How to treat: IgM related Disorders

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Belangenverklaring

In overeenstemming met de regels van de Inspectie van de Gezondheidszorg (IGZ)

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Organisatie: Amsterdam UMC, locatie AMC

☑☐ Ik heb geen 'potentiële' belangenverstrengeling

☑☐ Ik heb de volgende mogelijke belangenverstrengelingen:

Type van verstrengeling / financieel belang	Naam van commercieel bedrijf
Ontvangst van subsidie(s)/research ondersteuning:	
Ontvangst van honoraria of adviseursfee:	
Lid van een commercieel gesponsord ‘speakersbureau’:	
Financiële belangen in een bedrijf (aandelen of opties):	
Andere ondersteuning (gelieve te specificeren):	
Wetenschappelijke adviesraad:	

MGUS: 42th year anniversary

Monoclonal Gammopathy of **Undetermined** Significance

Kyle, Robert A

The American Journal of Medicine , Volume 64 , Issue 5 , 814 – 826, ***1978***

What if it *is* significant: coining concepts

- **- IgM related disorders**
- (Owen et al 2003)

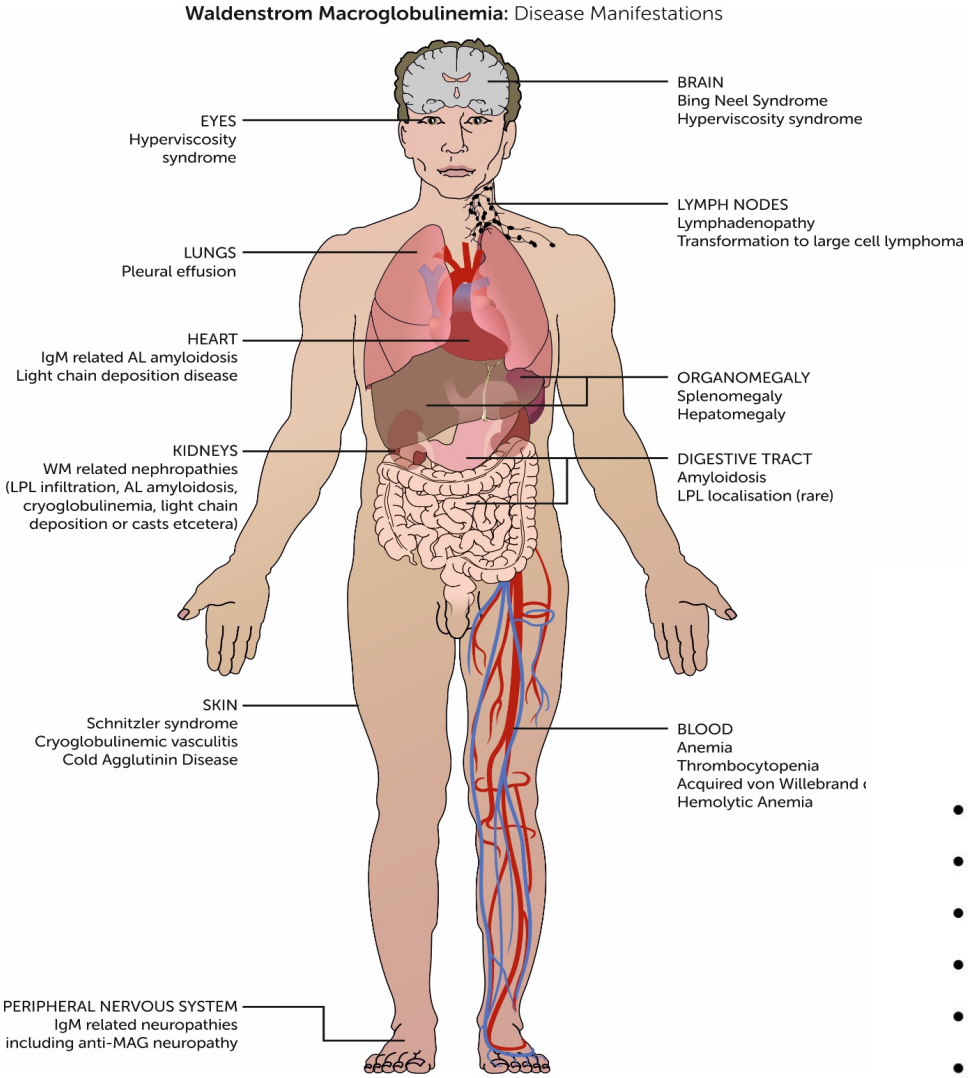
- - **Dangerous** small clones
- (Merlini, 2006)

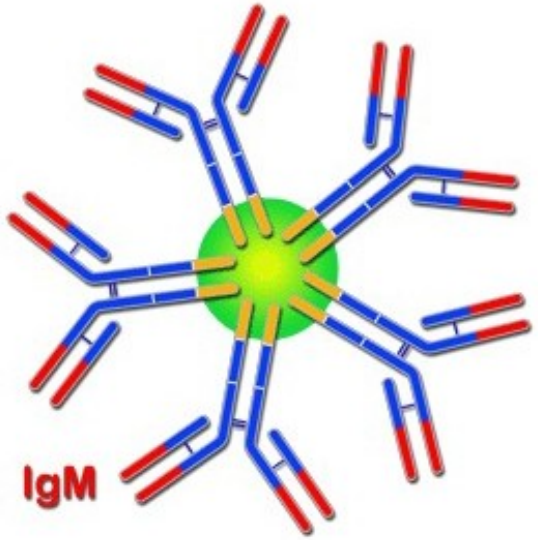
- - Monoclonal gammopathy of **renal** significance (MGRS)
- (Leung et al 2012)

- - Monoclonal gammopathy of clinical significance (MGCS)
  (Fermand et al 2018)

Zooming in on IgM paraproteins

- MGUS prevalence: ±3% in individuals > 50 yrs
- 15% = IgM MGUS





Biological Functions of IgM

- Good at virus neutralization
- Poor at toxin neutralization
- Excellent at bactericidal activity
- Excellent at causing agglutination of antigens
- Excellent at causing precipitation of antigens
- Excellent at complement fixation

Diagnosis?

- IgM paraproteinemia 15 g/L , discovered coincedentally
- Asymptomatic
- Bonemarrow: 8% infiltration monoclonal LPL cells

1) MGUS
2) Smouldering Waldenstrom's Macroglobulinemia

New Dutch WM guideline

	IgM MGUS	Asymptomatische M. Waldenström	Symptomatische MW	IgM gerelateerde ziekte
IgM M-proteïne (serum)	Ja, ≤ 30 g/L	Ja	Ja	Ja, ≤ 30 g/L
Lymfoplasmocytair infiltraat (Beenmerg)	≤ 10%	Ja	Ja	≤ 10%
WM gerelateerde klinische verschijnselen	Nee	Nee	Ja	Ja
Beleid	Follow up	Wait and see	Behandeling	Mogelijk behandelen
Kans op progressie naar MW	1.5% per jaar	50-60% na 5 jaar	n.v.t.	onbekend

WHO 2017 criteria versus IWMM criteria for IgM MGUS

WHO 2017:

- Serum IgM monoclonal protein less than 3 gm/dL
- Bone marrow lymphoplasmacytic infiltration less than 10%
- No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder

(>10%: Waldenstrom's Macroglobulinaemia)

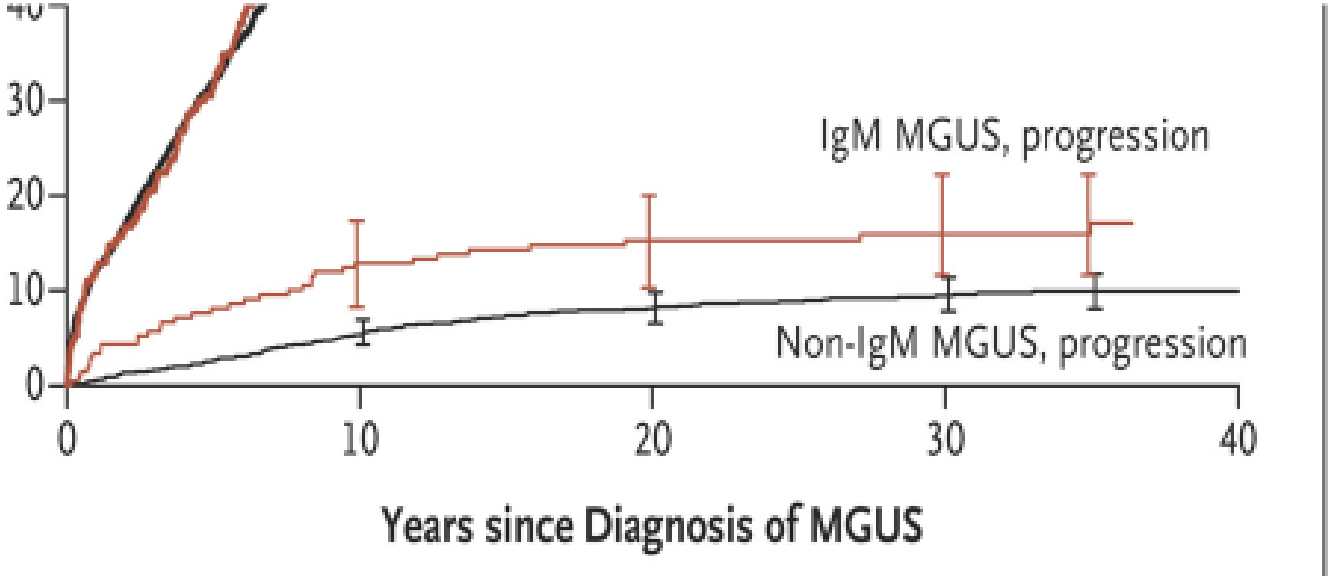
Owen et al IWMM-2 (2003) :

"IgM paraproteinemia of *any level* without *equivocal* BM infiltration and the absence of related symptoms"

(Any bonemarrow infiltration: Waldenstrom's Macroglobulinaemia)

Kyle data

- < 10% BM infiltration = Mayo = WHO definition
- IgM paraproteinemia < 3 g/dL and BM infiltration < 10% = good prognosis
- Proposed definition for new WM guideline
- Incidence of IgM related Disorders: unknown



IgM related Disorders: Pathophysiology

- **Deposition** of all or part of the IgM as aggregates, amorphous, crystalline, microtubular, or fibrillar forms
- **Autoantibody** activity against a tissue antigen
- **Physicochemical** properties of the IgM
- Formation of **immune complexes**
- **Complement activation**
- **Cytokine secretion**
- Unknown

IgM related disorders: “symptomatic MGUS”

- IgM related neuropathy – > 6 varieties, anti-MAG PN most common
- Cryoglobulinemia: type 1 & type 2
- Cold agglutinin Disease / Auto Immune hemolytic anemia
- Auto-Immune thrombocytopenia
- Nefropathy (MGRS, > 10 varieties)
- IgM related AL Amyloidosis
- Schnitzler syndrome
- Acquired van Willebrand syndrome

Gelukkig zijn we allemaal internist: breed blijven denken !

IgM related Polyneuropathy: epidemiology

PNP: 5% in IgG, 15% in IgA and **up to 30–50% in IgM MGUS** (?)

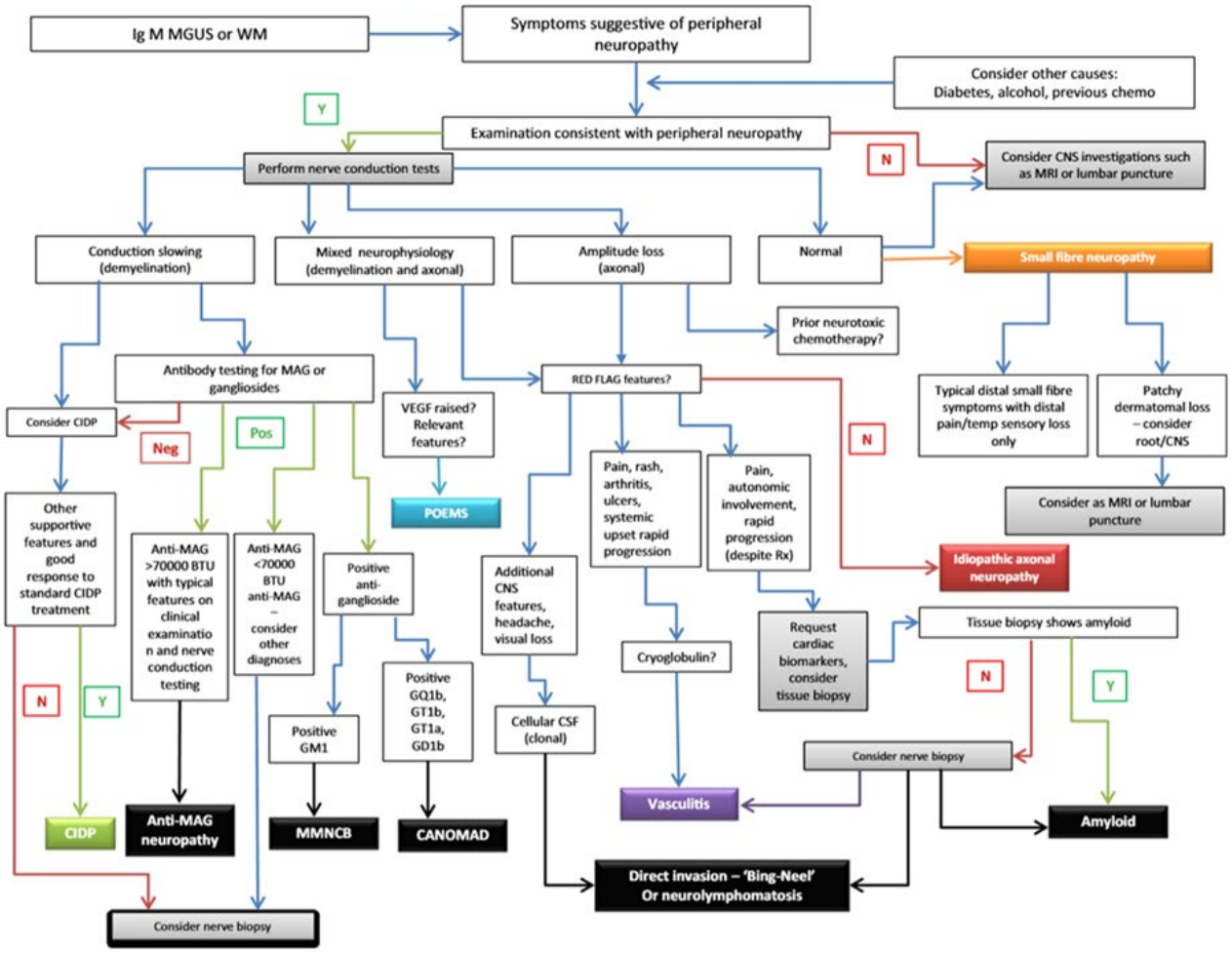
MGUS: **1%-8%** of population aged 50-90 yrs

PN: **2,4%,- 8,0%** (elderly)

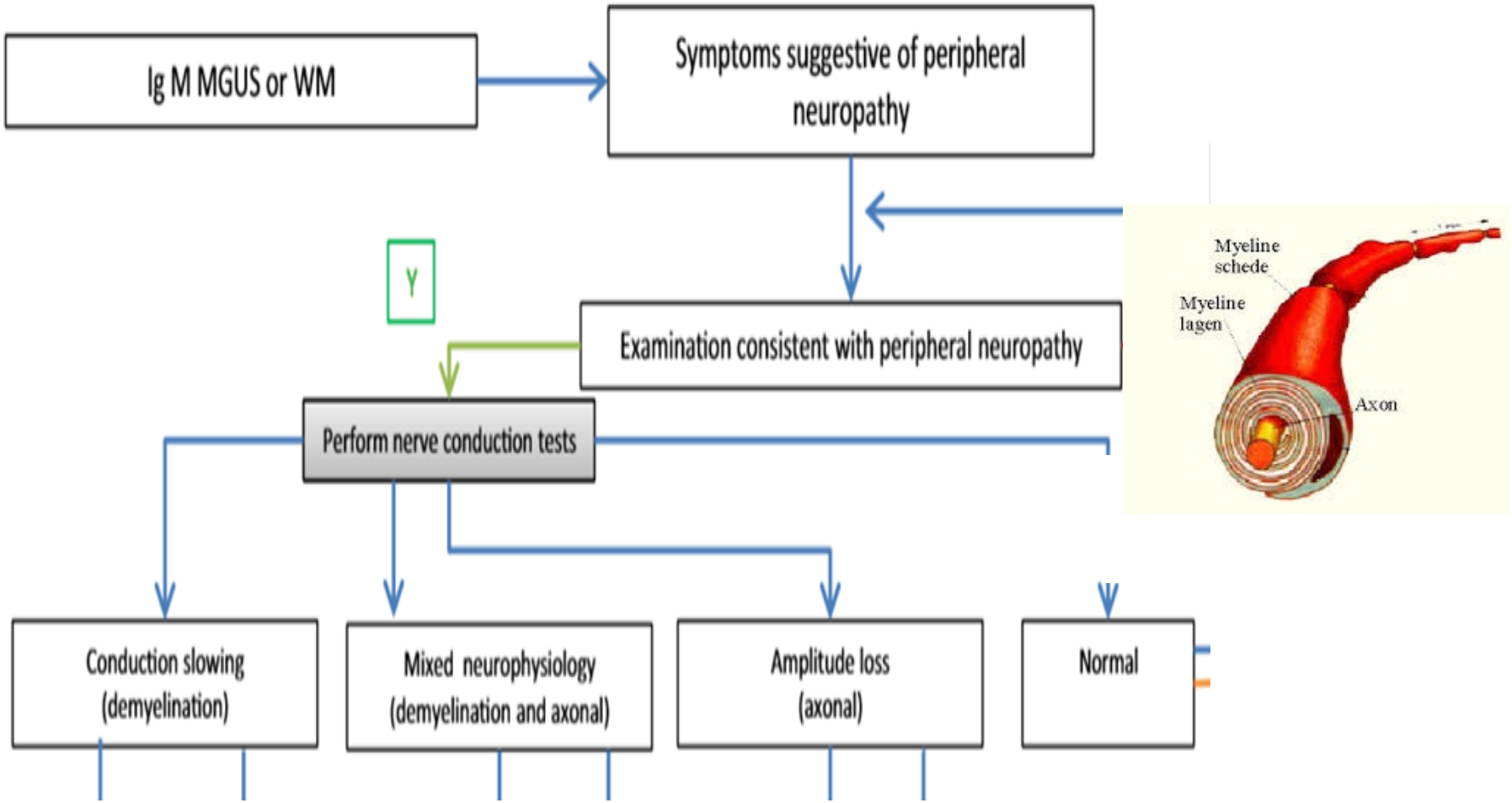
"A frequent challenge when two such conditions coexist is to relate a causative role of the MGUS versus coincidental association."

D'sa et al BJH 2017

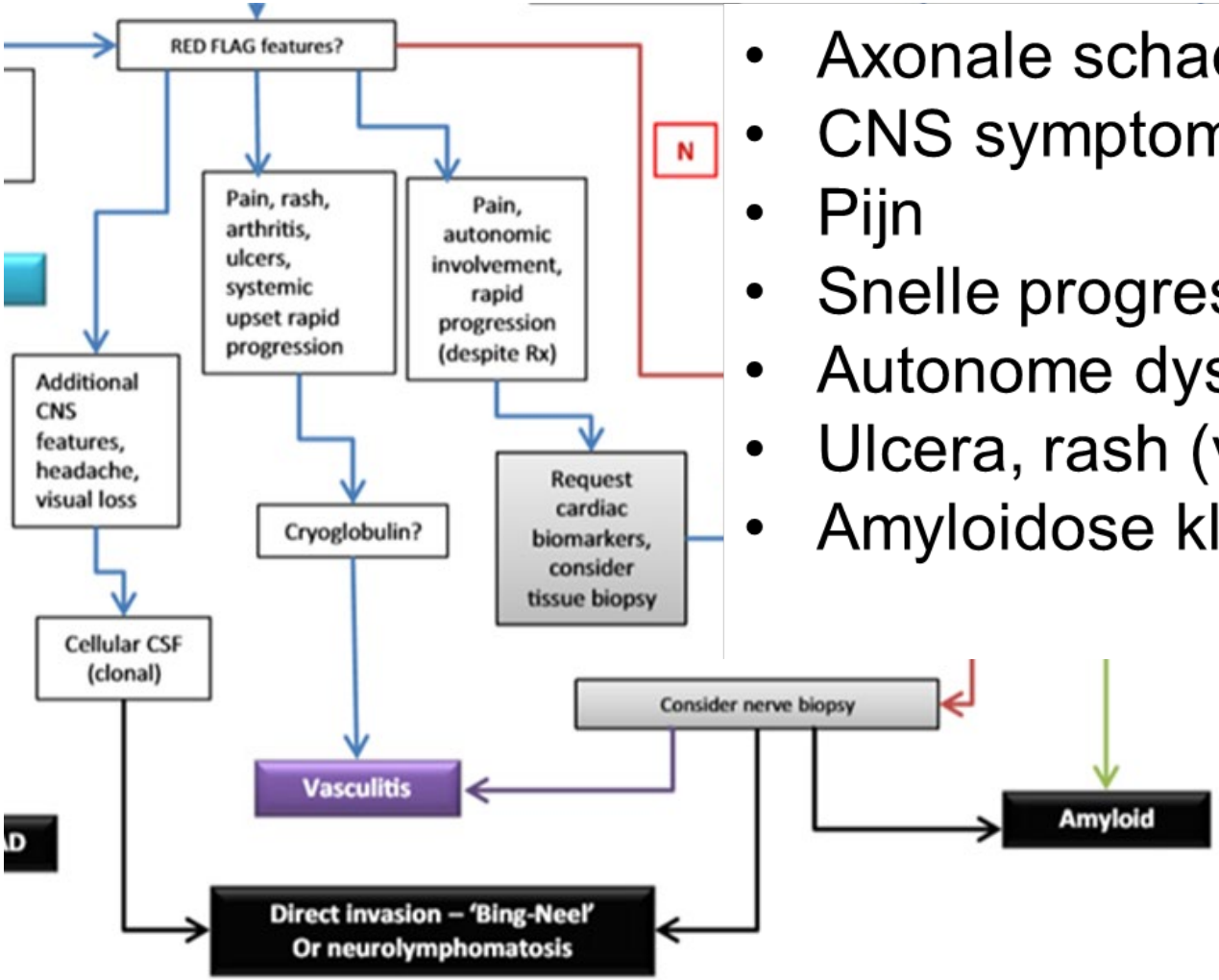
Diagnostisch stroomschema



Evaluatie: samen met neuroloog

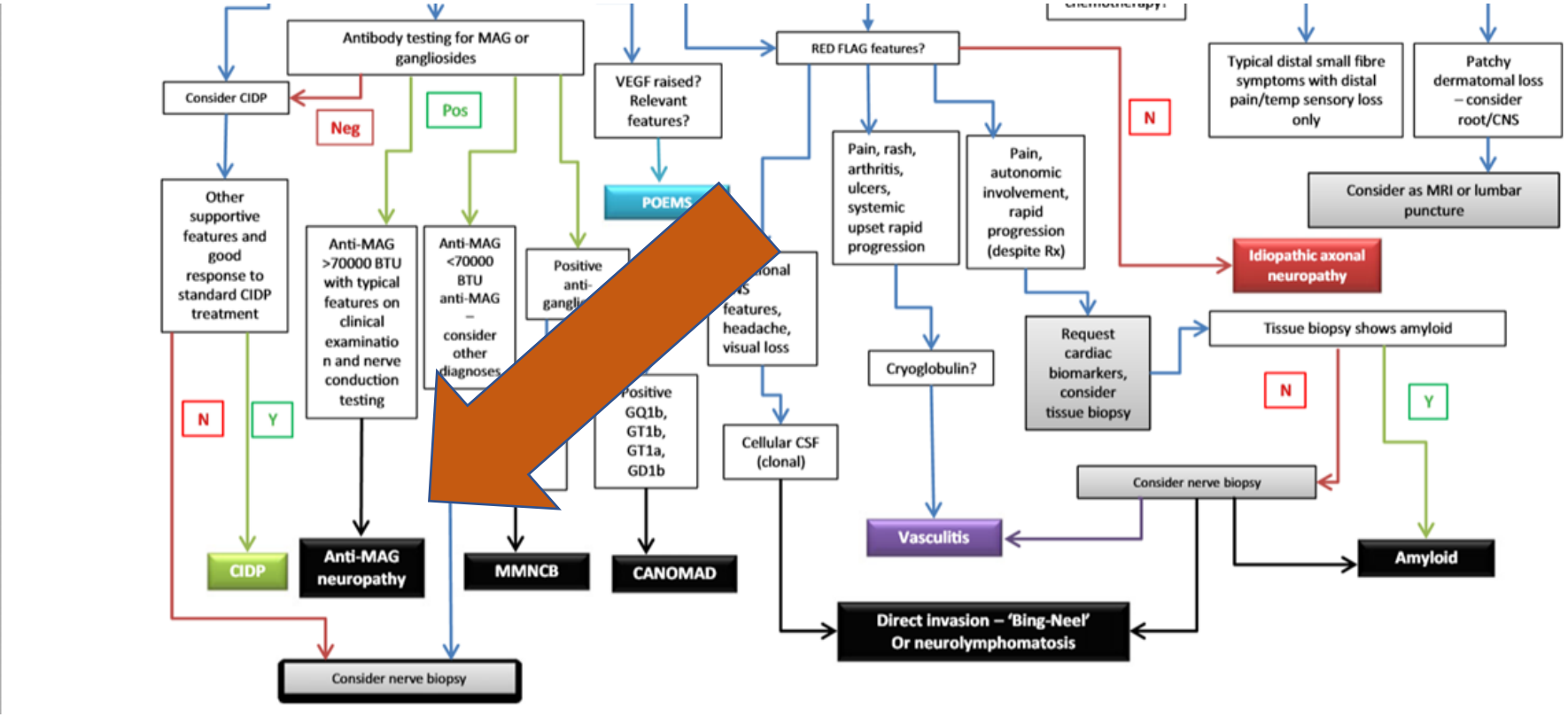


Red flags



- Axonale schade
- CNS symptomen
- Pijn
- Snelle progressie
- Autonome dysfunctie
- Ulcera, rash (vasculitis)
- Amyloidose kliniek

Most prevalent type: anti-MAG PN



Anti-MAG PNP: behandeling

- Treatment not always/ often not necessary
- If WM (rare): treat as WM
- If IgM MGUS:

➢ IVIG: only short term effect
➢ R-chemo: for aggressive, rapidly progressive cases
➢ Steroids: not effective
➢ For most cases: Rituximab

Anti-MAG PNP: Rituximab

- Cochrane meta-analyse: primary outcome measure: positive (disability scales, 2 trials, n=80, quality low)
- 4x weekly 375 mg/m2
- Is considered standard of care

- Identification of candidates for rituximab:
  - Short disease duration (< 5 years?)
  - Progressive disease
  - IgM/titers: not predictive
  - Before start of axonal damage?
  - Patients with less sensory nerve damage on EMG had better outcomes after rituximab

- Lunn & Nobile-Orazio, Cochrane 2016 ,

D'sa et al BJH 2017, Tang et al J Neurol 2019

Primary Cold Agglutinin Disease ≠ WM

- Hemolytic anemia, fatigue, acrocyanosis, increased risk of thrombosis
- DAT: C3D+/IgG neg (however 25% also (weakly) pos IgG)
- IgM kappa paraprotein (90%)
- 75%: LPL-type infiltrate, Median Bonemarrow infiltration 10%.

- MYD88 wildtype (100%, 17/17)
- Different IGHV gene usage compared to WM
- Distinct histopathology (no mastcells, no plasmacytosis or paratrabecular infiltrates)

→ **Primary CAD**

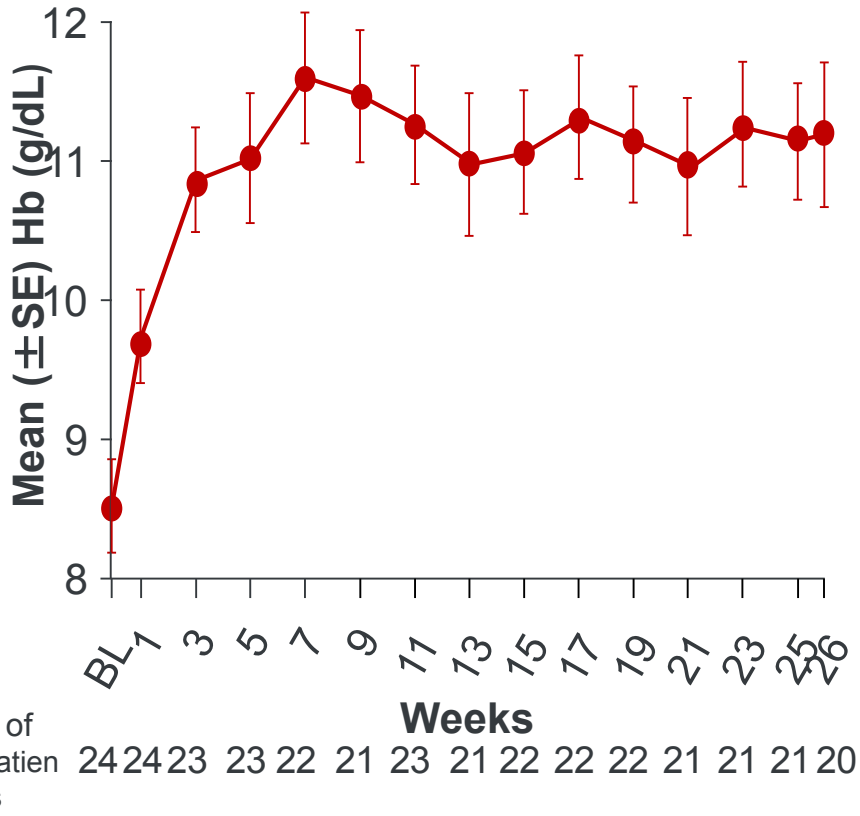
Berentsen et al Haematologica 2014

Cold Agglutinin Disease: treatment

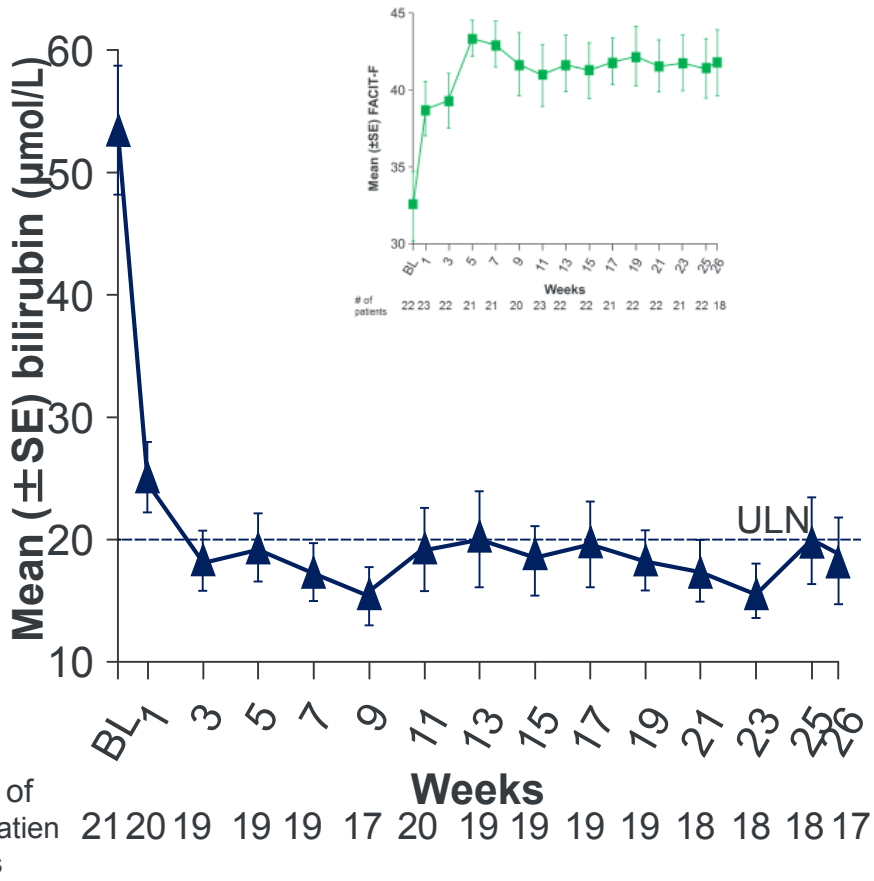
- Treatment: **Avoid** steroids and splenectomy (ineffective)
- Keep warm, folic acid (mild cases)
- **Rituximab: ±50% response, PFS ± 1 year**
- Bortezomib (4 giften, n=19):
  - 32% major response
  - After 16 months 66% persisting response
- **R-bendamustine (x4, n=45):**
  - 71% Major Response (40%CR, 31% PR)
  - median HgB rise ± 3.7 g/dL (2,2 mmol/L)
  - After 2,5 years > 90% persisting response

Rossi Blood 2018, Berentsen Blood 2017

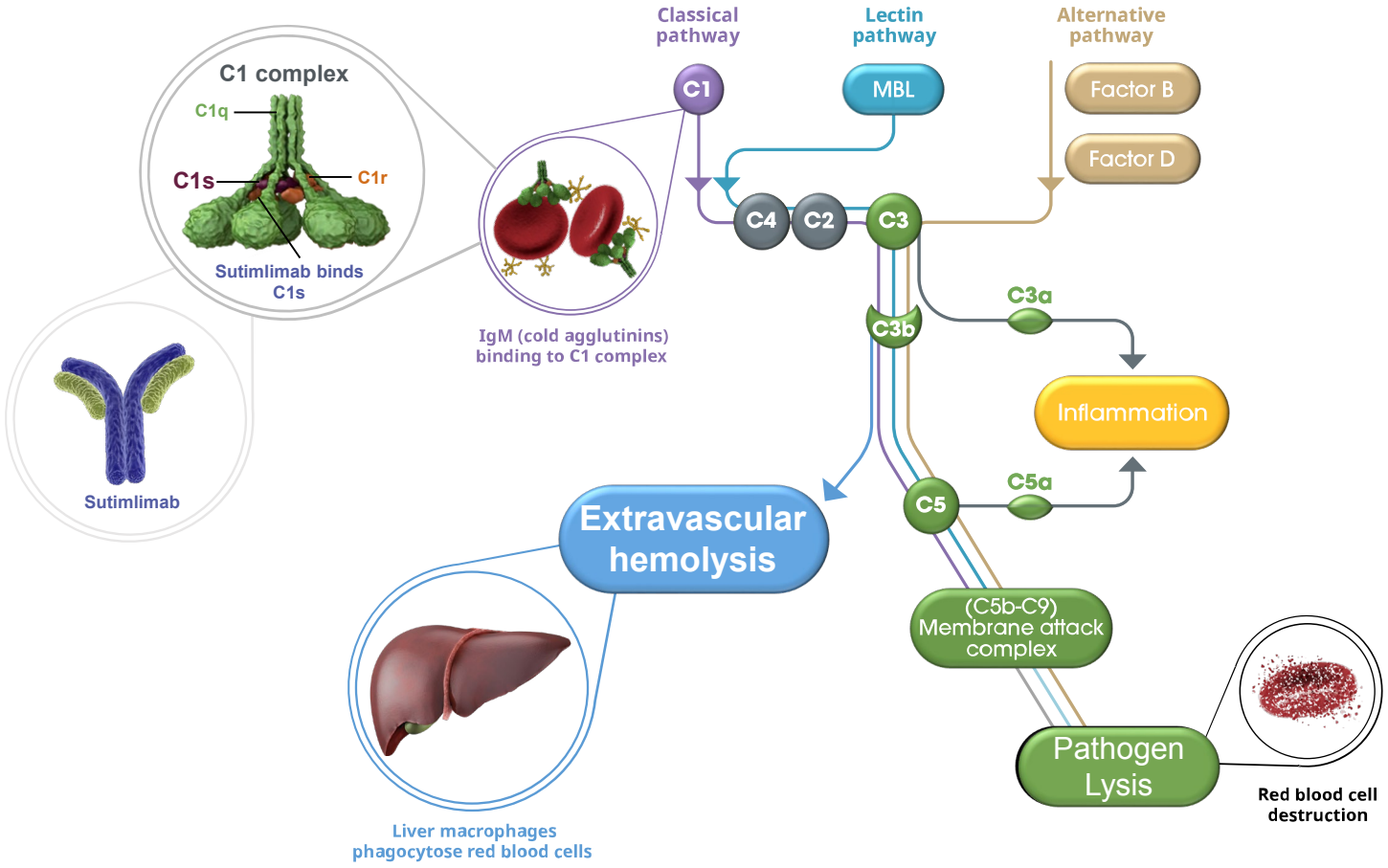
Sutimlimab: late breaking abstract ASH 2019
Cardinal study: CAD with recent transfusion

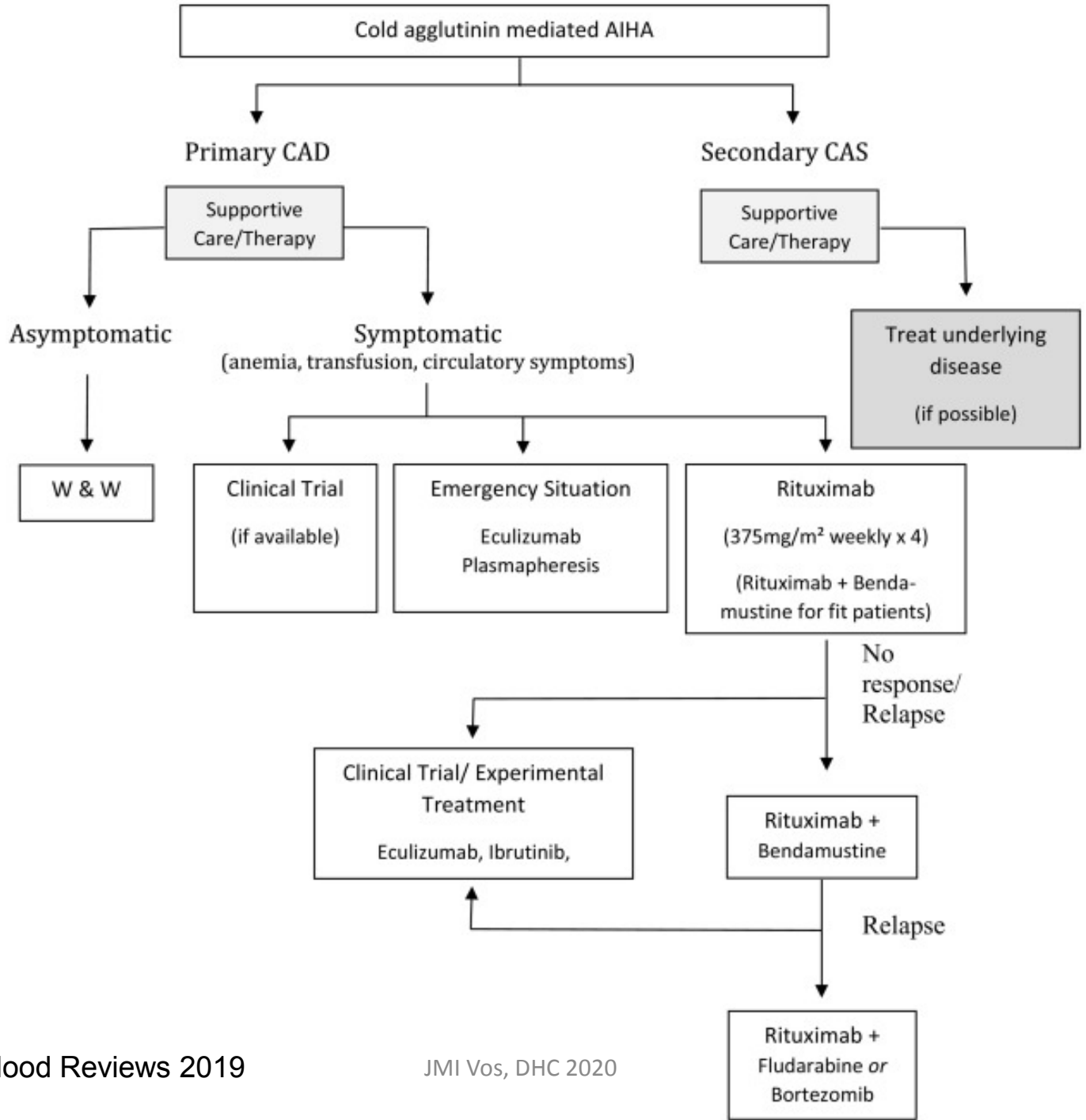


Quality of life



Sutimlimab Selectively Targets Complement C1s, Inhibiting Classical Complement Pathway Activation





Jaeger et al, Blood Reviews 2019

Huidige studies in Nederland

Chronische CAD

A Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Sutimlimab in Patients with Primary Cold Agglutinin Disease Without a Recent History of Blood Transfusion, Hb < 6.3

Open in AMC & LUMC

Acute complement gemedieerde hemolyse, transfusiebehoefte:

C1-inhibitor study (cinryze)

Open in AMC

hemat.trial@amsterdamumc.nl

Summary

- IgM related disorders: be aware, MGUS is not always innocent
- IgM related polyneuropathy: red flags
- Cold Agglutinin Disease: what if “ keep warm “ doesn’t work

Questions?

Cardinal study (n=24) : results

- Safety: No infusion reactions; 2 infections 1x respiratory tract and 1x streptococcal sepsis; 2x hypertension

- Mean Hb increase 2,6 g/dL = 1,6 mmol/L
- 20 of 24 (83.3%) patients had a clinically meaningful response (mean change from baseline Hb ≥1 g/dL = 0.6 mmol/L)
- Seventeen (70.8%) patients remained transfusion-free from Weeks 5 to 26