Appendix I

Practical recommendations regarding surveillance and therapy (adapted to the international consensus treatment guidelines as published by the FARF)

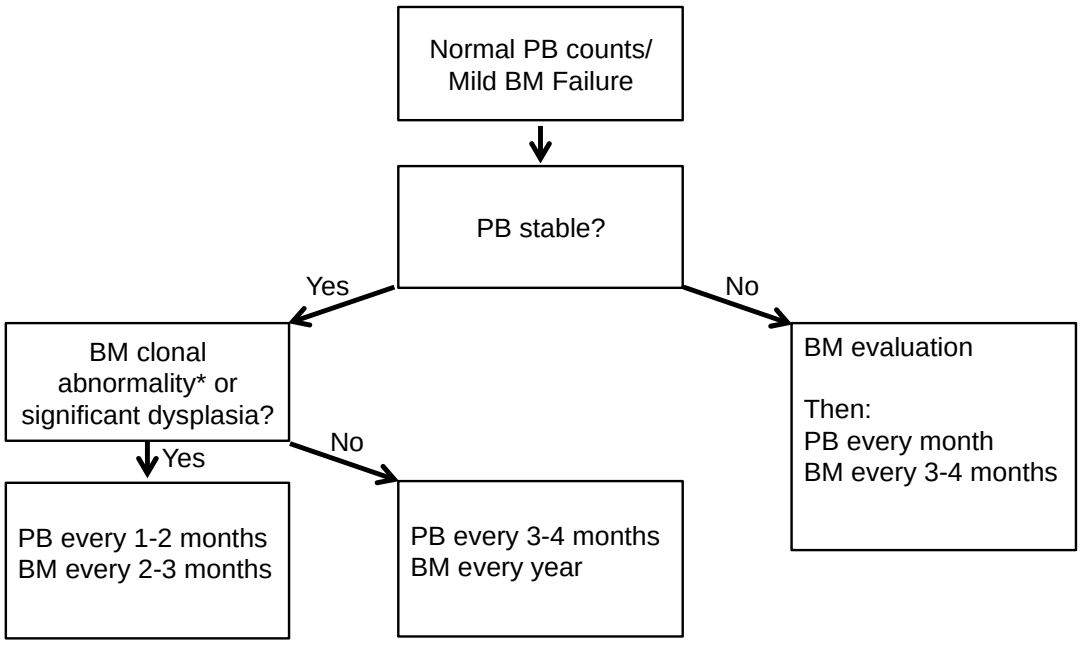
Severity of Bone Marrow Failure

	Mild	Moderate	Severe
ANC	<1,500/mm^3	<1,000/mm^3	<500/mm^3
Platelets	50,000 - 150,000/mm^3	<50,000/mm^3	<30,000/mm^3
Hb	≥8 g/dl*	<8 g/dl	<8 g/dl

*Less than norm for age but >8 g/dl

To meet these criteria for marrow failure, the cytopenias must be persistent and not transient or secondary to another treatable cause, such as infections, medications, PB cell destruction/loss or nutritional deficiencies.

Clinical Monitoring of Bone Marrow Failure



*Specific clonal abnormalities may warrant immediate treatment intervention or closer monitoring.

Figure 1. Suggested monitoring of bone marrow failure

- In stable situations, annual evaluation of the BM is recommended, commencing from two years of age.
- In case of compliance issues, one can consider skipping annual BM investigations (replacing it by testing for -7/+3q and chromosome 1 anomalies on peripheral blood), but only if all the following criteria are met: (1) stable blood counts; (2) no increase in monocytes; (3) no recent changes in MCV; (4) stable clinical situation; (5) absent known cytogenetic changes;
- BM examination should consist of an aspirate, trephine biopsy, cytogenetics with G-banding and FISH with specific probes for MDS/AML in FA
- Interphase FISH cytogenetic analysis in PB cells with specific probes for MDS/AML in FA (if available) may reduce the frequency of bone marrow examinations to longer than one year; however the approach has not yet been published to be effective.

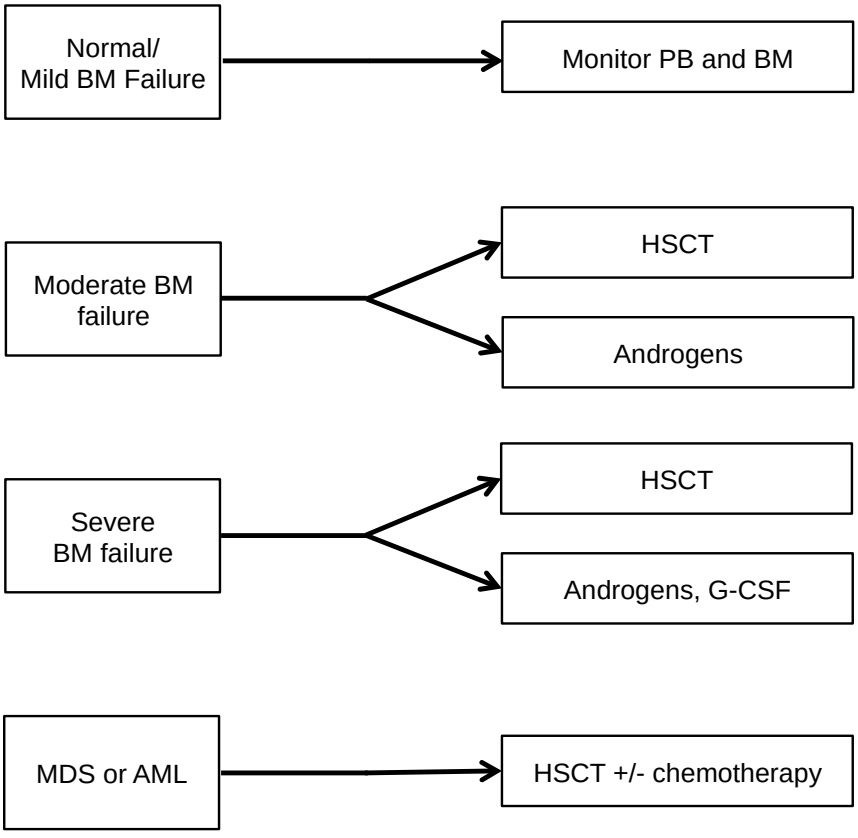


Figure 2. Bone marrow failure algorithm

A consensus HSCT regimen can be found in *Klin Padiatr 2015;227:157-65*
https://www.ncbi.nlm.nih.gov/pubmed/25985449

Androgen use in patients with Fanconi Anemia

- The effect of androgen therapy is to increase/stabilize the hemoglobin (it can also improve/stabilize the platelet count)
- Androgen therapy can be considered when the patients develops moderate bone marrow failure or has clinical signs of insufficient counts, however should start when the patient's hemoglobin drops below 8 g/dl or the platelet count falls below 30,000/mm^3. Of course, strategic discussions with the patient and the family about the use of androgens or whether to proceed to transplant need to start earlier. Prior to commencing treatment a bone marrow investigation is necessary to rule out MDS/AML. Discussion with the registry team is recommended.
- A few reports in the literature show that both male and female patients can be treated at starting dose of approximately 5 mg/kg/die (in one dose) with an attenuated synthetic androgen, danazol, which produces few virilizing effects. A recent retrospective study did demonstrate the effectiveness of danazol in 7 of 8 FA patients treated (starting dose 3.5-7.7 mg/kg/die).
- Most patients respond within 3-6 months to the initial dose with stabilization or increase in the hemoglobin or platelet levels.
- If a response occurs, the general strategy then is to slowly taper the daily dose in 10-20% decrements every 6 months until a dose is obtained which is still effective and side effects minimal/acceptable.
- The side effect of height and weight gain effectively reduces the individual's dose per kilogram body weight. The "real" dose per kg should be recalculated prior to making dose adjustments.
- Every effort should be made to minimize the side effects by tapering the dose whenever possible.
- Long-term androgen usage at higher doses might lead to testis atrophy in males, due to suppression of the hypothalamic-pituitary-gonadal axis.
- If no response is seen after 6 months, in the absence of other causes of cytopenias (such as viral or bacterial infection), alternative treatment options need to be considered; Please contact registry team.
- Blood tests for LFTs as well as lipid status are recommended every 3-6 months, and a liver ultrasound is recommended every 6-12 months.
- Transaminases do not always correlate with the degree of liver inflammation on liver biopsy. If liver transaminases increase to 3-5 times above normal, the androgen dose needs to be carefully tapered to see if the peripheral blood transaminase levels improve.
- Androgen-associated liver adenomas may develop with long-term androgen treatment, however predominantly with oxymetholone.
- These may resolve after androgens are discontinued, but some may persist even years after androgens are stopped.
- Liver adenomas are not a contraindication for stem cell transplantation.
- If screening tests raise a concern for adenocarcinoma, a liver biopsy using a technique appropriate to the patients bleeding risk should be considered.
- Malignant transformations of liver adenomas only occur after years of androgen treatment.

Side Effects of Androgens

- Virilization (mainly with the use of oxymethalone) (acne, facial hair growth/scalp hair loss, deepening of voice, pubic hair, enlargement of penis or clitoris, painful erection in small boys)
- Growth spurt followed by premature closure of epiphyses and short adult stature
- Hyperactivity and behavioral changes (puberty, aggressiveness)
- Cholestatic jaundice or transaminitis
- Abnormal lipid metabolism
- Hepatic adenoma or hepatoma, hepatocellular carcinoma
- Peliosis hepatis
- Hypertension

Cytokines

- Treatment with G-CSF may be considered if the neutropenia is associated with recurrent or serious infections, particularly if the neutrophil counts persistently fall below 500/mm^3 or fail to rise in response to infection. Treatment should generally be discontinued if the neutrophil count fails to improve after eight weeks of G-CSF therapy.
- A bone marrow aspirate/biopsy with cytogenetics is recommended prior to the initiation of cytokine treatment.
- It is reasonable to monitor the bone marrow morphology and cytogenetics every six months while patients are treated with cytokines.

Transfusion of blood products

- Acute transfusions with red blood cells may be necessary to manage symptoms of anemia or before surgery.
- Platelet transfusions are indicated in case of significant bleeding (thrombocytopenia) or prior to surgery.
- A patient should be transfused to maintain minimal trough hemoglobin levels, usually 7-8 g/dl, to ensure that they remain asymptomatic for the level of activity they choose to maintain.
- A post-transfusion hemoglobin of 10-12 g/dl is generally sufficient to allow for normal activity, growth, and development in children with a 3-4 week interval between transfusions.
- Amicar or related compounds may be used as an adjunct to platelet transfusion in a patient with mucosal bleeding. These drugs are generally contraindicated in patients with hematuria.
- Additional factors that increase bleeding risk should be minimized. Drugs that inhibit platelet function, such as aspirin or non-steroidal anti-inflammatory drugs (e.g., ibuprofen), should be avoided. A soft toothbrush should be used. Stool softeners should be administered if constipation poses a risk of GI mucosal trauma. Activities carrying a high risk of significant trauma (particularly to the head or trunk) should be avoided. To date there are no data supporting the efficacy of thrombopoietin-mimetic drugs.

Treatment of MDS or AML

- Treatments should be carefully discussed with experts such as study team members of the Fanconi anemia and EWOG-MDS protocols.

HPV vaccination

- HPV vaccination is recommended because it cannot be excluded that HPV contributes to FA-associated neoplasms. Both genders should be vaccinated.

ENT

- The high incidence of head and neck SCCs, combined with the limited therapeutic options for FA patients, underscore the importance of regular and rigorous surveillance and early surgical interventions in order to achieve cure.
- As two thirds of head and neck SCCs in FA patients are located in the oral cavity, surveillance should ideally be performed by a specialist and should also include naso-, oro-, and hypopharynx as well as larynx and possibly esophagus, especially in older patients and immediately if there are any signs of reflux or dysphagia.
- Without prior transplantation, 6-monthly screening by an FA mouth expert may start at the age of 15 years.
- 6 monthly surveillance is only recommended for patients who don't have any visible lesion.
- In case of a visible lesion, documentation employing mouth photography and a mouth map as well as a brush biopsy (analyzed at the reference cytopathology lab in Düsseldorf, Dr. Martin Schramm) are recommended every three months.
- In case of changes of the visible lesion over time or abnormal results on brush biopsy (ploidy as well as microscopy) a biopsy is necessary.
- A teaching video demonstrating the brush biopsy procedure will be placed on our website: www.cancer-predisposition.org
- Semiannual examinations may be indicated as early as 10 to 12 years of age and particularly, if the patient had undergone HSCT.
- In case of reasonable suspicion of head and neck cancer, a complete survey (panendoscopy) of the upper aerodigestive tract including representative biopsies or a diagnostic excision of the suspected lesion must be performed.
- The complete tumor extension must be documented and secondary carcinomas must be diagnosed/excluded.

Gynecology exams

- Gynecologists caring for FA patients need to have a good understanding of the unique health issues associated with FA patients at different ages.
- Female FA patients face a variety of gynecological problems such as structural abnormalities, delayed puberty, decreased fertility, early menopause, and a high risk of SCC of the cervix, vagina, vulva, and anus. They can also develop other cancer such as breast cancer later in life.

- Birth control for female FA patients needs to be carefully evaluated and discussed with the families. If not transplanted, hormonal contraception may not be ideal due to the effects on the hematopoietic system.
- In general, the pregnancy rates in untransplanted FA women are in the range of 10%-20%, depending on other manifestations of FA and especially on the hematological parameters and the transplant status.
- Pregnancy in an FA woman is classified as high-risk and menopausal symptoms may present at a young age.
- Some centers recommend early yearly gynecological evaluation by 18 years of age (or earlier in case of sexual activity) and annual cervical examinations by age 18 years. Biopsy is encouraged for any suspicious appearing lesions if reasonably accessible. The role of HPV in FA associated SCCs of the lower genital tract is unclear, however, as outlined above, HPV vaccination in all FA patients seems appropriate given the vaccines' strong safety profiles.
- If gynecological malignancies occur, therapeutic approaches for treatment are surgery and irradiation. Chemotherapy agents need to be carefully considered.
- FA patients will have a very high susceptibility in all organs for the toxic side effects of platin derivatives and bi- or tri-functional alkylating agents (busulfan, melphalan, mitomycin C). Thus, we encourage discussion of treatment options with registry team.

Annual endocrine evaluations

- Endocrine abnormalities occur frequently in FA patients. The affected systems often include but are not limited to GH regulation, thyreoid hormons, glucose metabolism, cortisol levels and gonadal hormone productions.
  Appropriate testing may include: 8:00-10:00 a.m. serum cortisol, TSH and FT4, oral glucose tolerance test, HbA1c, 25OH vitamin D.
  If the growth rate is too slow: AM FT4, TSH, IGF-I, IGFBP3, bone age,
  If delayed puberty: LH, FSH, Estradiol or Testosterone, DXA (bone density scan), bone age
- Use of Growth hormone:
  Brain MRI is recommended prior to commencing GH treatment, which is indicated in children who are growth deficient due endocrinologically proven growth hormone deficiency.