Welcome to today's Webinar: MS101

Your Presenter is: Prof Jeannette Lechner - Scott

Your Facilitator is: Ms Nicola Graham

Handouts

Handouts have been sent separately.
This contains a copy of the slides presented today.

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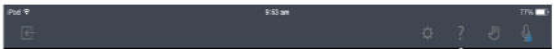
Control Panel

Control panel appears on the right of screen

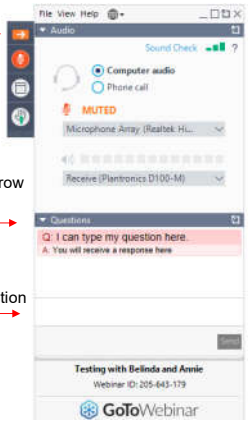
If you are using a Mac, a tablet or an iPad, you need to look for the control icons across the top, side or bottom of your screen;



Click to minimize or maximise

Click the down arrow on the Questions pane to open

Type in your question and click send



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Polls

Polls are used throughout our client webinars as a way of making the webinars interactive.

To familiarise you with how they work I will run one now…

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Acknowledgement

We acknowledge and pay respect to the traditional custodians past and present on whose lands we meet today.

We acknowledge the deep feelings of attachment and the relationship of Aboriginal people to country and respect the cultural authority of the elders in each community

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Welcome to today's Webinar: MS101

Your Presenter is: Prof Jeannette Lechner - Scott

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Introduction to Presenter

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Informed Choice

This presentation has been prepared and is presented by an independent expert.

The views presented are not necessarily the views of Multiple Sclerosis Limited.

Individuals are encouraged to seek further advice regarding the relevance of the information presented for their situation.

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Overview of Multiple Sclerosis

Webinar February 2019
Prof Jeannette Lechner-Scott
Head of MS Clinic John Hunter Hospital
Newcastle

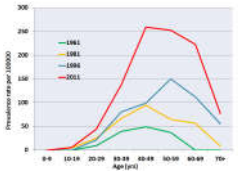
Overview

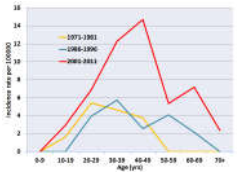
- Pathophysiology
- Epidemiology
- Clinical course
- Therapeutic option
  - Disease modifying therapies
  - Symptomatic therapies
  - Life style changes

Increasing prevalence and incidence of MS in young women

Year	Census population	Prevalence	Sex ratio (F:M)
1961	137,428	18.5 (13.7-25.0)	1.18
1981	138,719	35.1 (29.0-53.4)	1.97
1996	131,303	83.9 (40.3-73.2)	2.52
2011	148,535	124.2 (104.7-140.3)	3.10

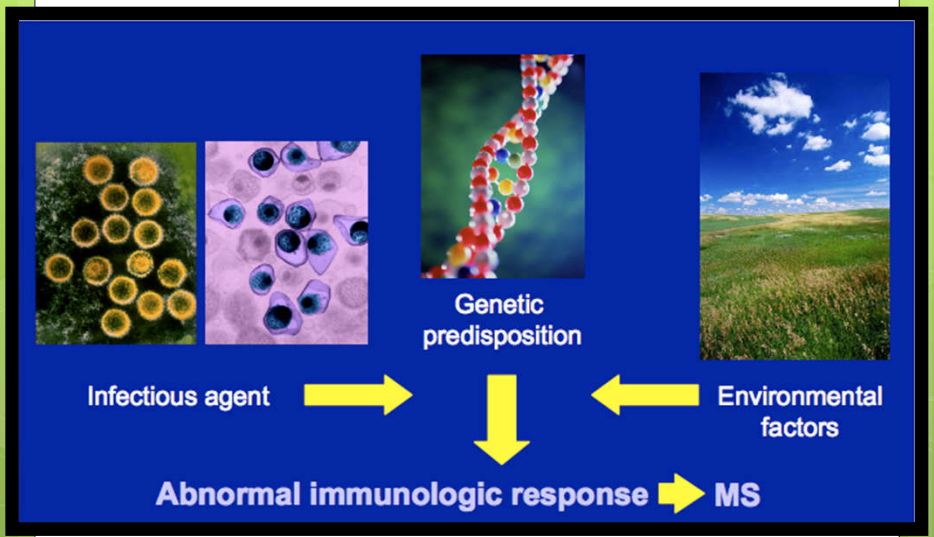
Year	Incidence	Sex ratio (F:M)
1971-1981	2.54 (1.33-3.37)	1.13
1986-1996	2.44 (1.68-3.47)	2.21
2001-2011	6.70 (5.39-8.01)	3.10



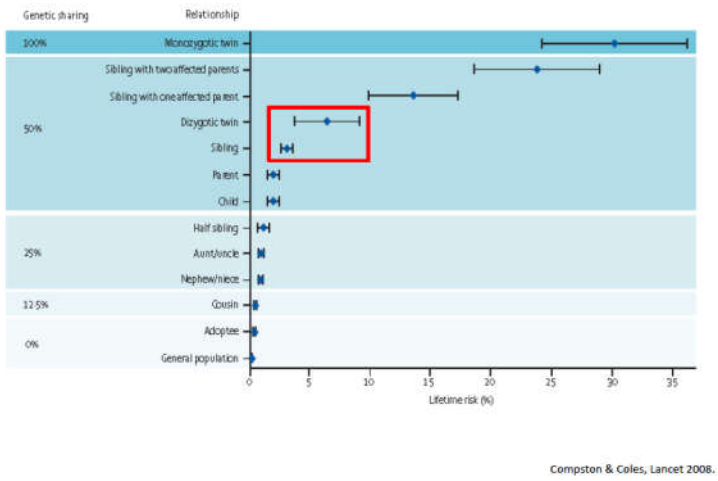


Ribbons K. et al. Mult Scler. 2017 Jul;23(8):1063-1071

Etiology

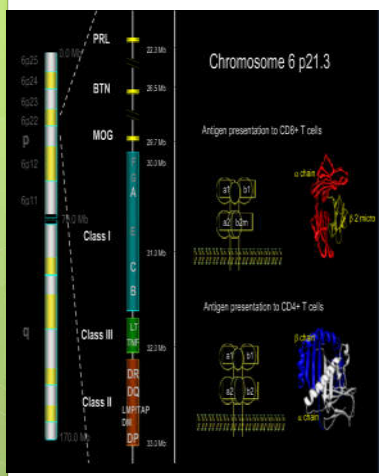


Genetics



Compston & Coles, Lancet 2008.

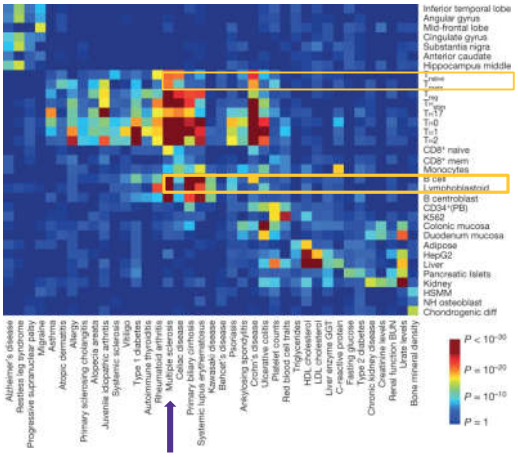
Genetics



- HLA-DRB1*1501 main susceptibility factor
- HLA-DRB1*0801 increases risk
- HLA-DRB1*1401 decreases risk

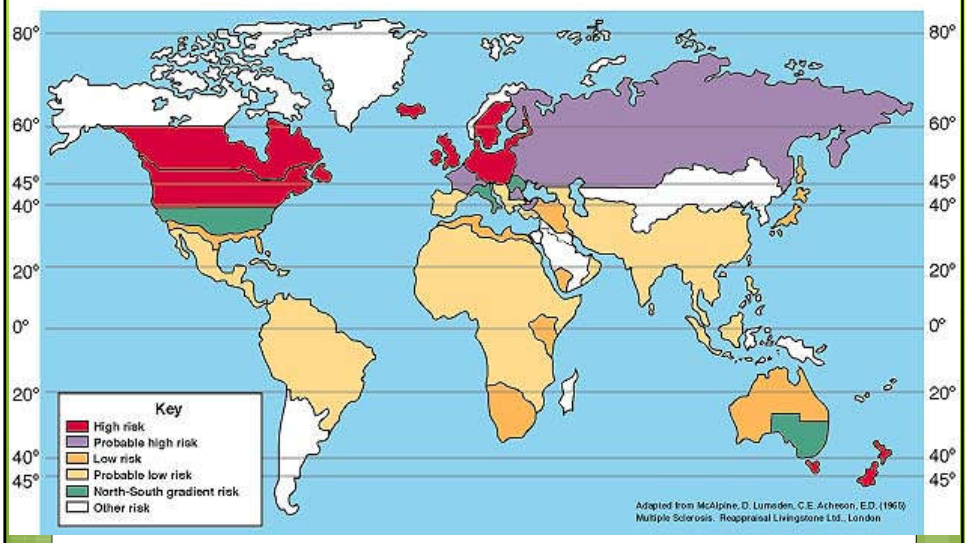
15

Genes affected by autoimmune disease



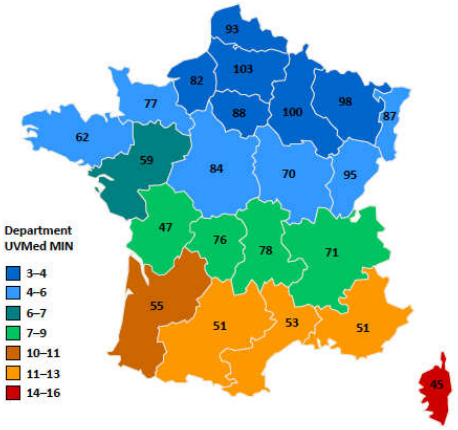
K K-H Farh *et al. Nature 518*, 337-347 2015

World Distribution of Multiple Sclerosis



UVB and MS prevalence in France

MS Prevalence by Department
Against UVMED Minimum



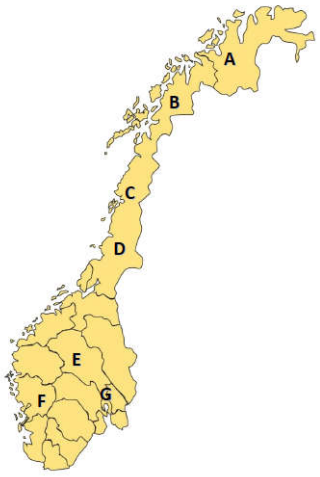
Orton et al. Neurology. 2011 Feb 1;76(5):425-31.

Prevalence of MS in Norway

- Prevalence data for counties in Norway (/10^5):

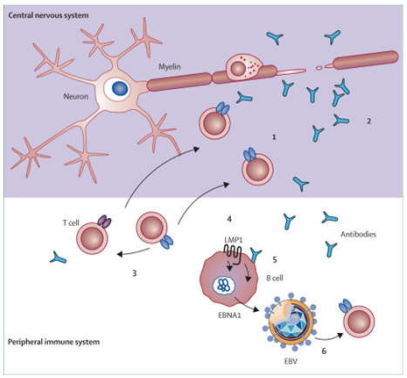
A Finnmark[1] (2003)	>83
B Troms[1] (2003)	>104
C Nordland (1999)	106
D Nord Trøndelag (1999)	164
E Oppland[2] (2002)	190
F Hordaland (2003)	151
G Oslo[2] (2005)	154

- In Norway, MS prevalence does not rise with increasing latitude, unlike other northern European countries and the USA
- As expected, measured UV radiation levels decrease with increasing latitude



Kampman et al, 2007

Infectious agent as cause of Autoimmune disease



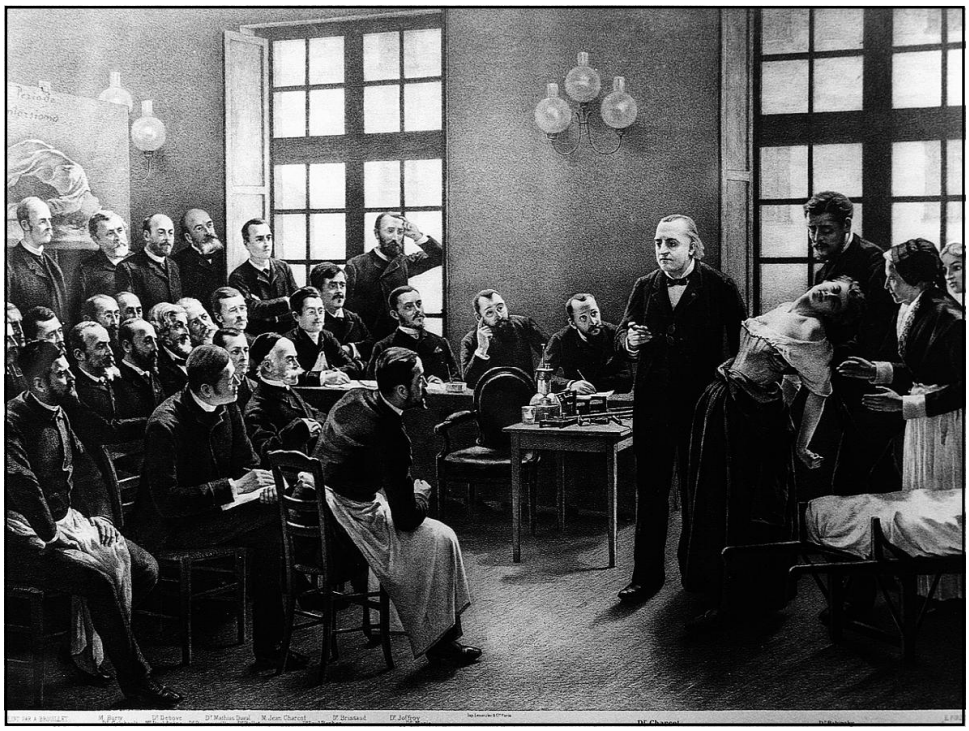
Giovannoni, Lancet 2006

Question 1
Which one is true?

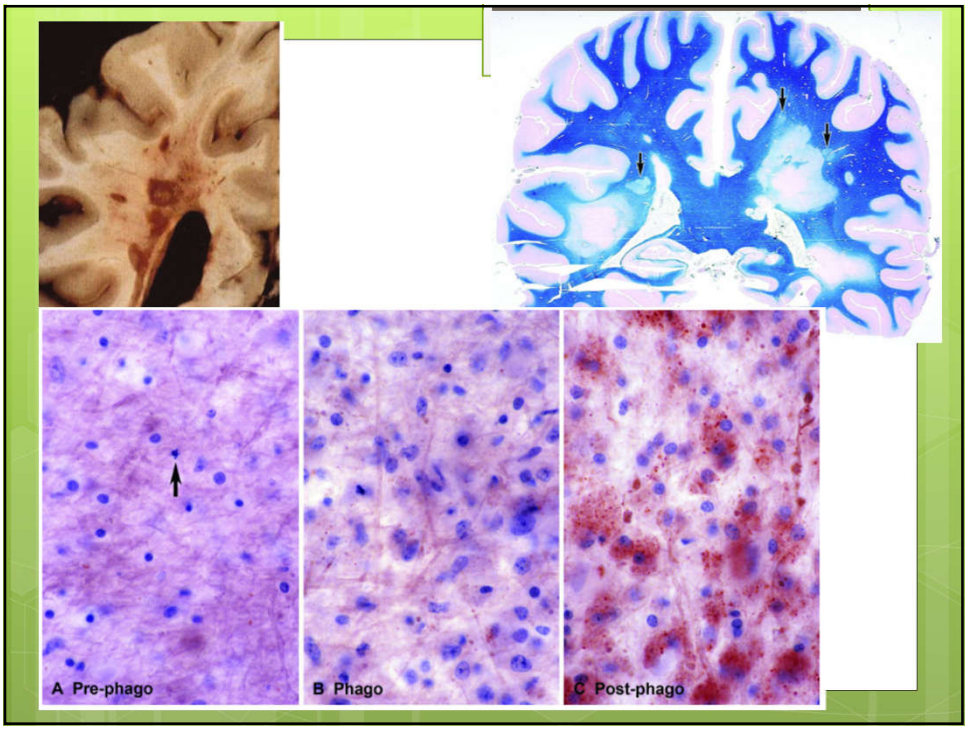
a) MS is an infectious disease
b) Children of PwMS have a 50% chance to get MS
c) MS is increasing in prevalence and incidence
d) Sun exposure can trigger MS
e) MS protects from other autoimmune diseases

What is MS ?

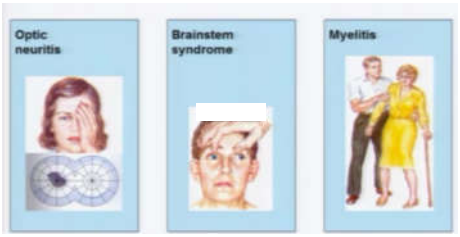
St. Lidwina of Schiedam




Carswell 1838


A Pre-phago
B Phago
C Post-phago

What are the first symptoms of MS? Clinically isolated syndromes (CIS) or First demyelinating events (FDE)



40% 20% 30%

10% presents with OTHER symptoms:

- Paroxysmal (stiffness, limb spasm)
- Bladder
- Cognitive
- Pseudo-radiculopathy or Trigeminal neuralgia

- Episodic Fatigue
- LHermittes (shock-like sensation when neck is flexed)
- Sexual dysfunction

CLINICAL SYMPTOMS OF MULTIPLE SCLEROSIS (MS)

- Fatigue
- Visual disturbances
  - Blurred vision, diplopia, nystagmus, red-green color dissociation
- Motor
  - Spasticity, paresis, dysarthria, spasms, ataxia, muscle weakness
- Sensory changes
  - Paraesthesia, neuralgia
- Cognitive deficits
  - Memory loss
- Bladder / bowel urgency and incontinence

Deficit reported	Presenting	During course
visual/oculomotor	49	100
paresis	42	88
paraesthesia	41	87
incoordination	23	82
urinary/bowel	10	63
cerebral	4	39

Uhtoff's phenomenon

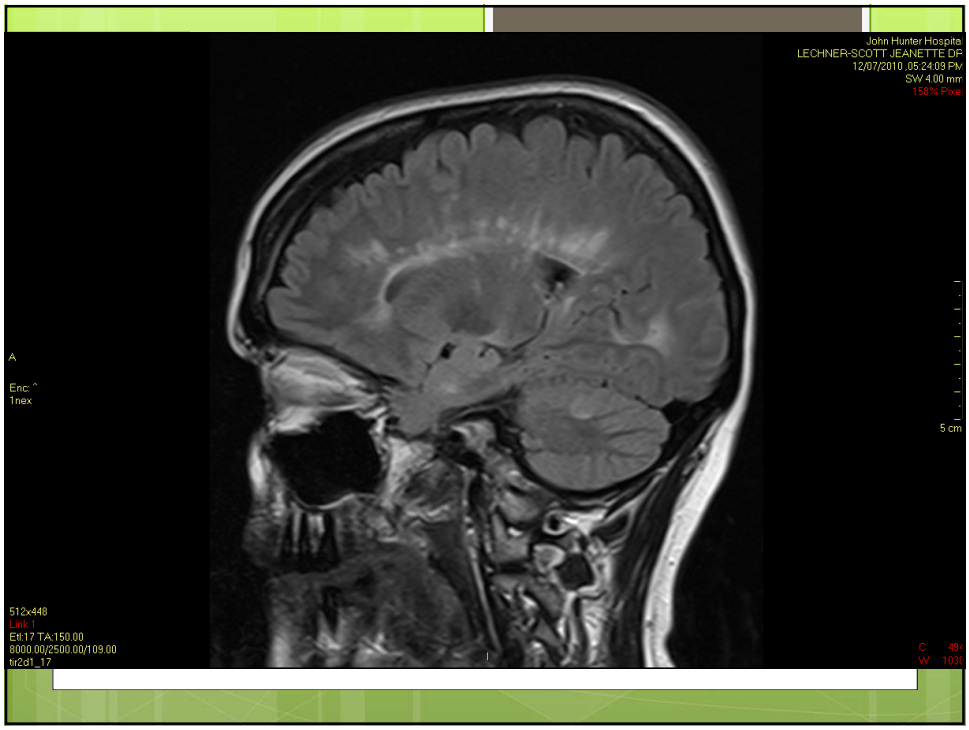
- Reversible and usually predictable decrements in physical (running walking reading etc) and cognitive (memory, thinking speed)
- Due to increased ambient body temperature and exercise
- Nerve conduction slowing and perhaps conduction block due to small (~0.5°C) increases in core temp

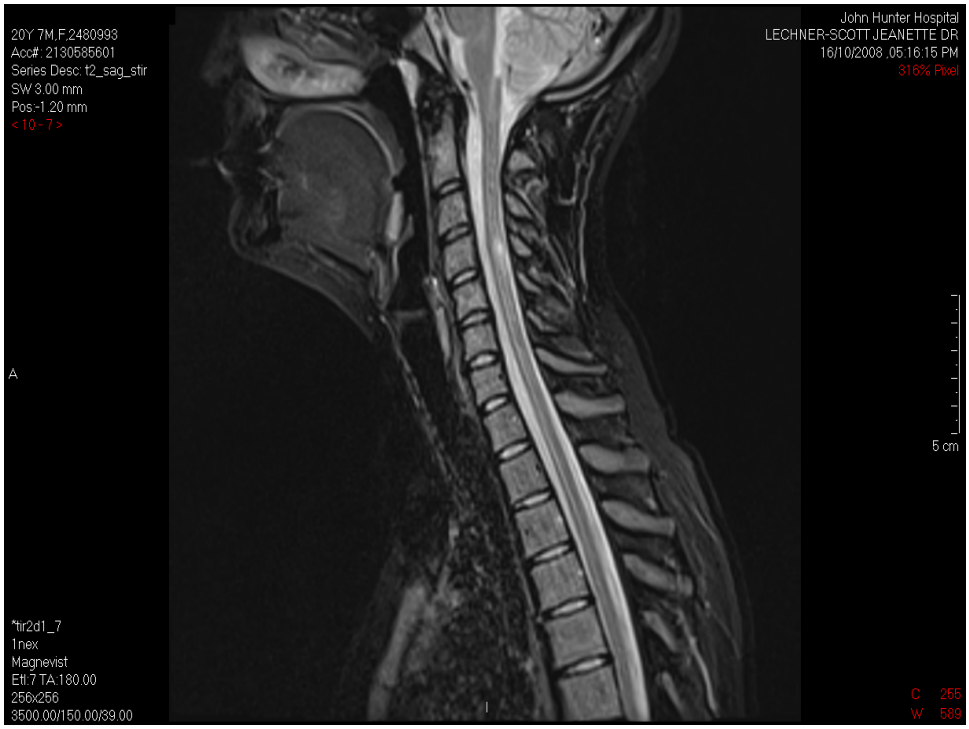
Pseudo-relapse – Uhthoff's phenomenon

- Reversible worsening of symptoms associated with increased body core temperature:
  - Fever
  - Vigorous exercise
  - Hot water baths / showers
  - Environmental heating

Question 2
Which statement is correct?

a) MS is a disease of modern society.
b) The symptoms depend on where the lesions are.
c) Bladder symptoms are unlikely to be due to MS.
d) A sudden onset of blindness is the most common presentation of optic neuritis.
e) Fatigue is not a characteristic symptom of relapse.

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John Hunter Hospital
LECHNER-SCOTT,JEANETTE DR
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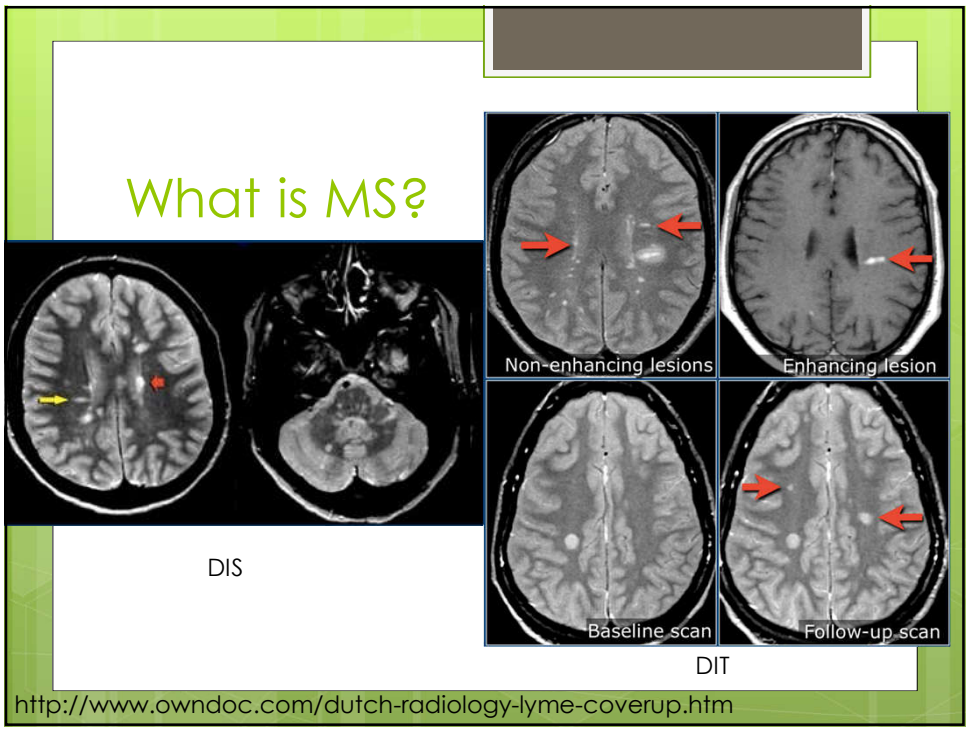
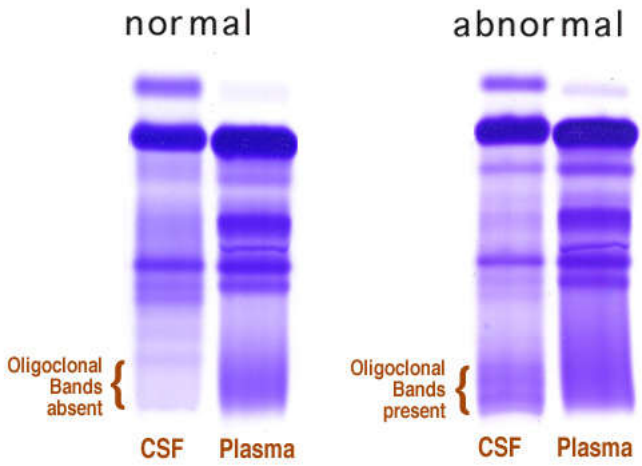
C 255
W 589

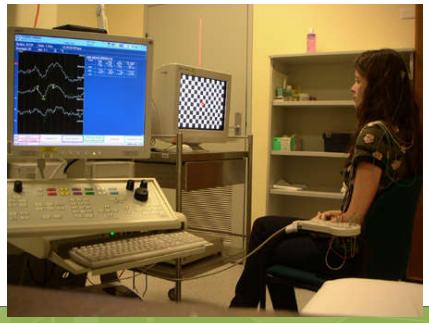

What is MS?
Non-enhancing lesions
Enhancing lesion
DIS
Baseline scan
Follow-up scan
DIT
http://www.owndoc.com/dutch-radiology-lyme-coverup.htm

Oligoclonal Bands in CSF



Visual Evoked Potentials (VEP)

- Stimulus presented to eyes
- Record electrical response from occipital lobe visual cortex
- Delay in response implies **demyelination** in the visual pathways
- Positive in 30% of patients after CIS, 50% after 2 attacks

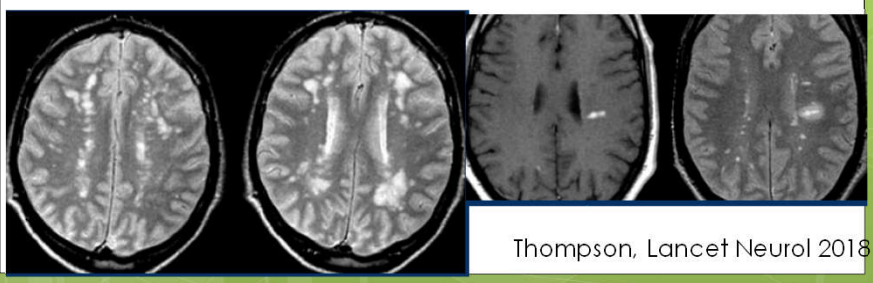


Doctor of Medicine

35

2017 MS diagnostic criteria

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶



Thompson, Lancet Neurol 2018

36

2017 MS diagnostic criteria

***Panel* 6: 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterised by progression from onset (primary progressive multiple sclerosis)**

Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

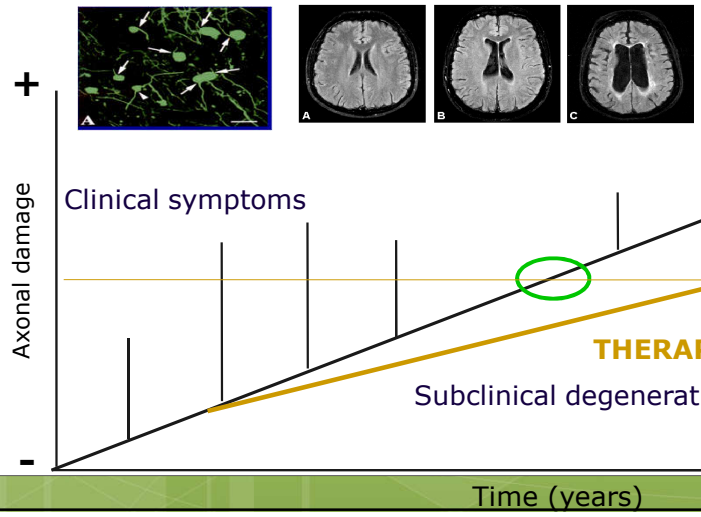
*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Thompson, Lancet Neurol 2018

Question 3
Which statement is not correct?

a) MRI is the major diagnostic tool for MS.
b) A lumbar puncture can confirm the diagnosis.
c) Evoked potentials can confirm dissemination in space.
d) You need to wait at least 6 months before the diagnosis of MS is confirmed.
e) Giving contrast for an MRI can help with dissemination in time.

Disease course



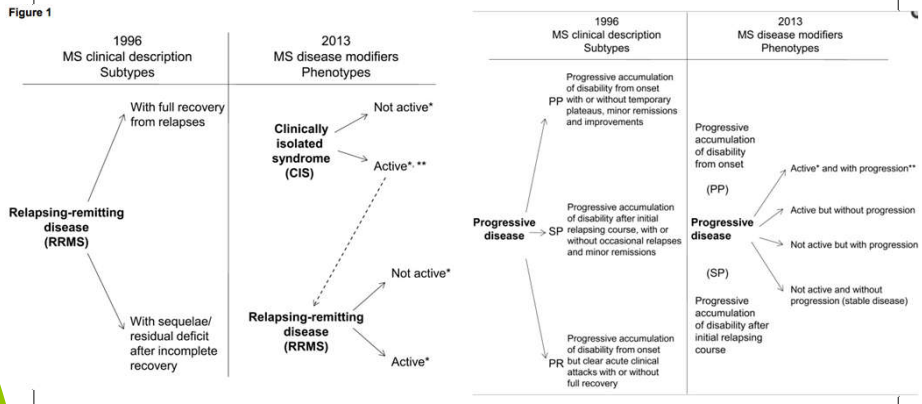
Prognosis

highly variable

40

Lublin criteria

Figure 1



Neurology. 2014 Jul 15;83(3):278-86

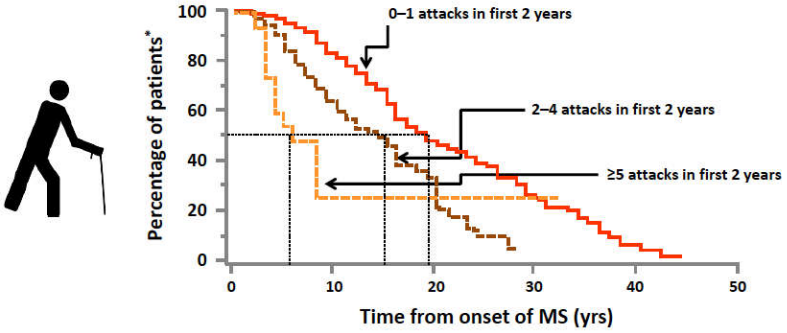
Brain (1989), 112, 1419–1428

THE NATURAL HISTORY OF MULTIPLE SCLEROSIS: A GEOGRAPHICALLY BASED STUDY

2. PREDICTIVE VALUE OF THE EARLY CLINICAL COURSE

by B. G. WEINSHENKER, B. BASS, G. P. A. RICE, J. NOSEWORTHY, W. CARRIERE, J. BASKERVILLE *and* G. C. EBERS

(From the Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada)



* The percentage of patients not having reached DSS 6 is shown after stratification according to the number of attacks in the first 2 years from onset of MS.
The difference between the groups is significant ($P < 0.0001$).
Patients with chronically progressive MS were excluded.

Weinshenker BG, *et al. Brain* 1989; 112:1419–1428

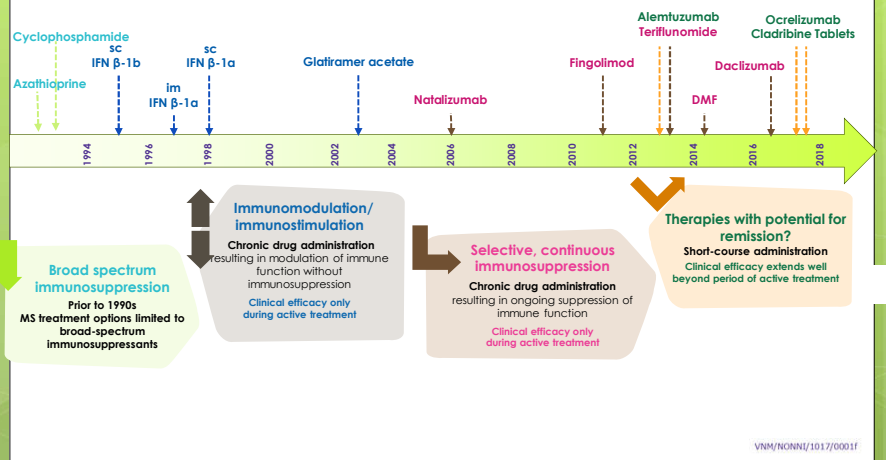
Predictor	Cox proportional hazard model	
	SDP1	
	HR	*p*
At baseline		
Clinical		
EDSS	1.32	0.023
Number of relapses before baseline	0.94	0.37
MRI		
Number of T2 lesions	1.01	**<0.001**
T1 lesion volume	1.19	**<0.001**
T2 lesion volume	1.03	**<0.001**
Brain parenchymal fraction	0.90	0.047
GM fraction	0.99	0.058
WM fraction	0.99	0.031
Thalamic fraction	0.73	**<0.001**
Corpus callosum fraction	0.52	**0.004**
At 12 months		
Clinical		
Number of new relapses before 12 months (0, 1, or >1)	1.31	0.027
EDSS	1.64	**<0.001**
EDSS change	2.13	**<0.001**
MRI		
Number of new or enlarging T2 lesions	1.03	**0.005**
T1 lesion volume absolute change	1.53	0.055
T2 lesion volume absolute change	1.04	0.54
Whole brain volume % change	0.87	0.16
GM volume % change	0.97	0.33
WM volume % change	1.02	0.59
Thalamus volume % change	1.00	0.93
Corpus callosum volume % change	0.91	**<0.001**

Predictors of progression

- Disability at baseline
- Brain atrophy
- Number of new lesions

Uher, Mult Scl January 2017

Most drugs rely on continuous administration with continuous immunosuppression or immunomodulation to treat MS



DMF, dimethyl fumarate; IFN, interferon; im, intramuscular; sc, subcutaneous

Disease modifying treatment

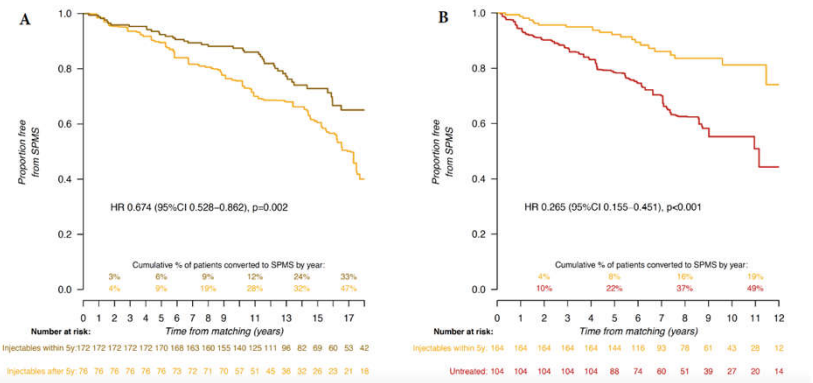
"I'D PREFER NOT TO RECOMMEND ANYTHING, M'SIEUR -- IT'S YOUR LIFE."

ESCALATE

- Escalation vs Induction debate
  - Pro Induction
    - Best evidence of high efficacy DMT in early inflammatory disease
  - Contra Induction
    - No de-escalation strategy
      - Rebound from Natalizumab and Fingolimod
      - High risk profile
      - Long term effect/ risk of interval therapy (Alemtuzumab/ Cladribine)
      - Benign MS

Brown W et al.

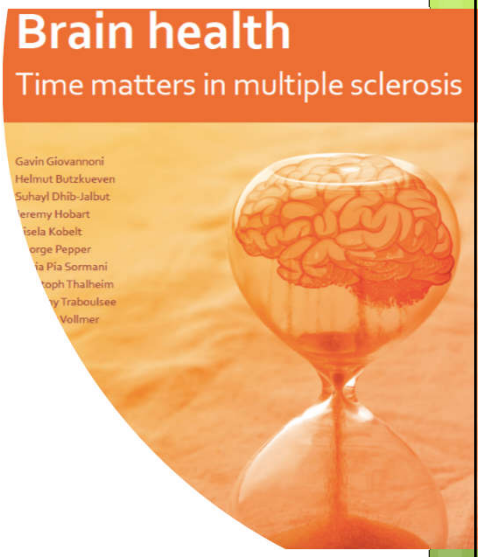
MSBase Neuro-Immunology Registry



What can be done?

EARLY DIAGNOSIS

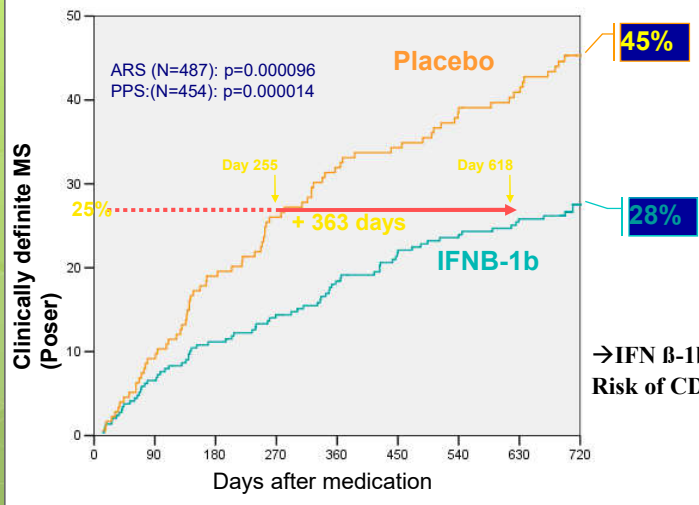
EARLY ACCESS TO EFFECTIVE THERAPY



Injectables

- Betaferon
- Rebif
- Avonex
- Copaxone od/ 2nd daily
- Plegridy

BENEFIT Trial (2005) – Time to CDMS



→IFN ß-1b reduces Risk of CDMS by 50%

Kappos et al., Neurolgy 2005

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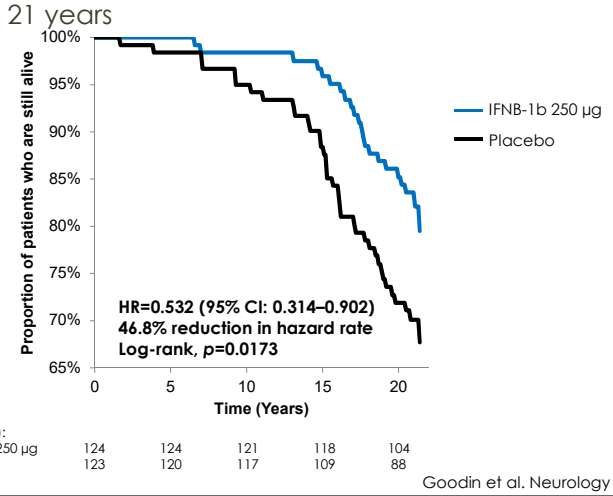
Time from Study Randomisation to Death

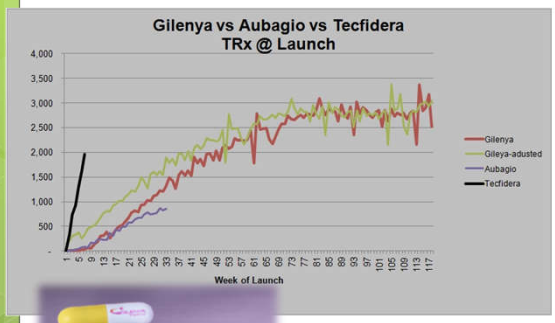
Early treatment with Betaferon 250µg compared with initial placebo treatment was associated with a 46.8% reduction in the risk of death at 21 years

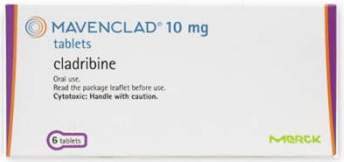


At risk (n):					
IFNB-1b 250 µg	124	124	121	118	104
Placebo	123	120	117	109	88

Goodin et al. Neurology 2012

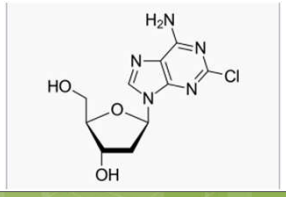
Oral medication





Cladribine

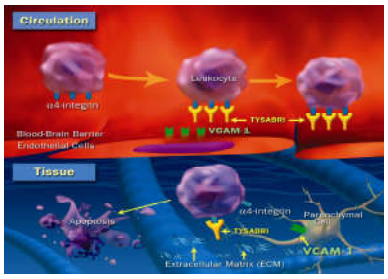
- Month one
  - Oral tbl weight adjusted for 5d
- Month two
  - Oral tbl weight adjusted

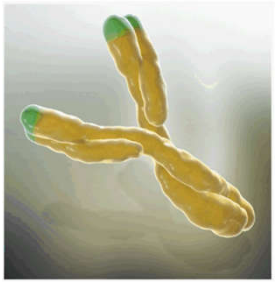


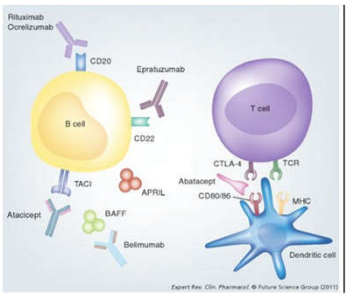
- Long lasting effect for minimum of 4 y
- Well tolerated
- Crosses BBB
- Irreversible effect

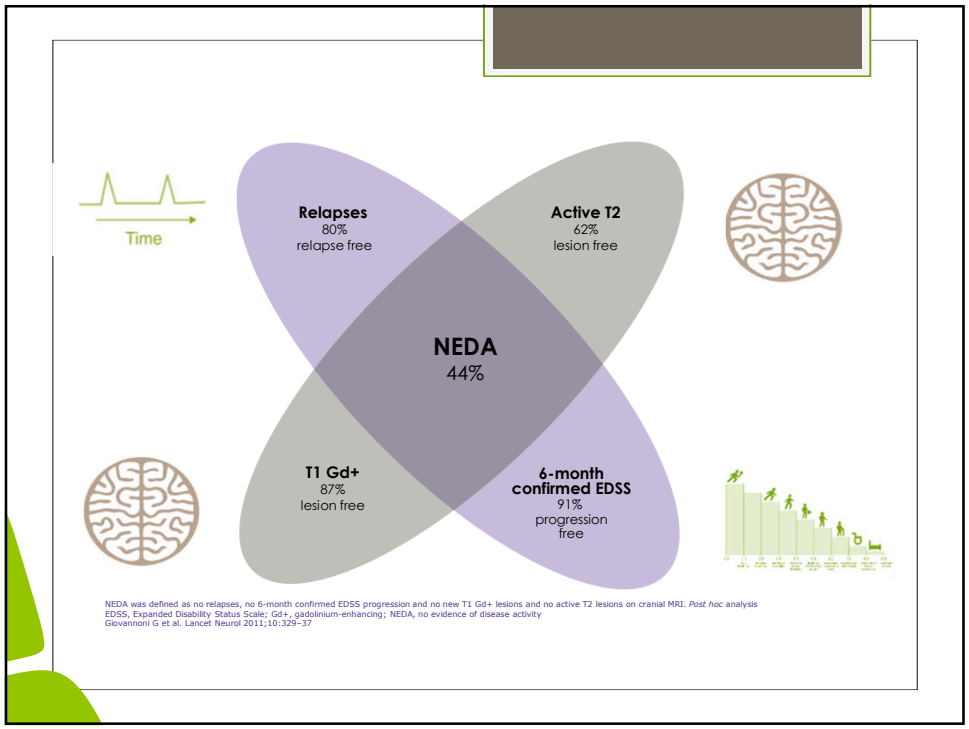
Infusions

- Natalizumab
- Alemtuzumab
- Ocrelizumab

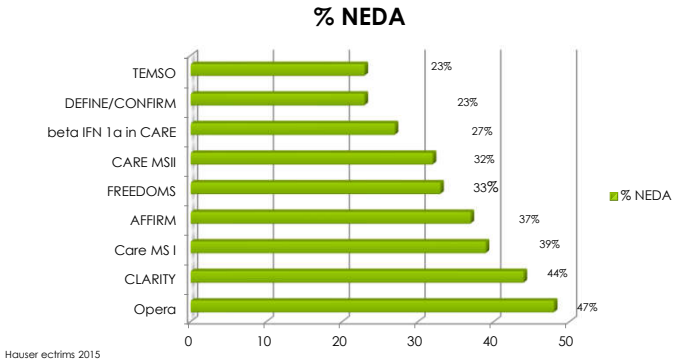




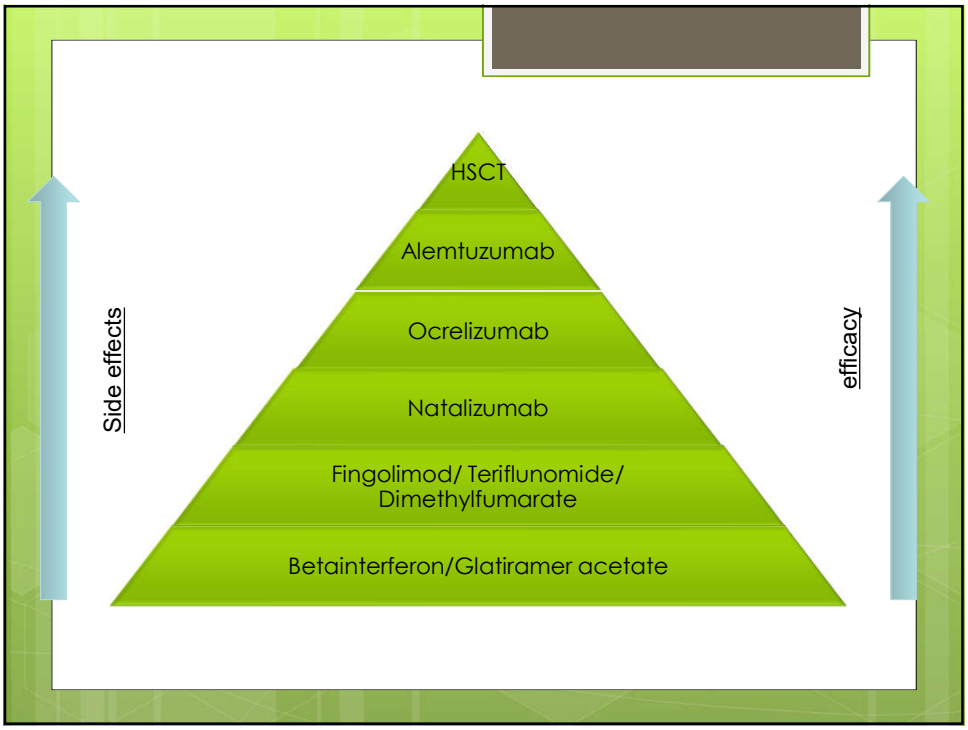


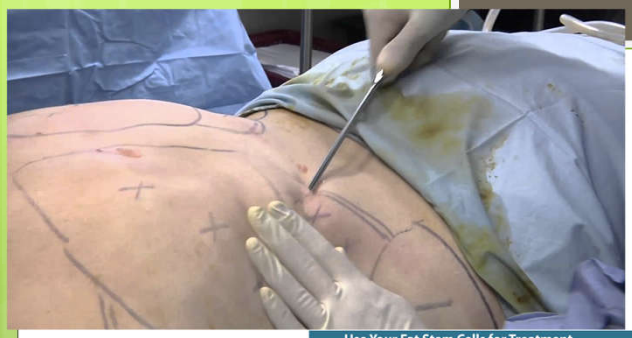

Time
Relapses
80%
relapse free
Active T2
62%
lesion free
NEDA
44%
T1 Gd+
87%
lesion free
6-month
confirmed EDSS
91%
progression
free
NEDA was defined as no relapses, no 6-month confirmed EDSS progression and no new T1 Gd+ lesions and no active T2 lesions on cranial MRI. Post hoc analysis
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; NEDA, no evidence of disease activity
Giovannoni G et al. Lancet Neurol 2011;10:329–37

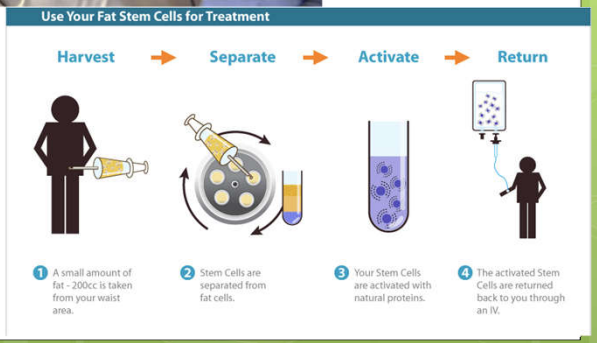
Comparison of NEDA outcome over 2 years



Hauser ectrims 2015
Giovannoni, Lancet Neurology 2011
Nixon, Adv Therap 2014;31:1134
Havdrova, Lancet Neurol 2009
Havdrova, Therp Adv Neurol Dis 2014



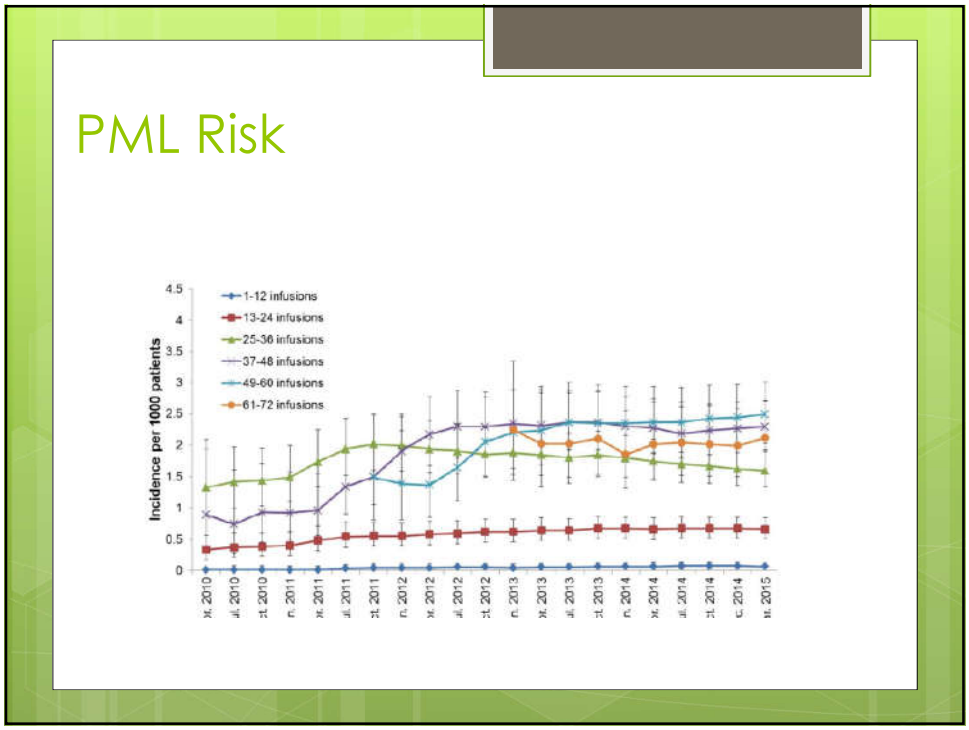




Question 4
Which statement is correct?

a) Stem cell therapy is effective in all MS types.
b) Treatment decisions need to be made for each patient individually according to their risk and benefit ratio.
c) You should always start with injectables first.
d) Infusions are the safest therapy.


Infusion related side-effects
Cytokine release syndrome
Rash
Headache
Transient worsening of neurological deficit
Chest tightness
SEPSIS KILLS
RECOGNISE • RESUSCITATE • REFER
1
2
3
4


PML Risk
Incidence per 1000 patients
1-12 infusions
13-24 infusions
25-36 infusions
37-48 infusions
49-60 infusions
61-72 infusions
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5

Serious side effects with Alemtuzumab

Identified Risk		Rate in Alemtuzumab-Treated Patients	Notes
ITP	Autoimmune Events	~1% (1 fatality prior to implementation of monitoring program)[1]	• Onset generally occurred 14-36 mo after first exposure[1] • Most cases responded to first-line medical therapy[1]
Nephropathies	Autoimmune Events	0.3% (anti-GBM n=2)[1]	• Generally occurred within 39 mo after last administration[1] • Responded to timely medical treatment and did not develop permanent kidney failure[2]
Thyroid disorders (Hypo-/hyper-)	Autoimmune Events	~36%[a] (serious, 1%)[1]	• Onset occurred 6-61 mo after first Alemtuzumab exposure; peaked in year 3 and declined thereafter[3] • Most mild to moderate, most managed with conventional medical therapy, however, some patients required surgical intervention[1] • Higher incidence in patients with history of thyroid disorders[1]
IARs		>90% (serious, 3%)[1]	• Occurred within 24 h of Alemtuzumab administration[1] • Most mild to moderate; rarely led to treatment discontinuation[1] • May be caused by cytokine release following mAb-mediated cell lysis[1]
Infections		71% (serious, 2.7%)[1]	• Incidence highest during first mo after infusion; rate decreased over time[2] • More common with Alemtuzumab; mostly mild to moderate[1] • Generally of typical duration; resolved following conventional medical treatment[1]

[a]Through 48 mo after first exposure.
ITP, immune thrombocytopenia; **GBM**, glomerular basement membrane; **mAb**, monoclonal antibody.

1. Alemtuzumab Summary of Product Characteristics. Oxford, UK: Genzyme Therapeutics, Ltd; 2013; 2. Wynn D, et al. Presented at: European Committee for Treatment and Research in Multiple Sclerosis; 2013; Copenhagen; P597; 3. Coles AJ, et al. *Neurology*. 2012;78:1069-1078.

Life style recommendations

- Baseline
  - FBC, UEC, LFT
  - HSV, HIV, VZV, CMV, Hepatitis, EBV, Quantiferon Gold, JCV-Ab, Measles, Mumps
  - MRI
  - ECG and OCT for Fingolimod
  - TSH, TPO for Alemtuzumab
  - Urine analysis for Alemtuzumab and Dimethylfumarate
- Follow up
  - 3 month post start OCT for Fingolimod (cave new medication)
  - Monthly FBC, UEC, LFT, TSH, TPO and urine analysis for Alemtuzumab (for 5 years after last infusion) and Teriflunomide
  - 6 monthly JCV-Ab
  - Yearly MRI
    - If JCV positive 6 monthly
  - Yearly dermatology review +/- PAP smear

Life style recommendations Diet

- Roy Swank 1948
  - Low polysaturated fats
- Terry Wahl
  - Raw foods, berry, fruits Paleo diet
  - Rich in nutrients for mitochondria
    - animal-based omega-3 fats, creatine, and coenzymeQ10, while your myelin needs vitamins B1, B9, B12, omega-3, and iodine
- Vitamin D

Cochrane Database Syst Rev. 2012 Dec 12http://www.msra.org.au/prevanz
Jagannath VA, Filippini G, Di Pietrantonj C, Asokan GV, Robak EW, Whamond L, Robinson SA. Vitamin D for the management of multiple sclerosis. Cochrane Database of Systematic Reviews. 2018(9).

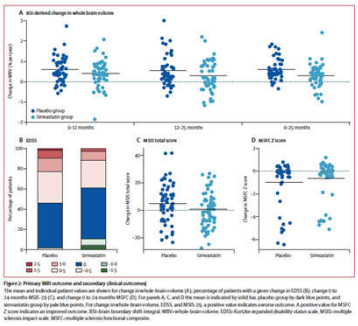
Life style recommendations Diet

- 63% of PwMS in Australia take supplements
- 41% of PwMS in Germany are on modified diets
- Evidence of impact on disease outcome is limited
- Proven benefit on weight reduction and well being

PLoS One. 2016; 11(10): e0165246
ASN Neuro. 2015 Feb 18;7(1)

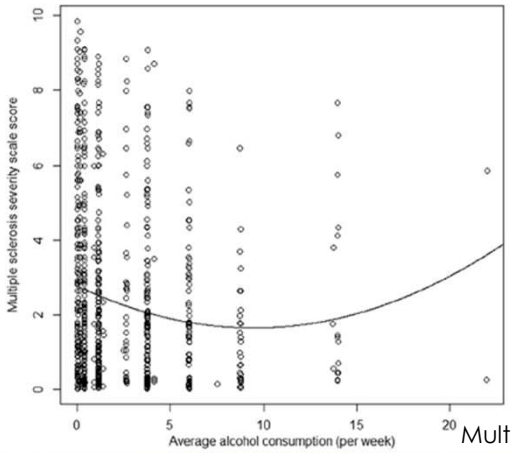
Life style recommendations

- High cholesterol associated with progression of disease.
- Simvastation 80mg associated with reduction in brain atrophy rate but not relapses or lesion load
- Positive effect on cognitive function



Chataway J Lancet. 2014 Jun 28;383(9936):2213-21
Gafson ARSci Rep. 2018; 8: 17026.
Chan D Lancet Neurol. 2017 Aug;16(8):591-600

Life style recommendations Alcohol



Mult Scl Rel Dis 2017; 47-53

Life style recommendations

Predictors of median 10-year EDSS change, n=2,466

	Unadjusted models		#Adjusted model	
Predictor	β coefficient (95% CI)	p-value	β coefficient (95% CI)	p-value
Gender				
Female	Reference	-	Reference	-
Male	0.00 (-0.20., 0.20)	0.999	0.14 (-0.02, 0.31)	0.089
Age at onset (10 year units)	0.00 (-0.10, 0.10)	0.999	0.41 (0.32, 0.50)	$5.8x10^{-18}$
Disease duration at baseline (5 year units)	0.16 (0.10, 0.23)	$9.7x10^{-7}$	0.36 (0.29, 0.43)	$1.8x10^{-23}$
Post-baseline relapses (ARR in first 10 years of follow-up)	1.11 (0.87, 1.35)	$4.1x10^{-19}$	1.14 (0.91, 1.37)	$1.9x10^{-22}$
Cumulative exposure to IFNβ/GA therapy	-0.73 (-1.03, -0.43)	$1.8x10^{-6}$	-0.86 (-1.13, -0.58)	$1.3x10^{-9}$
Number of pregnancies during follow-up				
Male	Excluded	-	Excluded	-
0	Reference	-	Reference	-
≥1	-0.50 (-2.18, 1.18)	0.560	-0.36 (-0.62, -0.09)	0.009

Quantile median regression analysis.
#Adjusted modelling included adjustments for first DMT identity, baseline EDSS score and country.
EDSS Expanded disability status scale; CI Confidence Interval; DMT Disease Modifying Therapy; ARR Annualised Relapse Rate

Jokubaitis et al., Annals of Neurology, May 2016

DMTs before pregnancy

- MSBase 893 pregnancies

Table 4. Factors predictive of relapse occurring in the first 3 months of the postpartum period. CI: confidence interval.

Variable	Unadjusted odds ratio (95% CI), p value	Adjusted odds ratio[a] (95% CI), p value
Age at onset of MS	1.00 (0.97, 1.04), 0.873	1.01 (0.96, 1.08), 0.594
Duration of MS at conception	1.00 (0.96, 1.04), 0.934	1.04 (0.98, 1.11), 0.199
ARR in 2 years pre-conception	13.39 (8.83, 20.32), <0.001	14.12 (9.09, 21.93), <0.001
ARR during pregnancy	1.71 (1.25, 2.34), 0.001	[b]
EDSS at conception		
<2.0	1.00	1.00
≥2.0	2.99 (1.75, 5.12), <0.001	1.10 (0.52, 2.33), 0.813
DMT use 2 years pre-conception		
No	1.00	1.00
Yes	0.55 (0.36, 0.84), 0.006	0.55 (0.32, 0.96), 0.034

[a]Hosmer and Lemeshow Goodness of Fit Test = 1.000.
[b]When ARR during pregnancy was included, the Hosmer and Lemeshow Goodness of Fit Test demonstrated a poor fit, and this covariate was therefore omitted from the model shown.

Hughes S et al Mult Scler 20,739-746.

Will my MS affect pregnancy outcome?

- Babies born from MS mothers are slightly smaller for gestational age by weight
- There is no difference in Apgar scores in babies of MS mothers
- There may be a slightly increased rate of operative deliveries in MS patients
- There is no increase in birth defects, perinatal mortality, or other adverse fetal outcomes.

Hellwig et al. Acta Neurol Scand 2008, 118 (1):24-28; Chen et al., Mult Scler. 2009; 15(5):606-612; Hellwig, J Neurol 2009, 256(5):830-831

Breastfeeding

One can prevent post-partum MS relapses by exclusive breast feeding: No
Sandra Vukusic and Christian Confavreux
Mult Scler 2013 19: 1565
DOI: 10.1177/1352458513503054

One can prevent post-partum MS relapses by exclusive breast feeding: Yes
Annette Langer-Gould and Kerstin Hellwig
Mult Scler 2013 19: 1567
DOI: 10.1177/1352458513505161

Answers to frequently asked questions
Symptom management

- Symptom relief
  - Spasticity
    - Fampridine
    - Cannabis
    - Botox
    - Intrathecal Baclofen
  - Bladder
    - Post void bladder scan
    - Oxybutinin/ Solifenacin
    - Botox
  - Fatigue
    - Physical exercise
    - Sleep regulation
    - Amantadine/Modafinil
  - Cognition
    - Treat depression/anxiety
    - Mental exercise

http://www.nationalmssociety.org/

Question 5
Which statement is correct?

a) If I have Alemtuzumab, I don't need to see my doctor any more.
b) Natalizumab has the highest risk of PML infection.
c) To prevent my MS from getting worse I need to go on a vegan diet.
d) Once diagnosed with MS you should not have any babies.

MSL Services

Multiple Sclerosis Limited

MSL Services - MS Practice

MS Practice is a free, online education series designed to support allied health professionals in the symptom management of people with MS.

https://www.msaustralia.org.au/about-ms/ms-practice

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- Support Coordination/Connection – assistance to help make your plan active (All areas)
- Short term accommodation (Vic)
- Community Participation (NSW)
- Exercise physiology and personal training (NSW)
- Specialist Continence Assessment (NSW and Vic)
- Physiotherapy and Occupational Therapy (NSW and Vic)

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1800 042 138

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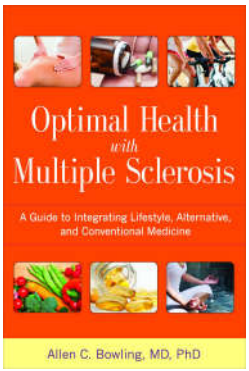

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