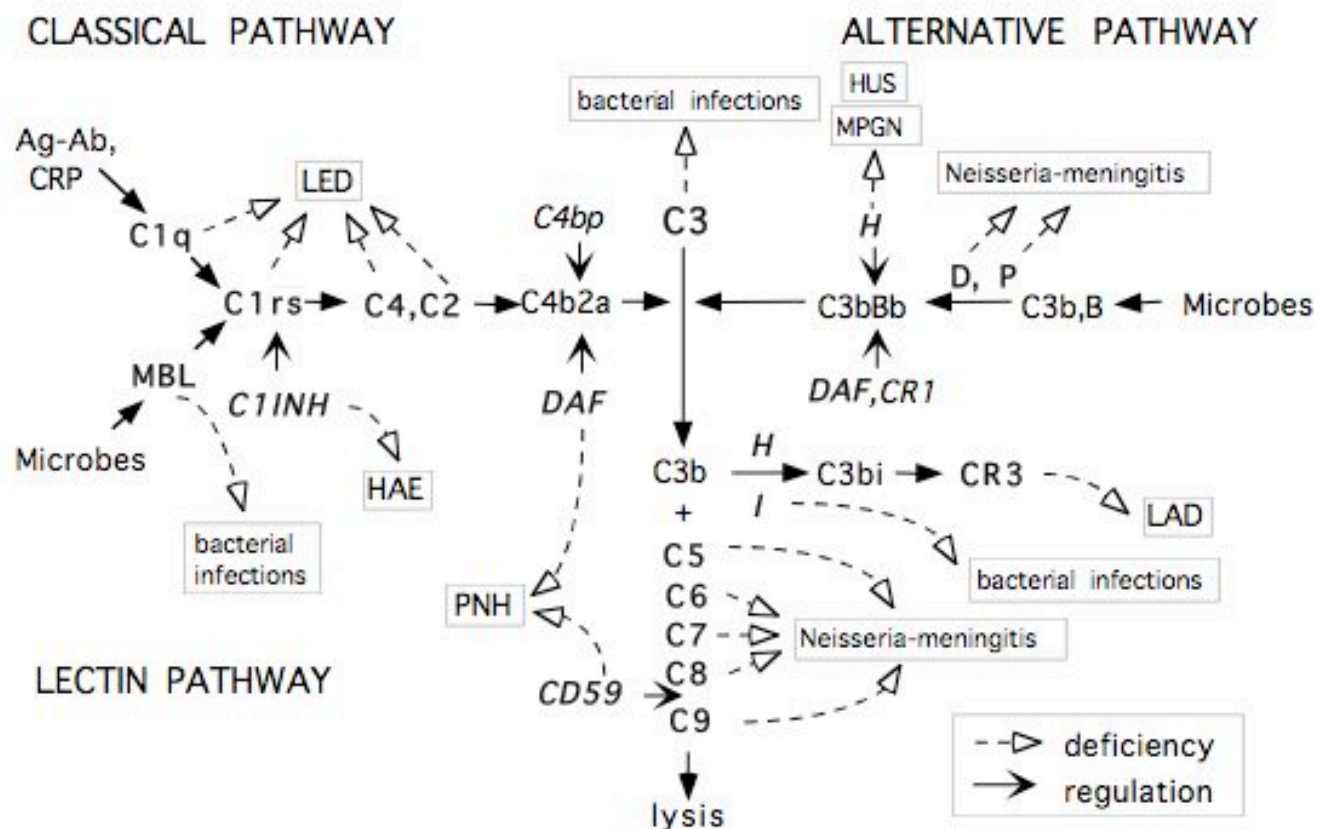


A quick reference guide for complement diagnostics Seppo Meri, Haartman Institute & Huslab



Complement activation pathways and deficiencies

Abbr: C1-INH, C1-inhibitor; DAF, decay accelerating factor; CR1 and CR3, complement receptors type 1 and 3; HAE, hereditary angioedema; PNH, paroxysmal nocturnal hemoglobinuria; MPGN2, membranoproliferative glomerulonephritis type 2 (dense deposit disease); HUS, hemolytic uremic syndrome (familial form); LAD, leukocyte adhesion deficiency; MBL, mannose binding lectin; P, properdin

Disturbances of the classical pathway

Disease	Abnormality	Diagnostics
Hereditary angioedema	C1-INH deficiency - type 1 (85%) - type 2 (15 %) - acquired: - lymphoma - AAE	C1-INH ↓, C4↓ (S-HAE), C1-INH biochemical activity↓, C4↓ C1-INH biochemical activity↓, C4↓ (C1-INH-antibodies +)
Hypocomplementemic urticarial vasculitis syndrome (HUVS)	Autoantibodies to C1q	C4↓, CH50↓ (S-C-Def) (C1q-antibodies +)
Systemic lupus erythematosus (SLE, SLE-like)	Deficiency of C1q, C1r, C1s, C2 or C4A Immune complexes -> C consumption Autoantibodies to C1q	CH50↓ (C1q/r/s, C2 or C4↓) (S-C-Def) C4A 0,0 (null/null) phenotype (S-C4-Ty) CH50↓, C2↓, C4↓ (C1q-antibodies +)
Pyogenic infections	Deficiency of C1, C2, C4B	CH50 ↓, C1q/r/s↓, C2 ↓ (S-C-Def) C4 ↓ (C4B 0,0) (S-C4-Ty)
Behçet's syndrome	Deficiency of C4bp or protein S (rare)	C4bp↓, protein S↓

Abbr: C1-INH, C1-inhibitor; AAE, acquired angioedema; CH50 (**S-CH100Cl**), total classical pathway hemolytic activity;
S-C-Def, study of complement deficiency (= C3 + C4 + CH100Cl + CH100Al) SMeri 2008

Disturbances of the alternative and lectin pathways

Disease	Abnormality	Diagnostics
Increased incidence of infections by encapsulated bacteria	Deficiency of C3 or factor I (rare) (or MBL (common))	CH50↓, AH50↓ C3↓ (factor I↓) MBL↓, MBL genotyping
Leukocyte adhesion deficiency (LAD)	CR3 deficiency (rare)	CD18 (integrin β-chain) ↓ on leukocytes
Membranoproliferative glomerulonephritis type II (dense deposit disease, DDD)	C3 nephritic factor (= anti-C3bBb) factor H deficiency or factor H antibodies	C3↓↓, C3Nef + dense deposits in EM of kidney biopsy (immunofluorescence: C3, P, C5b-9) factor H↓ factor H-antibodies +
Hemolytic uremic syndrome (familial)	Dysfunctional factor H (or factor I or CD46)	C3↓, AH50↓ functionally abnormal factor H (analysis for factor H , factor I or CD46 mutations)

Abbr: CH50 (**S-CH100C1**), total classical pathway hemolytic activity; AH50 (**S-CH100A1**), alternative pathway hemolytic activity; MBL, mannose binding lectin; C3Nef, C3 nephritic factor; P, properdin

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Disturbances of the terminal pathway

Disease	Abnormality	Diagnostics
Neisserial infections (meningococcal meningitis, disseminated gc)	Deficiency of C5, C6, C7, C8 or P	CH50↓, AH50↓ (S-C-Def) lack of C5, C6, C7, C8, (C9), or P
Paroxysmal nocturnal hemoglobinuria (PNH) (somatic mutation in <i>PIG-A</i> gene in BM precursor cells)	Lack of GPI-anchored proteins from blood cells (hemolysis, venous thrombosis)	B-PNH (FACS for CD59 and CD55)
Acute phase response; rheumatoid arthritis; reactive arthritis	tissue injury by MAC complexes (arthritis, vasculitis)	CH50↑, AH50↑ C3↑ reactive lysis +

Abbr: P, properdin; CH50, total classical pathway hemolytic activity; AH50, alternative pathway hemolytic activity; BM, bone marrow; MAC, membrane attack complex