EPI-NEWS
NATIONAL SURVEILLANCE OF COMMUNICABLE DISEASES

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COMPLEMENT DEFECTS

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The complement system (CS) is an important part of the immune defences and consists of a strictly regulated cascade of at least 24 serum proteins. CS contributes to the elimination of antigen-antibody complexes, damaged cells and pathogenic micro-organisms, and plays an important role in the development of inflammatory reactions.
CS may be activated by any of three reaction pathways:
1) the classical pathway, 2) the alternative pathway and 3) the lectin pathway; all three of which lead to the formation of terminal complexes.
Hereditary defects of individual complement proteins are rare conditions, with a prevalence that is probably about 1/10,000 in the population. With the exception of C1 inhibitor deficiency, the clinically relevant defects are either total or partial. Inheritance is as a rule autosomal recessive. Complement defects (CD) typically predispose to bacterial infections and to the development of immunological diseases such as systemic lupus erythematosus (SLE), table 1. Acquired CD, generally of several complement proteins, are due to increased consumption of complement and are more frequent.

Table 1. Complement defects and consequent diseases

Component	Diseases
C1q, C1r, C1s and C4	Inflammatory diseases (SLE or SLE-like with/without glomerulonephritis). Recurrent bacterial infections.
C2	As for C1 og C4 but more frequently with serious bacterial infections.
C3	Recurrent bacterial infections.
C5-C8	Recurrent infections with neisseria species, particularly N. meningitidis.
C9	Frequent occurrence in the Japanese population, possibly associated with N. meningitidis infections.
Factor D	Bacterial infections including recurrent systemic nerisseria infections.
Properdin	Infections with N. meningitidis.
C1 inhibitor	Hereditary/acquired angioneurotic oedema. SLE-like disease in some patients.
C3 nephritic factors (C3 NeF)	Acquired C3 deficiency. Membranoproliferative glomerulonephritis (MPGN), partial lipodystrophy and bacterial infections.
Factor I and factor H	Recurrent bacterial infections caused by secondary C3 deficiency. Inflammatory diseases. Factor H deficiency may cause MPGN.
MBL	Recurrent infections, SLE, recurrent spontaneous abortions.

Defects in the classical pathway
C2 deficiency is the most commonly occurring CD in humans, occurring in approximately 1/40,000 of Caucasians. The clinical manifestations of genetic C1, C4, C2 and C3 deficiency vary widely, table 1, however, a rheumatological disease such as SLE, discoid lupus, dermatomyositis, scleroderma or membranoproliferative glomerulonephritis (MPGN) often develops. Particularly in the case of C2 or C3 deficiency, there is an increased susceptibility to infection (bacteraemia, septicaemia, meningitis, osteomyelitis) with encapsulated bacteria (e.g. pneumococci, meningococci, H. influenzae type b).
C1 inhibitor (C1-INH) deficiency follows an autosomal dominant inheritance and leads to hereditary angioedema (HAE). The characteristic manifestations of HAE are attacks of 2-3 days' duration of angioedema with intestinal and respiratory obstruction due to oedematous mucous membranes. Paraclinical findings, apart from impaired or non-functional C1-INH, include decreased levels for C4 and C2 due to increased consumption of complement and uncontrolled activation. The levels are lowest during attacks, but also between attacks. Acquired angioedema (AAE) is often associated with lymphoproliferative diseases and is due to an increased breakdown of C1-INH, however, idiopathic disease also occurs. The symptoms are of recurrent angioedema or urticaria. Severe infections may also occur. As a rule, patients have M component and/or circulating autoantibodies that bind C1-INH. The mechanism for the increased breakdown is still unclear.
Auto-antibodies to C1q occur in severe SLE and are manifest as a low C1q level and C1q antibodies. In addition, C1q antibodies appear in hypocomplementaemic urticarial vasculitis syndrome (HUVS), and may also appear in other immunological diseases.

Defects in the alternative pathway
Factor D deficiency has been described in recurrent invasive infections, primarily with N. gonorrhoeae and N. meningitidis. Properdin deficiency is a sex-related recessive (X-linked) hereditary disease, which bears a strong predisposition to meningococcal disease. Fulminant infections have been described.
C3 nephritic factors (C3 NeF) are auto-antibodies to enzymes that regulate the conversion of C3 to C3b, involving dysregulation of the alternative pathway and acquired complement deficiency due to increased breakdown of C3 and/or C5. The appearance of C3 NeF is associated with MPGN, partial lipodystrophy and increased tendency to infection.

Defects in the lectin pathway
Mannan-binding lectin (MBL) deficiency occurs as a genetically impaired production or reduced stability of the protein and is associated with increased tendency to infection in children and adults. In addition, MBL deficiency is suspected to be associated with severe erosive rheumatoid arthritis, juvenile chronic arthritis, SLE and recurrent spontaneous abortions.

Defects in the terminal complex (Membrane attack complex, MAC)
Deficiencies of C5, C6, C7, C8 and C9 typically involve recurrent invasive infections with N. gonorrhoeae and N. meningitidis.

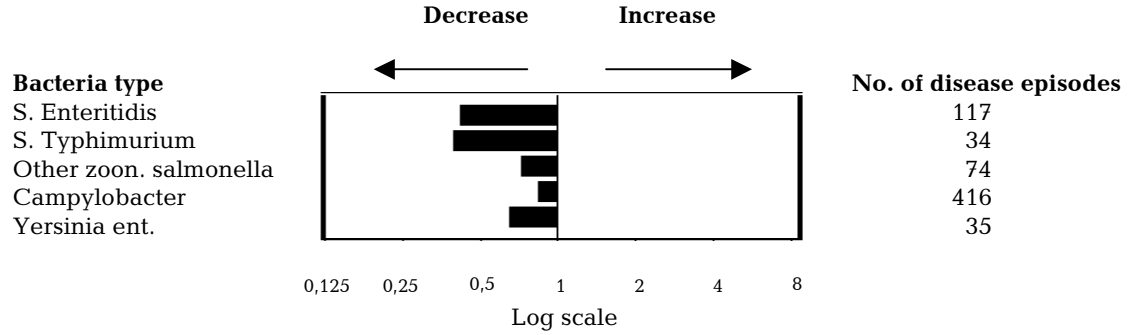
Diagnostic strategy
Most kinds of congenital or acquired CD can be excluded by a normal result of analysis of complement function (haemolytic assay), together with C3 and C4 measurement.
In the event of abnormal function investigation results, analysis for other components in CS and for specific antibodies may be indicated. In collaboration with the Department of Clinical Microbiology and Immunology at the University Hospital in Lund, the Dept. of Autoimmunology offers investigation of complement function and extended complement analysis, with measurement of complement proteins as well as factors and antibodies relevant for the investigation of complement deficiency. Measurement of MBL concentration in serum is performed by the Department of Clinical Biochemistry, SSI.
(R. Pelck, Department of Autoimmunology)

15 January 2003

Patients with positive cultures of pathogenic intestinal bacteria, November-December 2002

	S. Enteritidis		S. Typhimurium		Other zoon. salmonella		Campylobacter		Yersinia ent.	
County	Nov	Dec	Nov	Dec	Nov	Dec	Nov	Dec	Nov	Dec
Copenhagen Munic.	7	1	2	1	6	5	33	21	3	1
Frederiksberg Munic.	-	-	1	-	-	1	5	2	-	-
Copenhagen	4	2	3	-	6	3	20	16	3	-
Frederiksborg	4	1	2	-	-	4	16	9	-	1
Roskilde	5	5	-	-	-	4	16	7	1	1
West Zealand	2	-	-	-	1	1	3	2	-	-
Storstrøm	1	4	1	1	-	3	12	8	4	1
Bornholm	2	-	-	-	-	-	1	1	-	-
Funen	10	4	3	3	6	5	22	8	2	3
South Jutland	9	2	2	3	2	3	10	9	-	-
Ribe	6	4	-	3	1	2	16	9	-	-
Vejle	7	1	1	-	1	2	23	14	1	1
Ringkøbing	3	4	-	-	3	1	20	12	2	1
Aarhus	11	4	1	2	3	3	27	16	4	-
Viborg	4	1	-	2	-	2	8	5	-	2
North Jutland	6	3	3	-	5	1	33	10	4	-
Unknown	-	-	-	-	-	-	2	-	-	-
DK Nov/Dec 2002	81	36	19	15	34	40	267	149	24	11
DK Nov/Dec 2001	86	40	23	38	53	38	346	180	20	17

Barometer for pathogenic intestinal bacteria, November-December 2002

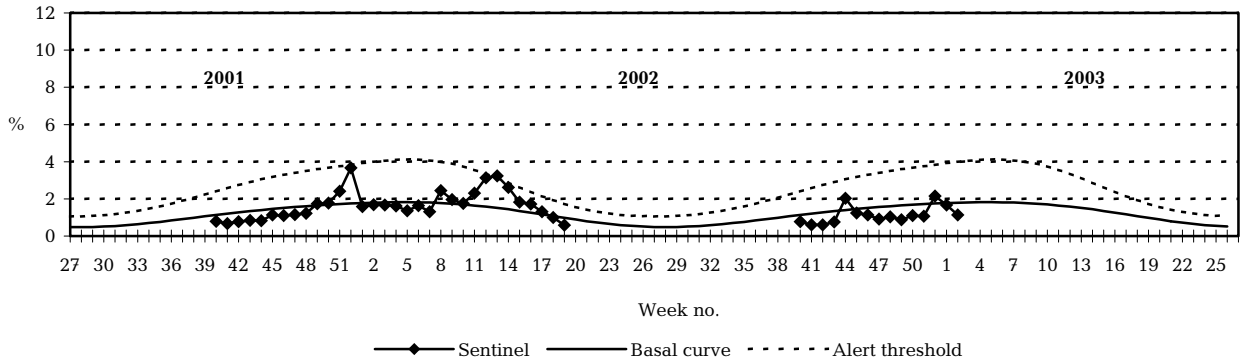


The barometer shows number of disease episodes in the two relevant months compared with the average of 15 two-month periods in the last five years. Further surveillance data may be obtained at www.germ.dk.

(Dept. of G-I Infections)

Sentinel surveillance of influenza activity

Weekly percentage of consultations, 2001/2002/2003



Sentinel: Influenza consultations as percentage of total consultations
Basal curve: Expected frequency of influenza consultations under non-epidemic conditions
Alert threshold: Possible incipient epidemic

(Dept. of Epidemiology)