Complementdiagnostiek: pre-analytische fase, diagnostische workflow en interpretatie

Critically appraised topic

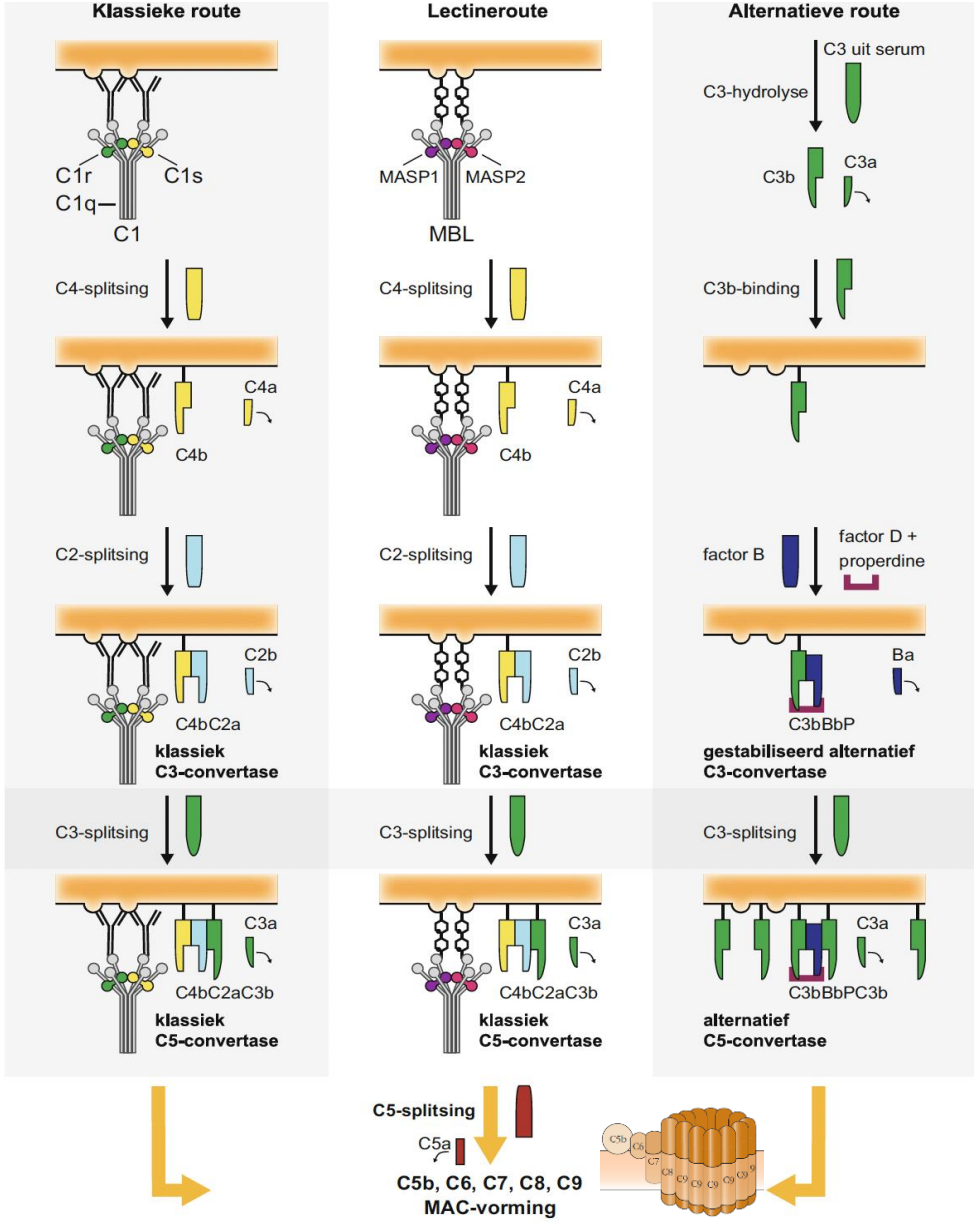
Tomas Gajdos

Overzicht

- Het complementsysteem
- Voornaamste indicaties voor complementdiagnostiek
- Diagnostiek (assays, pre-analytische fase & interpretatie):
  - complementfunctie
  - individuele componenten
  - activatiecomponenten
- Diagnostische workflow: complementdeficiëntie
- Mannose bindend lectine aanvragen GZA
- To do’s

Het complementsysteem

- Aangeboren immuunsysteem
- >30 eiwitten
- Synthese via de lever
- **Drie routes:**
  - klassieke route (CP)
  - lectineroute (LP)
  - alternatieve route (AP)
- **Activatie**
  - CP: antigen-antilichaam immuuncomplexen
  - LP: suikergroepen van microörganismen
  - AP: spontane hydrolyse
- **Effect:**
  - Cellysis (MAC)
  - Inflammatie (C3a, C4a & C5a)
  - Opsonisatie (C3b)



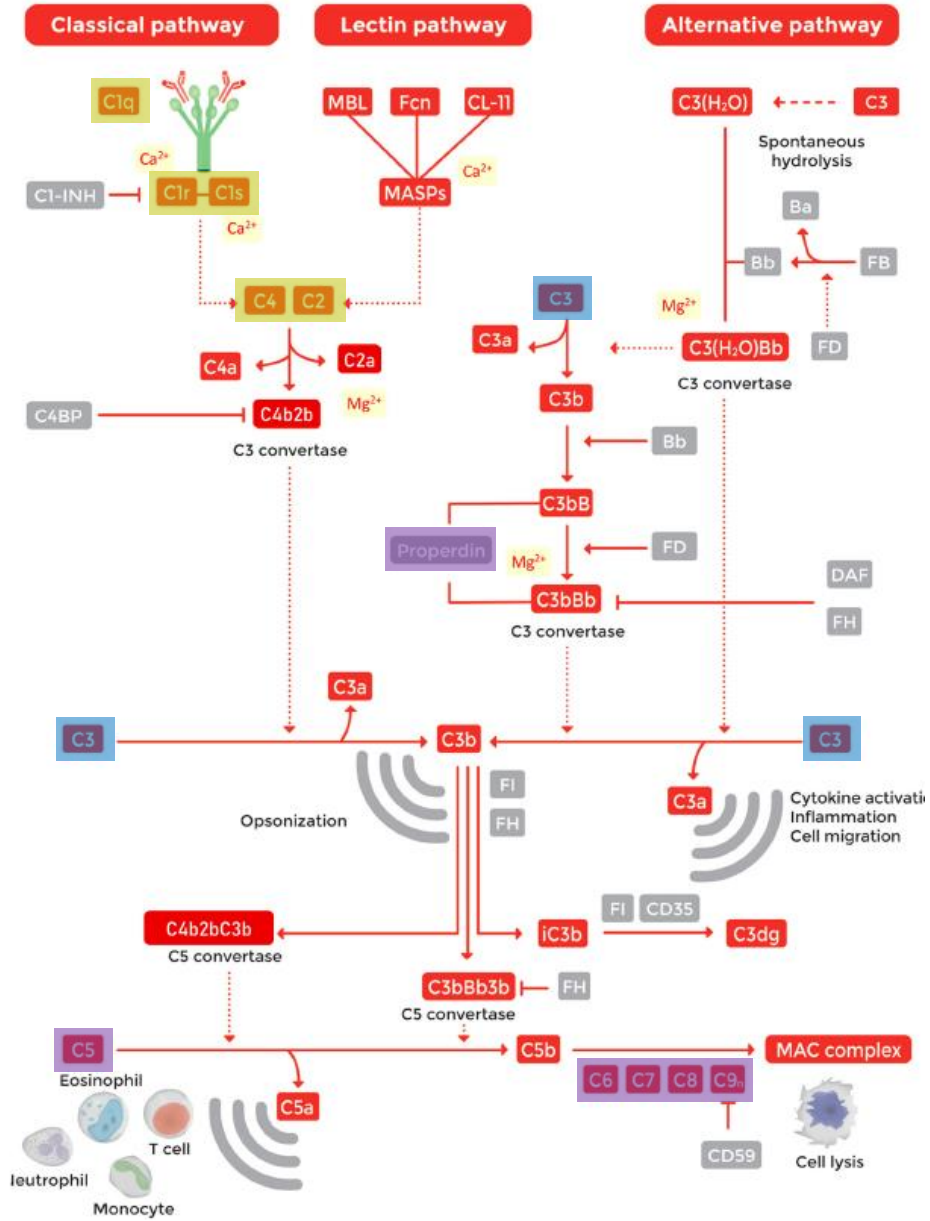
Bron: R. Benner, et al. Medische immunologie. 2016

Het complementsysteem: overzicht

- **Calcium**: activatie van proteasecomplexen (C1r, C1q, MASP's) van de CP en LP
- **Magnesium**: binding van C2 aan C4b om de C3 convertase te vormen
- **Regulatoren**: C1INH, DAF, CR1, C4Bp, factor H, factor I, MCP, properdine, …

→ **Deficiënties**

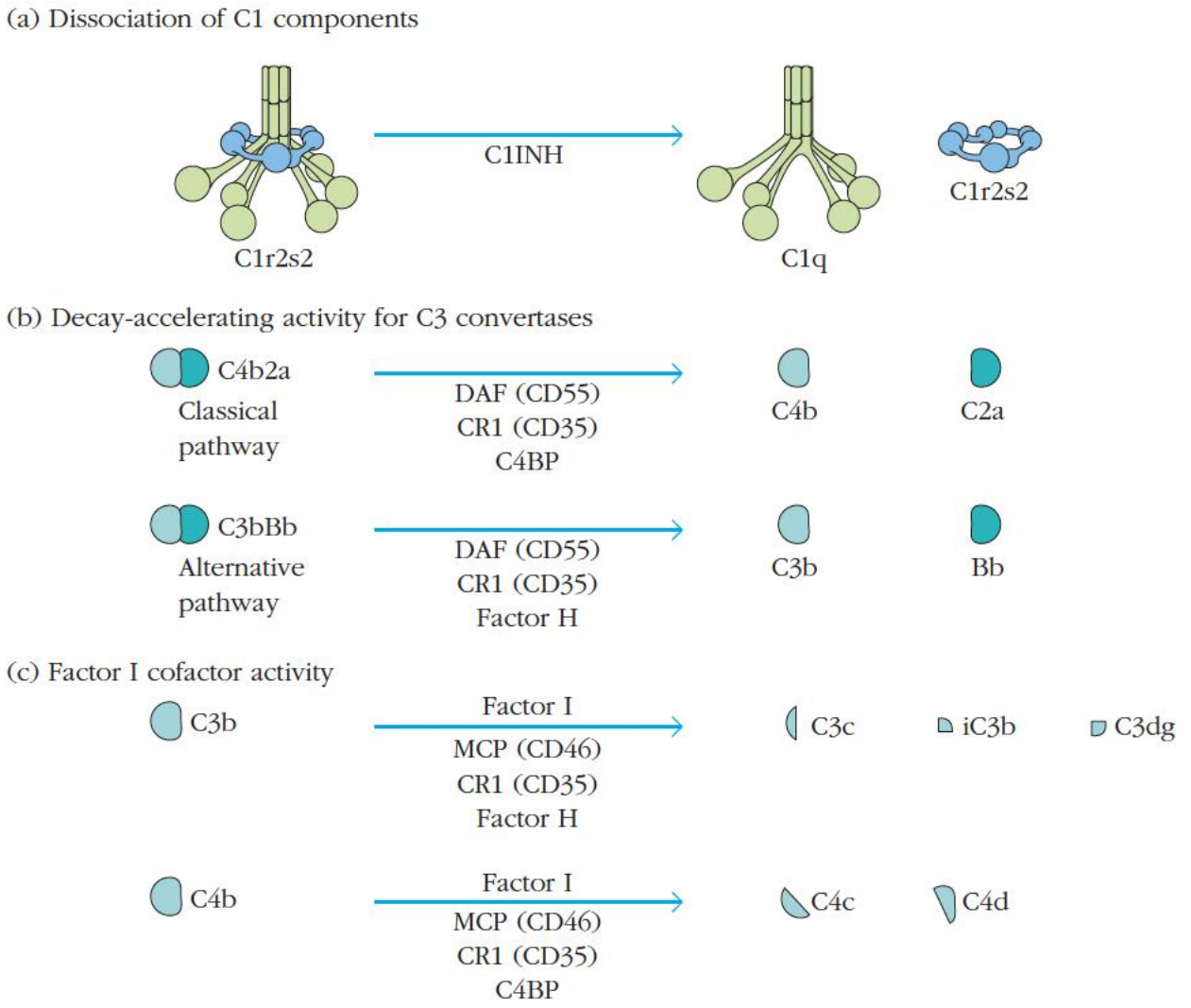
- AIZ
- Ernstige bacteriële infecties + AIZ
- *Neisseria* infecties



Bron: Brandwijk et al., frontiers in immunology, 2022

Het complementsysteem: regulatoren

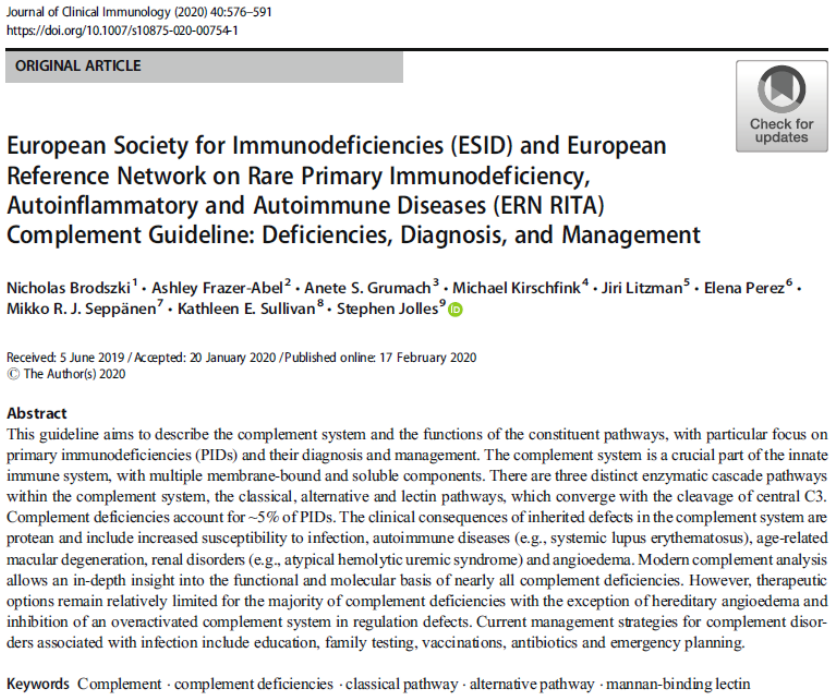
- C1INH deficiëntie → **HAE/AAE**
- DAF afwezigheid → **PNH**
- Mutaties, autoantistoffen tegen Factor H, I, MCP→ **aHUS**



Bron: J. A. Owen, et al., Kuby immunology, 2013, Figuur 6-16

Voornaamste indicaties voor complementdiagnostiek

1. Vermoeden van **complementdeficiënties**
   - Recidiverende bacteriële infecties (*S. pneumoniae*)
   - Ernstige infecties met omkapselde bacteriën
   - Meningokokken-meningitis >5 J oud
   - Auto-immuunaandoeningen (SLE)
   - Angio-oedeem zonder urticaria (HAE, AAE)



Journal of Clinical Immunology (2020) 40:576–591
https://doi.org/10.1007/s10875-020-00754-1

ORIGINAL ARTICLE

Check for updates

European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management

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Received: 5 June 2019 / Accepted: 20 January 2020 / Published online: 17 February 2020

Abstract
This guideline aims to describe the complement system and the functions of the constituent pathways, with particular focus on primary immunodeficiencies (PIDs) and their diagnosis and management. The complement system is a crucial part of the innate immune system, with multiple membrane-bound and soluble components. There are three distinct enzymatic cascade pathways within the complement system, the classical, alternative and lectin pathways, which converge with the cleavage of central C3. Complement deficiencies account for ~5% of PIDs. The clinical consequences of inherited defects in the complement system are protean and include increased susceptibility to infection, autoimmune diseases (e.g., systemic lupus erythematosus), age-related macular degeneration, renal disorders (e.g., atypical hemolytic uremic syndrome) and angioedema. Modern complement analysis allows an in-depth insight into the functional and molecular basis of nearly all complement deficiencies. However, therapeutic options remain relatively limited for the majority of complement deficiencies with the exception of hereditary angioedema and inhibition of an overactivated complement system in regulation defects. Current management strategies for complement disorders associated with infection include education, family testing, vaccinations, antibiotics and emergency planning.

Keywords Complement · complement deficiencies · classical pathway · alternative pathway · mannan-binding lectin

Voornaamste indicaties voor complementdiagnostiek

2. Vermoeden van **complementontregeling**
   - SLE
   - Urticariële vasculitis
   - Cryoglobulinemie
   - C3 glomerulopathie
   - TMA (aHUS)
   - …

Voornaamste indicaties voor complementdiagnostiek

3. Opvolgen van **therapie**
   - Eculizumab, Ravulizumab (anti-C5) bij aHUS, PNH

Complementdiagnostiek: onderdelen

Onderdeel	Klassieke route	Lectineroute	Alternatieve route	Terminale route
1. Functie	- CH50 hemolyse - ELISA CP - Liposomaal CP	- ELISA LP	- ELISA AP - AH50 hemolyse	- CH50 + AH50 hemolyse - ELISA CP, AP, LP
2. Individuele componenten	- C1, C2, C3, C4	- MBL, C2, C3, C4	- Factor B - Factor D	- C5, C6, C7, C8, C9
3. Activatiecomponenten	- C3d	- C3d	- C3d - Factor Bb	- sC5b-9
4. Controle-eiwitten	- C1-INH		- Factor H - Factor I - Properdine	
5. Autoantistoffen	- Anti-C1q - Anti-C1 Inhibitor - C4Nef (anti-C4bC2a)	- Anti-MBL - Anti-ficoline	- Anti-FH - Anti-FI - Anti-FB - C3Nef (anti-C3bBb)	- C5Nef (anti-C3bBbC3b)

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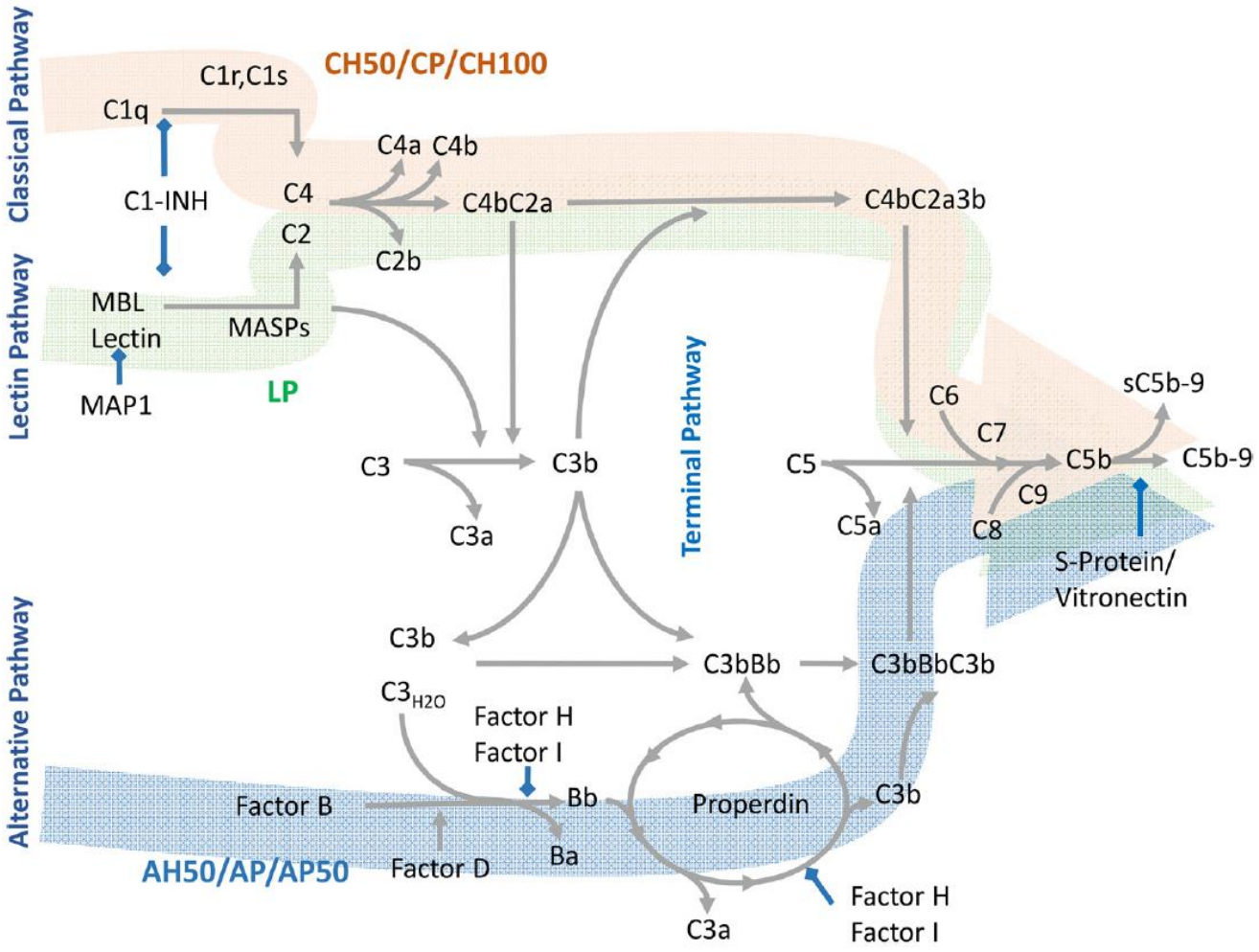
Complementdiagnostiek: complementfunctie

Methodes:

- Hemolytische assays
- ELISA
- Liposoom immunoassay

- ELISA

- Hemolytische assays
- ELISA

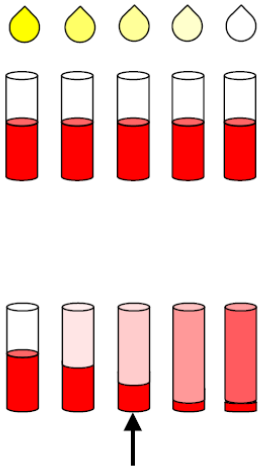


Bron: Prohászka et al., Molecular immunology, 2018

Complementfunctie: type assays

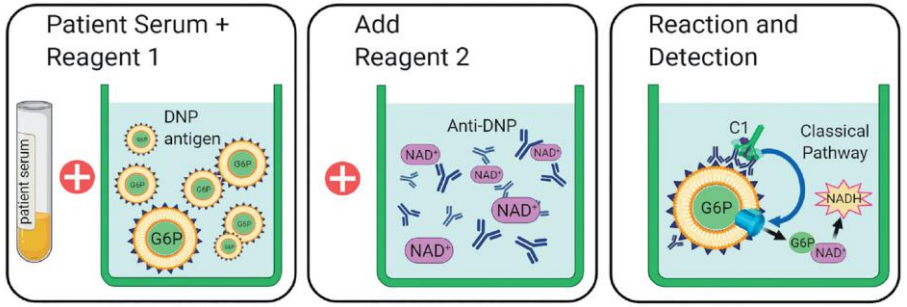
Hemolytische assay

1. Serially diluted serum
   Mix with
   Sensitized sheep erythrocytes
2. Incubate at 37°C for 30 min
3. Measure hemolysis
4. Identify amount of serum that lyses 50% of defined amount of erythrocytes



- Dierlijke erytrocyten
- Properdinedeficiëntie kan gemist worden

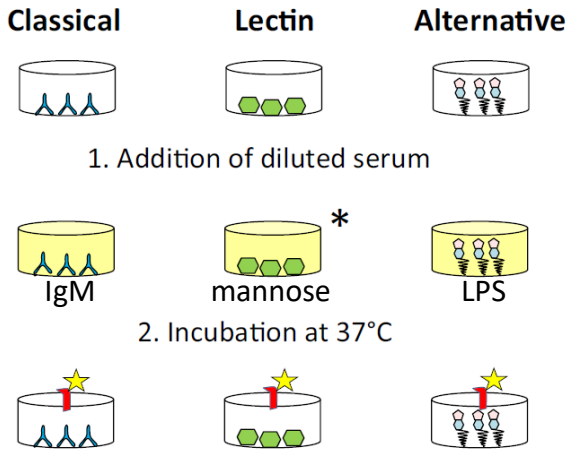
Liposoom immunoassay



- Enkel CP

+ Geautomatiseerd

ELISA



*Lectin pathway; C1q blocked by specific antibody

+ Gemakkelijk uit te voeren
+ Accuraat
+ Detectie properdinedeficiëntie
+ Kan alle 3 de routes testen

Complementfunctie: pre-analytische fase

- Serum (stollingsfactoren kunnen C3 splitsen)
- Afname op ijs
- Centrifugatie op 4°C voor 10 min
- Bewaring op -80°C
  - -20°C bevriest te traag
- Verzending: diepgevroren

Complementfunctie: pre-analytische fase

Parameter	Uitvoerend laboratorium				
	UZL	UZA	UZG	VUB	ULB
CP activiteit					
Staaltype	Serum	Serum	Serum	Serum	Serum
Verzendingsconditie	Ingevroren	Diepgevroren	Ingevroren	Ingevroren	Ingevroren
Methode	ELISA	ELISA	Liposome Immunoassay	Turbidimetrie	Turbidimetrie
AP activiteit					
Staaltype		Serum	Serum		Serum
Verzendingsconditie		Diepgevroren	Ingevroren		Ingevroren
Methode		ELISA	ELISA		ELISA
LP activiteit					
Staaltype		Serum	Serum		Serum
Verzendingsconditie		Diepgevroren	Ingevroren		Ingevroren
Methode		ELISA	ELISA		ELISA

Complementfunctie: interpretatie

- **Daling**
  - Complementdeficiëntie: PID of Eculizumab/Ravulizumab therapie
  - Verminderde synthese: leverpathologie
  - Complementconsumptie
- **Stijging**
  - Inflammatie (acute fase)

	Functionele assays		
Component	**CP**	**LP**	**AP**
C1q, C1r, C1s	↓	nl	nl
C4, C2	↓	↓	nl
MBL, MASP2	nl	↓	nl
Factor B, D, P	nl	nl	↓
C3, C5, C6, C7, C8, C9	↓	↓	↓

Complementdiagnostiek: onderdelen

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Complementdiagnostiek: complementcomponenten

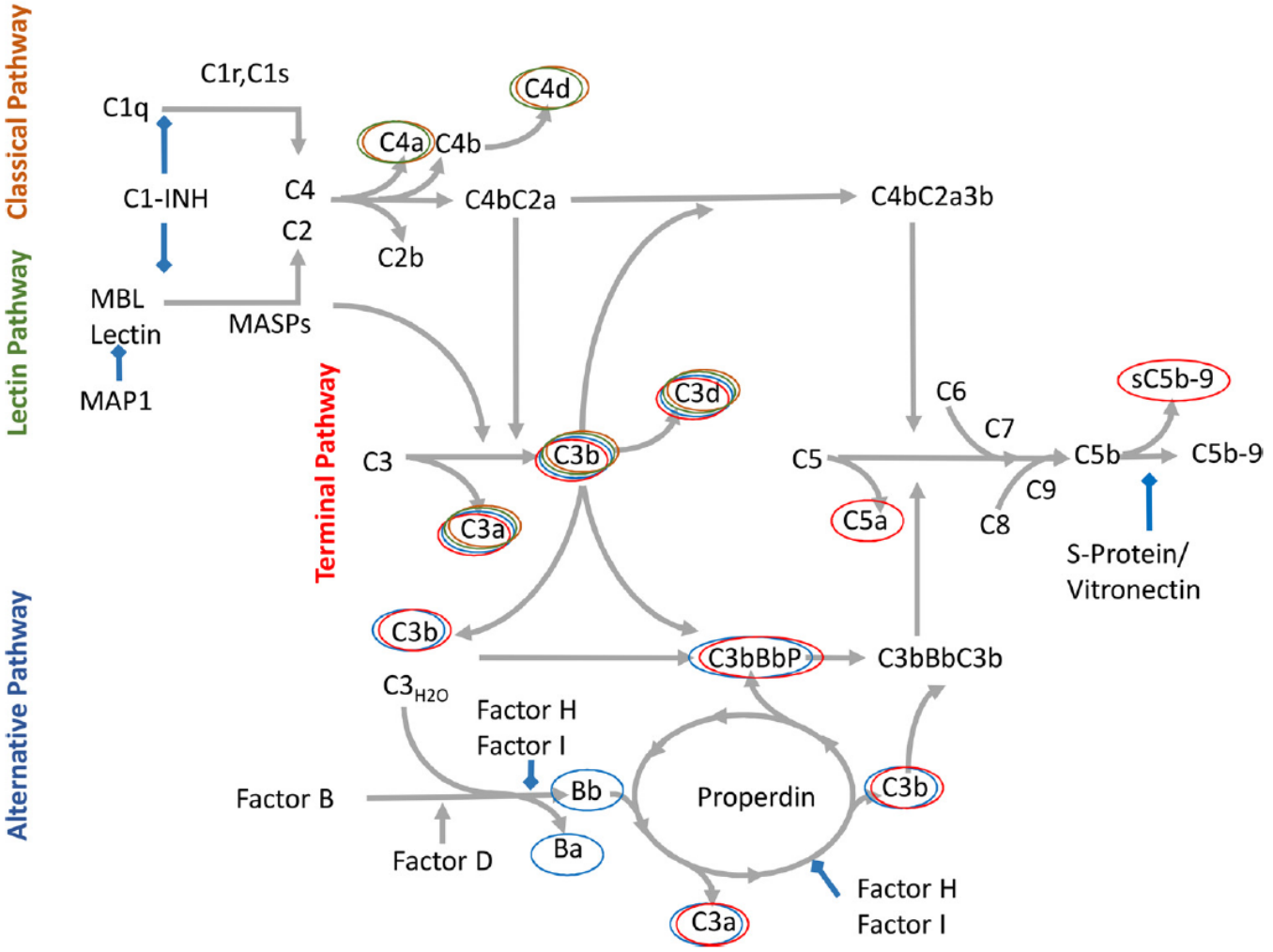
Methodes

Individuele componenten

- Turbidimetrie
- Nefelometrie
- ELISA
- RID

Activatiecomponenten

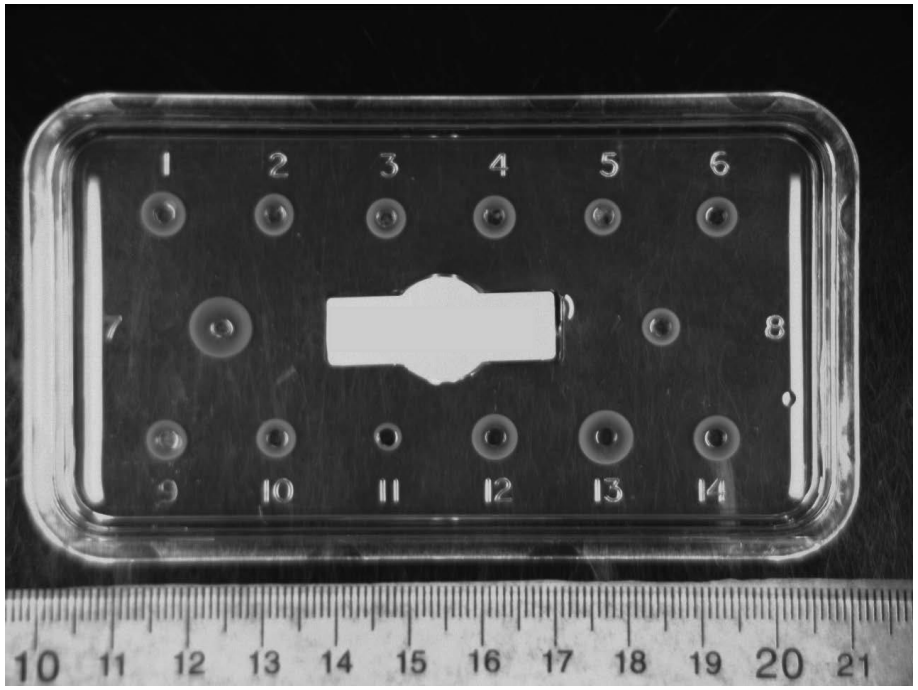
- Nefelometrie na PEG precipitatie
- ELISA

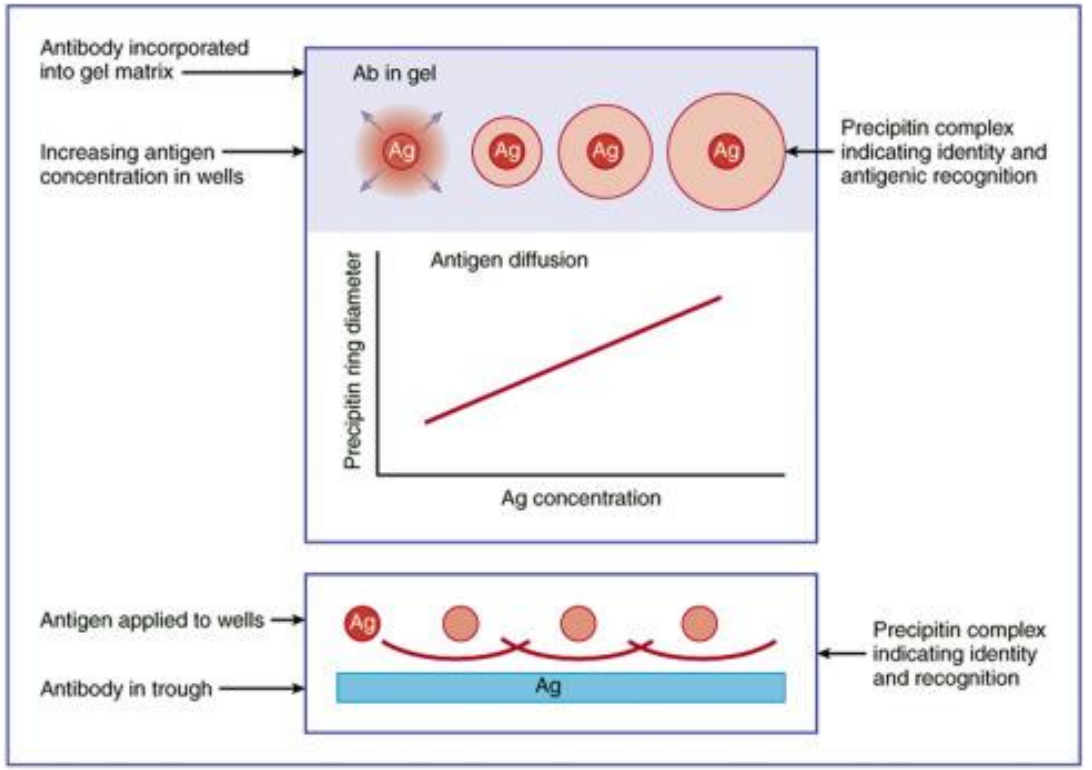


Bron: Prohászka et al., Molecular immunology, 2018

Complementcomponenten: type assay

- RID (= radiale immunodiffusie)
  - Bv. C2, C6 dosage



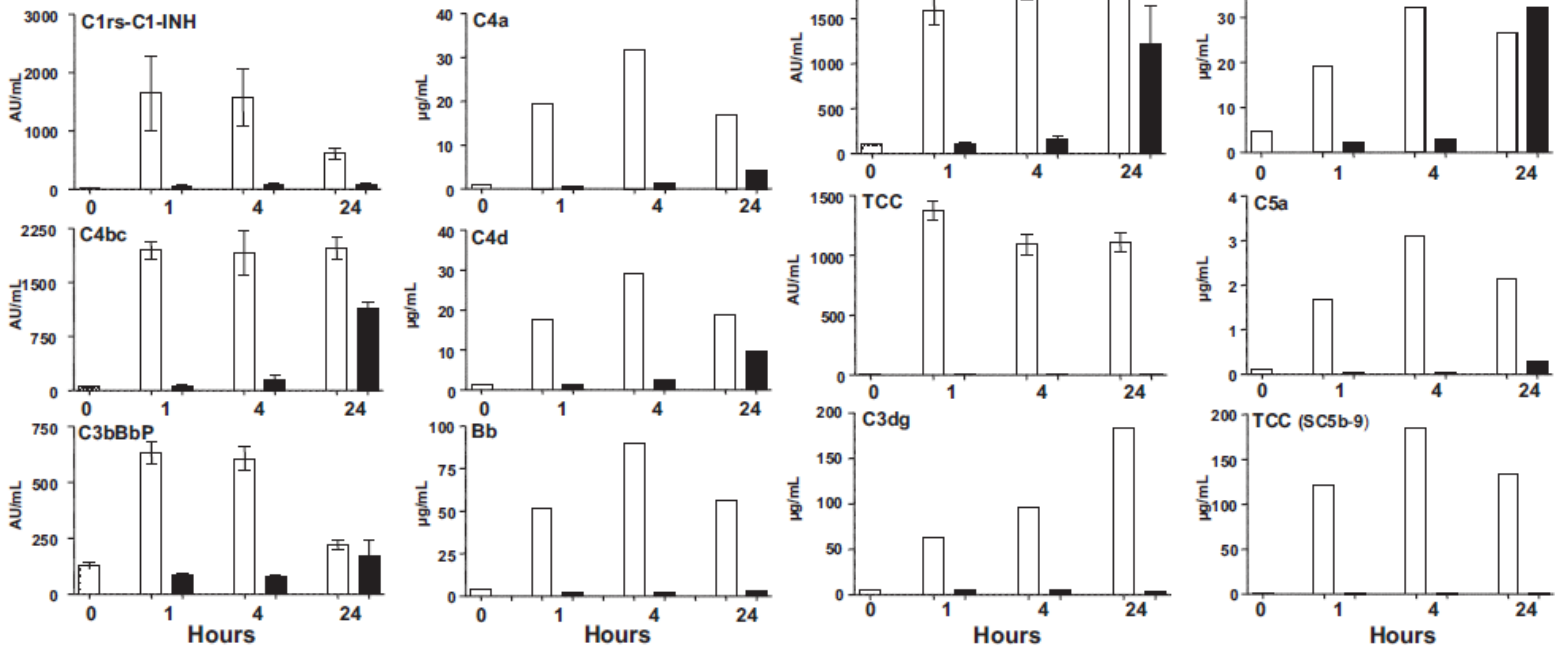


Bron: Henry A. Homburger, Ravinder Jit Singh, in Clinical Immunology (Third Edition), 2008

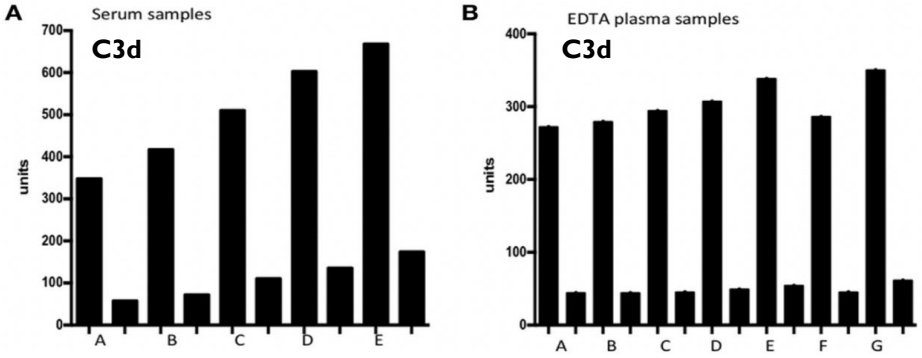
Complementcomponenten: pre-analytische fase

- <u>Afzonderlijke componenten</u>
  - Turbidimetrie: polyklonale As → meten ook activatieproducten! (C3 → C3a, C3b, iC3b, C3c, C3d)
  - Pre-analytisch minder streng (C3, C4): gekoeld/KT
  - **Serum**
  - ELISA: EDTA + invriezen
- <u>Activatieproducten</u>
  - Zeer lage concentraties (ng/mL) + snel in vitro geproduceerd
  - **EDTA** (cheleert Ca^{2+} en Mg^{2+} en zo complementactivatie)
  - Nafamostaat mesylaat (serine protease inhibitor)

Complementcomponenten: pre-analytische fase



Bron: G. Bergseth et al., Molecular Immunology, 2013

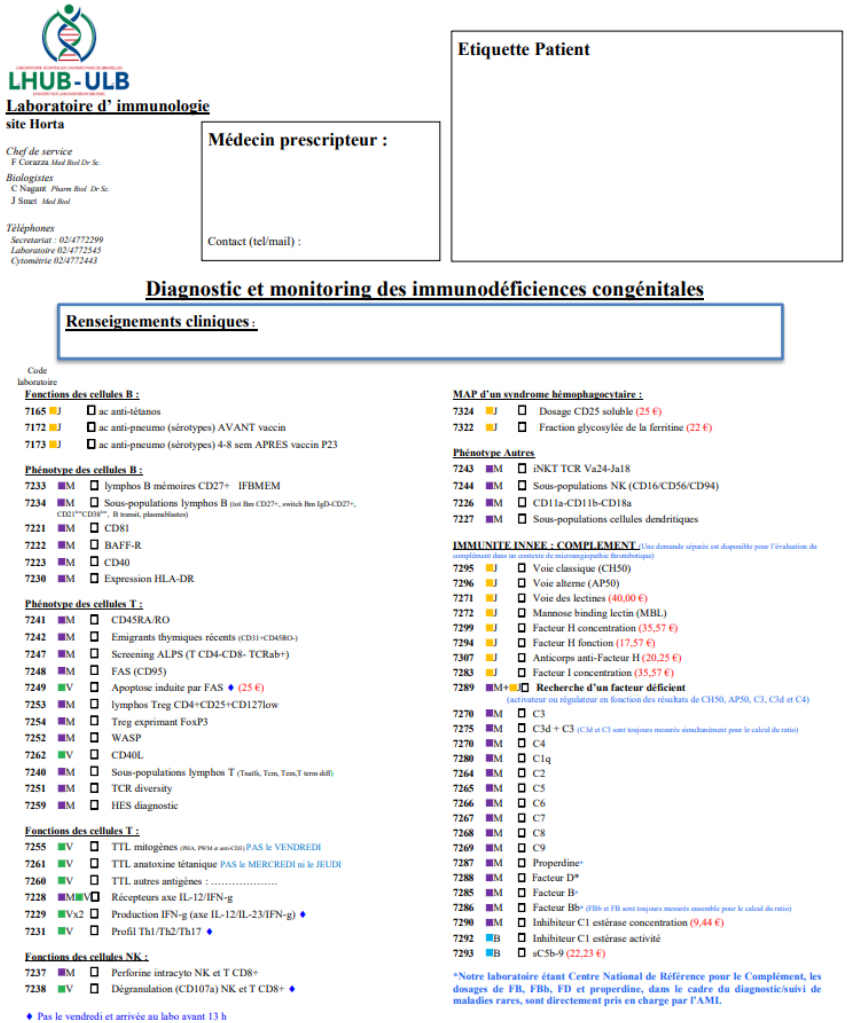


Bron: Troldborg A, et al., Front Immunol. 2018

Complementcomponenten: pre-analytische fase

Parameter		Uitvoerend laboratorium				
		UZL	UZA	UZG	VUB	ULB
Individuele componenten						
	C1q					
	Staaltype	Serum				EDTA
	Verzendingsconditie	Ingevroren				Ingevroren
	Methode	Nefelometrie				Nefelometrie
	C2					
	Staaltype	Serum				EDTA
	Verzendingsconditie	Ingevroren				Ingevroren
	Methode	Radiale immunodiffusie				Radiale immunodiffusie
	C3					
	Staaltype	Serum	serum	Serum/heparine	Heparine	EDTA
	Verzendingsconditie	Ingevroren	Kamertemperatuur	Ingevroren		Ingevroren
	Methode	Nefelometrie	Turbidimetrie	Turbidimetrie	Turbidimetrie	Turbidimetrie
	C4					
	Staaltype	Serum	serum	Serum/heparine	Heparine	EDTA
	Verzendingsconditie	Ingevroren	kamertemperatuur	Ingevroren		Ingevroren
	Methode	Nefelometrie	Turbidimetrie	Turbidimetrie	Turbidimetrie	Turbidimetrie
	C5					
	Staaltype	Serum				EDTA
	Verzendingsconditie	Ingevroren				Ingevroren
	Methode	Nefelometrie				Nefelometrie
Activatiecomponenten						
	C3d					
	Staaltype	EDTA	EDTA			EDTA
	Verzendingsconditie	Ingevroren	Ingevroren			Ingevroren
	Methode	Nefelometrie	Nefelometrie			Nefelometrie

Referentielabo complementdiagnostiek: LHUB-ULB



LHUB-ULB

Laboratoire d' immunologie
site Horta

Chef de service
F Corazza *Med Biol Dr Sc*

Biologistes
C Nagant *Pharm Biol Dr Sc*
J Smet *Med Biol*

Téléphones
Secretariat : 02/4772299
Laboratoire 02/4772545
Cytométrie 02/4772443

Médecin prescripteur :

Contact (tel/mail) :

Etiquette Patient

Diagnostic et monitoring des immunodéficiences congénitales

Renseignements cliniques :

Code laboratoire

Fonctions des cellules B :
7165 J ☐ ac anti-tétanos
7172 J ☐ ac anti-pneumo (sérotypes) AVANT vaccin
7173 J ☐ ac anti-pneumo (sérotypes) 4-8 sem APRES vaccin P23

Phénotype des cellules B :
7233 M ☐ lymphos B mémoires CD27+ IFBMEM
7234 M ☐ Sous-populations lymphos B (tot Bm CD27+, switch Bm IgD-CD27+, CD21low CD38low, B transit, plasmablastes)
7221 M ☐ CD81
7222 M ☐ BAFF-R
7223 M ☐ CD40
7230 M ☐ Expression HLA-DR

Phénotype des cellules T :
7241 M ☐ CD45RA/RO
7242 M ☐ Emigrants thymiques récents (CD31+CD45RO-)
7247 M ☐ Screening ALPS (T CD4-CD8- TCRab+)
7248 M ☐ FAS (CD95)
7249 V ☐ Apoptose induite par FAS ♦ (25 €)
7253 M ☐ lymphos Treg CD4+CD25+CD127low
7254 M ☐ Treg exprimant FoxP3
7252 M ☐ WASP
7262 V ☐ CD40L
7240 M ☐ Sous-populations lymphos T (Tnaïfs, Tcm, Tem,T term diff)
7251 M ☐ TCR diversity
7259 M ☐ HES diagnostic

Fonctions des cellules T :
7255 V ☐ TTL mitogènes (PHA, PWM et anti-CD3) PAS le VENDREDI
7261 V ☐ TTL anatoxine tétanique PAS le MERCREDI ni le JEUDI
7260 V ☐ TTL autres antigènes : ……
7228 M V ☐ Récepteurs axe IL-12/IFN-g
7229 Vx2 ☐ Production IFN-g (axe IL-12/IL-23/IFN-g) ♦
7231 V ☐ Profil Th1/Th2/Th17 ♦

Fonctions des cellules NK :
7237 M ☐ Perforine intracyto NK et T CD8+
7238 V ☐ Dégranulation (CD107a) NK et T CD8+ ♦

♦ Pas le vendredi et arrivée au labo avant 13 h

MAP d'un syndrome hémophagocytaire :
7324 J ☐ Dosage CD25 soluble (25 €)
7322 J ☐ Fraction glycosylée de la ferritine (22 €)

Phénotype Autres
7243 M ☐ iNKT TCR Va24-Ja18
7244 M ☐ Sous-populations NK (CD16/CD56/CD94)
7226 M ☐ CD11a-CD11b-CD18a
7227 M ☐ Sous-populations cellules dendritiques

IMMUNITE INNEE : COMPLEMENT (Une demande séparée est disponible pour l'évaluation du complément dans un contexte de microangiopathie thrombotique)
7295 J ☐ Voie classique (CH50)
7296 J ☐ Voie alterne (AP50)
7271 J ☐ Voie des lectines (40,00 €)
7272 J ☐ Mannose binding lectin (MBL)
7299 J ☐ Facteur H concentration (35,57 €)
7294 J ☐ Facteur H fonction (17,57 €)
7307 J ☐ Anticorps anti-Facteur H (20,25 €)
7283 J ☐ Facteur I concentration (35,57 €)
7289 M+J ☐ **Recherche d'un facteur déficient**
(activateur ou régulateur en fonction des résultats de CH50, AP50, C3, C3d et C4)
7270 M ☐ C3
7275 M ☐ C3d + C3 (C3d et C3 sont toujours mesurés simultanément pour le calcul du ratio)
7270 M ☐ C4
7280 M ☐ C1q
7264 M ☐ C2
7265 M ☐ C5
7266 M ☐ C6
7267 M ☐ C7
7268 M ☐ C8
7269 M ☐ C9
7287 M ☐ Properdine*
7288 M ☐ Facteur D*
7285 M ☐ Facteur B*
7286 M ☐ Facteur Bb* (FBb et FB sont toujours mesurés ensemble pour le calcul du ratio)
7290 M ☐ Inhibiteur C1 estérase concentration (9,44 €)
7292 B ☐ Inhibiteur C1 estérase activité
7293 B ☐ sC5b-9 (22,23 €)

*Notre laboratoire étant Centre National de Référence pour le Complément, les dosages de FB, FBb, FD et properdine, dans le cadre du diagnostic/suivi de maladies rares, sont directement pris en charge par l'AMI.

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7265 M ☐ C5
7266 M ☐ C6
7267 M ☐ C7
7268 M ☐ C8
7269 M ☐ C9
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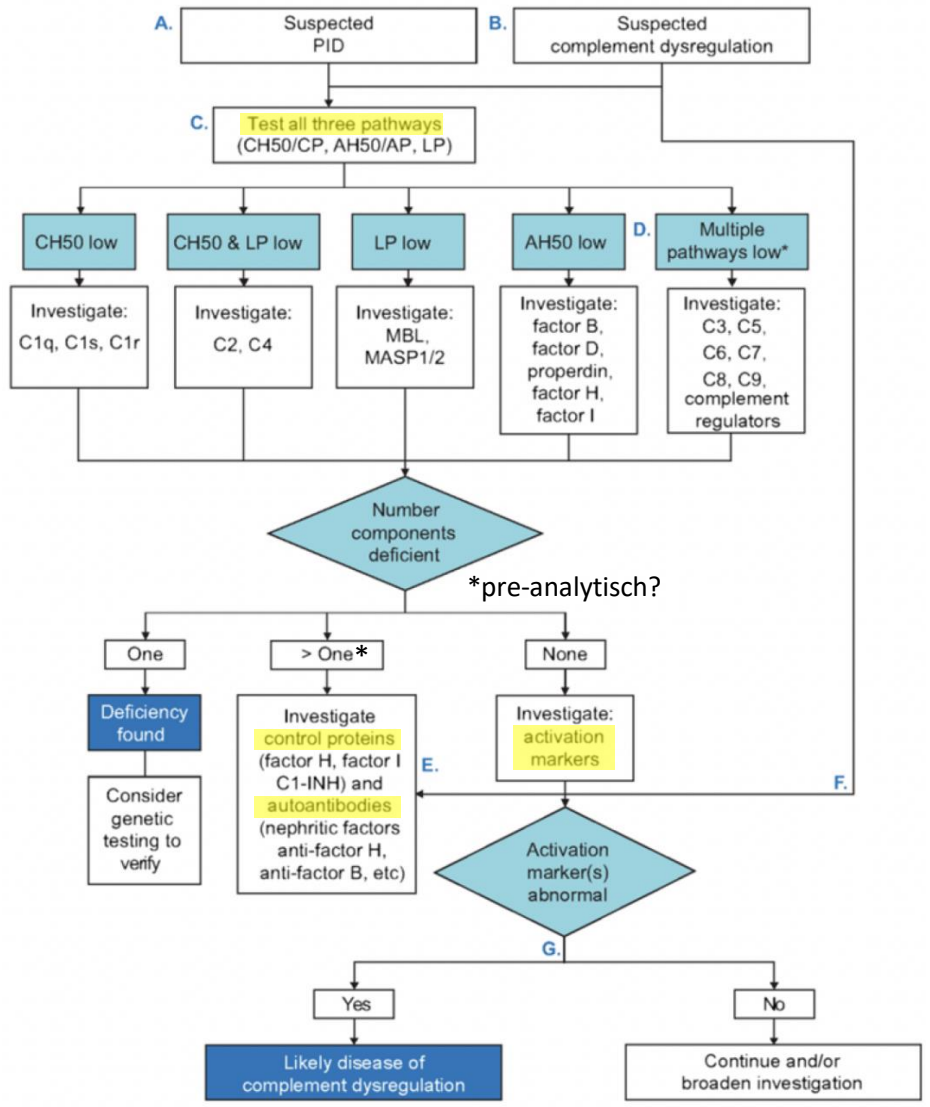
Diagnostische workflow: complementdeficiëntie



Journal of Clinical Immunology (2020) 40:576–591
https://doi.org/10.1007/s10875-020-00754-1

ORIGINAL ARTICLE

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European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management

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Received: 5 June 2019 / Accepted: 20 January 2020 /Published online: 17 February 2020

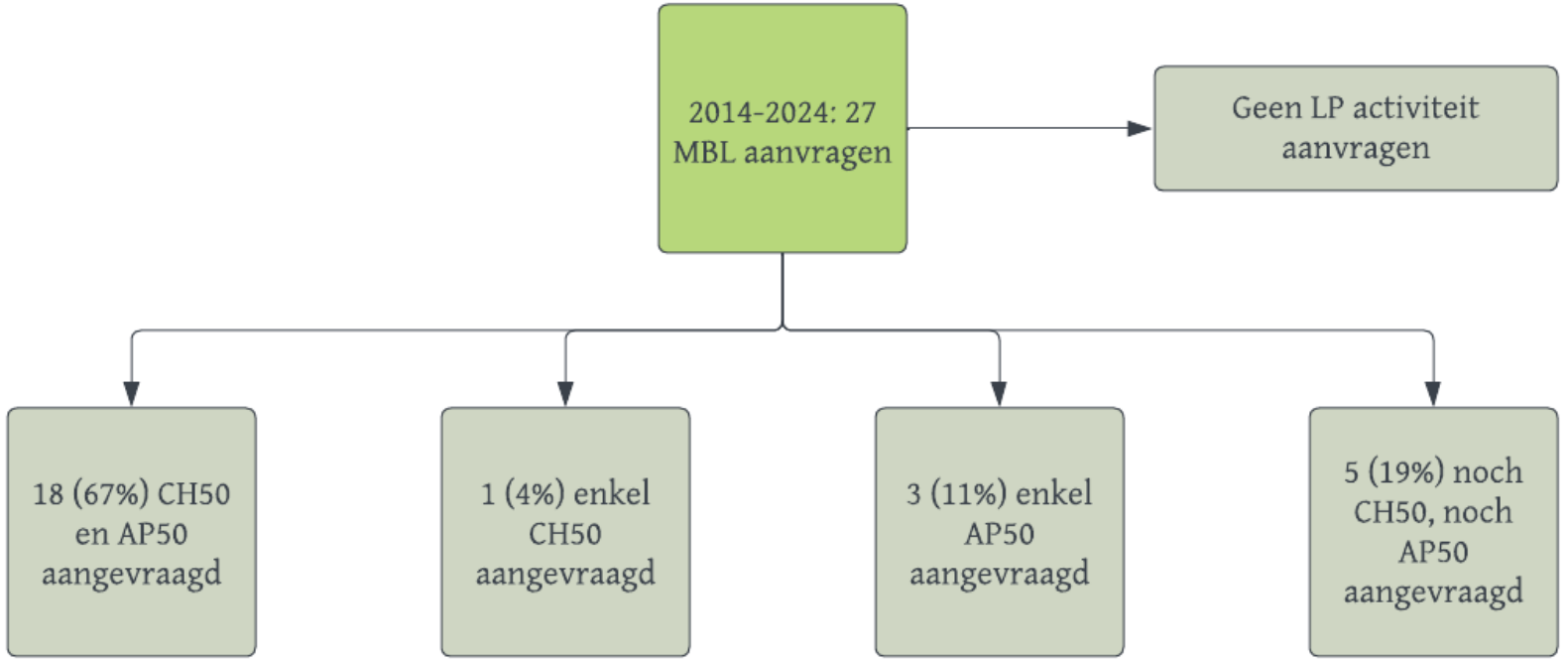
Abstract
This guideline aims to describe the complement system and the functions of the constituent pathways, with particular focus on primary immunodeficiencies (PIDs) and their diagnosis and management. The complement system is a crucial part of the innate immune system, with multiple membrane-bound and soluble components. There are three distinct enzymatic cascade pathways within the complement system, the classical, alternative and lectin pathways, which converge with the cleavage of central C3. Complement deficiencies account for ~5% of PIDs. The clinical consequences of inherited defects in the complement system are protean and include increased susceptibility to infection, autoimmune diseases (e.g., systemic lupus erythematosus), age-related macular degeneration, renal disorders (e.g., atypical hemolytic uremic syndrome) and angioedema. Modern complement analysis allows an in-depth insight into the functional and molecular basis of nearly all complement deficiencies. However, therapeutic options remain relatively limited for the majority of complement deficiencies with the exception of hereditary angioedema and inhibition of an overactivated complement system in regulation defects. Current management strategies for complement disorders associated with infection include education, family testing, vaccinations, antibiotics and emergency planning.

Keywords Complement · complement deficiencies · classical pathway · alternative pathway · mannan-binding lectin

Mannose bindend lectine aanvragen GZA

	Nummer	Leeftijd	Geslacht	Kliniek	MLB (ng/mL)	CH50 (U/mL)	AP50 (%)
2018	1.	<1	V	Pneumokokkenmeningitis	1037	51,3	65
	2.	2	M	Recidiverende otitiden	3380	50	64
2020	3.	1	M	Recidiverende otitiden	>4000	59,9	28
	4.	3	V	Recidiverende BWI, zus heeft MBL deficiëntie	163	54,3	32
	5.	3	V	Pneumokokkensepsis, recidiverende virale infecties	188	60,8	37
2021	6.	2	V	Ernstige pneumonie met abces	tws	59,6	57
	7.	1	V	Pneumonie met abcesvorming	3422	45,9	29
2022	8.	3	M	Recidiverende otitiden	>4000	42,3	NA
	9.	3	M	Otitis media, broer gekend met PID	1735	NA	NA
	10.	1	M	*H. influenza* meningitis	>4000	76,1	85
	11.	2	V	Recidiverend ziek (viraal)	tws	Tws	81
	12.	1	V	Recidiverende otitiden	>4000	NA	NA
	13.	4	V	Recidiverende bronchieëctasiën, negatieve CF genetica	330	NA	93
2023	14.	1	M	Atelectase, multipele pneumonieën	tws	44,6	NA
	15.	<1	M	2x mastoïditis met een acute mastoïdectomie	reagens probleem	tws	71
	16.	<1	M	Recidiverende BWI	8121	25,1	50
	17.	1	M	RSV, griep, buikgriep, keelonsteking, 3x otitis	3491	38,1	72
	18.	4	M	Recidiverend ziek (viraal)	5789	43	91
	19.	<1	M	Bronchiolitis met recidiverende otitiden	nut (staal niet op ijs)	NA	NA
	20.	2	M	Recidiverende bronchopneumonie (4x)	reagens probleem	41,5	58
	21.	2	V	Persiterende otitis serosa	reagens probleem	56,7	80
	22.	3	V	Recidiverende pneumonie, pneumosepsis	reagens probleem	57,4	NA
2024	23.	<1	V	Bronchiolitis	nut (staal niet op ijs)	46,3	nut (staal niet op ijs)
	24.	2	M	Recidiverende otitiden	50%	67,7	86
	25.	1	M	Otitis media	20	54,3	47
	26.	<1	V	Recidiverende BWI	nut (staal niet op ijs)	NA	NA
	27.	1	M	Recidiverende otitiden	nut (staal niet op ijs)	NA	NA

Mannose bindend lectine aanvragen GZA



To do’s

1. Strenger toezien op de pre-analytische fase
   1) Staal correct aangekomen op het labo (op ijs, correct recipiënt?)?
   2) Staal binnen de nodige tijd verwerkt?
   3) Verzending diepgevroren?

   → indien niet correct → nieuw staal

2. Correcte indicaties a.d.h.v. de ESID/ERN RITA richtlijnen

   → aanvragende arts informeren + juiste analyse(s) aanvragen

3. MBL aanvragen omzetten naar lectine activiteit

   → normaal resultaat = “Een normale activiteit van de lectine pathway (>10%) sluit een MBL deficiëntie uit”

Vragen?