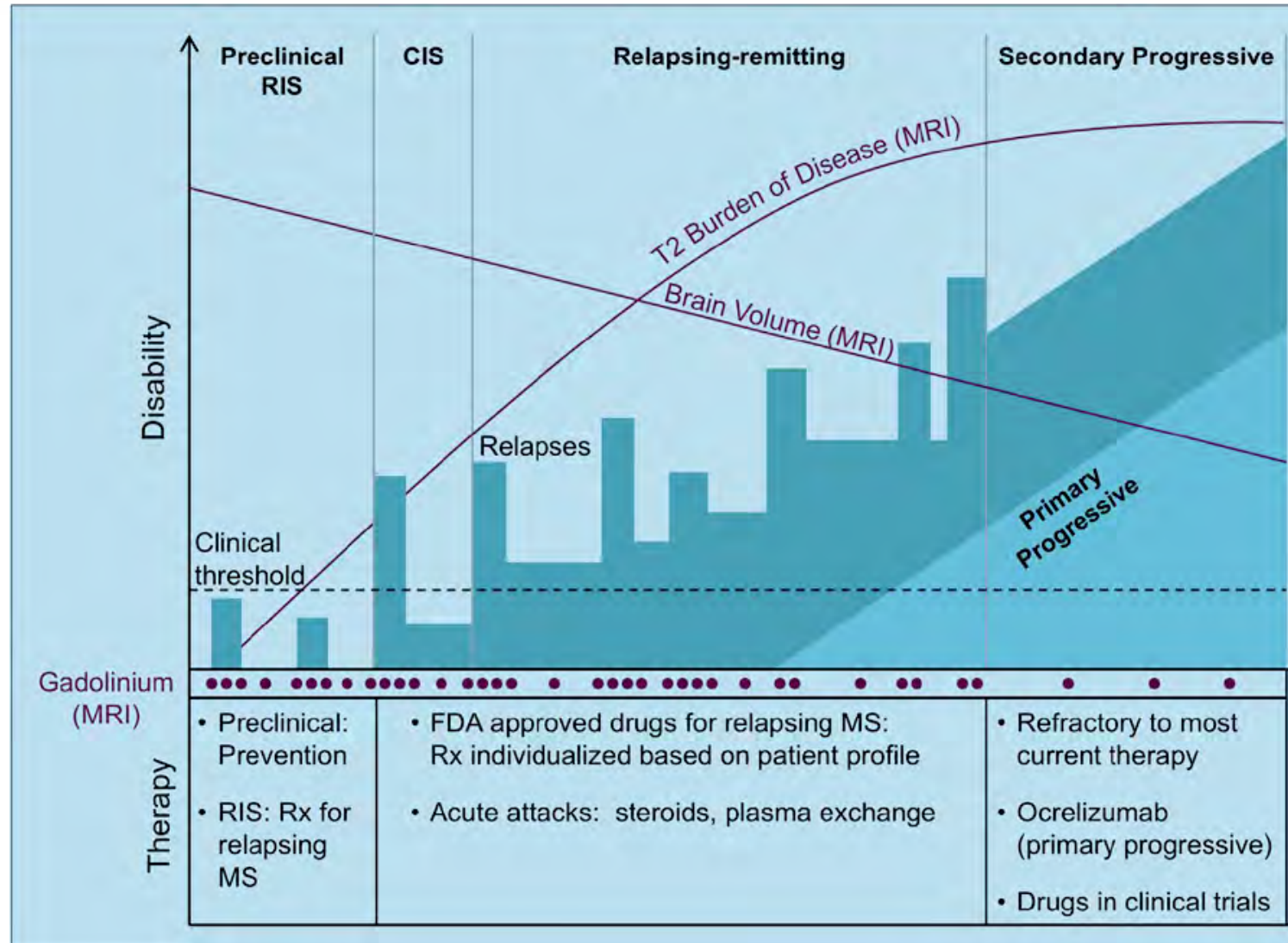
- Genetics
 - 1st degree relatives 2-5% risk vs Monozygotic twins 25-50% risk
 - No evidence of Mendelian inheritance
 - Role in susceptibility?
- Environment
 - Latitude & Migration (influence of Vitamin D & UV radiation)
 - Higher risk (Smoking) vs Lower risk (alcohol, caffeine) – impact on immune system?
- Infection
 - No single infectious agent (increased risk with EBV; role of gut microbiome?)

Neuron 2018; 97:742-768



NEJM 2018; 378: 169-180





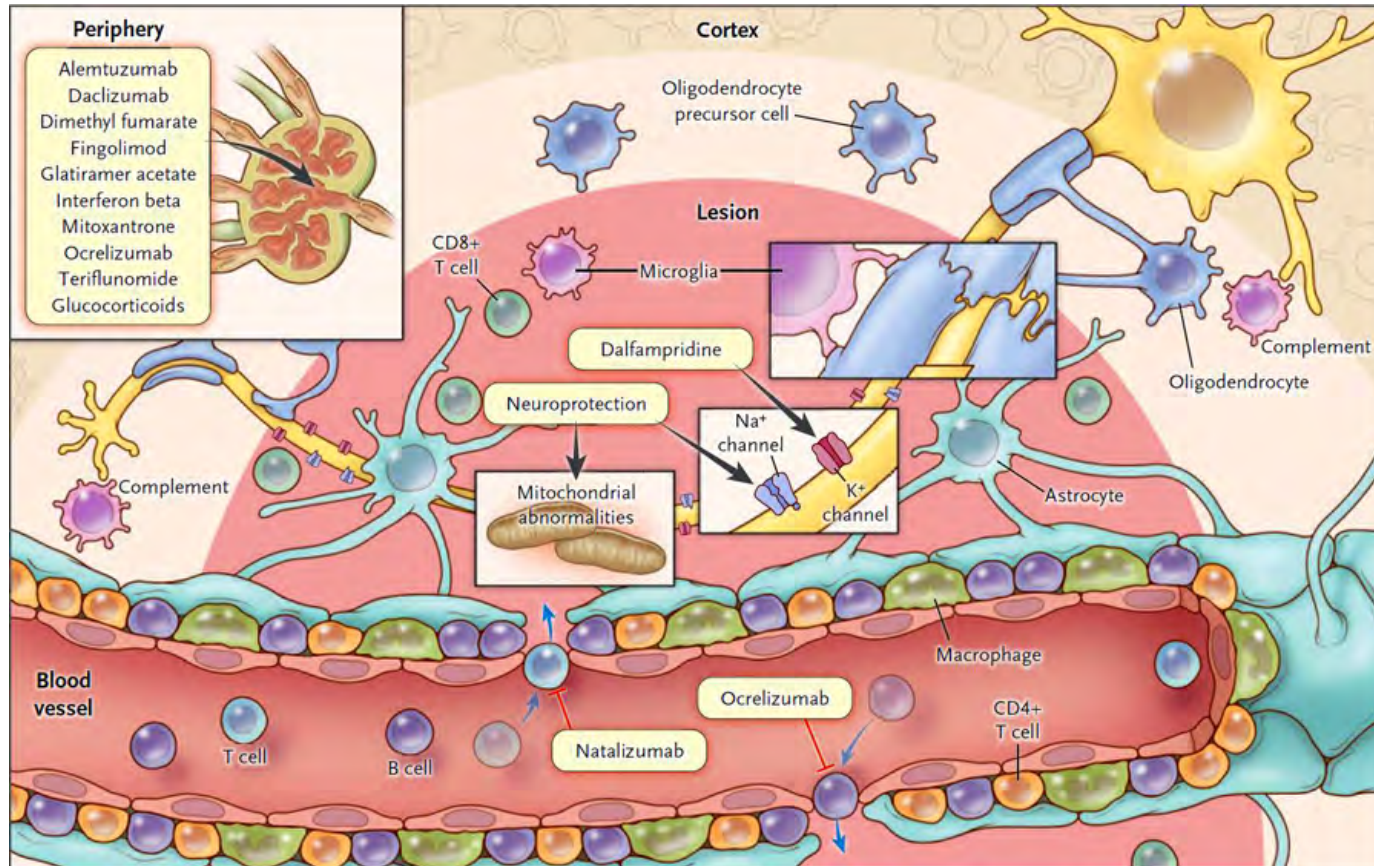
Challenges

- Lack of biomarkers
- Desire to treat early and with most appropriate medication versus inability to predict who will have a more aggressive clinical course
- Risks of medications (infection, autoimmune disorders, cancer)
- Current lack of curative therapies
- No disease reversing therapies

Medications – The last 20 years

- Steroids
- Platform Drugs
- Oral Therapies
- Infusions
- Others

Medications – Site of Action (as far as we know)



Prednisone and Methylprednisolone

- Reduces cytokine release
- Decreases T cell activation
- Accelerates relapse recovery but no benefit for disability accumulation or future relapses

Platform Drugs

Drug	Dosing	Action	Lab Changes	Monitoring
Interferon β 1b	0.25 mg SC 3x/wk	Decreases Th17 cells and decreases IL-17	Leucopenia Increased LFTs	CBC & LFTs, Thyroid
Interferon β 1a	30 μ g IM 1x/wk 22 or 44 μ g SC 3x/wk	Decreases Th17 cells and decreases IL-17	Leucopenia Increased LFTs	CBC & LFTs, Thyroid
Glatiramer acetate	20 mg Sc daily or 40 mg SC 3x/wk	Induce & activate T suppressor cells, interferes with antigen presentation	None	None
Pegylated Interferon β 1a	125 μ g SC q2wks	Decreases Th17 cell and decreases IL-17	Leucopenia Increased LFTs	CBC & LFTs, Thyroid

Oral Therapies

Drug	Dosing	Action	Adverse Events	Monitoring
Fingolimod	0.5 mg once daily	Sequesters lymphocytes in lymph nodes	Hypertension AV block Macular edema PML	CBC & LFTs q 6 months MRI
Dimethyl fumarate	240 mg BID	Activates Nrf2 transcriptional pathway	Facial flushing GI PML	CBC, LFTs & U/A q 6 months MRI
Teriflunomide	14 mg BID	Inhibits secretion of proinflammatory cytokines	Alopecia Diarrhea Increased LFTs	CBC & LFTs q 6 months
Cladribine	10-20 mg daily for 4 or 5 days and repeat 1 month later repeat 1 year later (cumulative dose 1.75 mg/kg per year)	Depletes T & B cells	Infection Lymphopenia ?PML	CBC 9 weeks after start (need for acyclovir?) & prior to dose 1 year later MRI

Infusion Medications – Humanized mAb

Drug	Dosing	Action	Adverse Events	Monitoring
Natalizumab	300 mg IV q 4 weeks	Prevents B & T cell migration into the CNS	Infusion reaction (20%) PML	LFTs JCV Ab, JCV Index q 3-6 months MRI q 6-12 months
Alemtuzumab	12 mg IV once daily X5 days 12 months later 12 mg IV daily X3 days	Depletes B & T cells	Infusion reaction (90%) Herpes infection (16%) Autoimmune diseases <ul style="list-style-type: none"> • Thyroid (30%) • ITP (2%) • Glomerulonephritis (0.3%) 	CBC, Cr monthly X5 years TSH q 3 months X 5 years Annual: <ul style="list-style-type: none"> • Skin exams (melanoma) • HPV screening
Ocrelizumab	1 st dose divided (single 300 mg IV dose, repeat 2 weeks later); subsequent doses 600 mg iv q 6 months	Depletes CD+ B cells	Infusion reaction (35%) URTI Herpes infection Breast cancer	

Other Therapies – Past and Present and Future?

- Daclizumab – recently withdrawn from market
- Cyclophosphamide
- Azathioprine
- Methotrexate
- Bone marrow transplant
- Stem cell transplant
- High dose Biotin

When do we worry, refer or reassure? - **Clinical**

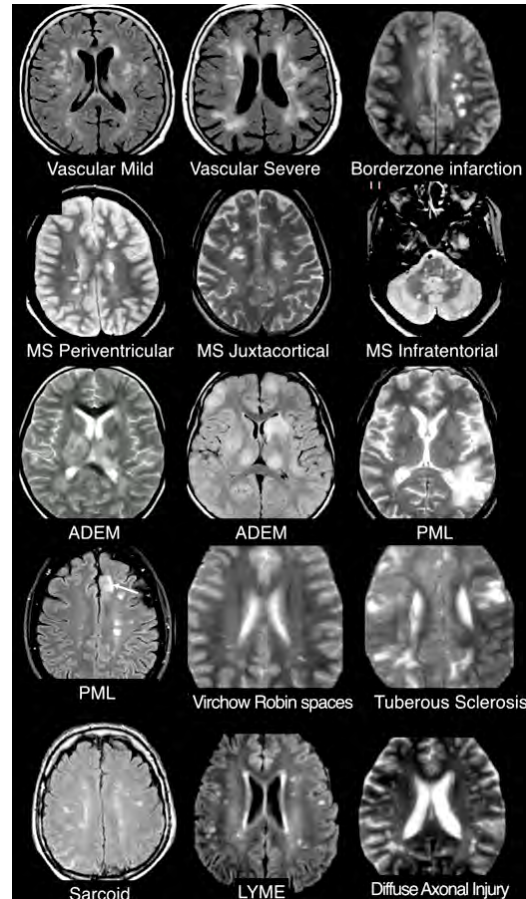
- Relapses occur, sometimes spontaneously and often in a setting of infection or immune activation
- Look for evidence of recent infection, treat if appropriate and reassure patient that the relapse will likely settle over the next several weeks
- Steroids offer option to shorten a relapse but carry some risk – limit to attacks with significant motor or visual deficits or patients at high risk of falls/injury – limit $\leq 3-4X/\text{year}$? – not as effective in longstanding MS
- With a significant relapse, a follow-up MRI may be required

When do we worry, refer or reassure? - Clinical

Vaccine	Type	Use in people with MS
Injectable seasonal flu vaccine	Inactivated	Considered safe
Flu-Mist® flu vaccine	Live attenuated	Not recommended
Fluzone® high-dose flu vaccine	Inactivated	Not recommended
Gardasil® human papillomavirus vaccine (HPV)	Inactivated	Probably safe
Hepatitis B vaccine	Inactivated	Considered safe
Measles-Mumps-Rubella vaccine	Live attenuated	Probably safe in individuals not on immunosuppressant medications
Pneumovax® 23 and Prevnar® 13 pneumococcal vaccines	Inactivated	Considered safe
Polio	Inactivated in most countries	Probably safe
Rabies	Inactivated	Probably safe; benefit likely outweighs any risks
Tetanus vaccine	Inactivated	Considered safe; may reduce relapses
Varivax® and Proquad® varicella vaccines	Live attenuated	Probably safe. Required prior to treatment with Fingolimod, Alemtuzumab and cladribine in patients without previous exposure
Yellow fever vaccine	Live attenuated	May not be safe; should not be used by individuals on immunosuppressant medications
Zostavax® zoster vaccine	Live attenuated	Probably safe for any adult who has had chicken pox

Adapted from Williamson EML, Chahin S, Berger JR. Vaccines in multiple sclerosis. *Curr Neurol Neurosci Rep* 2016; 16:36.

When do we worry, refer or reassure? - Radiologic



<http://www.radiologyassistant.nl/en/p4556dea65db62/multiple-sclerosis.html>

When do we worry, refer or reassure? - Radiologic

- Cerebral Small Vessel Disease
- Inflammatory
 - Vasculitis
 - Sarcoid
 - ADEM (Acute Disseminated Encephalomyelitis)
- Infectious
 - Lyme
 - Syphilis
 - HIV
 - PML
- Metastatic disease

When do we worry, refer or reassure? – Medication

- Management of MS has become much more complex in the last 20 years, including use of more potent medications with increased monitoring requirements
- Many of the medications has been used in other fields (GI, Rheumatology, Dermatology) and may be familiar to most Internists
- Some therapies carry specific risks:
 - PML (can mimic MS flare-up) may require MRI and potentially LP for JCV
 - Cancer
 - Autoimmune disorders (thyroid, ITP, glomerulonephritis) causing a neurologist to seek you out

NEDA

- Most MS patients on therapy now followed by neurologists – many through an MS Clinic
- Even if the relapse resolves, Neurologist will need to follow-up to determine if additional investigation required or change of therapy needed.

Conclusion

- MS is a prevalent condition and the young age of onset means that these patients will likely end up seeing an Internal Medicine physician at some point
- First presentation of MS can present some challenges from diagnostic perspective
- Management of relapses can often be handled by any physician but warrant referral back to MS Clinic for follow-up
- Current therapies require careful monitoring and may result in a neurologist seeking you out if complications arise

Thank you for your attention!

Questions?