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These guidelines were approved for the first time in May 2007 and were later revised. This fifth edition was approved in June 2015. A new revision will take place no later than May 2017.

The guidelines are approved by: ***SLIPI*** *– Swedish Physician Association for Primary Immune Deficiency. These guidelines can also be found at www.slipi.nu (see "medicinsk info").*

PIO *– Primary Immunodeficiency Organization (Swedish patient organization for PI)*

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Guidelines

For Assessment, Diagnosis and Treatment of Immunodeficiencies

Introduction

There can be many reasons why a person is suffering from recurrent infections. One explanation may be a total or partial lack of some of the components of the immune system. Primary immune deficiency is not as uncommon as we previously thought. It's easy to overlook this condition among all patients seeking counsel for infections. The physicians treat the current infection, but might forget to ask about the number of infections in the patient's medical history. Chronic lung disease for example is not only caused by smoking but can be the result of repeated infections due to underlying immunodeficiency. Many patients with immunodeficiency needing treatment are probably still undiagnosed. Today, it's estimated that there are approximately 40 000 people in Sweden with a primary immunodeficiency (PID). Many, but not all of these individuals suffer from recurrent infections. Since many of the people with PID have yet to be diagnosed, the treatment they receive might not be the correct one.

We considered it particularly important to formulate guidelines since many physicians rarely consider immunodeficiency as a differential diagnosis to recurrent infections. These guidelines provide opportunities for patients to receive similar treatment across the country.

The guidelines you now hold in your hand were developed by a working group within SLIPI (Swedish Physician Association for Primary Immune Deficiency). The working group consists of physicians with special interest in primary immunodeficiency diseases and includes both pediatricians and various specialists working in adult medicine. The Swedish patient association for primary immunodeficiency also gave valuable input to these guidelines.

The guidelines should be viewed as recommendations for the minimum that needs to be investigated and followed up. Every patient, of course, must be assessed individually and may therefore require additional investigation or further treatment. The guidelines are updated at regular intervals. This is the updated fifth edition and is expanded with more diagnoses of primary immune deficiencies and a section on immunoglobulin substitution was added as well

These guidelines were adopted in May 2007 and revised in 2015.
A new revision will be carried out no later than May 2017.

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Contents

Evidence grading system

We have chosen to use the same evidence grading system as the one used by the Swedish Association for Specialists in Infectious Diseases, which is in turn based on the system used by the Infectious Disease Society of America (IDSA). Each recommendation consists of a letter that indicates whether we recommend following it or not, and the strength of that recommendation. A Roman numeral indicates the basis for the recommendation, and each recommendation is given in parentheses after the relevant assertion.

Not all the recommendations are scientifically substantiated, nor can they be. Proven experience has consequently served as an important basis for the necessary compromises.

STRENGHTH OF RECOMMENDATION	DEFINITION
A	Good evidence to support a recommendation for use/intervention
B	Moderate evidence to support a recommendation for use/intervention
C	Poor evidence to support a recommendation for use/intervention
D	Moderate evidence to support a recommendation against use/intervention
E	Good evidence to support a recommendation against use/intervention

QUALITY OF EVIDENCE	DEFINITION
I	Evidence from at least one proper randomized controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees

The Warning Signs for Primary Immunodeficiency in children and adults

Symptoms

THE WARNING SIGNS FOR PRIMARY IMMUNODEFICIENCY (PID) IN CHILDREN

If one or more of the following warning signs are present, a workup for primary immunodeficiency should be considered:

1. 6 or more ear infections per year. Ear infections with complications such as chronic perforation or mastoiditis
2. ≥ 2 episodes of sinus infections per year
3. Infections that do not respond properly on antibiotic therapy
4. ≥ 2 episodes of pneumonia per year
5. Failure of an infant to gain weight or thrive, if other causes are ruled out
6. Recurrent, deep skin or organ abscesses
7. Persistent oral thrush or dermal fungal infections
8. Infections on unusual locations and/or caused by an unusual infectious agent
9. Two or more serious sinus infections per year
10. A family history of primary immunodeficiency disease

Step 1

SUGGESTED WORKUP IN CASE OF REPEATED BACTERIAL INFECTIONS

- WBC with differential count
- Immunoglobulin quantification: IgG, IgA, IgM
- Documentation of infections – Infection Diary
- Growth chart

Step 2

Contact a specialist in the field.

Symptoms

THE WARNING SIGNS FOR PRIMARY IMMUNODEFICIENCY (PID) IN ADULTS

If one or more of the following warning signs are present, a workup for primary immunodeficiency should be considered:

1. ≥ 4 upper airway infections requiring antibiotics per year, such as otitis media, sinusitis, bronchitis or pneumonia
2. Little or no effect from antibiotic therapy or recurrent relapsing infections
3. ≥ 2 severe bacterial infections, such as osteomyelitis, meningitis, sepsis or soft-tissue infections
4. ≥ 2 radiologically confirmed episodes of sinusitis or pneumonia over a period of 3 years
5. Infections with unusual localizations and/or caused by unusual agent
6. Known primary immunodeficiency disease in the family

Step 1

SUGGESTED WORKUP IN CASE OF REPEATED BACTERIAL INFECTIONS

- WBC with differential count
- Immunoglobulin quantification: IgG, IgA, IgM
- IgG subclasses: IgG1 - IgG4
- Documentation of infections – Infection Diary

Step 2

Contact a specialist in the field.

X-linked Agammaglobulinemia

(Bruton's disease, XLA)

Definition

ICD-10: D80.0A
Incidence: 1:70 000–300 000 newborns

DEFINITE DIAGNOSIS

Male with no or very low B cell count *and either*

- Confirmed mutation in *BTK* (the gene for Bruton's tyrosine kinase) *or*
- Absence of the BTK-protein (flow cytometry)

PROBABLE DIAGNOSIS

- Male with no or very low B cell count (CD19/CD20)
- Onset of bacterial infections during first year of life
- Serum IgG, IgA, and IgM severely depressed after maternal serum IgG has been consumed. Serum IgG often <2 g/L and almost total absence of serum IgA and IgM
- Male relative on mother's side with confirmed *BTK* mutation

Differential Diagnosis

- Autosomal recessive forms of agammaglobulinemia such as:
- Defective immunoglobulin molecule µ-chain (µ-heavy chain deficiency) (*IGHM* mutation)
  - λ5 deficiency *(IGLL1* mutation)
  - BLNK (B cell linker protein) -defect
  - TACI (transmembrane activator and CAML interactor) defect
  - CD19 deficiency
- Common Variable Immunodeficiency (CVID)
- Other causes of agammaglobulinemia: see Differential Diagnoses p. 79

Symptoms and Signs

- Disease onset usually at 4-8 months of age, in rare cases during the second year of life
- Recurrent and prolonged bacterial respiratory infections
- Increased risk of serious bacterial infections such as septicemia and meningitis
- Special problems:
  - Chronic *H. influenzae* colonization in the airways and conjunctivae
  - Encephalitis of uncertain etiology, possibly caused by an infection (particularly enterovirus) or autoimmune process. Often with slow progression of the disease, where the symptoms may be vague, e.g. delayed cognitive development and/or problems at school
  - Infections by various *Mycoplasma* species in the airways, urinary tract and joints
  - Increased frequency of intestinal infections
  - Increased incidence of autoimmune diseases
  - Absence of tonsils and small or non-palpable lymph nodes
  - Absence or low level of specific antibodies to previous vaccinations or infections
  - Peripheral B cell count (CD19/CD20) is usually very low, but may be normal in isolated cases
  - Impaired function and/or reduced count of T cells may be present on rare occasion

Assessment

To be done in cooperation with a PID specialist.

LABORATORY EVALUATION

- Hb, WBC with differential, platelets
- ESR, CRP
- ASAT, ALAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Lymphocytes (CD3, CD4, CD8, CD19, CD56)
- Analysis of antibodies pathogens to which the patient was vaccinated against or was infected with e.g. pneumococci, hemophilus, tetanus and polio
- If encephalitis is present:
  - Brain MRI
  - Cerbrospinal fluid analysis, including bacterial culture and PCR for possible neurotropic viruses, primarily the herpes group, JC virus and enterovirus
- If chronic diarrhea is present:
  - microbiological diagnosis
  - consider investigations for inflammatory bowel diseases
- DNA-based analysis confirms the diagnosis

PRIOR TO IMMUNOGOBULIN TREATMENT

- Save serum
- HBsAg and PCR for HIV and HCV

OTHER EXAMINATIONS

- Pulmonary function (dynamic and static spirometry and diffusion capacity and if available inert gas washout)
- Growth chart for children, weight for adults
- Offer genetic counseling and carrier diagnostics for adult female relatives

Treatment

- Immunoglobulin substitution. Dose: 100 mg per kg body weight/week. Aim for high serum IgG levels, preferably >10 g/L as trough level. Higher doses of 150-200 mg per kg body weight/week can be given if necessary **(AI)**. High serum concentrations of serum IgG lower the risk of bacterial infections **(BII)**. High serum IgG may also act prophylactically against encephalitis **(CIII)**. Please, see the chapter on immunoglobulin substitution for further information

OTHER TREATMENT OPTIONS

- Appropriate antibiotic treatment
  - Possible long-term treatment with an appropriate antibiotic
  - In cases of chronic lung damage, follow the guidelines for respiratory care of cystic fibrosis with drainage and intermittent antibiotic treatment with sepsis doses **(AIII)**
- Contraindication: Live vaccines **(BIII)**
- Contact physiotherapist, dietician and/or counselor as needed

Follow-up

After 6 months

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum IgG, IgA, IgM

After 12 months and at yearly follow-ups

- Same as for 6 months
- Save serum

Every 3 years, unless clinically warranted earlier

- Pulmonary function

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Common Variable Immunodeficiency

(CVID)

Definition

ICD-10: D83.0
Prevalence among adults: 1:20 000

- Serum IgG <3 g/L, serum IgA<0.07 g/L and normal or reduced levels of serum IgM
- >4 years of age
- Exclusion criteria: See Differential Diagnoses p. 79

Low IgG/IgA ICD-10: D83.8

- Serum IgG 3 g/L up to the lower reference range and serum IgA between 0.07 g/L and lower reference range for the laboratory
- >4 years of age
- The clinical significance is unclear
- Exclusion criteria: See Differential Diagnoses p. 79

Symptoms and Signs

- Disease onset usually between the ages of 10 to 30 years, although both younger and older individuals can develop this disease
- Recurrent/prolonged bacterial respiratory infections
- Increased frequency of lung disease/lung damage
- Increased risk of serious bacterial infections such as sepsis and meningitis
- Chronic *H. influenzae* colonization in the airways and conjunctivae
- Increased frequency of intestinal infections
- Increased incidence of autoimmune disease
- Increased risk of granulomas (sarcoidosis-like) most commonly in the lungs, lymph nodes, liver and spleen
- Slightly increased risk of malignancy (lymphoma and stomach cancer)
- Infections by various *Mycoplasma* species in the airways, urinary tract and joints
- Encephalitis of uncertain etiology, possibly caused by infection (such as enterovirus) or autoimmune process. Often presents with slow progression, in which the symptoms may be vague, such as cognitive developmental delay or problems at school
- Analysis of antibodies to pathogens against which the patient was vaccinated or was previously infected, with e.g. pneumococci, hemophilus, tetanus and polio
- Leukocytes and thrombocytes may be reduced
- Peripheral B cell count (CD19 or CD20) may vary, can be normal, low or zero
- Reduced function and/or reduced number of T cells may be present

Assessment

To be done in cooperation with a PID specialist.

DIAGNOSTIC TESTS

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- Analysis of specific antibodies against pathogens which the patient was previously infected with or was vaccinated against, e.g. pneumococci, hemophilus, tetanus and polio
- Fractionated serum proteins
- B12 and folate
- TSH and tyroxin (T4)
- Screening for complement deficiencies. Please see Assessment in chapter about complement deficiencies

PRIOR TO IMMUNOGOBULIN TREATMENT

- Save 0 serum
- HBsAg and HIV-Ag and PCR for HCV

OTHER EXAMINATIONS

- Weight in adults, growth chart in children
- CT of thorax, upper abdomen (ask about thymoma, lymph nodes and granuloma in liver and spleen). HRCT of the lung in cases of suspected lung injury. CT can be replaced by chest X-ray and ultrasound abdomen in patients with mild symptoms
- Bone marrow aspiration (to rule out malignancy, and count of plasma cells – reduced in CVID)
- Lung function tests (dynamic and static spirometry and diffusion capacity, and if available, inert gas washout)

BASED ON INDIVIDUAL ASSESSMENT

- CT of sinuses
- Screening for subclass-specific antibody deficiency
- *Pneumococcus* antibodies
- *Hemophilus* antibodies

If respiratory infection is present

- Nasopharyngeal, sputum and/or throat culture
- Mycoplasma species (PCR)

If intestinal symptoms are present

- Fecal culture
- Feces-PCR for protozae or fecal microscopy (cysts and worm eggs)
- If *Giardia* is suspected, do gastroscopy with duodenal biopsy
- Clostridium *difficile* cytotoxin
- Consider inflammatory bowel disease and celiac disease

If urinary tract symptoms are present

- Urine dipstick test and culture
- *Mycoplasma hominis*/*Ureaplasma urealyticum* PCR and/or culture (in urine)

Treatment

- Liberal use of antibiotics, even for long-term, if signs of bacterial respiratory infection are present
- Based on an individual assessment, it may be appropriate to vaccinate against pneumococci, Hib and influenza, as this may reduce the frequency of infections in some patients

INDICATIONS FOR IMMUNOGLOBULIN TREATMENT (AI)

- All patients with CVID should receive immunoglobulin treatment to normalize serum IgG measured as trough level **(AI)**
- The aim is to reduce the number of infections and consequent organ damage **(AI)**
- The presence of serum anti-IgA antibodies should be checked for prior to treatment. The presence of these antibodies is not normally an impediment to subcutaneous immunoglobulin treatment, but caution must be observed if intravenous substitution **(BIII)**

IMMUNOGLOBULIN TREATMENT

- Most patients are treated either subcutaneously or intravenously
- Recommended dose is 100 mg per kg body weight/week **(AI)**
- Primary treatment option: 100 mg per kg body weight/week administered as subcutaneous infusions (SCIG) **(AI)**
- If impaired lung function or a continued high frequency of infection, consider increasing the dose to 150-200 mg per kg body weight/week **(AII)**
- The dose may need to be further increased in rare cases of increased serum IgG loss, particularly in connection with inflammatory bowel disease **(AIII)**
- The treatments are initially often given more frequently in order to raise the serum IgG levels quickly, i.e. via daily subcutaneous infusions (100 mg per kg body weight) for five days, followed by weekly infusions as described above **(CIII)**

OTHER TREATMENTS

- Contact a physiotherapist, dietician and/or counselor if necessary
- If granulomas are found consider steroids **(BIII)**
- In case of bacterial respiratory infections liberal use of antibiotics and prolonged periods of treatment should be considered

Follow-up

IF IMMUNOGLOBULIN TREATMENT

After 6 months

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Analysis of specific antibodies against pathogens which the patient was previously infected with or was vaccinated against, e.g. pneumococci, hemophilus, tetanus and polio
- Evaluation of infection frequency and possible new findings such as autoimmunity, arthritis and inflammatory bowel disease

After 12 months and at yearly follow-ups

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Analysis of antibodies to pathogens against which the patient was vaccinated or was previously infected, with e.g. pneumococci, hemophilus, tetanus and polio
- Evaluation of infection frequency and possible new findings such as autoimmunity, arthritis and inflammatory bowel disease

BASED ON INDIVIDUAL ASSESSMENT

Every 3 years, unless clinically warranted earlier

- Lung function

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IgG Subclass Deficiency

Definition

ICD-10: D80.3
Estimated prevalence among adults: 1:250–500

- At least two low values for the same IgG subclass at an interval of least 12 weeks during any infection-free period
- >4 years of age. Some children may normalize their serum IgG subclass level a few years later, and a definitive diagnosis should not be made until the child reaches school age
- Serum IgG1 <2.8 g/L
- Serum IgG2 <1.15 g/L
- Serum IgG3 <0.24 g/L
- Exclusion criteria: see Differential Diagnoses p. 79

Children 3–18 years of age

	3–6 years	6–9 years	9–18 years
IgG1	<2.7 g/L	<3.5 g/L	<3.7 g/L
IgG2	<0.65 g/L	<0.85 g/L	<1.00 g/L
IgG3	<0.16 g/L	<0.20 g/L	<0.22 g/L

Symptoms and Signs

- Without any symptoms
- Recurrent and/or chronic respiratory infections
- Increased frequency of lung disease/lung damage

Assessment

To be done in cooperation with a PID specialist.

DIAGNOSTIC TESTS

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Fractionated serum proteins
- B12, folate
- TSH, T4

PRIOR TO IMMUNOGLOBULIN TREATMENT

- Save 0 sample (serum)
- HbsAg, anti-HCV and anti-HIV

BASED ON INDIVIDUAL ASSESSMENT

- Screening for subclass-specific antibody deficiency
- Screening for complement deficiency
- Lung function (dynamic and static spirometry and diffusion capacity)
- Chest X-ray, CT sinus
- Vaccination against pneumococci and/or Hib, with measurement of antibody levels before and 3–6 weeks after vaccination

If respiratory infection is present

- Nasopharyngeal, sputum and/or throat culture

Treatment

- Liberal use of antibiotics if signs of bacterial respiratory infection are present
- Based on an individual assessment, it may be appropriate to vaccinate against pneumococci and influenza, since it might lower the frequency of infections in some patients

INDICATIONS FOR IMMUNOGLOBULIN TREATMENT (BII)

The need for treatment must be documented prior to any immunoglobulin treatment.

- The patient should keep an infection diary
- ≥ 4 respiratory infections requiring antibiotics per year for at least two years in adults
- Underlying signs of lung disease/lung damage strengthen the indication for treatment
- Otherwise based on individual assessment

IMMUNOGLOBULIN THERAPY

- Recommended initial dose is 100 mg per kg body weight/week **(BII)**. If the clinical response is satisfactory, the dose can be reduced to 50 mg per kg body weight/week **(CIII)**. However, there are no studies showing the effect of the lower dose of 50 mg per kg / week but there is clinical experience from several clinics with adult patients with IgG subclass-deficiency that have adequately responded to this low dose **(CIII)**
- In case of severely decreased lung function and continued high frequency of bacterial infections it may be necessary to increase the immunoglobulin dose to 150–200 mg per kg body weight/week **(CIII)**

EVALUATION OF TREATMENT EFFICACY

- Before immunoglobulin treatment is started, the patient should be informed that a treatment trial period of 12–18 months is planned, and that a period of controlled treatment withdrawal will be needed to evaluate the efficacy of the treatment. The withdrawal period should last at least 6 months, possibly longer
- The patient must keep an infection diary. Bacterial infections should be confirmed by cultures
- Patients with severely decreased lung function (FEV_1 <30 %) and positive therapeutic response to immunoglobulin treatment should continue their substitution and they should not have a withdrawal attempt
- The immunoglobulin treatment should be reinstated in cases of increased frequency of infections (see above) during the treatment withdrawal. The indication for reinstatement is strengthened if the patient has an underlying lung disease such as asthma or COPD, or if the lung function deteriorates.
- A new trial withdrawal may then be considered after 3–5 years. Thereafter, any additional treatment interruption should be done at longer intervals, after individual assessment. Controlled treatment withdrawal means that the patient has an infection diary and regular check-ups. Documenting all infections with primarily respiratory cultures (sputum and nasopharyngeal) and if necessary blood tests (CRP and WBC) and X-ray should be mandatory

OTHER TREATMENTS

- Contact a physiotherapist, dietician and/or counselor as needed

Follow-up

IF IMMUNOGLOBULIN TREATMENT

After 6 months

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency

After 12 months and at yearly follow-ups

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency and, if relevant, new symptoms

IgG SUBCLASS DEFICIENCY WITHOUT IMMUNOGLOBULIN TREATMENT

SYMPTOMATIC
1–3 year interval, depending on the clinical presentation

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency
- Lung function test

ASYMPTOMATIC

- The patient should be informed about complications to immunodeficiency
- Follow-up visits as needed

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IgA Deficiency

Definition

ICD-10: D80.2
Prevalence among adults: 1:600

- Serum IgA<0.07 g/L, normal level of serum IgM and normal or elevated level of serum IgG
- >4 years of age. Some children may normalize their serum IgA a few years later; a definitive diagnosis should not be made before the age of 12 years
- Exclusion criteria: see Differential Diagnoses p. 79

Symptoms and Signs

- Without any symptoms
- Increased frequency and/or duration of respiratory infections particularly viral ones
- Increased risk of autoimmune diseases, such as celiac disease, thyroid disorders, Type I diabetes and SLE
- Progression to CVID has been reported (1:50)
- Normal or reduced vaccine IgG antibody response to polysaccharide antigens

Assessment

To be done in cooperation with a PID specialist.

DIAGNOSTIC TESTS

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Fractionated serum proteins
- B12, folate
- TSH, T4
- Serum anti-transglutaminase IgG antibodies

BASED ON INDIVIDUAL ASSESSMENT

- Screening for subclass-specific antibody deficiency
- Secretory IgA
- Screening for complement deficiency
- Lung function tests (dynamic and static spirometry and diffusion capacity)

If respiratory infection are present

- Sputum and/or throat culture
- Chest and sinus X-rays

If intestinal symptoms are present

- Fecal culture
- Feces-PCR for protozae or fecal microscopy (cysts and worm eggs)
- If *Giardia* is suspected, do gastroscopy with duodenal biopsy
- *Clostridium difficile* cytotoxin
- Consider inflammatory bowel disease and celiac disease

Treatment

- Antibiotics: bacterial infections should be treated in the usual manner
- If problems with sinusitis: assessment by an ENT specialist
- Based on an individual assessment, it may be appropriate to vaccinate against pneumococci, hemophilus and influenza, as this can lower the frequency of infections in some patients
- If necessary, refer to physiotherapist for mobilizing airway secretions
- Some patients with frequent bacterial infections may benefit from immunoglobulin therapy although there are no controlled trials supporting this **(CIII)**. For treatment strategy, dosage and controls: see IgG Subclass Deficiency p. 12

OTHER

- Patients with anti-IgA antibodies should be provided with written information that can be shown prior to any blood transfusion

Follow-up

SYMPTOMATIC PATIENT
1–3 years interval, depending on the clinical presentation

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- B12, folate
- TSH, T4

ASYMPTOMATIC PATIENT

- The patient should be informed regarding possible complications due to IgA deficiency
- Follow-up visits as needed

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Hyper-IgM Syndromes

(HIGM)

Definition

ICD-10: D80.5
Incidence: at least 1: 500 000 newborns

The hyper-IgM syndromes (HIGM) are a heterogeneous group of immunodeficiencies caused by defect immunoglobulin class switch recombination, (CSR) from IgM to IgG, IgA and IgE production, leading to low levels of serum IgG and serum IgA, with normal to high levels of IgM. The diseases are inherited in either an X-linked or autosomal recessive fashion.

PRACTICAL CLASSIFICATION

- Combined T and B cell defects
  - CD40 ligand deficiency (CD40L, CD154), X-linked form, constitutes about 75 % of all HIGM
  - CD40 deficiency, which is as well as the forms below are automsomal recessive inherited. PASLI: Defect activation of phosphatidyl inosito-3-phosphatase with mutations in *PIK3CD* or *PIKR1*
  - B cell defects
  - AID
  - AID C-terminal
  - UNG
  - NFkB
  - PMS2

There are additional forms of HIGM that are not yet genetically defined.

CERTAIN DIAGNOSIS

Patients with multiple bacterial and/or opportunistic infections, low serum IgG and serum IgA, with normal to high serum IgM and one of:

- Male patient with a mutation in the gene for CD40L
- Male or female patient with a mutation in one of the genes coding for AID, CD40, AID C-terminal, UNG, NFkB or PMS2

POSSIBLE DIAGNOSIS

- Serum IgG and serum IgA significantly reduced, with normal to high serum IgM after maternal IgG is consumed for male or female patients with the onset of bacterial and/or opportunistic infections during the first years of life

Differential Diagnosis

Several other hypogammaglobulinemias may be considered such as:

- X-linked agammaglobulinemia (Bruton's disease, XLA)
- CVID
- Autosomal recessive forms of hypogammaglobulinemia such as
  - Defective immunoglobulin molecule µ-chain (Mutation in *IGHM* gene)
  - λ-deficiency (mutations in the gene *IGLL1*)
  - BLNK (B cell linker protein) defect
  - TACI (Transmembrane activator and CAML interactor) defect
  - CD19 deficiency
- SCID and CID
- Transient hypogammaglobulinemia
- Some DNA repair disorders such as ataxia-telangiectasia and Nijmegen Breakage Syndrome may sometimes present with HIGM-like features
- Congenital rubella syndrome occasionally reveals HIGM-like features

Symptoms and Signs

In all forms

- Early onset with a median age of diagnosis before the age of 1 year
- Recurrent and prolonged bacterial infections of the lung, ear and sinuses. Recurrent pneumonias sometimes leading to bronchiectasis
- Increased incidence of serious bacterial infections such as septicemia and meningitis
- Encephalitis, probably caused by infection, especially enteroviruses presenting with progressive neurodegenerative disease with developmental delay and/or school problems
- Increased frequency of intestinal infections, sometimes without any identifiable microorganism
- Oral ulcers, gingivitis, proctitis and perianal ulcers
- Absent or low levels of specific antibodies against vaccine antigens or infections

In case of CD40L- or CD40-defect: opportunistic infections and other diseases such as

- Pneumonia with *Pneumocystis jiroveci* (onset infection in 40 %)
- 40 % have neutropenia at diagnosis, 60–70 % develop neutropenia over time
- Chronic cryptosporidiosis with persistent diarrhea and poor growth. Complications such as cholangiopathy, chronic hepatitis and liver cancer
- Increased incidence of *Toxoplasma*, Cryptococci and atypical mycobacterial infections
- Chronic infections with CMV and parvovirus
- Increased incidence of autoimmune diseases such as seronegative arthritis, IBD, ITP, hemolytic anemia and thyroid disease
- Osteopenia
- Bilary tract and liver malignancies
- In case of AID-defect: generalized lymphadenopathy

Assessment

To be performed in cooperation with a PID specialist.

LABORATORY WORKUP

- Hb, WBC with differential, platelets
- ESR, CRP
- ASAT, ALAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Lymphocytes (CD3, CD4, CD8, CD19, CD56)
- Analysis of specific antibodies against pathogens which the patient was previously infected with or was vaccinated against, e.g. pneumococci, hemophilus, tetanus and polio
- If encephalitis
  - MRI of brain and spinal tap including cultures and PCR for neurotropic viruses such as the herpes group, JC virus, astrovirus and enterovirus

OTHER TESTS

After individual assessment and depending on symptoms

- Lung function, dynamic and static spirometry and diffusion capacity, and if possible inert gas washout
- abdominal CT or MRI is indicated if hepatomegaly, cholangitis, or abnormal liver tests
- Chest X-ray and sinus CT
- Bronchoscopy and BAL in patients with chronic lung disease who do not respond to antibiotics or if suspected infection with *Pneumocystis jiroveci*
- Endoscopy with biopsy in case of chronic diarrhea
- Liver biopsy in liver disease alternative pathological liver tests

Provide genetic counseling and mutation carrier analysis for adult female relatives.

Treatment

Immunoglobulin-substitution. If possible, subcutaneous administration.

Initial dose 100 mg/kg body weight / week **(AI)**. If needed, higher doses of 150–200 mg/kg body weight/week may be given. Aim at serum IgG values, >10 g/L as trough or steady state level. Serum levels of IgG >10g/L reduces the risk of bacterial infections **(BII)**. High serum IgG might also protect against encephalitis **(CIII)**

PRIOR TO IMMUNOGLOBULIN TREATMENT

- Save pre-treatment serum
- HBsAg and PCR for HIV and HCV

OTHER TREATMENTS

- Appropriate antibiotic treatment
- PCP prophylaxis with trimethoprim-sulfamethoxazole for patients with CD40L or CD40 defect
- G-CSF treatment for neutropenia since immunoglobulin substitution usually do not normalize neutropenia
- If necessary, prophylactic treatment with antibiotics
- In case of chronic lung injury, follow the advice that applies to respiratory care in cystic fibrosis with drainage and intermittent antibiotic therapy in sepsis doses **(AIII)**
- Contraindication: live vaccines **(BIII)**
- Contact with physiotherapist, dietician and/or counselor as needed

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

In patients with defects in CD40L or CD40 and opportunistic infections, HSCT should be considered. If possible, this is performed as early as possible with an HLA-identical sibling or unrelated HLA-identical donor

Follow-up

After 6 months

- Hb, WBC with differential, platelets
- ESR, CRP
- ASAT, ALAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM

After 12 months and at yearly follow-ups

- Same as for 6 months

Every 3 years, unless clinically warranted earlier

- Lung function test
- Patients with chronic lung disease should be evaluated regularly, if possible with inert gas washout test

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Specific Antibody Deficiencies with Normal Ig Concentrations

Definition

ICD-10: D80.8
Estimated prevalence among adults: 1:5000

- Poor immune response, against polysaccharide antigens such as *S. pneumonia* and *H. influenzae* type B
- Serum IgG, within normal range
- Regarding *S. Pneumonia*:
  - At 2-5 years of age. Normal response is >50 % of the antigens tested with a fourfold increase after vaccination or a serum level >1.3 µg/ml per antigen. Investigation before the age of two years is not recommended
  - At 5 years of age or more. Normal response is <70% of the antigens tested with a fourfold increase after vaccination or a serum level >1.3 µg/ml per antigen
- Regarding *H. influenza*:
  - Children and adults are not considered protected against invasive pneumonia if serum level is <0.15 mg/L. A serum level of 0.15-1.0 is supposed to give protection for a short time. Serum level >1.0mg/L may give a longstanding immunity for H. influenza type B with the polysaccharide capsule
- Exclusion criteria: see Differential Diagnoses p. 79

Symptoms and Signs

- Healthy
- Recurrent and/or chronic respiratory tract infections
- Increased frequency of lung disease/lung damage
- Missing or low levels of specific antibodies against previous vaccinations and infections, especially of IgG2 specific antibodies
- Increased risk of bronchiectasis
- Increased risk of pneumonia
- Increased risk for chronic or recurrent rhino-sinusitis and otitis
- May be in connection with IgA, IgG2 and/or IgG3 deficiencies

Assessment

- Cooperation with a PID specialist is recommended
- Referral to a pediatrician is recommended if "Warning Signs" for children indicates an increased risk, see p. 5
- Infection diary to follow the patient's infections is valuable
- Analyses of antibodies against *S. pneumonia* are commonly done with only 3 antigens in Sweden, which is not in accordance with international recommendations most often suggesting 7 or more antigens
- A more comprehensive analysis of *S. pneumonia* can be done in Finland: Vaccination Programme Unit, Department of Health Protection, National Institute for Health and Welfare, Helsinki, Finland
- Analyses of *H. influenza* are done by most immunological laboratories in Sweden

DIAGNOSTIC TESTS

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- B12, folic acid
- TSH, T4
- Fractionated proteins
- Analysis of specific antibodies to pathogens against which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio

PRIOR TO IMMUNOGLOBULIN TREATMENT

- Save 0 sample (serum)
- HBsAg, anti-HCV and anti-HIV

BASED ON INDIVIDUAL ASSESSMENT

- Screening for subclass specific antibody deficiency
- Screening for complement deficiency. Please see Assessment in chapter about complement deficiencies
- Lung function tests (dynamic and static measurements as well as diffusion capacity and, if available inert gas washout)
- Chest X-ray, CT sinus

If respiratory infection is present

- Nasopharyngeal, sputum and/or throat culture
- Chest X-ray, CT sinuses

Treatment

- Liberal use of antibiotics if signs of bacterial respiratory infection are present
- In case of poor immune response against *S. pneumonia*, it is recommended to vaccinate with conjugated pneumococcal vaccine followed by analysis of the vaccine response against the strains in the conjugated vaccine after 3-6 weeks. After another 8 weeks unconjugated vaccine can be given followed by analysis of the response to strains in the unconjugated vaccine after another 3-6 weeks. The immune response against other pathogens ought to be evaluated taking in consideration the patient's previous vaccinations and infections. If the immune response continuously is inappropriate and the frequency of infections is high, treatment with immune globulins may be considered
- In case of poor immune response *H. influenzea*, vaccinate using conjugated vaccine and measure the immune response after 3-4 weeks. The immune response against other pathogens ought to be evaluated taking in consideration the patient's previous vaccinations and infections. If the immune response continuously is inappropriate and the frequency of infections is high, treatment with immune globulins may be considered

PRIOR TO IMMUNOGOBULIN TREATMENT

- Save 0 serum
- HBsAg and HIV-Ag and PCR for HCV

INDICATIONS FOR IMMUNOGLOBULIN TREATMENT (BII)

The need for treatment must be documented prior to any immunoglobulin treatment is instituted.

- Patients should keep an infection diary
- ≥ 4 respiratory infections requiring antibiotics per year for at least two years in adults
- Underlying signs of lung disease/lung damage strengthen the indication for treatment as does chronic changes in sinuses and ears
- Poor antibody response to immunizations tested according to the above recommendation
- Otherwise based on individual assessment

IMMUNOGLOBULIN THERAPY

- Recommended initial dose is 100 mg/kg body weight/week **(BII)**. If the clinical response is satisfactory, the dose can be reduced to 50 mg/kg body weight/week **(CIII)**. However, there are no studies showing the effect of the lower dose of 50 mg/kg body weight/week but there is clinical experience from several clinics with adult patients with IgG subclass deficiency which has adequately responded to this low dose **(CIII)**
- In case of severely decreased lung function and continued high frequency of bacterial infections it may be necessary to increase the immunoglobulin dose to 150–200 mg/kg body weight/week **(CIII)**

EVALUATION OF TREATMENT EFFICACY

- Before immunoglobulin treatment is started, the patient should be informed that a treatment trial period of 12–18 months is planned, and that a period of controlled treatment withdrawal will be needed to evaluate the efficacy of the treatment. The withdrawal period should last at least 6 months, possibly longer
- Patients should keep infection diaries. Bacterial infections should be confirmed by cultures
- Patients with severely decreased lung function (FEV_1 <30 %) and positive therapeutic response to immunoglobulin treatment should continue their substitution with immune globulins and they should not have a withdrawal attempt
- Immunoglobulin treatment should be reinstated in case of increased frequency of infections (see above) during the treatment withdrawal. The indication for reinstatement is strengthened if the patient has an underlying lung disease such as asthma or COPD, or if the lung function deteriorates
- A new trial withdrawal may be considered after 3–5 years. Thereafter, any additional treatment interruption should be done at longer intervals, after individual assessment. Controlled treatment withdrawal means that the patient has an infection diary and regular check-ups. Documenting all infections with primarily respiratory cultures (sputum and nasopharyngeal) and if necessary blood tests (CRP and WBC) and X-ray should be mandatory

OTHER TREATMENTS

- Contact a physiotherapist, dietician and/or counselor as needed

Follow-up

IN CASE OF IMMUNOGLOBULIN TREATMENT

After 6 months

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency
- Analysis of specific antibodies to pathogens against which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio

After 12 months and at yearly follow-ups

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency and, if relevant, new symptoms
- Analysis of specific antibodies to pathogens against which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio

SPECIFIC ANTIBODY DEFICIENCY WITHOUT IMMUNOGLOBULIN TREATMENT

SYMPTOMATIC
1–3 year interval, depending on the clinical presentation

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Urine dipstick
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Evaluation of infection frequency
- Lung function test
- Analysis of specific antibodies to pathogens against which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio

ASYMPTOMATIC

- Patient should be informed about known complications to their immunodeficiency
- Follow-up visits if needed

AFTER INDIVIDUAL EVALUATION

Continuous antibiotic treatment as an alternative therapy.

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Severe Combined Immunodeficiency

(SCID)

Definition

ICD-10: D81
Incidence: approximately 1.5:100 000 newborns

- Absence of T and B cell function, sometimes in combination with absence of/defective NK cell function
- Continuous transition to combined defects with partial T cell function
- Heterogeneous condition with many underlying genetic etiologies
  - Mutations that affect development and function of T cells and sometimes B cells or NK cells
  - Mutations that lead to dysfunction or absence of thymus, and thus indirectly to defective T cell development
- Practical classification
  - T-, B+, NK±
    - XSCID (mutation in the gene for the common gamma chain of many cytokine receptors, *IL2RG*)
    - *JAK3* mutation (mutation in the gene for Janus kinase 3)
    - *IL7RA* mutation (mutation in the gene for the alpha chain in the interleukin 7 receptor)
  - T-, B-, NK+
    - RAG1/2 deficiency, including abortive forms such as Omenn's syndrome and leaky SCID
    - Artemis deficiency
  - ADA (adenosine deaminase) deficiency
  - Reticular dysgenesis. Mutation in *AK2*, which encodes a mitochondrial enzyme and results in absence of both lymphocytes and myeloid cells
  - Thymus
    - Complete DiGeorge's syndrome (heterogeneous syndrome including CHARGE association, 22q11-deletion syndrome, etc.)
    - Human nude SCID (*FOXN1* mutation)
  - Other unusual conditions, including defects in T cell receptor activation and intracellular signal defects

Differential Diagnoses

- HIV
- Various combined immune defects (MHC class II defect ("bare lymphocyte syndrome"), ZAP-70 defect, etc)
- X -linked hyper-IgM syndrome (CD40 ligand defect) usually presenting at about 6 months of age with interstitial pneumonitis

Symptoms and Signs

Immediately contact a tertiary center with particular expertise in this disease as soon as SCID is suspected. Do not wait for local assessment results. 100 % mortality unless stem cell transplant is performed early in life.

- Onset during first months of life. Note that the initial symptoms may be vague
  - Chronic cough and obstructive lung disease
  - Diarrhea and malabsorption
  - Recurrent *Candida* infection of the mouth and diaper region
- Poor weight and height gain
- Skin rash, often pronounced, as a manifestation of maternal T cell engraftment or Omenn's syndrome
- Respiratory failure due to interstitial pneumonia caused by *Pneumocystis jiroveci* or virus (CMV, parainfluenzae etc), often seen late in the clinical course, at the age of 4–6 months
- Sudden death among infants in the immediate or extended family
- BCG-itis with extensive local infection and possible osteitis or generalized infection

Assessment

- The most important screening test is total lymphocyte count in peripheral blood <2 x 10^9 /L
- CD3+ cells <1 x 10^9 /L
- Analysis of T and B cell function
- TRECs
- DNA-based analysis to identify disease-causing mutation(s). NOTE Not all forms of SCID have their molecular genetic etiology defined yet
- Offer genetic counseling to the family and mutation carrier diagnosis in adult female relatives in the X-linked forms

Treatment

- Prophylaxis with trimethoprim sulfa **(AI)** and fluconazole **(BII)**
- Contraindications: live vaccines **(AII)**
- Filtered, irradiated and CMV-negative blood products ONLY **(AII)**
- Hematopoietic stem cell transplant **(AI)** within 4–6 weeks after diagnosis **(AIII)**
- Gene therapy **(AII)** (Not done in Sweden)

OTHER TREATMENTS

- Offer the family support from a counselor/psychologist if needed

Follow-up

- Following the stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined with visits to the local pediatric/adult clinic for day-to-day care

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Combined Immunodeficiencies

Definition

ICD-10: D81.8
Incidence: Unknown

Combined immunodeficiency is a vague term that includes disorder with varying etiologies and clinical pictures. The term includes certain monogenic disorders with a milder T cell defect than severe combined immunodeficiency (SCID) as well as hypomorphic mutations in genes that otherwise cause SCID.

Symptoms and signs vary from "leaky" SCID, i.e. a picture similar to SCID, to that of common variable immunodeficiency with T cell defects and to only granulomatous lesions in the skin or to even only selective IgA deficiency.

Hypomorphic mutations in genes that normally are associated with SCID

- Mutations in *RAG1/2*
- Mutations in *DCLREIC* (Artemis)
- Late onset adenosine deaminase deficiency (ADA deficiency)

Other monogenic disease such as

- Purine nucleoside phosphorylase deficiency (PNP-deficiency) with mutation in *PNP*
- Hyper-IgM syndrome with CD40 ligand or CD40 defect (see that chapter)
- CD3γ deficiency
- CD8 deficiency
- ZAP70 deficiency
- MHC class I and II deficiency

Differential Diagnoses

- Severe combined immunodeficiency
- Common variable immunodeficiency

Symptoms and Signs

- Viral infections
- Bacterial infections
- Infections with *P. jiroveci*
- Autoimmunity (PNP deficiency: autoimmune hemolytic anemia)
- Neurological symptoms in PNP deficiency
- Pyoderma gangrenosum in MHC class I deficiency

Assessment

To be performed in cooperation with a PID specialist.

LABORATORY WORK-UP

- Hb, WBC with differential and platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- T and B cell functional tests
- Analysis of specific antibodies against pathogens to which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio
- SDNA analysis

Treatment

- Prophylaxis with trimethoprim-sulfa and fluconazole
- Immunoglobulin substitution
- Contraindications: live vaccines
- Filtered, irradiated and CMV-negative blood products ONLY
- Hematopoietic stem cell transplantation

Follow-up

- Following the stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined with visits to the local pediatric/adult clinic for day-to-day care

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DOCK8 Deficiency

(Dedicator of Cytokinesis 8 Deficiency)

Definition

ICD-10: D82.4W

Incidence: Unknown, probably underestimated as the disease is lately characterized.
Autosomal recessive inheritance with mutation in *DOCK8* gene.

DOCK8 deficiency is often included among the hyper-IgE syndrome, but the disease lacks symptoms outside the immune system and the persons can have normal IgE levels. Severe chronic viral infections of the skin are typical features. As the name hints, the mutation results in defect cytoskeleton and actin activation that are thought to cause mechanical damage to lymphocytes when passing through, for example in the skin.

Differential Diagnoses

- If high serum IgE: autosomal dominant and autosomal recessive hyper-IgE syndromes
- Combined T and B cell deficiencies

Symptoms and Signs

- Severe persistent skin infections caused by viruses such as HSV, VZV, HPV and MCV *(Molluscum contagiosa virus)* and Staphylococci
- Life threatening infections (septicemia, meningitis, severe pneumonias)
- Other bacterial infections
- Mucocutaneous candidiasis
- Malignancy (in about 20 % of non-transplanted patients)
- Severe generalized eczema
- Allergies (food allergy common)
- Autoimmunity
- Cerebral vascular catastrophes and leucoencephalitis

Assessment

To be performed in cooperation with a PID specialist.

LABORATORY WORK-UP

- Hb, WBC with differential and platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum IgE
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- T and B cell functional tests
- Analysis of specific antibodies against pathogens to which the patient was vaccinated or was infected with e.g. pneumococci, hemophilus, tetanus and polio
- Specific DNA analysis

Treatment

Immunoglobulin substitution. Dose: 100 mg per kg body weight/week. Aim for high serum IgG levels, preferably trough levels of >10 g/L. Higher doses, 150-200 mg per kg body weight/week, can be given if necessary. High serum concentrations of serum IgG lower the risk of bacterial infections.

PRIOR TO IMMUNOGOBULIN TREATMENT

- Save serum
- HBsAg and PCR for HIV and HCV

OTHER TREATMENTS

- In case of chronic lung injury, follow the advice that applies to respiratory care in cystic fibrosis with drainage and intermittent antibiotic therapy in sepsis doses
- Contraindication: live vaccines **(CIII)**
- Refer to physiotherapist, dietician and/or counselor as needed
- Infectious prophylaxis (trimethoprim-sulfa and fluconazole)
- Interferon α-2b
- Hematopoietic stem cell transplantation

Follow-up

After 6 months

- Hb, WBC with differential and platelets
- ALAT, ASAT, LD, ALP
- Serum IgG, IgA, IgM

After 12 months and at yearly follow-ups

- As for 6 months
- Patients with chronic lung disease should be evaluated regularly, if possible with inert gas washout test
- Following the hematopoietic stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/ adult clinic for day-to-day care

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Wiskott-Aldrich Syndrome

(WAS)

Definition

ICD-10: D82.0
OMIM: 301000
Incidence: approximately 0.3:100 000 newborns

- Defective function of WASp (Wiskott Aldrich Syndrome protein) that affects the function of the cytoskeleton in all hematopoietic cells
- Caused by mutations in *WASP*
- X-chromosome-linked recessive
- Very rarely caused by mutations in *WIPF1* encoding WIP (WASP interacting protein) that stabilizes and prevents degradation of WASp

Differential Diagnosis

- Congenital hereditary thrombocytopenia
- TAR syndrome (thrombocytopenia, absent radius)

Symptoms and Signs

- WAS is a progressive combined immunodeficiency with symptoms and signs mentioned below if no hematopoietic stem cell transplantation is performed
- Presents immediately after birth with thrombocytopenia. This may be the only symptom of a mutation in *WASP* and the disease is then called XLT (X-linked thrombocytopenia)
- In addition to thrombocytopenia, the disease causes a qualitative thrombocyte defect. Boys are at risk to suffer from severe bleedings when the platelet count falls below 30 x 10^9/L. This is most pronounced during systemic viral infections
- Bleeding from the gut during the first year of life is common
- The bleeding tendency often decreases after 2–3 years of age; the reason why is unknown
- During the first year of life patients with the typical disease suffers from atopic dermatitis with bleeding and secondary skin infections
- Later in life other allergic manifestations, such as asthma and hay fever, are often seen
- From 6–12 months of age, patients have recurrent bacterial infections, particularly of the respiratory tract but also more serious infections like meningitis and sepsis
- From about 10 years of age patients are at high risk of lymphoid malignancy
- From adolescence, high incidence of autoimmunity such as hematologic autoimmunity that can aggravate thrombocytopenia
- In typical cases high/very high IgE, high IgA, normal IgG (IgG2 low many times) and moderately reduced IgM

Assessment

To be done in cooperation with a PID specialist.

- The most important screening test is the detection of microthrombocytes. Platelets should be analyzed by manual measurement of platelet diameter. Many automatic cell counters calculate platelet volume, but counters are usually not calibrated to analyze microthrombocytes (4.5 fl) and will give false normal result
- Hb, WBC with differential, platelets
- ESR, CRP
- ASAT, ALAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum IgE
- Lymphocytes (CD3, CD4, CD8, CD19, CD56)
- T cell functional test
- TRECs
- DNA-based analysis to identify disease-causing mutation

NB. The results of lymphocytes and T cell function are often normal during first year of life

Treatment

- Immunoglobulin substitution
- Contraindications: Live vaccine **(AII)**
- **Only filtered, irradiated and CMV negative blood products (AIII)**
- Hematopoietic stem cell transplantation **(AI)** before the age of 3–4 **(AIII)**

OTHER TREATMENT

- Provide family support from a counselor and/or psychologist if needed
- Offer genetic counseling to the family and carrier diagnostics to adult female relatives

Follow-up

- Following the hematopoietic stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/adult clinic for day-to-day care

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Ataxia Telangiectasia

(AT)

Definition

ICD-10: G11.3
OMIM 208900
Incidence: 2–3:1 million newborns

- Ataxia telangiectasia is primarily a progressive neurological disease with cerebellar ataxia, telangiectasia, and varying degree of immunodeficiency
- Inheritance is autosomal recessive
- Is caused by the mutations in the *ATM* gene encoding ATM kinase. ATM kinase plays a central role in the cell's mechanisms to repair damaged DNA

Differential Diagnosis

- Ataxias of other etiologies

Symptoms and Signs

- Progressive ataxia from 1–2 years of age, which confines most children to wheelchairs by age 10/early teens
- Mental retardation does not belong to the clinical picture
- Telangiectasias develop from 1–2 years of age or later. These are mainly found in the cornea, cheeks, earlobe, on the neck and the upper part of the thorax
- Progressive immunodeficiency with mainly bacterial respiratory infections
- IgA deficiency, low IgG subclasses and sometimes more extensive immunological abnormalities. The degree of immunodeficiency vary
- Very high risk of malignancy, particularly lymphoma and in teenagers also cancer
- Endocrine dysfunction is common, for example growth hormone deficiency and hypogonadism
- Premature aging with graying and aged skin, often already as a teenager
- Elevated α-fetoprotein

Assessment

- Serum IgG, IgA, IgM
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- α-fetoprotein
- DNA analysis of *ATM*

Treatment

- Strict restriction of all radiation (diagnostic and therapeutic) and alkylating chemotherapy due to the inability to repair DNA. Diagnosis and treatment of pneumonia should be based on clinical signs and not by X-ray **(AII)**
- After individual assessment, immunoglobulin substitution **(AIII)**

OTHER TREATMENT

- Habilitation from early age. Aids shall be introduced early so that the child/youth still have the ability to learn to use these
- Offer genetic counseling to the family

Follow-up

- Hb, WBC with differential and platelets
- Control susceptibility to infection and immunoglobulins for the assessment of whether and when the substitution should be initiated
- Pulmonary function test, if necessary
- Preferably cared for in collaboration between neurologist/habilitation and immunologist

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22q11 Deletion Syndrome

(DiGeorge Syndrome)

Definition

ICD-10: Q93.5
OMIM: 188400
Incidence: 25:100 000 births

- Micro-deletion syndrome with wide-range clinical presentations and severity such as various malformations, immunodeficiency, speech and language difficulties, learning disabilities and neuropsychiatric problems
- Defect: 22q11 deletion
- Inheritance - autosomal dominant, but about 90 % are caused by a new mutation
- Other names used: DiGeorge syndrome (DGS) and velocardiofacial syndrome. The majority of these are caused by the 22q11 deletion
- The name DiGeorge syndrome is often used when severe immune deficiency dominate the clinical picture in infants with heart defects and / or hypocalcemia with or without 22q11 deletion. If 22q11 deletion is present, it is appropriate to use the term 22q11 Deletion Syndrome

Differential Diagnosis

- DiGeorge syndrome phenotype without 22q11 deletion
- SCID
- CHARGE syndrome
- 22q11 Duplication syndrome

Symptoms and Signs

- Heart failure, usually of conotruncal type (e.g. interrupted aortic arch, truncus arteriosus communis, Fallot's anomaly, VSD)
- Thymic aplasia or -hypoplasia
- Immunodeficiency: usually mild-moderate with symptoms of frequent and/or prolonged respiratory tract infections, recurrent otitis and chronic otitis. About 1 % has severe immunodeficiency (SCID T- phenotype, sometimes Omenn syndrome like)
- Immunological abnormalities: low T cells, low IgG, IgA deficiency, IgG subclass deficiency or developing CVID-like phenotype
- Autoimmune diseases (such as ITP, autoimmune hemolytic anemia, hypothyroidism, rheumatoid arthritis)
- Hypocalcemia, hypoparathyroidism
- Feeding difficulties (infant)
- Characteristic facial features
- Delayed speech and language development
- Velopharyngeal insufficiency (nasal speech)
- Mild motor developmental delay and motor problems
- Learning disabilities
- ADHD, autism spectrum disorder
- Mental health problems/disorders in adolescents and adults
- Miscellaneous malformations/deformities (kidneys, spine, feet)
- Dental abnormalities, enamel disturbances, increased risk of caries
- Hearing loss (usually mild to moderate)
- Refractive errors, strabismus

Assessment

Detection of 22q11 deletion by MLPA, FISH or CGH array.

Blood tests:

- The immune system:
  - Hb, WBC with differential and platelets
  - Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
  - TRECs
  - Analysis of T cell function if CD4 + cells <0.4 x10^9/L
  - Serum IgG, IgA, IgM
  - IgG subclasses as needed (>6 years)
  - Analysis of antibodies against tetanus and pneumococci (>1–2 years)
- Investigation of parathyroid function
  - ionized serum Ca, serum phosphate, plasma PTH
- Investigation of thyroid function
  - TSH, T4

Other Assessments

- Heart
- Speech and language (speech therapist)
- Ear, hearing
- Eye
- Teeth
- Neurological development: motor skills, neuropsychology, neuropsychiatry
- Kidneys (ultrasound to detect abnormalities)
- Spine (scoliosis)

Treatment

- After individual assessment, immunoglobulin substitution **(AIII)**
- Antibiotic prophylaxis if necessary
- Immunoglobulin substitution if hypogammaglobulinemia is present
- Specific treatment of other symptoms
- Calcium should be checked before and after surgery

OTHER TREATMENT

- Provide family support – counselor and/or psychologist if needed
- Offer genetic counseling to the family
- Habilitation from early age.
- Referral to speech therapist at 1 year of age or even earlier
- Educational support activities

IF SEVERE IMMUNE DEFICIENCY (SCID T- PHENOTYPE)

- Prophylaxis with co-trimoxazole and fluconazole
- Immunoglobulin substitution
- Thymus transplantation or hematopoietic stem cell transplantation
- Contraindications: live vaccines
- ONLY filtered, irradiated and CMV-negative blood products

Follow-up

Patients are preferably cared for in collaboration between a team of specialists, primary care physicians, habilitation team and other specialists, depending on individual needs.

Follow up according to Ref 1. Practical Guidelines.

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Hyper-IgE Syndrome

(HIES with mutation in STAT3, HIES with mutation in PGM3)

Definition

ICD-10: D 82.4
OMIM: 147060
Incidence: The exact incidence is not known; in Sweden there are less than 20 known cases. The syndrome has been reported in Caucasians and individuals of Asian and African origin. The male/female distribution is equal.

HIES is a syndrome with recurrent infections (mainly bacterial) caused by mutations in the *STAT3* gene or in rare cases caused by mutations in the *PGM3* gene

- Inheritance is autosomal dominant in case of STAT3 defect. Inheritance is autosomal recessive in case of PGM3 deficiency
- HIES is a multiple organ defect syndrome (immune, vascular, bone, teeth, etc.)
- The mutations cause impaired function of Th17 cells, which seems to be the main cause of vulnerability to infection. The main pathogen is Staphylococcus

Differential Diagnosis

- Atopic dermatitis
- Wiskott-Aldrich syndrome
- SCID (Severe Combined Immunodeficiency)
- DOCK8 deficiency
- Other eosinophilic syndrome
- CGD

Symptoms and Signs

- Skin: papulopustular, itchy rash that can be seen in infants already a few week old - similar to atopic dermatitis. Leads to recurrent abscesses, furuncles, and cellulitis, frequently progressing to lymphadenitis that usually are "cold", lacking the classical signs and symptoms of inflammation. The most common agents are *Staphylococcus aureus* and *Candida albicans*
- Respiratory: Chronic respiratory infections - bacterial otitis media, mastoiditis, sinusitis, pneumonias. Note: the infections can be severe even though the patient remains asymptomatic. Pulmonary complications such as abscesses, bronchiectasis and pneumatoceles are common. Opportunistic infections, including fungal infections of the lungs occur later during life
- Skeleton:
  - Characteristic dysmorphic facial features develop with time making the patients resemble each other
  - Fracture proneness
  - Primary teeth are often retained
  - Scoliosis is very common
  - Poor growth
- Laboratory Findings:
  - Very high serum IgE, typically >2000 kU/L
  - High levels of eosinophils

NOTE: There is an absence of other atopies despite high IgE.

A scoring system for the diagnosis is available on
http://www.niaid.nih.gov/LabsAndResources/labs/aboutlabs/lcid/stat3base/Documents / scoringsystem.pdf

Assessment

- Hb, WBC with differential, platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum IgE
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- DNA analysis of *STAT3* and *PGM3*

Treatment

- Appropriate skincare
- Antibiotic prophylaxis - particularly against staphylococcal infections
- Aggressive treatment of infections. Important to try to find the pathogen involved. Essential to protect the lungs. If necessary, immunoglobulin substitution
- Possible fungal prophylaxis
- Contact with physiotherapist, pulmonologist, dietician, dentist, orthopedic surgeon and/or counselor as needed

Follow-up

- Hb, WBC, with differential and platelets
- Check lung function as pulmonary complications are the most common cause of death

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Familial Hemophagocytic Lymphohistiocytosis (FHL)

Definition

ICD-10: D76.1
OMIM: 267700, 603553, 608898, 603552, 613101
Incidence: 2–3:100 000 births

- A group of inherited diseases with defective production of cytotoxic granules within T and NK cells leading to uncontrolled proliferation and activation of macrophages and cytotoxic T cells. This in turn leads to a general acute and intense inflammatory reaction
- Defined either by
  - Detection of mutations in one of the genes that cause FHL 1–5 (FHL1 unknown, FHL2 *PRF1*, FHL3 *UNC13D*, FHL4 *STX11*, FHL5 *STXBP2*) X-chromosome-linked lymphoprolipherative syndrome (XLP) type 1 (*SH2D1A*,) and 2 (*BIRC4*) Griscelli syndrome type 2 (*RAB27A*) and Chediak-Higashi syndrome (*CHS1*) or
  - 5 of the following 8 clinical and laboratory criteria and exclusion of secondary forms
    - Fever
    - Splenomegaly
    - Cytopenia ≥2 cell lines
    - Hemoglobin <90 g/L (before 4 weeks of age <120 g/L)
    - Thrombocytes <100 × 10^9/L
    - Neutrophils <1 × 10^9 /L
    - Hypertriglyceridemia and/or hypofibrinogenemia
    - Fasting: Triglycerides ≥3 mmol/L
    - Fibrinogen <1.5 g/L
    - Ferritin ≥500 mg/L
    - Soluble IL2 receptor ≥ 2400 U/ml
    - Reduced or no NK cell function
    - Hemophagocytosis in bone marrow, spinal fluid, or lymph node

Differential Diagnosis

- Various secondary hemophagocytic lymphohistiocytoses (HLH) associated with malignancies, infections and autoimmune diseases. Particularly common are secondary HLH as a complication to systemic JIA (frequently called macrophage activating syndrome or MAS)
- Visceral leishmaniasis
- Lysosomal acid lipase deficiency (OMIM 278000)

Symptoms and Signs

- Onset is usually during the first year of life. Approximately 10 % presents already in the neonatal period. It is important to note that late-onset forms exist and that vague symptoms that may cause suspicion of another primary immunodeficiency can precede the onset of FHL with several years
- Typical symptoms are prolonged "undefined" fever with hepatosplenomegaly and cytopenia. Detection of hemophagocytosis may be delayed
- Among laboratory tests, ferritin is a valuable and easily analyzed marker. The criteria include serum ferritin >500 mg/L, but usually ferritin is much higher and can reach values of 100 000 mg/L or higher. A value of 10000 has a very high sensitivity and specificity for HLH
- All clinical findings or laboratory abnormalities are nonspecific but the often marked abnormal values and the total spectrum of findings are typical and gives the diagnosis
- During the course of the disease almost all patients will have CNS inflammation
- Griscelli syndrome type 2 and Chediak-Higashi syndrome also have typical pigment abnormalities
- Without treatment FH is 100 % fatal

Assessment

- In case of suspected FHL the laboratory tests described in the criteria should be analyzed
- In case of suspected FHL: you must contact the regional immunology center immediately

Treatment

- Induction of remission. In Sweden, this (today 2015) is usually achieved with chemotherapy (etoposide) in combination with cyclosporine and dexamethasone and intrathecal methotrexate **(AIII)**
- Only filtered, irradiated and CMV negative blood products **(AII)**
- Hematopoietic stem cell transplantation **(AI)** as soon as possible after remission

At follow-up it is important to consider the high risk of damage to the CNS.

OTHER TREATMENT

- Provide family support from a counselor and/or psychologist if needed

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Chediak-Higashi Syndrome

Definition

ICD-10: E70.3
Incidence: Estimated to 1–2 children per 1 million newborns
Autosomal recessive inheritance with mutation in *LYST*

Microtubuli polymerization defect that influences the formation of phagosomes and the empting of granule of the phagosomes. This causes defect killing of phagocytized bacteria. Also, the formation of granule in cytotoxic T cells is defect, which is the basis for viral infections such as EBV causing hemophagocytosis. The latter is called accelerated phase

Differential Diagnosis

- Griscelli syndrome type 2
- Hermansky Pudlak syndrome type 3
- Hemophagic syndrome (HLH) at other diseases

Symptoms and Signs

- Partial albinism with silvery hair, photophobia and sensitivity to light
- Bacterial infections
- Peripheral neuropathy
- Hepatosplenomegaly
- Anemia, neutropenia
- Giant lysosomes observed within neutrophil granulocytes
- HLH (accelerated phase)

Assessment

- Hb, WBC with differential and platelets
- CRP and ESR
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum IgE
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- Bone marrow aspirate: Large inclusion bodies (lysosomes) within the myeloid cells
- Hair shafts show even distribution of enlarged melanin granule (but not lumps of melanin as seen in syndrome). Typical finding with use of polarized light

DNA-analysis confirms the diagnosis

Treatment

- Antibiotics for infections
- Hematopoietic stem cell transplantation (before accelerated phase)

Follow-up

- Following the hematopoietic stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/adult clinic for day-to-day care

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Griscelli Syndrome Type 2

(partial albinism with immunodeficiency)

Definition

ICD-10
Incidence: Estimated to 1–2 children per 1 million newborns

There are three forms of Griscelli syndrome, but only type 2 is a primary immunodeficiency. *RAB27A* controls the formation of Rab27A that together with two other proteins transport the melanosomes out to the melanocytes' periphery. At a mutation in *RAB27A* melanosomes accumulate in the melanocytes. Together with other proteins Rab27A is also necessary for the transportation of the cytolytic granule in cytotoxic T cells, which explains the immunodeficiency.

Autosomal recessive inherited mutation in *RAB27A*.

Differential Diagnosis

- Chediak-Higashi syndrome
- Hermansky Pudlak syndrome type 3

Symptoms and Signs

- Partial albinism
- Bacterial infections
- Neutropenia
- Trombocytopenia
- Hypoglobulinemia
- Hemophagocytic syndrome (HLH)

Assessment

- Hb, WBC with differential and platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- Bone marrow aspirate:
- Hair shafts show uneven distribution of melanin (lumps of melanin). Typical finding with use of polarized light

DNA-analysis confirms the diagnosis

Treatment

- Antibiotics
- Hematopoietic stem cell transplantation

Follow-up

- Following the hematopoietic stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/adult clinic for day-to-day care

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Lymphoproliferative Syndromes

(XLP1 and XLP2)

Definition

ICD-10: D82.3
Incidence: XLP1 - estimated to 1 per 100,000 newborn boys; XLP2 to 1 per 5,000,000 boys

XLP type 1 is caused by mutation in the *SH2D1A*–gene that controls the formation of SAP (SLAM-associated protein). SAP is an adaptor protein necessary for the proper development of cytotoxic T and NKT cells, respectively.

XLP type 2 is caused by mutation in the *XIAP*-gene that controls the formation of X-linked inhibitor of apoptosis (XIAP). XIAP is a protein that prevents T cells from apoptosis. The relation to development of hemophagocytosis (HLH) is largely unknown.

Differential Diagnosis

- All different kinds of hypoglobulinemia (XLA, CVID etc.)
- PID with HLH

Symptoms and Signs

XLP1

- No or only very minor findings before an EBV infection
  - IgG-subclass deficiency
- Symptoms almost without exception triggered by an EBV infection
  - About1/3 develop hypoglobulinemia that can be misinterpreted as CVID
  - About 1/3 develop B cell lymphoma
  - About 1/3 develop HLH

XLP2

- After an EBV infection (about 60 %) or other herpes infection (e.g. HHV6 or CMV) HLH
  - NB. Also other herpes viruses and sometimes without documented infection: HLH. The patient often falls ill already at the age of a couple of months
- Inflammatory bowel disease, usually severe and resistant to therapy
- Recurrent splenomegaly often associated with fever. Considered to be a subclinical form of HLH
- Hepatitis

Assessment

- Hb, WBC with differential and platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- Investigation as for hemophagocytosis (see the chapter on Familial Hemophagocytic Lymphohistiocytosis, p. 38)

DNA-analysis confirms the diagnosis.

Treatment

- If hypoglobulinemia: Immunoglobulin substitution
- Lymphoma: rituximab sometimes in combination with cytostatic drugs followed by hematopoietic stem cell transplantation
- HLH. Remission induction according to HLH04 protocol followed by hematopoietic stem cell transplantation

Follow-up

- Following the hematopoietic stem cell transplant, the patient should be cared for on an alternating basis between the local pediatric clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/adult clinic for day-to-day care

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Mendelian Susceptibility to Mycobacterial disease (MSMD)

Definition

ICD-10: D82.8
Incidence: Not known

A condition with impaired IFN-γ-mediated immunity. The etiology is mutations in one of today (2013) 8 known genes involved in interleukin-12/23-(IL-12/ IL-23) dependent IFN-γ signaling.

- Autosomal recessive inheritance in case of mutation in any of the genes *IL12RB1*, *IL12B, IFNGR1, IFNGR2*
- Autosomal dominant inheritance in case of mutation in one of the genes *STAT1*, *IRF8*
- X-linked inheritance can in rare cases occur in patients with certain specific mutations in *CYBB* and *IKBKG* (encoding NEMO)

Symptoms and Signs

- MSMD are often, but not always, symptomatic
- The mutations may cause both partial and total defect of the IFN-γ-mediated immunity
- Is characterized by selectively increased susceptibility to mycobacterial infections including atypical mycobacteria and BCG strain
- Increased risk of infection with *Salmonella* and *Candida albicans* and slightly increased risk also for other intracellular microbes (*Nocardia, Paracoccidioidomyces, Histoplasma* and *Leishmania*) requiring similar immunological defenses as mycobacteria
- Complete lack of IFN-γR1 and IFN-γR2 and STAT-1, as well as complete IL-12p40- and IL-12Rβ1-defects, have a later onset and a better prognosis
- Mutations in *IKBKG* increase the risk of infections to varying degrees, and only certain mutations are associated with isolated susceptibility to mycobacterial infections
- Mutations *CYBB* cause X-linked CGD, but some mutations can cause isolated Mycobacterial infections only and no other manifestations of CGD
- MSMD has almost exclusively onset in childhood, before the early teens
- Infection in individuals with MSMD has a high mortality (30 %), especially in those with atypical mycobacteria (50 %). Prognosis improves with age

Assessment

To be done in cooperation with a PID specialist.

- Functional study of IL-12/IFN-γ signaling pathways with analysis of e.g. TNF and IFN-γ production after stimulation of monocytes and T lymphocytes
- DNA-based analysis to identify disease-causing mutations

Treatment

- Antibiotics for infections according to national guidelines for mycobacteria. Extended regimens may be needed if there is poor response to therapy **(BII)**
- IFN-γ treatment is effective in some of the known genetic defects **(CIII)**
- Surgical revision/drainage of infection site if it does not heal on drug therapy **(BII)**
- Appropriate treatment of any other simultaneously occurring infections caused by MSMD

OTHER TREATMENT

- Provide the family support from a counselor and/or psychologist if needed

Prophylaxis

- BCG vaccination is contraindicated **(AII)**
- Possibly prophylactic antibiotic treatment of susceptible patients **(CIII)**

Follow-up

- Close clinical monitoring to detect latent infections and to assess whether prophylactic treatment may be indicated
- In case of clinical TB infection, the recommended search for additional cases of TB among the patient's contacts must be done

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APECED (Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dysplasia)

Definition

ICD-10: E31.0
OMIM: 240300
Incidence: 2–3: 1 000 000 newborns
Prevalence in Finland 4: 100 000

- Etiology: mutations in *AIRE* encoding the transcription factor autoimmune regulator (AIRE) necessary for negative selection and apoptosis of autoreactive T cells in the thymus
- Inheritance is autosomal recessive

DEFINITIVE DIAGNOSIS

- Two of the following three key symptoms: mucocutaneous candidiasis, hypoparathyroidism and Addison's disease *or*
- One of the three findings above if siblings have a verified diagnosis *or*
- Proven mutation in *AIRE*

PROBABLE DIAGNOSIS

- One of following three key symptoms: mucocutaneous candidiasis, hypoparathyroidism, or Addison's disease (before 30 years of age) and at least one of the minor symptoms that are chronic diarrhea, keratitis, periodic rash with fever, severe constipation, autoimmune hepatitis, vitiligo, alopecia or enamel hypoplasia
- One of the key symptoms plus the detection of antibodies to interferons
- One of the key symptoms and detection of antibodies against NALP5, AADC (aromatic L-aminosyredecarboxylase), TPH (tryptophan hydroxylase) or TH (tyrosine hydroxylase)

Differential Diagnosis

- IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome
- Autoimmune polyendocrinopathy type 2

Symptoms and Signs

- Autoimmune hypoparathyroidism with onset in childhood or early adulthood. Later in life the majority will develop Addison's disease
- Marked mucocutaneous candidiasis, but no deep candida infections
- This triad of symptoms is seen at some point in 70 % of patients
- Later in life often chronic active hepatitis, malabsorption, pernicious anemia, alopecia, vitiligo and primary hypogonadism (but rarely hypothyroidism and type 1 diabetes mellitus)
- Enamel-hypoplasia, nail-dystrophy and other skin changes
- Rash with fever
- The disease is often complicated by bronchiectasis, fulminant autoimmune hepatitis and interstitial nephritis, and increased incidence of oral and oesophageal cancer
- Progress and symptoms vary greatly among individuals, even in the same family
- A variety of autoantibodies can be detected not only against endocrine organs but also against many cytokines

Assessment

- Detection of autoantibodies in serum
- Demonstration of candida in cultures from skin and mucous membranes
- DNA analysis of *AIRE*

Treatment

- Symptomatic treatment of hormone deficiencies (calcium, vitamin D, cortico- and mineralocorticoids etc.)
- Prolonged oral treatment with azoles for candida infections
- Symptomatic treatment with immunosuppression in autoimmune hepatitis, interstitial nephritis, etc.
- Before surgery be sure to check calcium and adrenal gland function. Provide family support from a counselor and/or psychologist if needed

Follow-up

- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Additional samples depending on organ involvement
- Control of autoantibodies that are associated with the development of specific autoimmunity
- The patient should be cared for in collaboration between endocrinologist and immunologist

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Autoimmune Lymphoproliferative Syndrome

(ALPS)

Definition

ICD-10: D72.8, D89.8
OMIM: 601859
Incidence: 2–3:100 000 births

- ALPS is caused by defective apoptosis of lymphocytes in the thymus .
- Inheritance is autosomal dominant, but modifying factors are likely. In the same family members can be found with the mutation but with no symptoms at all, while others will have a severe disease
- Approximately 75 % of ALPS is caused by defective FAS
- To ALPS also counts ALPS-related diseases with defective caspase-8 and RAS-associated ALPS (somatic mutations in *KRAS* and *NRAS*)
- Diagnostic criteria for ALPS
  - Mandatory criteria
    - Chronic (>6 months), non-malignant, non-infectious lymphadenopathy and / or splenomegaly
    - Increased number of CD3+TCR$\alpha\beta$+CD4-CD8 double-negative T cells (DNT) (>1.5 % of the total number of lymphocytes or >2.5 % of CD3+ TCR$\alpha\beta$+ lymphocytes) if the lymphocyte count is normal or elevated
  - Additional criteria

    Primary
    - Defective lymphocyte apoptosis at two different occasions
    - Mutation (congenital or acquired) in *TNFRSF6* (encoding Fas), *TNFSF10*, (encoding Fas ligand) or *CASP10*

    Secondary
    - In plasma increased sFASL levels (>200 pg/ml), IL-10 levels (>20 pg/ml), vitamin B12 levels (>1500 ng /L) and/or IL-18 levels>500 pg/ml
    - Typical immunohistological findings
    - Autoimmune cytopenias (hemolytic anemia, thrombocytopenia and/or neutropenia with elevated serum IgG levels (polyclonal hypergammaglobulinemia)
    - Family history of non-malignant/non-infectious lymphoproliferation with or without autoimmunity

For definitive diagnosis: Both of the required criteria plus a primary criterion.

Probable diagnosis: Both of the required criteria plus a secondary criterion.

Differential Diagnosis

- Splenomegaly of another etiologies such as malignancy and infection
- Autoimmune cytopenias due to other etiologies

Symptoms and Signs

- Median age at symptom onset is approximately 3 years, range 0 to >30 years
- Nearly 100 % develop splenomegaly and/or lymphadenopathy and about 65 % also have hepatomegaly
- Autoimmunity is seen in approximately 65 %; the most common are autoimmune cytopenias (autoimmune hemolytic anemia, ITP and neutropenia in that order). Other autoimmune disorders occur as well: uveitis, glomerulonephritis, alopecia, pancreatitis
- Increased risk of B cell malignancies and non-Hodgkin lymphoma
- In adults spontaneous improvement of the lymphadenopathy is often seen but no improvement of the autoimmune phenomena occurs
- Usually there is no clinical evidence of ALPS among parents of the patient with clinical disease even though they have the same mutation

Assessment

- On suspicion of ALPS, test first for double negative T cells. Note that this must be done for TCR$\alpha\beta$ + cells, not on the entire T cell population as T delta/gamma cells always are double negative
- IL-10, IL-18 and B12 are simple tests that often are helpful diagnostically
- On suspicion of ALPS contact the regional immunology center
- Offer genetic counseling to the family

Treatment

- Symptomatically with filtered, irradiated and CMV-negative blood products ONLY **(AII)**
- Sirolimus as first choice, and mycophenolate mofetil as second choice. Sirolimus often has dramatic effect on splenomegaly and anemia, but may have many side effects. Mycophenolate mofetil affects rarely the splenomegaly but the cytopenias may be affected favorably
  - In cases sirolimus or mycophenolate are insufficient, corticosteroids can be tried. Splenectomy may also be necessary
- In severe cases, hematopoietic stem cell transplantation **(AIII)**

OTHER TREATMENT

- Provide family support from a counselor and/or psychologist if needed

Follow-up

- Hb, WBC with differential, platelets
- Based on clinical investigation of autoimmunity, e.g. Coombs test
- The patient should be cared for on an alternating basis between the local clinic and the specialized center, i.e. with regular follow-ups at the specialized center on a life-long basis combined visits the local pediatric/adult clinic for day-to-day care

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Severe Congenital Neutropenia

(SCN)

Definition

ICD-10: D70.9B
Incidence: 1:250 000 newborns

DEFINITE DIAGNOSIS

- Severe neutropenia (neutrophil granulocytes (ANC) <0,5X10^9/L) and proven mutation in one of the following genes
  - *ELANE*
  - *HAX1* (= Kostmann disease)
  - *G6PC3*
  - *GFI1*
  - WASP (gain-of-function mutation)
  - *CSF3R* (congenital biallelic mutation)
  - *JAGN1*

PROBABLE DIAGNOSIS

- Severe neutropenia (ANC <0,5X10^9/L) and
- Maturation arrest at promyelocyte/myelocyte level found at bone marrow investigation

Differential Diagnosis

- Leukemia
- Drug induced neutropenia
- Autoimmune neutropenia in children during first years of life
- Alloimmune neonatal neutropenia due to transplacental transport of maternal antibodies against paternal antigens on the surface of the neutrophil granulocytes
- Cyclic neutropenia: Cycles of often 21 days, duration 3–6 days when neutrophils drop to 0,1 X10^9/L, with normal or subnormal ANC in between. More than 90 % have a mutation in *ELANE*
- Chronic idiopathic neutropenia. Neutropenias not known to be congenital, immunological or neoplastic. Heterogeneous group with unknown etiology
- Neutropenia in other primary immunodeficiencies such as antibody deficiency disorders, hyper-IgM syndrome, severe combined immunodeficiency (reticular dysgenesis or part of maternal engraftment with graft-versus-host disease) and WHIM syndrome. The WHIM syndrome is characterized by warts, hypogammaglobulinemia, infections and myelkatexsis (retention of mature granulocytes in bone marrow)
- Neutropenia as part of other diseases with distinctive features
  - Glycogen storage disease type 1b. Characterized by hypoglycemia, lactacidosis, hepatomegalia and short stature
  - G6PC3 deficiency. Associated with structural cardiac malformations, prominent superficial venous pattern and urogenital defects
  - Chédiak-Higashi syndrome. Partial albinism, defect NK cell function, bleeding problems and neurological findings
  - Griscelli syndrome type 2. Associated with partial albinism, (intermittent) neutropenia and defect function of cytotoxic lymphocytes
  - Leukocyte adhesion defects (LAD 1, 2 and 3)
  - Hermansky-Pudlak syndrome type 2. Associated with partial albinism and prolonged bleeding time due to thrombocyte dysfunction
  - p14 deficiency. Associated with short stature, immunoglobulin deficiency and defect function of cytotoxic lymphocytes
  - Shwachmann–Diamond syndrome. Characterized by pancreas insufficiency, growth inhibition, skeletal anomalies and bone marrow failure
  - Cohen syndrome. Characterized by microcephaly, muscle hypotonia, mental retardation and often dysymorphic features
  - Barth syndrome . Characterized by dilated cardiomyopathy, skeletal myopathy and carnitine deficiency
  - Pearson syndrome. Characterized by i.e. exocrine pancreas dysfunction, short stature, anemia
  - Cartilage hair hypoplasia syndrome. Characterized by short stature due to metaphyseal chondrodysplasia and hair that is lighter in color compared to the rest of the family

Symptoms and Signs

- Onset usually during the first weeks/months of life with severe bacterial infections such as omphalitis with septicemia
- Bacterial infections (otitis, pneumonia, tonsillitis, septicemia, and/or osteomyelitis) starting in skin and mucosa
- Painful non-herpetic aftae in mouth and parodontitis with early loss of permanent teeth
- Severe congenital neutropenia constitutes a congenital myelodysplastic syndrome. I 20–30 % a development to MDS and/or AML will occur

NB. isolated granulocytopenia is not associated with serious deep fungal infections. An Aspergillus infection or other invasive fungal infection is a sign that monocytes are defect or also missing as in aplastic anemia and iatrogenic neutropenia after treatment with cytostatic drugs.

Assessment

To be done in cooperation with a PID specialist.

- Hb, WBC with differential, platelets (SCN often associated with monocytosis and eosinophilia)
- WBC with differential x 3/week in 6 weeks (to exclude cyclic neutropenia)
- Bone marrow morphology (aspiration and biopsy), flow cytometry and chromosome analysis (look for defects such as monosomia 7 or trisomia 21)
- Serum IgG, IgA, IgM (SCN often associated with increased serum IgG)
- Neutrophil specific antibodies
- DNA-analysis

Treatment

- Substitution with human recombinant G-CSF (filgrastim or lenograstim), 5 µg/kg bodyweight subcutaneously or more once daily. If the patients needs 20 µg/kg or more, give G-CSF b.i.d. **(AII)**
  - Consider dose increase with 10–20 % in case of infection or surgery
- Appropriate antibiotic treatment
  - In cases of chronic lung damage, follow the guidelines for respiratory care of cystic fibrosis with drainage and intermittent antibiotic treatment with sepsis doses **(AIII)**
- Vaccinations. See Vaccinations in immunodeficiency p. 80

OTHER TREATMENTS

- Regular visits to dentist and dental hygienist
- Contact with physiotherapist, dietician and/or counselor as needed
- Genetic counseling to the family
- Hematopoietic stem cell transplantation

Follow-up

- Clinical visits with complete blood count every 3 to 6 months. The goal should be ANC between 1 and 1.5 (2) $\times 10^9$/L, which is enough to protect against most infections. NB. Lower ANC can be insufficient and the risk for severe and even lethal infections is high
- Yearly bone marrow aspiration (morphology, immune phenotyping, cytogenetic analysis and analysis of possible somatic mutation in the *GCSFR* gene is recommended due to the increased risk for MDS and AML

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Chronic Granulomatous Disease

(CGD)

Definition

ICD-10: D84.8

Incidence: Approx. 1:100 000– 200 000 newborns

- X-linked CGD: defect in the gp91^{phox} component of the NADPH oxidase in phagocytes
- Autosomal recessive CGD: defect in one of the p47^{phox}, p40^{phox}, p67^{phox} or p22^{phox} components of the NADPH oxidase in phagocytes

CERTAIN DIAGNOSIS

- Male or female patient with absent or reduced production of oxygen radicals in activated neutrophils (phagoburst or NBT) test:
  - Mutation in one of the genes that code for gp91^{phox}, p22^{phox}, p47^{phox}, p67^{phox} or p40^{phox},i.e. *CYBB, CYBA, NCSF1, NCSF2,* or *NCSF4* respectively
  - Absence of mRNA for any of the aforementioned genes
  - Male maternal cousins, uncles or nephews of a patient with X-linked CGD who have a defective NBT test or phagoburst
- Phagoburst can be evaluated using:
  - Dihydrorhodamine flow cytometry (sometimes referred to as metabolic activation or FAPIA in some labs)
- Testing for specific mutations is performed at certain specialized laboratories in Europe. Prenatal diagnosis is possible if the mutation has been identified previously in the family

POSSIBLE DIAGNOSIS

- Male or female patient with absent or reduced production of oxygen radicals in activated neutrophils (phagoburst or NBT) test and:
  - Deep infections such as liver abscess, perianal abscess, lung abscess, adenitis or osteomyelitis caused by *Staph aureus, Serratia marcescens*, Candida- or Aspergillus-species or other catalase-positive microorganism
  - Granuloma formation in the respiratory, gastro-intestinal or urogenital tract
  - Failure to thrive, hepatosplenomegaly or lymphadeno-pathy

Differential Diagnoses

For example

- Leukocyte adhesion deficiency (LAD)
- Granulomatous conditions such as Crohn's disease, tuberculosis, sarcoidosis, common variable immuno-deficiency
- Hyper-IgE syndrome

Symptoms and Signs

- Approximately 2/3 of patients with CGD have X-linked disease and 1/3 have autosomal recessive disease. The X-linked form often entails higher morbidity, earlier disease onset and higher mortality
- The onset of X-linked disease often occurs during the first years of life, but later onset can occur in the autosomal recessive forms, even in adulthood on rare occasion
- Bacterial and fungal infections, often with suppurating abscesses in the lymph nodes, lungs, liver, bones, other internal localizations and skin
- Sterile inflammation with granuloma formation occurs, frequently in the internal organs
- IBD-like inflammation in the gut, primarily in the colon, with granuloma and perianal fistula formation is common
- Infections caused by catalase-positive bacteria, particularly *Staph aureus*, *Serratia marcescens*, gram-negative intestinal bacteria and *Burkholderia cepacia*. Fungal infections caused by Aspergillus- and Candida-species. Many other less common catalase positive microorganisms occur as well.
- Specific problems: Infection with *Burkholderia cepacia*, which is often multi-resistant and difficult to culture. *Aspergillus* infections are often life threatening. Liver abscess caused by *Staph aureus*.

Assessment

Examine all the siblings, since CGD sometimes have late onset.

To be conducted in cooperation with an experienced PID or CGD specialist.

REGULAR DIAGNOSTIC TESTS

- Hb, WBC with differential and platelets
- ESR, CRP
- ASAT, ALAT and ALP
- Plasma protein fractionation
- Urine dipstick test

BASED ON INDIVIDUAL ASSESSMENT AND SYMPTOMS

- If focal infections are present, always perform aggressive microbiological diagnostics with internal biopsies and, for example, BAL for bacteria, mycobacteria and fungi. Institute an appropriate empirical antibiotic as soon as possible. Contact with a CGD expert or a microbiologist is recommended, given the unusual agents that may cause the infection
- Lung function assessment
- Chest X-ray, chest HRCT/MRI
- CT/MRI/ultrasound of internal organs
- Antibody levels for *Aspergillus fumigatus*
- Mutation analysis is performed at certain specialized laboratories in Europe. Prenatal diagnosis is possible through chorionic villi biopsy if the mutation is known

Treatment

PROPHYLACTIC TREATMENT

- Continuous treatment with trimethoprim-sulfamethoxazole at prophylactic dosage **(AII)** and itraconazole **(AI)**
- Consider treatment with interferon-gamma (IFN-γ) **(BII)**

ACUTE TREATMENT

- Surgical drainage of abscesses **(BIII)**
- Based on culture results, use antibiotics with good intracellular penetration into phagocytes, i.e. trimethoprim-sulfamethoxazole, clindamycin, ciprofloxacin and rifampicin. CGD requires often a much longer duration of the treatment compared with normal patients **(AII)**. Liver abscess may be treated with concomitant corticosteroids. Avoid penicillins since they exhibit poor intracellular penetration
- *Aspergillus* infections are preferably treated with voriconazole **(AI)** (avoid combination with rifampicin) or posaconazole **(BII)**
- Consider granulocyte transfusions under steroid protection in refractory and severe infections **(CIII)**

OTHER TREATMENTS

- Steroid therapy is indicated in prolonged inflammation of the gut and other organs under adequate antibiotic protection **(AII)**
- In patients with X-linked CGD or severe autosomal recessive CGD, hematopoietic stem cell transplantation (HSCT) should be offered as early as possible with either an HLA-matched sibling donor or matched unrelated donor, using a reduced intensity conditioning regimen **(AII)**
- Offer family support from a counselor/psychologist if needed

Follow-up

- Regular follow-ups every 3–6 months at the local clinic. Consultations and alternating visits to a CGD or PID specialist at the tertiary center. The aim is early identification of infections and/or inflammation

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IRAK4, MyD88, NEMO and IκBα Deficiencies

Definition

ICD-10: D82.8
Incidence: Unknown, but these diseases are very rare, and are known in a few hundred cases worldwide.
OMIM: IRAK4-deficiency 606883, MyD88 deficiency 612260, NEMO: 300291, IκBκdeficiency 612132

These diseases are innate immunodeficiencies, conferring defect intracellular signaling from Toll receptors (IRAK-4 and MyD88), i.e. receptors in the innate immune-defense or defect signaling from NF-κβ. These conditions lead to an increased number of bacterial infections, mainly invasive, severe infections with *S pneumoniae*, usually at an early age.

- RAK4 and MyD88 are inherited as autosomal recessive traits
- NEMO is inherited as an x-linked recessive trait
- IκBα is inherited as an autosomal dominant trait

Both NEMO and IκBα also involve ectodermal dysplasia, i.e. a syndrome of thin hair, defect teeth and a lack of sweat glands with hypohidrosis. In NEMO, the ectodermal dysplasia may be very mild and constitute only solitary spots of skin and a few teeth.

CERTAIN DIAGNOSIS:

- IRAK4, MyD88-deficiency: male or female patient with an increased number of invasive, bacterial infections and homozygous or compound mutations in the genes for *IRAK4* or *MYD88*
- NEMO-deficiency: male patient with an increased number of invasive, bacterial infections and a mutation in the gene for *IKBKG*. In 90 % of the cases, the patient has ectodermal dysplasia. However, it can be very mild and in some cases only present with a few misshaped teeth
- IκBα-deficiency: male or female patient with an increased number of invasive, bacterial infections and a heterozygote mutation in the gene *NFKBIA*

Differential Diagnoses

- Congenital asplenia
- Post splenectomy
- Complement deficiency

Symptoms and Signs

- All subgroups: usually before the age of 2 years: onset of severe, rapidly progressive, invasive, pyogenic infections, i.e. meningitis, septicemia, arthritis, osteomyelitis, deep tissue abscesses, lymphadenitis, pneumonia and ENT infections. A lack of a raised CRP as well as fever, is common, which may lead to high mortality because of under-diagnosing
- Infectious agents in invasive disease are mainly *S pneumoniae* and *P aeruginosa*. *S aureus* infections are common in non-invasive skin infections. A number of other Gram- and Gram+ bacteria also cause infection
- Non invasive skin infections also do occur
  - Patients with IκBα-deficiency also have infections with *Candida sp* and *P jerovicii*
  - Patients with NEMO deficiency also have increased susceptibility for a number of infectious agents such as viruses, mycobacteria and *Candida*, as well as the already mentioned
- After the teenage years, the increased susceptibility to infection seems to vanish

Assessment

- Hgb, WBC with differential count and platelets
- ESR, CRP
- AST, ALT and ALP
- Serum creatinine
- Urine dipstick test
- Serum IgG, IgA, IgM
- Serum IgG-subclasses (IgG1, IgG2, IgG3, IgG4)
- Lymphocyte markers CD3, CD4, CD8, CD19 and CD56
- T cell function
- Antibodies against vaccine antigens
- Screening for complement deficiencies
- Phagocyte function

The aforementioned analyses are usually normal with the following exceptions:

- Patients with NEMO mutations may have low levels of antibodies against polysaccharide antigens
- Patients with IκBα-deficiency have hypogammaglobulinemia and lack specific antibodies and sometimes even reduced T cell proliferation

DNA-analysis confirms the diagnosis.

Treatment

- Vaccinations with conjugated and non-conjugated vaccines in the same manner as in splenectomy (see chapter on Splenectomy and Asplenia in Children, p. 70)
- Lifelong prophylactic antibiotic treatment with a combination of sulphmethoxazole-trimethoprim and penicillin V
- On suspicion of an infection, empirical intravenous antibiotics should be administered, with coverage of *S pneumoniae* and *P aeruginosa*, independent on inflammatory markers, since the infections may have a very dramatic and fulminant course, without a raised CRP
- Immunoglobulin substitution to the patients with NEMO or IκBα-deficiency who have hypogammaglobulinemia
- Stem cell transplantation may be considered in severe forms of NEMO and IκBα-defiency
- Genetic counseling

Follow-up

- Continuous information of the risks with the disease
- Update antibiotic prophylaxis
- Update vaccinations
- For patients with hypogammaglobulinemia, trough values of IgG should aim at a concentration > 10g/L

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Chronic Mucocutaneous Candidiasis

Definition

ICD-10: D84.4A
Incidence: Unknown but most likely underestimated as mutations in *STAT1* are recently described.
Autosomal dominant inherited mutation in *STAT1*
Autosomal dominant inherited mutation in *IL17F*
Autosomal recessive inherited mutation in *IL17RA*

Isolated chronic mucocutaneous candidiasis with or without autoimmunity caused by gain-of-function mutation in *STAT1*. The disease causes constitutionally increased phosphorylation of STAT1 (signal transducer and activator of transcription1) and transcription of interferon coding genes. The patients also have decreased activity of STAT3 with less production of IL-17, which is thought to explain the chronic candida infections. In vary rare cases the etiology is mutations in genes that controls the formation of IL-17 and its receptors. Those cases are not associated with autoimmunity.

Differential Diagnosis

All T cell deficiencies and a number of other primary and secondary immunodeficiencies such as:

- Severe combined immunodeficiency
- APECED
- Hyper-IgE syndrome (mutation in *STAT3*)
- DOCK8 deficiency
- CARD9 deficiency
- ACT1 deficiency
- Poorly controlled diabetes mellitus
- Alcoholism
- HIV
- Treatment with broad spectrum antibiotics
- Treatment with corticosteroids

Symptoms and Signs

- Relapsing severe mucocutaneous candidiasis
- Autoimmunity for example
  - Autoimmune hepatitis
  - Alopecia, very common
  - Pernicious anemia
  - Autoimmune cytopenia

Assessment

To be performed in cooperation with a PID specialist after other causes than that of primary immunodeficiency were excluded.

LABORATORY WORK-UP

- Hb, WBC with differential and platelets
- ESR, CRP
- ALAT, ASAT, LD, ALP
- Serum creatinine
- Serum IgG, IgA, IgM
- Serum anti-IgA
- Serum IgG-subclasses (IgG1, IgG2, IgG3, IgG4)
- Lymphocytes (CD3, CD4, CD8, CD19 and CD56)
- Fungal and bacterial cultures
- Autoantibodies
- DNA-analysis

Treatment

- Repeated or continuous treatment with fluconazole **(BIII)**
- Treatment of autoimmunity (corticosteroids and in certain cases calcineurin blockers)
- In severe cases ruxolitinib (janus kinase inhibitor, NB not licensed for treatment of chronic mucocutaneous candidiasis with *STAT1*-mutation) **(CIII)** or hematopoietic stem cell transplantation
- Contact with physiotherapist, dietician and/or counselor as needed

Follow-up

- ASAT, ALAT, LD, ALP (autoimmune hepatitis, fluconazol toxicity)

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Autoinflammatory Disorders

(including periodic fevers)

Definition

ICD-10: E85.0 Familial Mediterranean fever, D89.8 All other autoinflammatory disorders
Incidence: these diseases are all rare. Some of them are so rare that they are only found in a few families worldwide. Familial Mediterranean Fever is estimated to affect about 130 000 individuals globally. Most of the other diseases have an incidence of around 1:100 000 individuals or less.

- The periodic fevers belong to the group of autoinflammatory diseases which is a heterogeneous group of diseases characterized by irregularly recurring episodes of autoinflammation with fever and general malaise, without signs of autoimmunity, malignancy or infection. This chapter deals with the diseases caused by single gene mutations in genes coding for different functional proteins in the innate immune defense (as opposed to the autoimmune diseases, caused by a defect in the adaptive immune system, leading to the formation of an auto-antibody)
- These diseases convey a powerful inflammatory response with a raised CRP, often >100 mg/L, raised serum amyloid protein A (SAA) and ESR. If this is lacking, the diagnosis should be sought elsewhere
- Lymphadenopathy, serositis, arthritis/arthralgia and dermal rash are part of the symptomatology for several of the diseases, but every disease also has specific symptoms that distinguish it clinically from the others
- Onset is often early, during the first years of life. Between the episodes of inflammation, the patients are usually well and without symptoms, but sometimes there is a subclinical inflammation with a remaining, slightly raised SAA, despite normal CRP
- The diseases are inherited as autosomal recessive or autosomal dominant traits
- Since the symptoms in periodic fever are similar to the symptoms of bacterial infection, many patients are misunderstood and have been the victims of unnecessary hospitalization and unnecessary antibiotic treatment
- The knowledge of these diseases is continuously increasing and the list of diseases is therefore growing. In January 2015 we have knowledge of 18 single gene disorders that belong to this group

OMIM:

- Familial Mediterranean Fever, FMF: 249100
- Tumor Necrosis Factor Alfa Receptor Associated Periodic Syndrome, TRAPS: 142680
- Mevalonate Kinase Deficiency (Hyper IgD Syndrome, HIDS): 260920
- Familial Cold Autoinflammatory Syndrome, FCAS: 120100
- Muckle Wells Syndrome, MWS: 191900
- Chronic Infantile Neurologic Cutaneous and Articular Syndrome, CINCA or Neonatal Onset Multiinflammatory Disease (NOMID) 607115
- Blau Syndrome: 186580
- Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne, PAPA: 604416
- Majeed Syndrome: 609628
- Familial Cold Autoinflammatory Syndrome 2, FCAS2: 611762
- Interleukin 1 Receptor Antagonist Deficiency, DIRA: 612852
- Early-Onset Enterocolitis: 613148
- Interleukin 36 Receptor Antagonist Deficiency, DITRA: 614204
- HOIL-1 Deficiency: 615895
- Autoinflammation and PLCγ2-Associated Antibody Deficiency and immune dysregulation, APLAID: 614878
- Proteasome Associated Autoinflammatory Syndrome, PRAAS: 256040
- Deficiency of ADA2, DADA2: 615688
- STING-associated Vasculopathy with Onset in Infancy, SAVI: 615934

CERTAIN DIAGNOSIS

Male or female patient with repeated episodes of fever and raised inflammatory laboratory markers. Infection, autoimmunity and other diseases should have been ruled out as far as possible. DNA analysis has revealed a mutation in a gene causing disease in one of the afore mentioned diseases. In FMF, a mutation is not always identified. The diagnosis is then confirmed by typical history, ethnicity and treatment response to Colchicine.

POSSIBLE DIAGNOSIS

Male or female patient with repeated episodes of fever and raised inflammatory laboratory markers. Infection, autoimmunity and other diseases have been ruled out as far as possible, and a risk for autoinflammatory disease exists.

Differential Diagnosis

- PFAPA (periodic fever, aphtous stomatitis, pharyngitis, adenitis)
- Cyclic neutropenia and other primary immune deficiency syndromes
- Leukemia, lymphoma and other malignancies
- Systemic Juvenile idiopathis arthrtitis, Adult Still's disease, Crohns' disease, Behçets disease. These diseases are now often classified as ¨multifactorial autoinflammatory disease¨, since the mechanism seems similar but the background is more likely polygenic

Symptoms and Signs

The most common diseases are listed in the table. Some specific symptoms are listed below to some of the more common diseases:

- FMF is the most common and first described disease in the group. The disease affects almost exclusively individuals with ethnic origin from the eastern Mediterranean area. In FMF, a protein named pyrin is defect because of biallelic mutations in the gene coding for this protein, *MEFV*. However, two mutations are only found in about 2/3 of the cases. The febrile episodes are short, usually 12–72 hours and recur at irregular intervals, without distinct triggers. Common symptoms are serositis (i.e. inflammation of the serous membranes of the body with pain in the abdomen and thoracic cavity), erysipelas like rash and monoarthritis. Less common are pericarditis as well as orchitis. If untreated, the disease leads to severe renal amyloidosis and premature death
- TRAPS is characterized by long episodes, 1–3 weeks, with spiking fever combined with periorbital edema, painful conjunctivitis, rash, migrating myalgia, sometimes under the dermal rash. The disease is inherited in an autosomal dominant trait and often affects one of the parents, however, de novo mutations are also common
- HIDS is caused by mutations in the gene coding for the enzyme mevalonate kinase, which catalyzes a step in the isoprenoid pathway. Patients usually are affected from the first year of life by irregularly recurring febrile episodes with a duration of 3–5 days and an interval of about 4–6 weeks. A strong inflammatory reaction with malaise, cervical lympadenopathy, abdominal pain, vomiting and diarrhea, a vasculitic rash and arthritis are common symptoms. Serum IgD is often highly raised but sometimes it is normal in the beginning of life. IgD is however raised in several conditions and is not specific. IgA is raised in about 80 % of the cases. With increasing age, the episodes become less frequent and not as aggressive. Between the episodes, the patients are well. The attacks usually start without a known reason but may be triggered by stress or vaccinations. HIDS is inherited as an autosomal recessive trait
- Cryopyrin associated periodic syndrome, CAPS, is a common denominator for MWS, FCAS and CINCA (NOMID). They are all caused by mutations in the *NLRP3* gene, coding for cryopyrin. The disorders are inherited as autosomal dominant traits
  - CINCA has the onset already during infancy, and is characterized by episodes of fever, arthropathy, urticarial rash and aseptic meningitis as well as mental retardation
  - MWS has later onset, sometimes as late as adolescence, with attacks of fever, arthralgia/arthritis, urticarial rash with a duration of 24–48 hours. It is often complicated by sensorineural hearing impairment and amyloidosis
  - FCAS leads to recurrent, short, 12–24 hour fever episodes with urticarial rash sometimes triggered by chill, shivers, sweating, arthralgia and conjunctivitis
- Concerning symptoms and signs for the other very rare conditions, see the reference list of articles

Assessment

A detailed medical history concerning symptomatology and family history is crucial for the assessment. The evaluation is preferably made in cooperation with a specialist in the field.

- Hb, WBC with differential count and platelets
- ESR, CRP, Serum Amyloid A (with fever and also without fever)
- ASAT, ALAT, LD and ALP
- Serum creatinine and/or plasma cystatin C
- GFR-cystatin-clearance
- Urine dipstick test
- ANA, ENA (ANA-screen), ANCA and ds-DNA
- Serum IgG, IgA, IgM
- Screening for complement deficiencies
- DNA-based diagnostics
- Streptococcal throat and urinary tract infections should be ruled out
- Throat and urinary tract infections should be ruled out

Treatment

Is usually prophylactic and should be designed specifically. The aim of the treatment is to prevent or decrease the effect of the febrile episodes, but also the development of amyloidosis in some of the diseases

- FMF is treated with Colchicine, which prevents or decreases the fever attacks as well as the development of amyloidosis. The dose 0.5–2 mg daily, divided in two doses can be given even to children. Even pregnant women are now recommended treatment since the risk for the fetus seems less with treatment than without. Colchicine resistant FMF often responds to inhibition of IL-1
- IL-1 inhibition with Anakinra (daily subcutaneous injections) or Canacinumab (monthly i.v. infusions) is efficient in TRAPS, HIDS, MWS, FCAS and most of the other conditions. Chest X-ray as well as a test to rule out tuberculosis should precede the treatment
- Corticosteroids can be efficient in some of the conditions, however, less efficient in others (e.g. HIDS)
- NSAID substances may relieve the attacks but is usually insufficient as monotherapy
- Offer psychological support to the family if necessary

Follow-up

- Careful follow-up and dose adjustment in FMF, since the target for treatment is absence of fever and prevention of amyloidosis
- In FMF kidney function is checked annually with cystatin-C, GFR-cystatin-C clearance, urine dip slide test, u-protein, u-creatinine and SAA
- Follow up should be adjusted specifically for the different diseases, depending on organ involvement

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	FMF	HIDS	TRAPS	FCU	MWS	CINCA
Inheritance	AR	AR	AD	AD	AD	AD
Ethnicity	Eastern Mediterranean area					
Chromosome	16p13	12q24	12p13	1q44	1q44	1q44
Gene	*MEVF*	*MVK*	*TNFRSF1A*	*NLRP3*	*NLRP3*	*NLRP3*
Affected Protein	Pyrin	Mevalonate kinase	TNFRSF1A	Cryopyrin	Cryopyrin	Cryopyrin
Duration of attacks	12–72 hours	3–7 days	>7 days –4 weeks	<24 hours	24–28 hours	Continuously
Skin rash	Often erysipelas-like	Vasculitis-like	Polymorphous	Urticarial	Urticarial	Urticarial
Clinical signs	Polyserositis often monoarthritis	Cervikal lymphadenopathy	Periorbital edema Myalgia	Induced by cold exposure	Hearing impairment	Aseptic meningitis
Lymph glands/ hepatosplenomegaly	Splenomegaly	Cervikal lymphadenopathy	Splenomegaly	No	Rare	Common
Thorax	Pleuritis		Pleuritis			
Abdomen	Peritonitis	Pain, vomiting, diarrhea	Peritonitis	Nausea	Pain	Unusual
Joints	Often monoarthritis	Arthritis/ arthralgia	Arthritis/ arthralgia	Arthralgia	Arthritis/ arthralgia	Arthropathy
Onset	Childhood / Adolescence	90 % <1 year	Variable <20 years	<6 months	Adolescence	<1 year
Amyloidosis	High risk	Rare	10–20 %	Unusual	About 25 %	Unknown

PFAPA (Periodic fever, Aphthous stomatitis, Pharyngitis and Cervical adenitis Syndrome)

Definition

ICD-10: D89.8
OMIM: Missing
Incidence: Unknown

- The diagnosis is clinical and defined according to the following: repeated, regularly appearing episodes of fever without signs of upper respiratory infections, with at least one of the following symptoms: adenitis, pharyngitis and/or aphtous stomatitis. CRP should be markedly raised during the febrile episode
- The disease currently lacks a genetic or etiological explanation as well as a laboratory marker
- Familial occurrence of PFAPA is rare

Differential Diagnosis

- Hereditary monogenetic autoinflammatory diseases:
  - Familial Mediterranean Fever
  - Tumor necrosis factor-alfa receptor associated periodic syndrome (TRAPS)
  - Mevalonate kinase deficiency (Hyper-IgD syndrome)
  - Familial cold autoinflammatory syndrome
  - Muckle Wells syndrome
- Systemic Juvenile idiopathis arthrtitis, Adult Still's disease, Crohns' disease, Behçets disease
- Cyklic neutropenia and other primary immune deficiencies
- Leukemia, lymphoma and other malignancies

Symptoms and Signs

- Regularly appearing fever episodes with 3–4 (up to 8) weeks interval and a duration of usually 3–6 days
- The onset is usually at 2–5 years of age and the disease has usually disappeared spontaneously within a few years. In one report, the mean duration was six years. In about 10 %, the onset was after 5 years of age. Although rare, the onset of PFAPA has even been described in adults
- It is typical that upper respiratory symptoms are lacking
- A sign of subsiding disease is shorter duration of febrile episodes and longer interval between the episodes
- In a large cohort of 301 patients, the following symptoms appeared:
  - Pharyngitis 90 %
  - Cervical adenitis 78 %
  - Aphtous stomatitis 56 %. Aphtous ulcers do not necessarily appear simultaneously with the fever
    - 43 % of all patients proved to have all three symptoms of the acronym
- 75 % of the patients also had other symptoms like:
  - Gastrointestinal symptoms 43 %
  - Arthralgia and/or myalgia 28 %
  - Rash 12 %
  - Neurological symptoms 2 %
    - Between the febrile episodes the children are asymptomatic and reveal no elevated laboratory inflammatory markers. The condition affects neither growth nor development among the children

Assessment

- Hb, WBC with differential count and platelets
- ESR, CRP, Serum Amyloid A (with fever and also without fever)
- ASAT, ALAT, LD and ALP
- Serum creatinine and/or plasma cystatin C
- GFR-cystatin-clearance
- Urine dipstick test
- ANA, ENA (ANA-screen), ANCA and ds-DNA
- Serum IgG, IgA, IgM
- Screening for complement deficiencies
- A detailed medical history concerning symptomatology and family history is crucial for the assessment. It is of great importance to rule out other hereditary forms of autoinflammatory disease. See chapter on autoinflammatory diseases
- Streptococcal throat and urinary tract infections should be ruled out

Treatment

- NSAID and acetaminophen are first line treatments during febrile episodes. There are no studies supporting prophylactic NSAID treatment
- Corticosteroids can be given as a single dose at fever, usually with prompt effect on the fever. A common negative effect of this treatment is that the interval to the next febrile episode is reduced, which may lead to frequent corticosteroid use with side effects as a consequence. Therefore, corticosteroids should be used with great caution to reduce the duration of a febrile episode
- Tonsillectomy is often efficient, however, febrile episodes may reappear after operation. This has to be taken into account since the disease has a good prognosis with spontaneous remission without operation
- Anakinra has been tried in some cases and has proved to be efficient

Follow-up

- After the diagnosis has been set, the need for follow up varies. Follow-up may be important in order to decide on tonsillectomy or other treatments
- Because of the similarity with PFAPA episodes and bacterial infection, it is common that these children have become the victims of unnecessary medical care e.g. they may have been prescribed antibiotics they do not need etc. Therefore, information from a specialist with experience of these diseases may be of great importance for the family

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Complement deficiencies

Definition

ICD-10: D84.1

Absence or impaired function of the factors involved in the activation or regulation of the complement system

Background

- The complement system consists of about 30 different components
- The complement system
  - Enhances chemotaxis (C3a, C5a)
  - Enhances phagocytosis by opsonization of bacteria via C3b
  - Enhances the antibody production (C3d)
  - Increases inflammatory response, for example in infection (C3a, C5a increases histamine release)
  - Has cytolytic effect through the membrane attack complex (MAC)
- The complement system has three activation pathways
  - The classical pathway (C1q, C4, C2)
  - The alternative pathway (C3, factor B, factor D)
  - The lectin pathway (MBL, MASP-1, MASP-2, C4, C2, ficoliner)

Symptoms and Signs

Depending on the missing component complement deficiency can cause an increased risk of severe infections, development of rheumatic disease or other autoimmune diseases or cardiovascular disease.

- C2 deficiency is the most common deficiency of the classical pathway (1:20 000). About 60 % of patients with C2 deficiency have severe infections (sepsis, meningitis, pneumonia) caused by pneumococci, *H. influenzae* and meningococci
  - Some patients also have low levels of IgG2 and IgG4, which may lead to further increased infection susceptibility
  - C2 deficient patients have a 5-fold increased risk of developing arteriosclerosis and with it associated diseases like stroke and heart attack
  - Approximately 40 % of the patients suffer from systematic lupus erythematosus (SLE), SLE-like disease, or other autoimmune disease
  - It is important to note that approximately 25 % of all individuals with C2 deficiency are fully healthy
- C1q is the first protein in the classical pathway and deficiency of C1q is strongly associated (>95 %) with the development of severe SLE disease. This association is less pronounced for deficiency of the other components of the classical activation pathway (C4 deficiency 60 %, C3 deficiency 20 %, C2 deficiency 10 %)
- Deficiencies of the alternative pathway, including properdin, and the terminal activation pathway result in an increased risk of *Neisseria* infections (*N. meningitidis* and *N. gonorrhoeae*)
  - Properdin deficiency type 1 is associated with a 250-fold increased risk of fulminant meningococcal disease with high mortality
  - No patient with complete absence of factor B has been described.
  - There are several reports associating factor D deficiency to severe meningococcal disease
- The most common defect of the lectin pathway is MBL deficiency (14 %)
  - MBL deficiency can lead to somewhat increased susceptibility to infections, especially in children under 1 1/2 years. The combination of MBL deficiency and other immune defects or illnesses has in several studies been associated with increased susceptibility to infection. The MBL deficient patients also showed significantly worse survival in case of severe infections.
  - MASP-2 deficiency is associated with recurrent infections and autoimmune disorders. The prevalence among Europeans is 1–3 % and about 20 case reports have been published.
  - Recently a association between ficolin-3 deficiency and increased risk of infections was found. The first described patient suffered from recurrent respiratory infections in childhood and of cerebral abscesses and multiple pneumonias later in life. Ficolin-3 deficiency is also associated with thrombocytopenia
- A deficiency of the terminal activation pathway is associated with increased risk of meningococcal disease. The course of the disease is less dramatic than expected likely due to the non-formation of MAC and lesser release of LPS
- Lack of C1 esterase inhibitor (C1-INH) may cause hereditary angioedema (HAE). See the section on HAE
- Lack of factor H can give rise to various diseases such as atypical hemolytic uremic syndrome (aHUS), thrombocytopenia and acute renal failure as well as age-related macular degeneration
- Lack of the membrane-bound complement inhibitors DAF and CD59 cause paroxysmal nocturnal hemolysis syndrome (PNH)

Assessment

To be done in cooperation with a specialist in the PID.

- Careful medical history
- Functional tests should be used for screening of complement deficiencies and should include the different activation pathways (e.g. by ELISA (WIELISA) or hemolytic analysis of the complement function. Measuring only C3 and C4 levels is not enough
- Immunochemical determination of individual complement proteins can be made either directly or as the next step after the functional test

OTHER INVESTIGATIONS

- Hb, WBC with differential and platelets
- ESR, CRP
- ASAT, ALAT, LDH and ALP
- Serum creatinine
- Urine dipstick test
- ANA, ENA, ANCA and ds-DNA
- Serum IgG, IgA and IgM
- Plasma protein fractionation
- B12 and Folate
- TSH and T4

Treatment

- Specific treatment is not available except for HAE (please, see separate section). Substitution with recombinant components to date have had mixed success
- Appropriate antibiotic treatment. Possibly long-term prophylactic antibiotics **(CIII)**
- Vaccination against encapsulated bacteria reduces the risk of serious infections in patients with complement deficiencies **(BII)**. In C2 deficiency vaccination against pneumococcus and *H. influenzae* reduces the risk of developing severe infections caused by these bacteria **(BII)**. Vaccination against meningococcal prevents relapse in deficiencies of the alternative pathway and terminal activation pathway **(BII)**
- In case of concomitant IgG deficiency consider treatment with immunoglobulin subcutaneously or intravenously **(BIII)**. Recommended initial dose is 100 mg per kg/ body weight/week **(BIII)**. The need for this treatment should be reconsidered after 3–5 years, especially if the patient has reached teenage or adulthood. In these age groups is very unusual to have reduced production of antibodies, as seen for example in C2 deficiency **(BII)**

Follow-up

- In case of deficiency that leads to increased susceptibility to infections, specific antibodies against pneumococci, *H. influenzae* and meningococci should be measured before any vaccination. The specific antibody levels should be monitored annually to assess if they are above protective levels
- Individual assessment of the patients depending on the type of deficiency and associated medical conditions
- Consider contacting a specialist in rheumatology, internist, ophthalmology, etc. for specific advice and treatment
- The defects are hereditary and testing of the family should be done
- Asymptomatic patients should be informed about the deficiency

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Hereditary and Acquired Angioedema

(HAE, AAE and ACEiAE)

Definition

HAE, ICD-10 D84.1
Prevalence of 1:50 000
AAE, ICD-10 D84.8
Prevalence estimated 1:250 000
ACEiAE
Prevalence estimated 1:200–1000 patients treated

- HAE type I. Both function (<50 %) and concentration of C1 inhibitor (C1-INH) are reduced. C1q level normal
- HAE type II. Reduced function (<50 %) but normal or increased concentration of C1-INH. C1q level normal
  - For children <1 years of age, the diagnosis is challenging due to difficulties to relate to age-matched reference values. Low values may, however, indicate HAE
- For both HAE type I and type II onsets usually occurs before 25 years of age (women 95–100 %, men 90–95 %). Onset in 50 % for both girls and boys before the age of 10
- Type I and II are caused by mutations in the *SERPING1* gene. Inheritance is autosomal dominant. New mutations are common
- HAE type III. Both function and concentration of C1-INH and C1q are normal. Women from Mediterranean countries constitute with overwhelming majority. Some cases are linked to defects of the coagulation protein factor XII. No patient diagnosed in Sweden so far (2015). Typical HAE symptoms and proven mutation in the gene encoding FXII and/or positive family history is required for the diagnose
- AAE. C1-INH is reduced to varying degrees. The concentration of C1q is usually low. Antibodies against C1-INH may result in decreased function without lowering the concentration of C1-INH. Disease onset occurs usually after the age of 40. AAE occurs only as a sequel, usually to underlying diseases with monoclonal immunoglobulins or malignancies. AAE may disappear if the underlying disease is eliminated
- ACEiAE. Induced by ACE inhibitors. ACEiAE usually develops within months after start of the offending drug, but can also appear several years after start of the drug. Even if the suspected drug is stopped, the swellings can continue and may require treatment

Symptoms and Signs

- Skin: Deep subcutaneous swellings that in general develop over several hours. The swellings often occur where skin and mucous membranes meet. The swellings often migrate and can affect various parts of the body (such as hands, feet, face, and abdomen). The swellings give discomfort and moderate to severe pain and most often no severe itch or urticaria. The attacks generally last longer in the skin then in other localizations
  - Attacks are often associated with the chicken wire like erythema, i.e. erythema marginatum, which can be mistaken for urticarial lesions, but it is without the classic severe itch and wheals
- GI tract: Severe stomach pain with nausea, vomiting and diarrhea. Abdominal swelling. The attacks often confine the patient to bed. Edema of the intestinal wall and ascites can be diagnosed by imaging (e.g. ultrasound, computed tomography or magnetic resonance imaging)
  - Many patients (about 30 %) are operated upon on suspicion of acute abdomen
- Respiratory: Every second patient experiences laryngeal edema sometime. Life-threatening laryngeal edema had previously high mortality, about 20–50 %
  - Still, today, death may occur due to complete airway obstruction as a result of insufficient treatment
- Urogenital: Symptoms such as cystitis or edema of scrotum and vulva. Vaginal deliveries rarely provoke attack
- Circulation: In case of severe attacks, mainly of the abdomen, there is a risk of hypovolemia and fainting. Plasma leakage can cause hemoconcentration and hematocrit up to 75 %
- Autoimmune disorders: There are numerous reports of increased frequency of autoimmune diseases
- Attacks are triggered by:
  - Injury after trauma (after for example physical exercise/sports, biking or horse riding
  - Trauma after surgery, especially in the mouth and throat area, major dental work or endoscopic examinations (e.g. gastroscopy, bronchoscopy)
  - Stress and infections
  - Increased estrogen levels during menstruation, pregnancy, birth control pills or estrogen substitution
  - ACE inhibitors often trigger attacks immediately in patients with HAE
- Correlation geno-phenotype: Poor, even within a family or between identical twins. Large variations even for the same individual over time
- Asymptomatic: About 10 % of individuals with proven mutation
- Other: HAE causes neither increased susceptibility to infections, although it is a complement deficiency, nor does it cause any known bleeding or thrombotic tendency

Assessment

Suspected HAE should be primarily investigated by general practitioners, in more complex cases, such as AAE, preferably in cooperation with a specialist in HAE/AAE.

- C4 is almost always low, especially during attacks (sensitivity>95 %), and can serve as a screening test
- Careful medical history focusing on deep swellings at several locations and severe abdominal pain is important. Review possible familial cases
- NB. About 20–25 % of the HAE type I and II are new mutations and therefore without family history
- Functional tests should be used for screening of complement deficiencies and should include the different activation pathways (e.g. by ELISA (WIELISA) or hemolytic analysis of the complement function)
- Quantitative test of C1-INH, C3 and C4 are not enough to safely exclude HAE or AAE. The investigation should be done preferably in specialized laboratories such as Departments of Clinical Immunology. in Lund and Uppsala. Always request instructions from these laboratories how to collect and transport the samples. Immunochemical determination of individual complement proteins can be done either directly or as a second step after the function tests
- When a test is abnormal a second confirmative test should be done after 1–3 months
- Prenatal diagnosis is possible in families with known mutations. HAE. C1-INH can also be measured in cord blood, but the levels are slightly lower than in adults (about 70 % of adult levels)

Treatment

- Symptoms of HAE and AAE are treated with C1-INH or bradykinin inhibitor as first choice **(AI)**. In severe cases of ACEiAE bradykinin inhibitor has been used **(AIII)** as well as C1-INH **(BIII)** with good effect. Steroids and antihistamines are most likely not effective
- In case of the upper airway involvement, intubation or tracheotomy must be considered early **(BIII)**, and should not be delayed by search of suitable drug
- All patients should have at least two doses available to allow for rapid treatment. Easy access to the drugs is important **(AIII)**
- Self-administration of C1-INH or bradykinin inhibitors are recommended since early treatment goes with increased treatment efficacy **(BII)**
- All patients should be offered training in self-administration **(BII)**
- In some cases, with frequent/severe attacks, C1-INH can be given as a long-term prophylaxis **(AII)**
- Prophylactic treatment with androgens in the lowest possible dose may be considered if frequent attacks occur **(AI)**. Some patients may use this as well as emergency treatment – however this is not anymore recommended
- In some cases, prophylactic treatment with tranexamic acid is effective, particularly in case of AAE. The drug was previously used even for acute treatment but this is not recommended any more **(CIII)**
- Short-term prophylaxis with C1-INH or possibly anabolic steroids can be given before an expected trauma, like surgery, endoscopy or intubation, when upper and lower respiratory tracts are involved and in case of major dental work, as well as before inevitable hard training with expected physical injury or before particularly stressful situations **(CII)**
- In an emergency, solvent/detergent-treated plasma can be used and as last measure fresh frozen plasma can be given **(AII)**
- Treatment of HAE I, II and AAE differs; in AAE tranexamic acid is considered to have a better effect compared to HAE
- No established recommendations for treatment of HAE III exists, but often the same drugs as for HAE I/II are used
- Immunization against hepatitis A an B is recommended **(BIII)**

Follow-up

Consider contacting a specialist for HAE.

- 0-sample should be saved since treatment often is given with plasma products
- HAE is hereditary and evaluation of the family should be done (50 % chance that the children inherit the disease)
- Asymptomatic individuals should be informed about the disease and about triggers and offered follow-up visits if necessary
- In case of prophylactic medication with androgens is given, liver function test, lipids profile and liver ultrasound should be analyzed every 6 months. Women of childbearing potential must be advised against pregnancy during androgen treatment
- Ensure that the patients have two medication doses to use if necessary and are provided with written information about their disease to show to other healthcare professionals

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Secondary Immunoglobulin Deficiency

Definition

Impaired immunoglobulin production or abnormal losses of antibodies due to underlying disease and/or drug treatment.

DISORDERS WITH REDUCED IMMUNOGLOBULIN PRODUCTION

- CLL / lymphoma
- Myeloma
- Hematopoietic stem cell transplantation (HSCT)
- Organ Transplantation
- Treatment with certain medications (see p. 79)
- Thymoma
- Infection
- Severe malnutrition

DISORDERS WITH ABNORMAL LOSS OF IMMUNOGLOBULIN

- Protein-loosing-enteropathy / lymphangiectasia
- Nephrotic syndrome
- Severe burns
- Plasmapheresis

DEFINITION OF SEVERE SECONDARY IMMUNGLOBULIN DEFICIENCY (SID)

Serum IgG <3 g/L, Serum IgA <0,07 g/L

DEFINITION OF LIGHT TO MODERATE SID

Serum IgG 3 g/L up to lower reference range, Serum IgA between 0.07 g/L and lower reference range for the laboratory

THE MOST COMMON DISEASES WHERE TREATMENT WITH IMMUNGLOBULINS MAY BE INDICATED:

- CLL/lymphoma
- Myeloma
- HSCT (rarely!)
- Organ Transplantation
- Treatment with anti-CD20 antibodies (rituximab, ofatumomab) and anti-CD52 antibodies (alemtuzumab)
- Use of recently licensed drugs such as inhibitors of BTK (ibrutinib) and PI3K delta (idelalisib) are expected to lead to hypogammaglobulinemia
- Thymoma with hypogammaglobulinemia

INFECTIONS IN SID

The most common infections in SID are repeated bacterial respiratory infections – otitis, sinusitis, bronchitis and pneumonia. Invasive infections such as sepsis and bacterial meningitis, primarily caused by encapsulated bacteria, also are frequent and so are intestinal infections. Infections with non-capsulated *H influenzae* also occur in these patients.

NOTE it is important to remember that not all patients with secondary immunoglobulin deficiency and reduced immunoglobulin levels have increased infection rates.

INVESTIGATION FOR INCREASED INFECTION PRONENESS / IMMUNGLOBULIN DEFICIENCY

- Serum IgG, IgA, IgM and the assessment of possible monoclonal (M) component
- Serum IgG subclasses (IgG1, IgG2, IgG3, IgG4)
- Specific antibody titers, for example, pneumococcal and Hib can be assessed by serologic titers after vaccination or after an infection
- Lymphocytes (CD3, CD4, CD8, CD19 / CD20, CD56)
- Infection Diary

IMMUNOGLOBULIN THERAPY MAY BE CONSIDERED

In a patient with Increased frequency of infections and low Serum IgG level as defined above, and with no other etiology explaining

- Severe bacterial infections such as meningitis, sepsis or pneumonia
- ≥ 4 antibiotics treatment for respiratory infections per year
- Poor healing of infections despite adequate antibiotic treatment

Signs of pulmonary / lung injury strengthens the indications for treatment

Treatment

If treatment is initiated, the dosages used will be determined individually depending on the clinical situation, for example:

- IVIG 100 mg/kg body weight/week every 3–4 weeks
- SCIg 100mg/kg body weight per week (usually home-treatment)

Evaluate after 6–12 months and if necessary adjust dose

SUGGESTED TREATMENT GOALS:

- Low/no infection – achieved at individual levels of IgG
- IgG trough level of at least 6 g/L

TREATMENT INTERRUPTION

- At the start of immunoglobulin therapy, one must always consider treatment interruption or discontinuation of the treatment
- Appropriate treatment period for assessment of the effect is approximately 12–18 months or sooner if the clinical situation changes
- An infections-diary can facilitate the evaluation of treatment need

Other treatments: see Antibiotics for Adults with Antibody Deficiencies, p. 82

DOCUMENTATION

1. HEMATOLOGICAL DISEASES

Numerous studies on immunoglobulin therapy in lymphoproliferative diseases and after HSCT are published but very few from recent years.

Lymphoproliferative diseases

For hypogammaglobulinemia in patients with lymphoproliferative diseases, mostly patients with CLL and myeloma, the most recent meta-analysis was published in 2009 by Raanani et al, and included nine randomized studies where IVIG were compared with no treatment. No survival benefit was seen in these studies. A reduced incidence of severe infections and reduction of clinically documented infections was seen in three studies. No study has demonstrated that IVIG treatment is cost effective.

A general recommendation for immunoglobulin treatment cannot be given. Individual assessment must be made of each patient as above.

HSCT

After HSCT, several patients have low Ig levels and increased susceptibility to infection before the immune system slowly recovers. Some patients remain vulnerable to infection, have residual GVHD problems, respiratory problems and persistent low Ig levels.

The most recent meta-analysis of Raanani et al included 30 studies with IVIG given after HSCT, with the goal of reducing mortality and infection rate. The IVIG was given 3 months to 1 year after transplantation and compared with controls not given IVIG. No difference in overall mortality or clinically documented infections could be demonstrated. IVIG increased the risk of veno-occlusive disease (VOD) but risk of graft-versus-host disease (GVHD) was not affected. In some studies the authors speculated whether IVIG could delay the immune reconstitution after HSCT.

In conclusion, there is no indication for the routine use of IVIG in HSCT.

However, there are no controlled studies of IVIG given later than one year after HSCT. Patients with persistent low IgG levels and infection problems need to be assessed individually regarding indication for immunoglobulin substitution. If treatment is initiated the effect must be evaluated after about 12–18 months.

2. ORGAN TRANSPLANTATION

After organ transplantation, especially after lung and heart transplantation, some patients may develop hypogammaglobulinemia and consequently higher risk for infections. In a retrospective study and some case reports treatment with IVIG, in patients with low IgG and history of severe infections, was shown to reduce infection frequency and increased survival. However, there are no prospective controll studies as to the effect of IVIG in organ transplant patients.

3. ANTI-CD20 ANTIBODY THERAPY (RITUXIMAB)

Rituximab (anti-CD20), used in patients with lymphoid malignancies and autoimmune diseases, can result in prolonged or even permanent decreased levels of immunoglobulins and in some cases repeated bacterial respiratory infections. Hypogammaglobulinemia usually takes time to develop and may even occur up to one year after stopping treatment. Initially decreased IgM levels are often seen, later followed by reduced IgG.

SWEDISH CLL GROUP CONCLUDES:

A general recommendation for immunoglobulin treatment in secondary immune deficiencies cannot be given, since there are only case reports and few studies of varying quality.

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Splenectomy and Asplenia in Children

Definition

- Splenectomy, congenital asplenia and functional asplenia lead to an immunodeficiency disorder associated with increased incidence of severe and sometimes life-threatening infections with fulminant sepsis, meningitis or pneumonia known as OPSI (overwhelming post-splenectomy infection). The risk of severe infection is highest in splenectomized children under the age of 2 years and in the years after the loss of the spleen. However, the risk for severe infection persists throughout life and is believed to increase again after the age of 50-years
- Functional asplenia or hyposplenism also early in life in individuals with sickle cell disease, and occurs as sequelae to other hematologic/oncologic disease. It also follows bone marrow transplantation, liver and intestinal diseases (celiac disease and IBD), in HIV / AIDS and other conditions

Differential Diagnoses

Possible differential diagnoses to undiagnosed asplenia include

- IRAK4 deficiency
- MyD88 defects
- Complement defects

Symptoms and Signs

Overwhelming post-splenectomy infection (OPSI):

- *Streptococcus pneumoniae* 50–90 %
- *Haemophilus influenzae* type b
- Meningococci
- Uncommon agents: *E Coli, Pseudomonas aeruginosa* and *Capnocytophaga canimorsus* (following dog bite)
- Increased risk of severe infection with falciparum malaria
- Increased risk for vascular complications in some patients after splenectomy

Assessment

There is a lack of specific and standardized tests to determine hyposplenism, but functional asplenia should be suspected if Howell Jolly bodies are detected in blood smears and the suspicion is even stronger if an increased number of "pitted erythrocytes" are found by interference microscopy evaluation.

Vaccinations

PRIOR TO SCHEDULED SPLENECTOMY

Pneumococcal vaccine

- If the child is <2 years and has not yet received the primary vaccination: follow Prevenar 13® primary vaccination programme
- If the child is >2 years and has not received the 13-valent pneumococcal conjugate vaccine, administer Prevenar 13®, 10 weeks before the planned surgery. Moreover, give the 23-valent pneumococcal vaccine, Pneumovax®, 8 weeks after Prevenar and at least two weeks prior to splenectomy. In case of tight schedule, the interval between Prevenar 13® and PneumoVax® can be reduced to 1 month

Hib vaccine

- If the child is <2 years and has not yet received the primary vaccination, follow the Act-Hib® primary vaccination schedule
- If the child is >2 years, give 1 dose at least two weeks before surgery, if the child has not yet received the primary vaccination

Meningococcal vaccine

- If the child is >2yrs give Menveo®, a 4-valent conjugate meningococcal vaccine group A, C, W-135 and Y, and Bexcero®, a conjugate meningococcal group B vaccine at least two weeks prior to surgery. There is evidence that supports the use of these vaccines even for healthy children from 2 months of age. Studies regarding their use before splenectomy are missing (Feb 2015)

IF CASEE OF TRAUMATIC SPLENECTOMY OR CONGENITAL ASPLENIA

- Give the same vaccines as above, 2 weeks after surgery, or at the time for diagnosis of asplenia. Menveo®, Bexcero and Prevenar13® are recommended for those who have received unconjugated vaccines

AFTER TRAUMATIC OR SCHEDULED SPLENECTOMY, ACTUAL ASPLENIA OR HYPOSPLENIA

- Pneumovax is given every three to five years. Consider repeating Prevenar13® but evidence is lacking. Nor do we know yet whether Menveo® and Act-Hib® should be repeated for this group of patients. Studies are warranted
- Annual influenza vaccination is recommended
- If patient lacks immunity to varicella, vaccination should be given
- It is important to understand that critical infection may occur despite adequate vaccinations. Vaccinations cover only the most common agents that cause infections in asplenia/post-splenectomy and furthermore, vaccines cover only the serotypes included in the vaccine

Information

- The patient and family must repeatedly be informed about the increased risk of serious infections and about measures to decrease the risks
- Patients and relatives should understand the danger of OPSI and how rapidly it develops
- Patients should be advised to seek medical attention for fever >38 degrees C, especially in case of shivers or systemic symptoms and they should be assessed as soon as possible. Animal bites should be treated in the same way
- Patients not on continuous antibiotic prophylaxis should in case of fever >38 degrees immediately take their prescribed antibiotics and thereafter seek medical attention
- Patients should inform the attending physician / dentist about their lack of a spleen
- Patient's medical record should have a warning, informing that the patient has undergone splenctomy oris suffering from functional asplenia, The warning text should give advice on assessment and treatment in case of a febrile episode

TRAVEL RECOMMENDATIONS

- People with asplenia should be advised about the importance of prophylactic treatment against falciparum malaria in endemic regions
- People who do not take preventive antibiotics should carry with them antibiotics for the entire travel time. The choice of antibiotics should take into account the local resistance patterns
- People with asplenia should protect themselves against environmental factors on the trip, that is, wearing protective clothing, avoiding mosquito bites and dog bites

Treatment

PROPHYLACTIC TREATMENT

- Phenoxypenicillium 12.5 mg / kg body weight and dose, 2 doses per day
- All splenectomized individuals should be treated for at least a minimum of 2 years post splectomy with prophylactic antibiotics, since this time confers the greatest risk
- All young children should have prophylactic antibiotics until at least the age of 5. After the age of 5 there are varying recommendations, such as continuous treatment until the age of 15–20, lifelong treatment or immediate treatment for each fever episode followed by direct contact with a physician. The later requires self-involvement and very good information. Since scientific studies still are lacking regarding best practices, the treating physician should individualize treatment for the patient and for the actual situation
- Choice of antibiotic, penicillin or amoxicillin, must be balanced against compliance, antimicrobial resistance and the occurrence of adverse effects

EMERGENCY TREATMENT OF PROVEN OR SUSPECTED BACTERIAL INFECTION

- Patients who develop a suspected bacterial infection despite prophylactic measures (antibiotics, vaccinations) should immediately be taken to hospital and given intravenous antibiotics. Although OPSI is usually caused by pneumococcal, meningococcal or *Haemophilus influenzae type b* infection, consider also other pathogens (see Background)

If the patient is seeking outpatient care:

- Give an iv dose of benzyl penicillin 100–150mg/kg body weight prior to transportation to hospital

At the hospital:

- Cefotaxime or ceftriaxone at sepsis dose

If there is local antibiotic resistance regarding *Strep pneumoniae*, this must be taken into account in empirical antibiotic treatment

Follow-up

At each visit

- Repeated information about the risks of OPSI after splenectomy
- Update the current antibiotic prophylaxis
- Update the vaccinations

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Vaccination in Case of Splenectomy in Adults

Splenectomy due to trauma

VACCINATION IN HEALTHY AND IMMUNOCOMPROMISED PATIENTS

Start preferably 14 days after the splenectomy.

The most important is pneumococcal vaccination

If there is likely that vaccination will not be given at two weeks post splenectomy, vaccination should be given during the hospital stay.

Pneumococcal vaccine

- One dose of Prevenar® (0.5ml) administered im. (13-valent pneumococcal conjugated vaccine)
- Two months later, one dose of Pneumovax® (0.5ml) im. (23-valent polysaccharide vaccine)
- After 5 years, one dose Prevenar® (0.5 ml) im. as a booster dose
- In patients previously vaccinated with one or more doses of 23-valent polysaccharide Pneumovax® and where more than 5 years has elapsed since last vaccination: One dose Prevenar® (0.5 ml) im.
- Newly diagnosed patients with functional or anatomic asplenia without other known diseases and with impaired immune system are vaccinated as in traumatic splenectomy (as above)

Meningococcal Vaccination

- A dose Menveo® (0.5ml) administered im (quadrivalent meningococcal conjugated vaccine)
- A booster dose with Menveo® (0.5ml) administered im after 5 years

Haemophilus influenzae type b vaccination

- One dose of Act-HIB® (0.5ml) administered im. Offered at the same time as pneumococcal vaccine
- No booster vaccination

Elective splenectomy

VACCINATION IN THE IMMUNOCOMPROMISED

Vaccination should be completed no later than 14 days before splenectomy.

The interval between vaccinations can be shortened to 1 month in case of urgency.

Most important is the pneumococcal vaccine.

Pneumococcal vaccine

- Two doses of Prevenar® (0.5ml) administered im. at 1–2 months interval
- Two months after the last dose of Prevenar® a dose of Pneumovax® (0.5 ml) im
- After 5 years, a dose Prevenar® (0.5 ml) im as a booster dose

Meningococcal Vaccination

- Two doses Menveo® (0.5ml) administered intramuscularly given at 2 months intervals
- A booster dose of Menveo® (0.5ml) administered im after 5 years

Haemophilus influenzae type b vaccination

- One dose of Act-HIB® (0.5ml) im. Offered at the same time as pneumococcal vaccine
- No booster vaccination recommended

Comments

- Patients treated with rituximab (MabThera®), alemtuzumab (MabCampath®) or similar drugs during the 6–9 months interval before splenectomy are very likely to have reduced vaccination responses and individual assessment should be made. One possibility is to give prophylactic antibiotics after splenectomy with ie phenoxypenicillium 1gx2 until about 1 year after the last treatment and thereafter begin vaccination
- Patients who have undergone hematological stem cell transplantation or patients with compromised immune systems and are planned for splenectomy are given 3 doses Prevenar® followed by Pneumovax® as above

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Immunoglobulin Substitution for Immunodeficiency

Indications for treatment in children & adults include

- Primary antibody deficiency (e.g. XLA, CVID, IgG-subclass deficiency) with recurrent respiratory tract infections. See each chapter respectively
- Many combined immunodeficiencies (e.g. SCID and WAS before HSCT, HIGM, DOCK-8 deficiency)
- Secondary immunodeficiencies (e.g. myeloma and chronic lymphatic leukemia) with recurrent infections (see page 68)

Route of administration

Immunoglobulin substitution can be given subcutaneously (SCIG), intravenously (IVIG) or, in exceptional cases, intramuscularly (IMIG). In adults, SCIG can be facilitated by infusion of recombinant human hyaluronidase (IGHy; currently available as HyQvia®). HyQvia® enables subcutaneous infusion of up to 600 ml immunoglobulin at each site and administration.

The following aspects should be considered when choosing immunoglobulin product and route of administration:

- *Patient´s preference and life situation*
- *Adverse events (see below)*
- *Venous access*
- *Patient´s abilities:* Patients with cognitive or physical disabilities might need to receive immunoglobulin treatment in a clinic setting. In such case, IVIG or facilitated SCIG can be beneficial, since this makes longer dosing intervals possible
- *Wear-off effect:* Patients who experience fatigue or malaise at the lower IgG-serum concentrations preceding the next dose may benefit from the stable serum concentrations achieved by the more frequent dosage usually applied for SCIG
- *Comorbidity:* Increased loss of immunoglobulin from the blood stream can occur in inflammatory bowel disease and in nephrotic syndrome, in which case the more gradual uptake achieved by SCIG can be preferable. On the other hand, IVIG might be more efficient in patients with autoimmune cytopenia with autoantibodies due to the immune modulating effect achieved at peak IgG concentration

Aim of treatment

The main aim of treatment is to reduce the incidence and severity of infections and to reduce the risk of organ damage, especially pulmonary damage. The effects of the treatment should be evaluated using patient´s infections-diary.

Pre-treatment assessment

- Save serum
- HBsAg and PCR for HIV and HCV

Presence of anti-IgA-antibodies increases the risk of severe systemic adverse events. Take precaution, especially if IVIG is to be given. However, treatment with SCIG is usually not a problem even if anti-IgA-antibodies are present **(BIII)**.

After 6 months

- Hb, WBC with differential and platelets
- ESR, CRP
- ASAT, ALAT and ALP
- Serum creatinine
- Serum IgG, IgA and IgM
- In patients with IgG-subclass deficiency:
  - Serum IgG-subclasses (IgG1, IgG2, IgG3, IgG4)
  - Evaluate effect of given treatment using patient´s infections-diary

After 12 months and at yearly follow-ups

- Hb, WBC with differential and platelets
- ESR, CRP
- ASAT, ALAT, ALP
- Serum creatinine
- Serum IgG, IgA and IgM
- In patients with IgG-subclass deficiency:
  - Serum IgG-subclasses (IgG1, IgG2, IgG3, IgG4)
  - Evaluate effect of given treatment using patient´s infections-diary

Dosage of immunoglobulin

Dosage of immunoglobulin should be individualized. IgG-trough levels may be used for guidance, but should be considered together with incidence of infections, need for antibiotic treatment, prevalence of bronchiectasis and underlying diagnosis (XLA or CVID). High IgG-trough levels (>10 g/L) reduce the risk for bacterial infections **(BII)**. High IgG-trough levels may also protect patients with XLA from encephalitis **(CIII)**.

IN SUBCUTANEOUS ADMINISTRATION

Recommended starting dose for SCIG is 100 mg/kg bodyweight/week **(AI)**. To reach steady state with sufficiently high IgG-trough levels, treatment can initially and for the first five days, be given once daily in dose in dose 100 mg per kilo /week, followed by weekly infusions with the same dose **(CIII)**. If patients with IgG-subclass deficiency have satisfactory effect on this dose, there is some clinical experience that supports that an attempt to lower the dose to 50 mg per kilo /week can be made. **(CIII)**. Traditionally, SCIG has been given once weekly, but intervals ranging from once daily to once every other week have successfully been used **(CIII)**.

A higher dose 150–200 mg/kg bodyweight/week is recommended in patients with pulmonary complications or frequent infections (XLA **(AI)**, CVID **(AII)**, IgG-subclass deficiency **(CIII)**). Further increase of dose might be needed, e.g. in protein loosing enteropathy **(AIII)**.

IN FACILITATED SUBCUTANEOUS ADMINISTRATION

Recommended dose for facilitated subcutaneous administration is 400 mg per kilo every 3 to 4 week. Initially the monthly dose is divided into weekly doses, and the dosing interval is gradually increased. Dose and dosing interval can be adjusted and individualized according to patient´s needs and treatment every second week is an option to achieve higher IgG-trough levels.

IN INTRAVENOUS ADMINISTRATION

Recommended starting dose for IVIG is 400 mg/kg bodyweight every 3 to 4 weeks. The dose should be adjusted based on IgG-trough levels and achieved effect of treatment.

Adverse reactions

Irrespective of route of administration, the first infusions of immunoglobulin may cause chills and pyrexia. These symptoms occur when immunoglobulin reacts with pathogens in the patient, and it is not an obstacle for future treatment with immunoglobulin.

Mild local reactions at the infusion site often occur in SCIG and in facilitated SCIG. These side effects are often transient, but persistent symptoms might require reduced infusion volume, more infusion sites, lowered rate of infusion or a switch to another product.

IVIG may cause systemic side effects, such as headache, nausea and pyrexia. These side effects mainly occur when serum concentration of IgG peaks during or soon after infusion. The risk for this kind of adverse events is reduced if the patient is well hydrated when receiving treatment, but it might be necessary to lower infusion rate or to give pre medication with anti-pyretics or anti-histamines. In case of severe or recurrent systemic side effects a change of batch or IVIG product should be considered, or change to SCIG or facilitated SCIG which gives a more stable serum concentration.

Treatment with immunoglobulin rarely causes anaphylactic reactions. Some rare side effects of treatment with IVIG include hemolytic anemia, aseptic meningitis, thromboembolic events and acute renal failure.

Devices for administration, infusion sites, volume:

SCIG can be given with a portable infusion pump or through "rapid push", using a regular butterfly needle and a syringe. The number of infusion sites and the maximum volume infused at each site is limited by what is comfortably tolerated by the patient. Adult patients usually tolerate volumes of 20-50 ml per infusion site. For children, infusion volumes should be individualized. Suitable infusion sites include the abdominal wall, the thigh, buttock or backside of arms. Manufacturers recommend infusion rates ranging from 10-25 ml per hour, but many patients seem to tolerate considerably higher infusion rates, with no more side effects **(CIII)**. When patients or parents have been educated they can often manage home administration of SCIG.

Facilitated subcutaneous administration can be given with a portable infusion pump. The number of infusion sites and the maximum volume infused at each site is limited by what is comfortably tolerated by the patient. Adult patients usually tolerate volumes up to 600 ml per infusion site. Suitable infusion sites include the abdominal wall or the thigh. The manufacturer recommends infusion rate of up to 300 ml /hour at each infusion site. When patients have been educated they can often manage home administration of facilitated SCIG.

Read more about devices for administration at www.sissi.nu

Due to the need for venous access IVIG is often administered in a clinic setting. As long as the patient has normal heart- and lung function, there is usually no concern regarding volume overload. If the manufacturers instructions regarding infusion rate is exceeded, the risk for systemic adverse events might increase.

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Vitamin D treatment (in adults with an increased susceptibility for respiratory tract infections)

Definition

If serum 25-OH vitamin D <50 nmol/L in combination with increased number of bacterial or viral respiratory tract infections, vitamin D treatment should be considered.

If serum 25-OH vitamin D is between 50–75 nmol/L, vitamin D can be prescribed after individual consideration.

Background

Studies have demonstrated that treatment with vitamin D can have a positive effect on the increased susceptibility for bacterial and viral respiratory tract infections.

A placebo controlled study in Sweden has shown that substitution with vitamin D results in a decreased consumption of antibiotics and less symptoms of infections in patients with an increased susceptibility for respiratory tract infections. However, other studies have not been able to demonstrate a positive effect on the frequency of infections. It is still difficult to compare the studies since they differ in a number of parameters such as; study population, vitamin D value at start of the study as well as dosing (dose and dose interval). Variations in study design can explain why some studies demonstrate a positive effect on respiratory tract infections while others have shown no effect.

Treatment

Treatment suggestion; products and doses

- Detremin, oral drops, solution 20 000 IE/mL (cholecalciferol vitamin D3) 3 drops daily (1500 IE daily)
- Divisun, tablets 800 IE (cholecalciferol, vitamin D3) 2 tablets daily (1600 IE)

Treatment with vitamin D is connected with few adverse events. Calcium ions, alternatively albumin corrected calcium, should be controlled before starting substitution treatment with vitamin D. After specific consideration it might be necessary to control plasma PTH before treatment initiation. Patients with hyperkalemia or kidney stone(s) should not be prescribed vitamin D in accordance with respectively SmPCs. Precautions should also be taken with patients suffering from sarcoidosis, renal insufficiency or active tuberculosis. It is recommended to contact a specialist in endocrinology in case of uncertainties.

Follow-up

The level of serum 25-OH should be measured after 6–12 months on vitamin D substitution treatment. Available studies have demonstrated that a level of 75-125 nmol/L is a suitable target value. There are no supportive data that a level >125 nmol/L have a more favorable effect on infections.

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Differential Diagnoses for IgG/IgA Deficiency

Pharmacologically induced

(Reported until September 2015)

ANTIEPILEPTICS

- Phenytoin
- Carbamazepine
- Lamotrigine
- Levetiracetam
- Valproate

IMMUNOSUPPRESSANT/ANTI-INFLAMMATORY TREATMENT

- Anti-CD20/CD19-therapy (rituximab etc)
- NSAID
- Glucocorticoids
- Gold salts
- Penicillamine
- Sulfasalazine

OTHER

- Captopril
- anti-malaria preparations

Hereditary disorders

Ataxia telangiectasia
Autosomal forms of SCID
Hyper-IgM syndrome
Chromosome 18p syndrome
Chromosome 18q syndrome
Monosomy 22 syndrome
Transcobalamine II defect and hypogammaglobulinemia
Trisomy 8 syndrome
Trisomy 21 syndrome
Some metabolic diseases
Wiskott-Aldrich syndrome
X-linked agammaglobulinemia
X-linked lymphoproliferative syndrome (XLP)(EBV-associated)
X-linked SCID

Infectious diseases

EBV
HIV
Congenital rubella
Congenital CMV
Congenital toxoplasmosis

Malignancy

Immune defect with thymoma
Chronic lymphatic leukemia
B cell malignancies/Multiple myeloma
Non-Hodgkin's lymphoma

Other conditions

EXTENSIVE IMMUNOGLOBULIN LOSS

- Lymphangiectasia
- Nephrosis
- Severe burns
- Severe diarrhea (including protein-loosing enteropathy)
- Severe starvation

Vaccinations in Immunodeficiency

Vaccinations in Immunodeficiency

The most common reason for vaccinating patients with confirmed / suspected immunodeficiency are

- As part of the investigation
- To provide protection against infections that patients can be particularly susceptible to, usually encapsulated bacteria and influenza
- After hematopoietic stem cell transplantation
- Splenectomy
- Travel vaccination

For most forms of primary immunodeficiency or patients with increased susceptibility to infection we are missing large, well-controlled vaccination studies. However, there are several studies and vaccination programs designed for patients who underwent allogeneic stem cell transplantation, splenectomy and for patients with complement deficiencies. In recent years, new vaccines, particularly pneumococcal and meningococcal, have been produced, but these vaccines have not been included or evaluated in the different vaccination programs.

The results of the above mentioned studies and our clinical experience are the basis for the recommendations below regarding patients with primary immunodeficiency/ susceptibility to infections.

For vaccination of patients with primary immunodeficiency who had stem cell transplantation we refer to the vaccination program of the transplanting centers.

The following vaccinations may be considered in cases of increased susceptibility to infections:

- Pneumococcal
  - Conjugate vaccine:
    - Prevenar 13®: 13 pneumococcal serotypes or
  - Polysaccharide: 23 serotypes
- Influenza vaccination against seasonal influenza each year
- Meningococcal Vaccine
  - Menveo® or Nimenrix®: conjugate vaccine containing serotypes A, C, W135 and Y (Menveo® is approved from 2 years in Sweden, in the US from 2 months of age, Nimenrix® from 1 year of age)
- H. influenzae type B (ActHib®):
  - Protects against encapsulated *Hemophilus influenzae type B* but is not effective against non-encapsulated *Hemophilus influenzae*

Vaccination with killed and subunit vaccines

Can be given to all if no contraindication against any of the components of the vaccine

- IgA deficiency
- IgG subclass deficiency
- Susceptibility to infections with no detectable immune deficiency
- They have no or doubtful efficacy in CVID and XLA. Some patients may have some antibody production and could therefore benefit from the vaccinations. A cell-mediated effect of the vaccine have been discussed but it is unclear if it exists
- Complement defects
- CGD

Vaccination with live vaccine

WARNING: Do not use in patients with

- T cell defects or if severely immunocompromised
- XLA
- CVID
- CGD – valid only for tuberculosis (BCG) and oral typhoid vaccine. Other live vaccines can be given

Can be used in patients with

- IgA deficiency
- IgG subclass deficiency
- Complement deficiency
- Severe congenital neutropenias

NB. Immunoglobulin therapy may inhibit the effect of live vaccine. If vaccination with live vaccine is needed, this if possible at earliest three months after the last immunoglobulin dose.

Vaccinations + splenectomy

Please refer to chapters Splenectomy and asplenia in children, and Vaccination in splenectomy in adults.

Killed and subunit vaccines
Diphtheria
Tetanus
Pertussis
Polio (inactivated vaccine, injectable form)
Hib
Meningococci
Pneumococci (polysaccharide and conjugate vaccines)
Influenza (non-nasal)
Hepatitis A and B
TBE
HPV (human papilloma virus)
Travel vaccines
Cholera and traveler's diarrhea
Typhoid (inactivated vaccine, injectable form)
Japanese B encephalitis
Rabies

Live vaccines
Morbilli – parotitis – rubella (MPR)
Varicella
Tuberculosis (BCG)
Yellow fever
Oral typhoid vaccine
Oral polio vaccine (OPV)
Certain influenza vaccines (nasal)
Rota virus vaccine

Antibiotics for Adults with Antibody Deficiencies

Patients with hypogammaglobulinemia – CVID or XLA

The use of antibiotics in respiratory infections in patients with CVID or XLA differs in several aspects from the customary Swedish recommendations. Patients often require longer duration of treatment, with antibiotics with a broader spectrum and that these are instituted early on.

Principles

Take culture of the relevant local infection. Clinically appropriate antibiotics are started as soon as the cultures are taken to avoid permanent tissue damage, for instance in the lungs. Adjust antibiotics according to the culture results (sputum, nasopharyngeal).

In patients with CVID / XLA the predominant infection are with non-encapsulated *Haemophilus influenzae*, followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis*.

In this patient group recurrent/chronic upper respiratory infections with *Hemophilus influenza* are also seen. Studies have shown that *Hemophilus influenza* can persist for long periods intracellularly in the epithelium of the nasopharynx.

Antibiotics with good intracellular penetration may be of value in the treatment of these infections. Examples of such antibiotics with good anti HI activity are quinolones (e.g. ciprofloxacin) and trimethoprim-sulfa. In difficult cases, oral rifampicin can be considered in combination with other antibiotics, possibly ceftriaxone (Rocephalin) im/iv once daily. This can be given on an outpatient basis.

Special Case A

Mycoplasma infections are particularly difficult to diagnose, but they are a relatively uncommon problem in this patient group (CVID/XLA). Examples are *Mycoplasma pneumoniae*, *Ureaplasma urealyticum* and *Mycoplasma hominis*. Patients with infection with any of these agents have slowly progressive symptoms from the affected organs. Most common organs involved are the respiratory tract, joints and urinary tract. For treatment see table.

Special Case B

Patients with recurrent respiratory tract infections with *Staph. aureus* or *Pseudomonas aeruginosa* upon repeated cultures in the sputum may have sustained lung damage and should be treated actively.

SUGGESTED ANTIBIOTIC THERAPY

- Normal dosage and duration of treatment to those with isolated upper / lower respiratory tract infections with uncomplicated course
- Extended duration of treatment and possibly higher dosage is needed to those with frequent episodes of infection and / or complicated course (e.g., acute otitis media, sinusitis, underlying lung disease)
- Individual assessment is necessary for patient with antibiotic hypersensitivity and if the bacteria are resistant to antibiotics

Patients with IgA Deficiency and/or IgG subclass deficiency

These patients may have an increased susceptibility to bacterial respiratory infections where pneumococcus, *Moraxella catarrhalis*, and *Hemophilus influenzae* are the most common. These patients do not have the same risk as patients with CVID / XLA to have chronic recurrent infections. They do not have the same increased susceptibility to mycoplasma infections either.

Antibiotic therapy is primarily guided by culture findings.

Treatment options for adults
duration 10–21 days

Streptococcus pneumoniae, susceptible to Pc

- phenoxymethylpenicillin, 1–2 g 1x3
- Amoxicillin 500mg 1x3
- Clindamycin 300 mg 1x3 (at Pc-hypersensitivity)
- In selected cases cephalosporin/macrolide

Moraxella catarrhalis

- Macrolides, for example
  – Erythromycin 250mg 2x2
  – Azithromycin 250 mg 2x1 d 1, followed by 1x1 4 days followed by 1 every other day. Duration 14 days or 500 mg 1x1 7–10 days
- Doxycycline 100 mg 1x2
- Ciprofloxacin[1, 4] 500–750 mg 1x2
- Amoxicillin with klavulansyra[3] 500mg 1x3

Haemophilus influenzae [2]

- Amoxicillin[2] 500 mg 1x3
- Amoxicillin with klavulansyra[3] 500mg 1x3
- Trimethoprim-sulfamethoxazole 400/80 mg 1–2x2
- Doxycycline 100 mg 1x2
- Ciprofloxacin[1, 4] 500–750 mg 1x2
- Cephalosporins (oral) – exception
- Ceftriaxone i.m./i.v. 2g x1

Without culture [5]

Treatment should normally cover pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis*

- Amoxicillin with clavulanic acid 500 mg 1x3
- Doxycycline 100 mg 1x2
- Trimethoprim-sulfamethoxazole 400/80 mg 1–2x2
- Moxifloxacin[1] 400mg 1x1 (use with caution due to side effects)

Proven or suspected mycoplasma infection

- Doxycycline 100 mg 1x2
- Quinolones: Ciprofloxacin 500-750 mg 1x2, moxifloxacin 400 mg 1x1
- Macrolides: Erythromycin 250mg 2x2, azithromycin 500 mg 1x1

1. Medication for use in recurrent or complicated infections with prolonged treatment duration (and possibly higher dose, applies mainly to penicillium and doxycycline)
2. Do not use amoxicillin if beta-lactamase producing *Haemophilus influenzae*
3. Effect also on beta-lactamase producing Haemophilus influenza and Moraxella catarrhalis
4. Poor effect on pneumococci but good on *Moraxella catarrhalis*
5. Ciprofloxacin and ceftibuten have poor effect on pneumococci. Macrolides have poor effect on *Haemophilus influenzae*

Prophylactic antibiotics

May be considered for patients with frequent recurrent bacterial respiratory infections and/or underlying lung injury. Some experts alternate between multiple preparations in the hope that this might reduce risk of microbial resistance and side effects. Each preparation can be given for example 4–6 weeks at a time in a set schedule, over a total of 4–8 months.

Suggested drugs

- Amoxicillin 750mg 1x1–2
- Amoxicillin with clavulanic acid 500-875 mg 1x1–2
- Ciprofloxacin 500–750 mg 1x1
- Doxycycline 100 mg 1x1
- Trimethoprim-sulfamethoxazole 400/80 mg 1x1–2

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