EBMT Registry

Bone marrow failure syndromes incl. Aplastic anaemia

Guide to the completion of the EBMT data collection form:

BMF_incl_AA_v2.0

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EBMT Registry

EBMT Clinical Research & Registry Department

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Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on EBMT website.

Bone marrow failure syndromes

Bone marrow failure syndromes are disorders of the haematopoietic stem cells leading to cytopenia that can involve one or more cell lineages. They can be acquired (non-constitutional) or genetic (constitutional).

This form must be completed for all patients whose primary disease for which the reported HCT, or IST is being given is BONE MARROW FAILURE SYNDROMES (BMF) incl. APLASTIC ANAEMIA (AA). In addition, the form can be completed if it was requested for a specific study.

No data items should be left blank unless specifically stated in the definition.

Disease

Date of diagnosis

Report the date of the first diagnosis of the disease, either clinical or genetic. Add the date when the sample was collected for examination or (in its absence) the date indicated by a physician within the patient's medical record.

For any genetic (congenital) disease, the date of birth should be reported as the diagnosis date.

If diagnosed in utero, report the date of birth as the diagnosis date.

Classification

Indicate if the disease was **Acquired** or **Genetic**.

Acquired bone marrow failure syndromes

Acquired bone marrow failure syndromes are non-constitutional syndromes: the etiology is not congenital or genetic.

If **Acquired** is selected, also specify the disease class by selecting one of the options from the list.

Aplastic anaemia (AA) is a bone marrow failure syndrome characterised by bicytopenia (decrease in two of three cell lines: erythrocytes, leukocytes, or platelets) or pancytopenia (decrease in all blood cell lines) in the peripheral blood. In addition to an aplastic (absence of cellular proliferation) or

hypoplastic/hypocellular (insufficient cell proliferation) bone marrow in the absence of major dysplastic features or neoplastic (malignant) cells and in the absence of chemotherapy- or radiation therapy-induced damage, or increased reticulin. Aplastic anaemia is classified by its severity as moderate, severe, and very severe aplastic anaemia based on peripheral blood counts as described in table 1. Therefore, it is important to get information on blood counts at the first immunosuppressive treatment episode.

Severity of Aplastic Anaemia (AA)

Please indicate the severity of the AA at diagnosis according to the patients' peripheral blood counts. See table 1 for the criteria for each severity grade.

Aplastic anaemia grade	**Description**
Moderate	• Reduced BM cellularity • Patients with pancytopenia who do not fulfill the criteria of severe disease And/or 2 out of 3 criteria: • Neutrophils < 1.5 x 109/L • Platelets < 50 x 109/L • Hb < 10 g/dL
Severe	BM cellularity < 30% (or < 50% if < 30% of BM are haematopoietic cells) *And 2 out of 3 criteria* • Neutrophils < 0.5 x 10^9/L • Platelets < 20 x 10^9/L • Reticulocytes < 60 x 10^9/L[1]
Very severe	*Same criteria as severe AA, but* Neutrophils < 0.2 x 10^9/L (*obligatory*)

Table 1. Description of the severity of aplastic anaemia.

Pure red cell aplasia (non-congenital PRCA) is an isolated impairment of erythropoiesis (generation of red blood cells), i.e. these patients suffer from anaemia only. In contrast to patients with aplastic anaemia, leukocyte and platelet counts are normal in these patients. There is absolute reticulocytopenia (reduction of the absolute number of reticulocytes below the lower limit of the normal range). The marrow is normocellular and there is a marked erythroid hypoplasia (lack or paucity of recognizable erythropoietic cells in the bone marrow).

Note: For congenital PRCA see question Genetic bone marrow failure syndromes.

[1] Using an automated analyser. < 20 x 10^9/L if manual.

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder of haemopoietic stem cells. PNH is always acquired. Its clinical course is characterised by haemolysis (chronic or acute) and/or thrombosis. Often it is associated with aplastic anaemia (might precede aplastic anaemia or might occur as a late clonal complication after aplastic anaemia). The combination of symptoms (haemolysis, thrombosis, bone marrow failure) and severity may vary greatly.

PNH presentation

Please indicate which of the symptoms PNH was associated with at diagnosis (***you can tick more than one box***):

Haemolytic - the patient presents complement-mediated intravascular haemolysis.

Aplastic - the patient presents symptoms of aplastic anaemia.

Thrombotic - the patient presents symptoms of thrombotic complications.

If the patient presents symptoms other than that mentioned in the list, select **Other** and specify the type of the symptoms in English.

If criteria for both aplastic anaemia and PNH is fulfilled, select **Aplastic anaemia** as the diagnosis and enter details on PNH later on in the diagnosis form when asked (see Bone marrow assessments).

Pure white cell aplasia (non-congenital PWCA) is an isolated impairment of the white cell lineages. It may be associated with thymoma and/or hypogammaglobulinemia.

Note: If PWCA is of genetic origin, it is called Shwachman-Diamond syndrome (see Genetic bone marrow failure syndromes).

Amegakaryocytosis / Thrombocytopenia (non-congenital) can be as:

- thrombocytopenia due to the reduction or absence of megakaryocytes (precursor cells of platelets) in the marrow;
- otherwise, normocellular bone marrow with normal erythropoiesis and granulopoiesis.

Note: For genetic Amegakaryocytosis / Thrombocytopenia see question Genetic bone marrow failure syndromes.

If the acquired syndrome is not mentioned in the list, select **Other acquired cytopenic syndrome** and specify the syndrome name in English in accordance with WHO classification.

Etiology of acquired Bone Marrow Failure Syndromes*

*Cause of the disease

· **Idiopathic**

No recognisable cause; in the majority of patients disease is classified as "idiopathic" (since there is no evidence for any other etiology like post-hepatitis, drug-induced etc)

- **Secondary to hepatitis**

Documented infection with a hepatitis virus preceding the onset of BMF. The virus inducing this hepatitis-aplastic anaemia syndrome has still not been identified.

- **Toxic (includes drug induced)**

Toxic some drugs can induce BMF (e.g. gold salts, penicillamine, phenylbutazone; ibuprofen, indomethacin; antiepileptics: hydantoins, carbamazepine; chloroquine, phenothiazines, antithyroid drugs, allopurinol, sulphonamides); also toxic elements (i.e. benzene) can induce aplastic anaemia.

- **Other, specify**

This can include infections with other virus: Epstein-Barr-Virus infections and other herpes virus infections and influenza A infections can, in some rare cases, be complicated by aplastic anaemia

Genetic bone marrow failure syndromes

For **Genetic** syndromes, also specify the disease class by selecting one of the options from the list. In addition, fill in the “Inborn Errors DCF” (optional).

Amegakaryocytosis / Thrombocytopenia (congenital) - see Amegakaryocytosis / Thrombocytopenia (non-congenital) in question Acquired bone marrow failure syndromes.

Fanconi Anaemia is a congenital aplastic anaemia characterised by progressive bone marrow failure, an increased risk of developing cancers (acute leukaemia and other malignancies); typical birth defects (skin pigmentation, short stature, hypoplasia of thumb and radius, microcephaly, microphthalmia, urinary tract defects, cardiac anomalies).

In vitro diagnostic tests:

- sensitivity to chromosomal breakage by DNA cross-linking agents (= positive "chromosomal breakage test");
- molecular basis: mutations in at least eight distinct genes (“Fanconi anaemia genes“ FANCA, B, C, D1, D2, E, F, G, FANCA, FANCC etc.).

Fanconi anaemia is characterised by bi-lineage or tri-lineage cytopenia and hypoplasia or aplasia in the bone marrow. It is genetically heterogeneous and the different genetic subtypes are known as “Fanconi

complementation groups". There are 12 known complementation groups that cause Fanconi Anaemia when they undergo pathogenic mutations. The groups are A, B, C, D1, D2, E, F, G, I, J, L, and M. The genes that correspond to these groups are given names like **FANCA** (the most common cause of FA), **FANCB**, **FANCC**, **FANCD1 (also called BRCA2)**, **FANCD2**, **FANCE**, **FANCF**, **FANCG**, **FANCL** (also called PHF9 and POG), and FANCM (also FAAP250). So 11 of at least 12 Fanconi Anaemia genes have now been identified, the only one outstanding to be identified is FANCI.

Indicate the mutated gene by selecting one of the options from the list. If the gene of interest is not mentioned in the list, select **Other** and specify the name of the gene in English in accordance with the HGNC nomenclature.[2]

Diamond-Blackfan anaemia (congenital PRCA) see **Pure red cell aplasia (non-congenital PRCA)** in question 2.1.

Shwachman-Diamond syndrome is a rare genetic disorder that affects many organs in the body, and symptoms could vary from individual to individual. The primary features include bone marrow problems (leading to inadequate production of some types of white blood cells e.g. neutropenia, pancytopenia with aplastic anaemia or myelodysplastic syndrome), an exocrine defect in the pancreas (leading to malabsorption), skeletal abnormalities such as metaphyseal dysostosis, and short stature.

Dyserythropoietic anaemia is a group of autosomal recessive anaemias characterised by ineffective erythropoiesis, bone marrow erythroblastic multinuclearity and secondary haemochromatosis.

Dyskeratosis congenita (DKC or Zinsser-Cole-Engman syndrome) is a rare progressive congenital disorder. It is characterised by a triad of symptoms:

- Cutaneous hyper-pigmentation;
- Nail dystrophy;
- Leukoplakia of the oral mucosa.

Other symptoms may include cirrhosis, lung fibrosis, osteoporosis, avascular necrosis of bone, continuous lacrimation, anaemia, and testicular atrophy. DKC is the typical disease of short telomeres. It is caused by a mutation in DKC1 (X-linked recessive), TERT, TERC or TINF2 genes (autosomal dominant) among other genes.

Congenital sideroblastic anaemia is a rare genetic disorder that leads to the accumulation of iron in the mitochondria of erythroblasts, resulting in the formation of ringed sideroblasts. These abnormal cells

[2] https://www.genenames.org/

cannot function properly, leading to anaemia. The severity of the condition varies depending on the specific genetic mutation involved. Treatment may involve blood transfusions, iron chelation therapy, and bone marrow transplantation in severe cases.

If the genetic syndrome is not mentioned in the list, select **Other congenital anaemia** and specify the syndrome name in English in accordance with WHO classification.

Chromosome analysis

Chromosome analysis done before main treatment (all methods including FISH)

In this section describe the results of the most recent complete chromosome analysis (performed at or after diagnosis but before the treatment). Indicate if chromosome analysis was done by selecting **Yes** - the chromosome analysis has been performed prior to treatment. If it was not done, select **No** - the chromosome analysis has not been done. Select **Unknown** if it is unknown whether the chromosome analysis has been done or not.

Output of analysis

Indicate if the output of the chromosome analysis will be reported as **separate abnormalities** or as a **full karyotype**.

What were the results?

Report the results of the analysis. **Normal -** the results of the analysis were normal. Select **Abnormal if** at least one of the results has been found to be abnormal. In addition, indicate the number of abnormalities present in the most recent analysis with abnormal results* (**number of abnormalities present**). Select **Failed** if the chromosome analysis was performed but failed

*If more than one analysis has been done since diagnosis but before treatment, indicate **abnormal results** if at least one analysis has been found to be abnormal. In this case, describe the results of the most recent analysis with abnormal results.

Date of chromosome analysis (if applicable)

Indicate the date of the chromosome analysis mentioned above. If the chromosome analysis was not done/failed leave the field blank. If the date of the chromosome analysis is unknown, select **Unknown**.

Chromosome analysis details

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was **Absent** or **Present**. If a chromosome abnormality was not evaluated, report **Not evaluated**.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality, marking whether it was **Absent** or **Present**.

Transcribe the complete karyotype

If it is necessary, transcribe the complete karyotype according to the International System for Human Cytogenetic Nomenclature (ISCN).

Chromosomal breakage test (for Fanconi only)

For Fanconi anaemia, indicate the outcome of the chromosomal breakage test by selecting **Negative** or **Positive**. Check **Not done or failed** if the chromosomal breakage test has not been done or failed. Select **Unknown** in case it is not known if the test was performed or not.

Molecular marker analysis

Molecular marker analysis done before treatment

If molecular markers were assessed before treatment, select **Yes** and provide details in subsequent questions of this section. If they were not assessed, select **No**. Select **Unknown** if it is unknown whether the analysis of the molecular markers has been done or not.

Date of molecular marker analysis

If applicable, report the date of the molecular marker analysis. If the date is unavailable, select **Unknown**.

Molecular marker analysis details

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent** or **Present**. If a molecular marker was not evaluated, report **Not evaluated**.

If a molecular marker was evaluated, but not listed as an option in the table, select **Other** and specify the marker, indicating whether it was **Absent** or **Present**.

TP53 mutation

If **TP53** mutation is present, indicate the mutation type if known. A TP53 mutation is considered a multi hit if it fulfils one of the following criteria:

- 2 or more distinct mutations of TP53 with a VAF of ≥ 10%
- 1 mutation and 1 deletion involving the TP53 locus
- 1 mutation with VAF ≥ 50%

- 1 mutation with complex karyotype

A TP53 mutation is considered single hit if either one of the following criteria is fulfilled:

- a single TP53 mutation with VAF < 50%
- loss of 17p13 involving TP53 locus without TP53 mutations

If the lab report does not specify the type, select **Unknown**.

Bone marrow investigation

Bone marrow assessments

If any bone marrow investigation was performed at diagnosis, provide details in subsequent questions of this section. If not, proceed to the next section.

Cellularity in the bone marrow aspirate

Report the result of the cellularity assessment performed by aspiration test by indicating if the bone marrow was **Acellular**, **Hypocellular**, **Normocellular**, **Hypercellular** or it had **Focal cellularity**.

Usually, the examination of the BM aspirate is done by a haematologist. The results can be found in the haematology laboratory report.

Cellularity	**Description**
Acellular	Absence of bone marrow cells (“dry tap”)
Hypocellular	Bone marrow has fewer cells than normal or expected
Normocellular	Bone marrow has normal cellularity
Hypercellular	Bone marrow has more cells than normal or expected
Focal cellularity	Bone marrow has fewer cells than normal or expected but with the local normal cellularity

Table 2. Definitions of bone marrow cellularity.

If the cellularity in the bone marrow aspirate was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the cellularity was assessed or not.

Cellularity in the bone marrow trephine

Report the result of the cellularity assessment performed by trephine biopsy by indicating if the bone marrow was **Acellular**, **Hypocellular**, **Normocellular**, **Hypercellular** or it had **Focal cellularity** (see the table above).

The results of the bone marrow trephine biopsy can be found in the pathology report.

If the cellularity in the bone marrow trephine was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the cellularity was assessed or not.

Fibrosis on bone marrow biopsy

Indicate if the bone marrow biopsy revealed any signs of fibrosis. Select **No**, if the biopsy did not show features of fibrosis. If the biopsy revealed histological features of fibrosis select **Mild**, **Moderate** or **Severe** depending on the fibrosis severity grade.

The results of the bone marrow biopsy can be found in the pathology report.

Check **Not evaluable** if the sample could not be analysed. If fibrosis was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the fibrosis was assessed or not.

CD34+ cell count percentage (%)

Indicate the percentage of CD34+ cells in the bone marrow sample. If the cell count was not assessed, report **Not evaluated**. Select **Unknown** in case it is not known if the cell count was measured or not.

Blast count percentage (%)

Indicate the percentage of blast cells in the bone marrow sample. If the cell count was not assessed, report **Not evaluated**. Select **Unknown** in case it is not known if the cell count was measured or not.

If the precise blast count is not available, please indicate if the percentage blasts in the bone marrow sample was below or above 5%.

PNH Tests

This section should be filled in only for Aplastic Anaemia and/or PNH.

A substantial proportion of AA patients carry a population of cells with a "PNH phenotype", i.e. cells which are missing the expression of a specific class of surface proteins (GPI-anchored proteins) due to an acquired mutation in the PIG-A gene.

Flow cytometric analysis of GPI-anchored proteins (e.g. CD55, CD58, CD59, CD14, CD16, CD66b, etc.) is the gold standard for the diagnosis of paroxysmal nocturnal haemoglobinuria.

PNH test done?

Indicate if the recipient had testing for PNH at the time of diagnosis of aplastic anaemia and/or PNH by selecting either **No** or **Yes**. If it is not known if the PNH test was performed select **Unknown.**

Date of PNH test

If the answer to the previous question is **Yes**, indicate the date of the PNH test. In case the date is not known, report **Unknown**.

PNH diagnostics by flow cytometry

Blood cells that have been affected by PNH are known as PNH clone cells. Indicate if the PNH clone cells were absent or present by selecting the appropriate option. If it is not known whether or not the PNH clone is absent or present, report **Unknown.**

Size of PNH clone in percentage (%)

If the **Clone present** option is selected, also specify the size of the clone in percentage (%). PNH clone size refers to the proportion of PNH-affected cells versus normal cells within the total cell population. This information can be found in the haematology report.

Flow cytometry assessment done on

Indicate the type of cells used for the PNH test by selecting one of the options from the list. If the cell type is not mentioned in the list, select **Other** and specify the cell type in English.

Clinical manifestation of PNH

Clinical manifestations of PNH include cytopenias, thrombocytopenia, neutropenia or anaemia, thrombotic complications such as the Budd Chiari syndrome (hepatic vein thrombosis) or thromboses in different locations and active haemolysis which may manifest by dark urine, flank pain or elevated LDH. PNH patients may also exhibit cramps of the bowel, oesophagus, or other muscles, as well as erectile dysfunction. Indicate if any of these PNH manifestations was observed in the patient by selecting either **No** or **Yes**.

Date of clinical manifestation

If **Yes**, also add the date when the clinical manifestation was first reported. In case the date is not known, report **Unknown**.

Anti-complement treatment given?

Indicate if any anti-complement treatment was given to the patient by selecting either **No** or **Yes**. Including compounds that inhibit the complement system, for example: C-5 inhibitors (Eculizumab & Ravulizumab) and C-3 inhibitors (Pegcetacoplan). If the anti-complement treatment that has been given is not listed please select: **Other; specify**.

If anti-complement treatment was given, please provide details.

Drug

If **Yes**, select the drug name from the list of options or use **Other** and report the generic drug/agent name(s) in the textbox in English.

Please consult the **LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS** on the EBMT website for drug/agent names. This document provides alternative names for many of the drugs/agents. Once you have found the drug/agent of interest on the list, add its database name to the table.

Start date

Indicate the date when the treatment was started. In case the date is not known, report **Unknown**.

Treatment stopped

Indicate if anti-complement treatment stopped. In case this information is unavailable, report **Unknown**.

Stop date

If the answer to the previous question is **Yes**, indicate the date when anti-complement treatment stopped. In case the date is not known, report **Unknown**.

If there were more drugs given during one line of treatment add more copies of the page, if using the paper form. It is also possible to add more fields in the online EBMT Registry application to report multiple drugs there.