Paroxysmal Nocturnal Hemoglobinuria (PNH)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases
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Table of contents

1 Definition and Basic Information ........................................ 2
  1.1 Definition ........................................................................ 2
  1.2 History ........................................................................... 2
  1.3 Epidemiology ................................................................... 2
  1.4 Pathophysiology .............................................................. 3

2 Clinical Presentation ......................................................... 3
  2.1 Hemolysis and Hemoglobinuria ........................................... 3
  2.2 Thrombophilia ................................................................. 3
  2.3 Secondary Aplastic Syndrome or AA-PNH-Syndrome .......... 4
  2.4 Renal Manifestation .......................................................... 4
  2.5 Unspecific Clinical Manifestations ........................................ 4

3 Diagnostics ........................................................................ 5

4 Therapy ............................................................................. 7
  4.1 Supportive Therapy ............................................................ 8
    4.1.1 General Considerations ................................................ 8
    4.1.2 Steroids .................................................................... 8
    4.1.3 Anticoagulation .......................................................... 8
    4.1.4 Immunosuppressive Therapy ........................................ 9
    4.1.5 Complement Inhibition with Eculizumab ...................... 9
    4.1.6 Pregnancy .................................................................. 10
  4.2 Potential Curative Therapy ................................................. 10
    4.2.1 Allogeneic Stem-Cell Transplantation ......................... 10

5 References ......................................................................... 11

7 Links .................................................................................. 15

8 Authors’ Affiliations ............................................................ 15

9 Disclosures ......................................................................... 16
Paroxysmal Nocturnal Hemoglobinuria (PNH)

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Compliance rules:
- Guideline
- Conflict of interests

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1 Definition and Basic Information

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired corpuscular hemolytic anemia which because of its highly variable clinical symptoms often makes diagnosis and prediction of its clinical course difficult. PNH is a clonal hematopoietic disorder, in which one or several pluripotent stem cells acquire the characteristic defect of glycosyl phosphatidylinositol (GPI)-anchored surface molecules and proliferate in the bone marrow. The development of eculizumab, a targeted inhibitor of the terminal complement cascade, has distinctly improved the clinical symptoms of PNH patients and gives us the option to treat disease-associated complications.

1.1 Definition

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired disease affecting the hematopoietic stem cells in the bone marrow. The clinical progression of the disease is extremely variable. Characteristics are intravascular hemolysis, thrombophilia with a propensity to thrombosis in typical and atypical locations, and cytopenia which in its manifestation may range from mild subclinical cytopenia to severe pancytopenia.

1.2 History

1882 Initial description by Strübing of a 29-year-old patient who sought treatment because of fatigue, abdominal pain and intravascular hemolysis, occurring particularly after physical exertion and excessive alcohol consumption [1]

1911 Marchiafava and Micheli reported hemolytic anemia associated with hemoglobinuria

1937 Introduction of the acid hemolysis test by Ham [2]

1954 Evidence of the central role of the complement system in the pathophysiology of PNH [3]

1985 Evidence of deficient complement-regulating surface molecules in PNH [4]


1.3 Epidemiology

PNH is a very rare disease with a prevalence (regarding the evidence of a significant GPI- (PNH) clone) of approx. 16 cases/1 million inhabitants, and an incidence rate of approx. 1.3 cases/1 million inhabitants (data from Great Britain/France). No reliable epidemiological data are avail-
able for the prevalence and incidence of PNH in Germany. Considering the clinical heterogeneity it must be assumed that the disease is distinctly “underdiagnosed” [7].

1.4 Pathophysiology

The cause of paroxysmal nocturnal hemoglobinuria is an acquired somatic mutation of the PIG-A-gene in either one or several pluripotent hematopoietic stem cells of the bone marrow [8, 9]. Not all stem cells of the bone marrow are affected, hence a so-called mosaic situation exists. Additional pathophysiological mechanisms may include an autoimmunity-mediated depletion of GPI+−, i.e. healthy stem cells leading to secondary accumulation of GPI-deficient PNH stem cells, and the existence of an intrinsic growth advantage by the GPI deficient stem cells [10]. The predominant consequence of GPI deficiency on peripheral blood cells is the absence of so-called complement-inactivating proteins, especially from the surface of erythrocytes. In this regard, particular mention must be made of CD55, the so-called “decay-accelerating factor (DAF)” and/or CD59, the “membrane inhibitor of reactive lysis (MIRL)” [11]. Once complement is activated the red blood cells become vulnerable to terminal complement-mediated lysis due to the constitutive absence of transmembrane molecules. As almost all PNH-specific symptoms are also described in a case with isolated CD59 defect, the CD59 molecule is of crucial importance to PNH pathogenesis [12].

2 Clinical Presentation

2.1 Hemolysis and Hemoglobinuria

Although the dark-brown morning urine belongs to the classic manifestation of PNH, this typical clinical sign can only be seen in about 26% of all PNH patients at the time of initial diagnosis. Many PNH patients do not have no clinically obvious hemoglobinuria or, at most, intermittent episodes which are not associated with the circadian rhythm. However, there is a connection between the occurrence of hemoglobinuria and the size of the PNH clone, i.e. the proportion of GPI-deficient cells in the peripheral blood. Physical weakness, fatigue, and stress dyspnea are the characteristic clinical symptoms of chronic hemolytic anemia. The intensity of fatigue is not strictly correlated with the severity of the anemia, however, a correlation does exist with the size of the PNH clone.

2.2 Thrombophilia

Thromboembolic complications are the most relevant clinical complications in patients with PNH and represent the main cause of the increased morbidity and mortality of this disease [13]. About 40 to 60% of all patients with PNH develop thromboses, which predominately affect the venous system. The probability to acquire thrombosis correlates with the size of the PNH clone, which can be measured in granulocytes, and the existence of classic symptoms, i.e. hemolysis and hemoglobinuria. Venous thromboses in PNH patients appear in typical and atypical locations such as the abdominal, particularly the hepatic or in the cerebral veins.

1. The Budd Chiari-Syndrome (BCS) is a typical manifestation of thrombosis in PNH patients [14, 15]. Clinical symptoms of hepatic vein thrombosis are abdominal pain, hepatomegaly, jaundice, ascites formation, and weight gain. The thrombosis might affect both the small and the large hepatic veins. The course and prognosis of BCS in PNH patients does not differ significantly from that of patients with BCS of other origin [16].

2. In addition to hepatic vein thromboses PNH patients also display an increased rate of portal vein thromboses, which occur at a distinctly lower rate than BCS [17]. In this case nausea, vomiting, abdominal pain, and hepatic dysfunction are the major clinical symptoms.
3. Another highly sensitive anatomic region for the appearance of venous thromboses in PNH patients are the cerebral veins, in particular the sagittal cerebral veins and sinuses. Clinical characteristics are headaches, which are occasionally associated with focal neurological deficits.

4. Apart from the typical and atypical venous manifestations of thromboembolic events, arterial thromboembolism also occurs and results in the occlusion of cerebral, coronary, visceral, and retinal vessels, leading to the characteristic symptoms. The frequency of these arterial occlusions was reported as high as 39 percent of all thromboembolic events in a Korean cohort [18]. However, according to observations made in other cohorts worldwide, this appears to be relatively high. Still, PNH should be considered also in case of arterial events, particularly in patients without pre-existing angiopathy.

2.3 Secondary Aplastic Syndrome or AA-PNH-Syndrome

There is a close clinical and pathophysiological connection between aplastic anemia and PNH:

1. The risk for developing a clinical PNH is at approx. 15-25% for patients with an acquired aplastic anemia.

2. At initial diagnosis >20% of patients with aplastic anemia display a small or moderate GPI-deficient population in the bone marrow [21].

3. Depending on the study, 10-20% of patients with aplastic anemia develop myelodysplasia in the course of their disease, often many years after termination of immunosuppressive therapy [22].

4. An aberrant cytogenetic findings prevails in approx. 20% of PNH patients already at initial diagnosis [23].

5. Allogenic stem-cell transplantation can prevent the secondary transformation of aplastic anemia in to PNH.

Hence it follows that secondary clonal diseases, e.g. PNH and MDS, characterize the natural course of aplastic anemia.

2.4 Renal Manifestation

Functional renal disorders are observed in two-thirds of all patients with PNH, in 21% even in advanced stage of renal failure [24]. Pathophysiology includes hemosiderin deposits in the proximal tubules as well as microvascular thromboses. Clinically dominant is an impaired tubular function and a gradually declining creatine clearance in the majority of patients [25].

2.5 Unspecific Clinical Manifestations

The distinctly pronounced fatigue is often the clinical symptom which is most obvious in PNH patients. Typically, this fatigue does not correlate to the severity of anemia but to the severity of hemolysis. In addition, intermittent esophageal spasms, chest pain, nausea and swallowing disorders appear, the latter especially in conjunction with hemolytic episodes. Male patients occasionally report of erectile dysfunction. In addition, moderate to sometimes intensive pain, in particular back pain, headaches, muscle pain and abdominal pain appears in association with hemolytic crises. As applies to the increased incidence of pulmonary-arterial hypertension, the pain is probably causally related to nitrogen oxide (NO) catabolism which is enhanced by intravascular hemolysis and results in the deregulation of endothelial and smooth muscle cells in the vascular wall and hence in a condition of vasculopathy. It can be influenced by treatment with the C5 antibody eculizumab (see below) [26].
3 Diagnostics

Diagnostics in case of suspected PNH should include the following steps [27]:

- Comprehensive family and medical history in order to distinguish whether an acquired disorder or congenital differential diagnoses (e.g. membranopathies, enzymopathies) are more likely.
- Medical history including targeted questioning about PNH-typical symptoms (symptoms of anemia, fatigue, dyspnea, urine discoloration, recurrent abdominal pain crises, dysphagia, headaches, erectile dysfunction, thromboembolic events, signs of hemorrhages, frequent infections).
- Physical examination (particular attention should be given to the following aspects: signs of anemia, jaundice, signs of acute or previous thromboses, signs of hemorrhages, obvious constitutional features as occur in congenital aplastic anemias (see elsewhere), splenomegaly).
- Sonography (upper abdomen, including color Doppler) paying special attention to the following aspects: dimensions of the liver and spleen; Doppler sonographic signs of acute or previous thromboses of the hepatic vein, portal vein, splenic vein, or mesenterial vein). If an acute thrombotic event is suspected, color Doppler and angiography of other regions (e.g. cerebral veins) is recommended, if feasible.
- Laboratory analyses [27-29]
  - Complete blood cell count, including leukocyte count with differential, reticulocytes
  - Erythrocyte morphology (particularly important to exclude the existence of fragmentocytes when distinguishing PNH from microangiopathic hemolysis).
  - Hemolytic parameters. Mandatory: LDH, total bilirubin, direct bilirubin; haptoglobin, hemopexin, urine status including hemoglobin analysis. Optional: free hemoglobin in the serum; hemosiderin in the urine.
  - Direct antiglobulin test (DAT); blood group.
  - Flow-cytometric analysis of GPI-anchored proteins (see Table 1)
  - Bone-marrow diagnostics including cytology, cytogenetics and histology, in patients with significant cytopenia of such an extent that PNH is suspected in the context of another hematological disease (esp. aplastic anemia; MDS).

If significant GPI-deficient populations are diagnosed in the flow cytometric analysis, the analytical profile should be extended by the following parameters:

- Creatinine, creatinine clearance.
- Ferritin, iron, transferrin, transferrin saturation, reticulocyte hemoglobin, soluble transferrin receptor.

In case of ferritin values > 1.000 ng/ml further clarification of potential organ damage due to an iron overload (echocardiography, blood glucose/diurnal blood-glucose profile; thyroid parameters, TSH; if possible, FerriScan).

- Plasma concentrations of folic acid and vitamin B₁₂
- In young patients with an indication for stem cell transplantation: HLA typing of the patient and siblings.
- If there is a positive family case history for thromboembolic events: Thrombophilia-screening (Factor V Leiden; prothrombin mutations; Protein C, Protein S etc.).
• Genetic analyses (PIG-A gene) to confirm the diagnosis will generally will not be necessary if the constellation of findings is typical. Genetic diagnostics might be reasonable in case of atypical clinical manifestations/atypical flow-cytometric results [30-32].

The standard method to determine a PNH-typical GPI-anchor defect consists in the analysis of multiparameter flow cytometry (at least granulocytes and red blood cells) [29, 33]. Indications are summarized in Table 1.

**Table 1: Indications for Flow-Cytometric Diagnostics GPI-Anchored Proteins [27-29]**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired, Coombs-negative hemolytic anemia (without signs of a microangiopathic hemolytic anemia)</td>
<td>Initial diagnostics according to Table 1</td>
</tr>
<tr>
<td>Intravascular hemolysis (haptoglobin not measurable, hemoglobinuria, elevated free plasma hemoglobin)</td>
<td>Flow cytometric analyses in intervals of six months during the first two years after diagnosis; thereafter annually if the course of the disease is stable.</td>
</tr>
<tr>
<td>Thromboses, if at least one of the criteria below is fulfilled:</td>
<td>Individual adjustment of the intervals of analysis.</td>
</tr>
<tr>
<td>◦ &quot;Atypical&quot; locations (sinus vein thrombosis, Budd-Chiari syndrome, mesenterial vein or portal vein or splenic vein thrombosis, dermal thromboses)</td>
<td>Repetition in annual intervals and/or if clinical symptoms are altered or in case of treatment changes.</td>
</tr>
<tr>
<td>◦ Thromboses (irrespective of their location) in patients showing signs of hemolytic anemia</td>
<td>Test every three months in case chimerism analysis reveals a positive recipient percentage, until the GPI-deficient population is no longer measurable, thereafter annual remission controls. Tests are to proceed within the interval if a relapse is suspected for clinical reasons.</td>
</tr>
<tr>
<td>◦ Thromboses (irrespective of their location) in conjunction with cytopenia</td>
<td>Test every three months in case chimerism analysis reveals a positive recipient percentage, until the GPI-deficient population is no longer measurable, thereafter annual remission controls. Tests are to proceed within the interval if a relapse is suspected for clinical reasons.</td>
</tr>
<tr>
<td>◦ Thromboses (irrespective of their location, including arterial thromboses) without risk factors</td>
<td>Test every three months in case chimerism analysis reveals a positive recipient percentage, until the GPI-deficient population is no longer measurable, thereafter annual remission controls. Tests are to proceed within the interval if a relapse is suspected for clinical reasons.</td>
</tr>
<tr>
<td>Patients with an unclear iron deficiency anemia (after meticulous exclusion of other causes) in association with signs of hemolytic anemia</td>
<td>At diagnosis, thereafter every 12 months should there be no signs of hemolysis.</td>
</tr>
<tr>
<td>Diagnosis or strong suspicion of aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>Diagnosis or strong suspicion of myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Recurrent abdominal pain crises of uncertain etiology or dysphagia, particularly if concomitant signs of hemolysis exist</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations for disease monitoring by flow cytometry are summarized in Table 2.

**Table 2: Frequency of Flow-Cytometric PNH Analyses [27, 28]**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of suspected hemolytic PNH</td>
<td>Initial diagnostics according to Table 1</td>
</tr>
<tr>
<td>In case of evidence of a significant GPI-deficient cell population</td>
<td>Flow cytometric analyses in intervals of six months during the first two years after diagnosis; thereafter annually if the course of the disease is stable.</td>
</tr>
<tr>
<td>In case of fluctuating proportion of GPI-deficient cells or distinct alteration of the clinical symptoms</td>
<td>Individual adjustment of the intervals of analysis.</td>
</tr>
<tr>
<td>Under eculizumab therapy</td>
<td>Repetition in annual intervals and/or if clinical symptoms are altered or in case of treatment changes.</td>
</tr>
<tr>
<td>After allogenic stem-cell transplantation due to PNH</td>
<td>Test every three months in case chimerism analysis reveals a positive recipient percentage, until the GPI-deficient population is no longer measurable, thereafter annual remission controls. Tests are to proceed within the interval if a relapse is suspected for clinical reasons.</td>
</tr>
<tr>
<td>In case of aplastic anemia</td>
<td>At diagnosis, thereafter every 12 months should there be no signs of hemolysis.</td>
</tr>
</tbody>
</table>

Several relevant aspects, especially also including pre-analytics, are shown in Table 3.

**Table 3: Flow-Cytometric Analysis of GPI-Anchored Proteins [25, 33-35]**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>Peripheral blood (preferentially EDTA anticoagulated). (No analysis of the bone marrow in the scope of routine diagnostics (!), as the physiological changes in the expression of GPI-anchored proteins in the context of hematopoietic differentiation makes the interpretation very difficult).</td>
</tr>
<tr>
<td>Interval between sampling and analysis</td>
<td>If possible &lt; 48 hours, 72 hours at maximum If transport times &gt; 24 hours the sample should be chilled (+1 to +10°C).</td>
</tr>
</tbody>
</table>
Cell lineages

At least granulocytes and erythrocytes; Analysis of the reticulocytes can provide relevant additional information. Analysis of lymphocytes and platelets is optional. At least two different markers per cell line should be analyzed (GPI-anchored proteins or the GPI-anchors themselves). The examined cell population should be identified with a non-GPI-anchored marker.

Reporting of Results

Reports should contain quantitative statements relating to the analyzed cell lines, including a separate report of the percentage of cells with a completely absent expression of GPI-anchored proteins (PNH type-III cells) and reduced expression (PNH type-II cells).

Sensitivity

Routine analyses should enable the identification of a GPI-deficient population exceeding a relative proportion of 1%.

For methodical aspects concerning test performance we refer to the specialized literature [33–35]. The participation in interlaboratory ring trials on flow-cytometric diagnostics which have been organized in Germany since 2011 is also recommended.

4 Therapy

A therapy algorithm is shown in Figure 1.

Figure 1: Algorithm for the Therapy of Patients with Paroxysmal Nocturnal Hemoglobinuria

Legend:

1 TE – thromboembolism: Status post previous TE or increased risk
2 In the event of a single occurrence of a hemolytic crisis steroids may be applied over a short period. However, the dose should be reduced soon and therapy gradually terminated.
4.1 Supportive Therapy

4.1.1 General Considerations

The following recommendations essentially relate to the therapy of hemolytic PNH. As far as the therapy of AA with a PNH clone is concerned, we refer to the Onkopedia Guideline Aplastic Anemia.

- Substitution with erythrocyte transfusions (washed erythrocyte transfusions are not necessary) [36].
- Administration of folic acid (1-5 mg/d, PO) and, if necessary, vitamin B₁₂ as well (in case of deficiency) due to the considerably enhanced compensatory erythropoiesis in the bone marrow.
- Oral iron substitution in case of a deficiency, under control of iron storage parameters (ferritin, transferrin saturation, reticulocyte hemoglobin). Intravenous administration of iron should be avoided as it might trigger a hemolytic seizure. Under therapy with ecuizumab the chronic iron deficiency due to hemoglobinuria and/or hemosiderinuria is stopped through an effective inhibition of intravascular hemolysis. Hence no uncontrolled administration of iron should proceed under therapy with ecuizumab. In case of a potential iron overload [37] (particularly in case of a residual transfusion demand) an iron depletion should be initiated, if possible.
- Bacterial infections should be treated with antibiotics early, as they might cause an exacerbation of PNH accompanied with hemolytic crises [28].
- Sufficient hydration during hemolytic crises.

4.1.2 Steroids

- Empirical therapy, without randomized studies [38-40].
- Short-term pulse therapy with steroids (e.g. 1-2 mg prednisone/kg b.w. over several days) might under certain circumstances exert a beneficial influence on severity and duration of the hemolytic crises.
- Permanent therapy with steroids is not recommended [28]

4.1.3 Anticoagulation

- Life-long secondary prophylactic anticoagulation after a thromboembolic event. Despite effective anticoagulation there still remains a relapse risk for thromboembolic events, which under certain circumstances may be an indication for therapy with ecuizumab [41].
- Therapy of thromboses at atypical locations, for example, a Budd-Chiari syndrome should be performed in a specialized center, if possible. It includes local or systemic lysis therapy, and initiation of ecuizumab therapy [42].
- Primary prophylactic anticoagulation should be considered in patients in whom therapy with ecuizumab is not applied [43]. PNH clone size (granulocyte clone > 50%) and other thrombophilic risk factors must be taken into consideration.
- Both coumarins and heparins can be applied for therapy and prophylaxis.


4.1.4 Immunosuppressive Therapy

- Immunosuppressive therapy as sole treatment of hemolysis activity is not indicated, see Onkopedia Guideline Aplastic Anemia. Eculizumab therapy should be discontinued before therapy with ATG is started, as there will usually be no indication in aplasia (none or only few GPI-deficient erythrocytes) and the efficacy of ATG might be limited (complement-mediated cell lysis).

4.1.5 Complement Inhibition with Eculizumab

A new therapeutic strategy consists in the inhibition of the terminal complement system. The humanized monoclonal antibody eculizumab (Soliris®) binds to complement factor C5, prevents its cleavage into the fragments C5a and C5b, and thus blocks the subsequent formation of the terminal complement complex C5b-9. Therapy is started two weeks after a protective immunization against meningococci. It consists in the administration of 600mg eculizumab weekly for four weeks, followed by 900mg eculizumab every two weeks over approx. 30 minutes plus a 60-minute observational follow-up [41, 44-47].

Indications:

Eculizumab is intended for use in the treatment of symptomatic patients with paroxysmal nocturnal hemoglobinuria. The drug should be administered particularly in case of complications such as transfusion-requiring anemia (in which case hemolysis-induced and cytopenia-induced anemias should be distinguished [48]), subsequent to previous thromboembolic events, PNH-associated renal failure, crises of abdominal pain, or other serious PNH-related symptoms [41, 49]. Therapy with eculizumab usually is a long-term treatment, as the underlying cellular defect, relative to the clone size, is not influenced by the administration of the antibody [46, 49]. Patients previously symptomatic (see above) can benefit from a long-term therapy with eculizumab as it reduces the symptoms and complications associated with the disease, while survival has also been significantly improved as compared to that of a historical control group treated at the same therapy center [49].
Risks and Problems:

- There is an increased risk for infections with capsule-producing bacteria, in particular meningococci, resulting from the inhibition of the terminal complement reaction sequence. Accordingly, protective immunization against meningococci with a tetravalent conjugate vaccine is mandatory at least two weeks prior to onset of therapy (to be repeated every three years; CAVE: There is a high prevalence of the B strains in Europe which have hitherto not been covered by the vaccination).

- In case of symptoms of meningococcal infection (e.g. headaches, accompanied by nausea or vomiting, fever, neck stiffness, skin rash, states of mental confusion) immediate medical diagnostics are required in an emergency plan (emergency ID card!). In addition, a stand-by prophylaxis with 750mg ciprofloxacin will be reasonable in case there are signs of a meningococcal infection (sudden fever, vigilance disorders, cardiovascular insufficiency, etc.).

- Complete blood cell count, reticulocytes, hemolysis parameters (particularly LDH), iron parameters (particularly ferritin), PNH clone size, folic acid, vitamin B₁₂ should be checked on a regular basis under therapy with eculizumab, along with a monospecific Coombs test to determine the existence of complement factors on the surface of erythrocytes (C3d, and, if possible, also C3c) as an indication of extravascular hemolysis [50, 51, 52].

- If there are signs of breakthrough hemolyses an adjustment of the eculizumab dose should be considered under certain circumstances, by shortening the time interval to 12 days [53]. Alternatively, increasing the dose to 1,200mg eculizumab every 14±2 days may be attempted.

- Elective surgical procedures should be scheduled directly after the last administration of eculizumab. In case of potential breakthrough hemolyses an additional dose administration of eculizumab should be taken into consideration. Irrespective of this circumstance perioperative thrombosis prophylaxis should be applied, e.g. with a low-molecular-weight heparin.

- In the event of discontinuation of eculizumab therapy the differential blood cell count and hemolysis parameters should be monitored frequently in order to prevent the occurrence of a serious hemolysis or hemolysis-associated complications [53].

4.1.6 Pregnancy

Pregnancies of female PNH patients are associated with a high rate of maternal and fetal lethality (11.6% and 7.2%, respectively [54]) and each pregnancy is of high risk. Case reports mentioned successful pregnancies under eculizumab without signs of teratogenicity, however, the number of cases was rather low [55]. An ongoing therapy with eculizumab should not be discontinued when pregnancy is diagnosed. If PNH patients have the desire to become pregnant eculizumab therapy should be considered individually after weighing all the risks and complications. Under certain circumstances a dose adjustment will be necessary because of the occurrence of breakthrough hemolyses during pregnancy (e.g. maintenance therapy with 900mg per week).

4.2 Potential Curative Therapy

4.2.1 Allogeneic Stem-Cell Transplantation

Indications:
An indication for allogeneic stem-cell transplantation in case of PNH ensues in cases of severe aplastic anemia, see *Onkopedia Guideline Aplastic Anemia*.

Complications like secondary bone marrow due to severe aplastic anemia, MDS, or transition to an acute leukemia, as well as recurrent thromboembolic complications despite thrombosis prophylaxis or eculizumab therapy might present potential situations from which an indication for allogenic stem-cell therapy might ensue.

Problem:

Considerable transplantation-associated morbidity and mortality due to high rates of transplant rejections particularly after conventional conditioning, complications due to infection, and GVHD (long-term survival rates: approx. 50%-60%) [56, 57]

## 5 References


7 Links

Interlaboratory ring trials: http://www.instandev.de/ringversuche/

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Disclosures

According to the rules of the DGHO (German Association of Hematology and Oncology), the recommendations of the AWMF (Version as by April 23, 2010) and international recommendations: