National Diagnostic and Treatment Protocol

Aplastic Anaemia
APLASTIC ANAEMIA
National Diagnostic and Treatment Protocol for a Rare Disease

February 2009
Abbreviations

FA  Fanconi anaemia
AA  Aplastic anaemia
MA  Marketing authorisation
ALAT Alanine aminotransferase
ASAT Aspartate aminotransferase
BMB Bone marrow biopsy
HSC Haematopoietic stem cells
CMV Cytomegalovirus
APC Apheresis platelet concentrates
EBV Epstein Barr Virus
EPO Erythropoietin
G-CSF Granulocyte colony-stimulating factor
GVHD Graft versus host disease
HLA Human leucocyte antigen
Hb  Haemoglobin
PNH Paroxysmal nocturnal haemoglobinuria
IgG Immunoglobulin G
IgM Immunoglobulin M
MMF Mycophenolate mofetil
PN Polynuclear neutrophils
LBP Labile blood products
MDS Myelodysplastic syndromes
APTT Activated partial thromboplastin time
PT  Prothrombin time
HIV Human immunodeficiency virus
Summary

This summary was produced from the national diagnostic and treatment protocol (PNDS – protocol nationale de diagnostic et de soins) available on the website www.has-sante.fr.

1. Aplastic anaemia (AA) is a quantitative bone marrow failure, secondary to the complete or partial disappearance of haematopoietic tissue, with no abnormal cell proliferation.

2. The cessation of the production of haematopoietic stem cells (HSC) is responsible for the general failure of haematopoiesis and pancytopenia.

3. There may be an intrinsic genetic cause in constitutional AA or an extrinsic or environmental cause in acquired AA. AA is described as idiopathic when the cause is not known.

4. AA is a rare disease with an incidence of 2 cases per million inhabitants per annum in Europe and the United States. Its prevalence is one person per 250,000 inhabitants.

5. The symptoms and severity of AA differ from one patient to another. Moderate forms of AA need only to be monitored.

6. Overall mortality, although falling significantly, is still high especially during the first few months of the illness. Death generally occurs following a major haemorrhage or a serious infection. There is a risk of onset of myelodysplasia or acute leukaemia.

7. The treatment programme for a patient with AA starts at the time of the first transfusion, in coordination with the blood transfusion centre and the specialists informed of the diagnosis.

8. In severe acquired AA, the combination of anti-thymocyte globulins (ATG) and ciclosporin is the treatment of choice in the absence of an HLA-identical donor amongst the patient’s siblings. This treatment improves survival (a five-year survival rate of 80%). However, it is efficacious in only 50 to 60% of patients, whose condition stabilises or improves to varying degrees. The main disadvantage is the time taken before its effects are apparent (an average of 3 months).

9. A haematopoietic stem cell (HSC) transplant can achieve a recovery in 70 to 80% of cases of severe acquired AA. Graft versus host disease (GvHD), which is potentially fatal, is the main complication.

10. HSC transplantation is the only treatment for constitutional forms.
1. Introduction

1.1. Objectives

The objective of this national treatment protocol (PNDS - *protocol nationale de diagnostic et de soins*) is to explain to health professionals the current optimum management approach and the care programme for a patient with aplastic anaemia (AA) as a chronic condition in relation to bone marrow failure.

This Protocol is a practical tool to which the general practitioner, in collaboration with the specialist, can refer when establishing the management of the patient, particularly at the time of drawing up the care protocol\(^1\) in conjunction with the consultant and the patient.

This Protocol cannot however cover all specific cases, all comorbidities, all therapeutic options, hospital treatment protocols, etc. It cannot claim to be an exhaustive review of possible approaches to the patient’s management nor can it replace the responsibility of each individual doctor to his patient. This protocol does however explain the essential management structure for a patient with AA, and will be updated as new data are validated.

1.2. Epidemiology

AA is a rare disease, the incidence of which is less than ten cases per million per annum, which is twenty times less than multiple myeloma and ten times less than acute leukaemias. Two points should be mentioned:

- although earlier studies may have overestimated the number of cases, it appears that the frequency of the disease has fallen in the last thirty years;
- the disease is more common in Asia than in Europe and America. The incidence is currently in the order of 2 cases per million inhabitants per annum in Europe, rising to 6 in Thailand and 7.4 in China.

The incidence of AA follows a bimodal curve with a first peak in young subjects and another for those over 50 years of age. More cases were reported in males in France in 1984-1985, in the 15-29 age-group, corresponding to severe cases. This peak did not re-occur in the next two years. In the same way, the incidence peaks reported in young people or adolescents in the USA appear not to have been reproduced from one site and one year to another, which would suggest epidemic factors. On the other hand, in Asia the incidence peak in the less than 25 age group is constant.

\(^1\) Alternatively, particularly when the diagnosis is made in a hospital or in an emergency context, another doctor may prepare the treatment protocol. A 100% management programme may be started for a period of 6 months, which may be renewed.
and is four times the rate reported in Europe and Israel in the same age group. The proportion of serious cases is generally higher in young subjects. In both sexes, regardless of continent, incidence rates increase over the age of 60.

AA occurs more frequently in underprivileged socio-economic classes: in a case/control study conducted in Bangkok and two rural areas of Thailand, the risk of onset of AA was correlated to a lower number of years in education and inversely correlated to monthly income. Higher levels of AA have not been reported in rural areas in France, contrary to what was suspected ten years earlier. On the other hand, the number of cases detected in small towns (fewer than 2000 inhabitants) is significantly higher. Finally, in France, 2/3 cases are severe. The time between the first symptoms and the diagnosis is significantly shorter in young people and in severe forms. These figures suggest that severe acute aplasia in young subjects, predominantly male, and chronic hypoplasia in subjects over 50 years of age, more common in women, are two different diseases.

1.3. Physiopathology

The various physiopathogenic hypotheses for AA, which previously conflicted, tend today to be based around a general concept of mechanisms which could lead to bone marrow failure.

Classically, three mechanisms are thought to be responsible for the onset of such bone marrow failure:

- an intrinsic haematopoietic stem cell deficiency:
  This constitutes the main, or even the only, cause of constitutional AA, and a significant proportion of cases of acquired aplasia;

- a bone marrow micro-environment deficiency:
  Its role is probably minimal in acquired and constitutional AA;

- a haematopoiesis deficiency associated with dysregulation of the immune system:
  This is the preponderant mechanism in acquired AA and its role has not been proven in constitutional aplasia.

With regard to acquired AA, it is unlikely to be found that just one of the mechanisms referred to can be held solely responsible for bone marrow failure in AA, with the possible exception of AA induced by toxic agents acting directly on the stem cell such as ionizing radiation or benzene. The term AA covers a range of illnesses with related physiopathological mechanisms.

The efficacy of immunosuppressant treatment can achieve an improvement in the blood count and myelogram, but these patients still have clearly abnormal and decreased haematopoiesis. Furthermore, the primary disorder persists and can constitute the first step towards cellular transformation (initiation) which will lead some patients to develop a myelodysplastic
syndrome. On the other hand, the immune system can be the *primum movens* in other cases. The hypothesis put forward is then that the immune system recognises an epitope of pharmacological or viral origin present on the stem cell which then becomes the target of the immune system (and leads to depletion of the stem cell pool). In this case, following immunosuppressant treatment, residual haematopoiesis is also significantly impaired and subject to transformation.

1.4. Working method

The working group consulted the main international recommendations on the management of AA, together with meta-analyses, clinical trials and cohort studies published since 1990, in English and indexed in the Medline database under the description “aplastic anaemia”. The level of proof for studies and the grade of the recommendations were evaluated using the methodological guide published by the ANAES [National Health Accreditation and Evaluation Agency] on the analysis of literature and grading of recommendations (January 2000).

This Protocol does not apply to pancytopenia occurring immediately after antimitotic chemotherapy or to isolated cytopenia (anaemia, thrombopenia and neutropenia), whether acquired or congenital, which are outside the recognised field of expertise of the “aplastic anaemia” rare diseases reference centre.
2. Initial assessment

2.1. Main objectives

- To confirm the diagnosis of AA.
- To assess its severity.
- To investigate the cause of this aplasia.

2.2. Professionals involved

The initial management of the AA patient involves:

- systematically:
  - the general practitioner,
  - the adult or paediatric haematologist,
  - the paediatrician in the case of children;

- according to the clinical picture, any other specialist whose opinion is required:
  - radiologist (assistance in the diagnosis of complications),
  - microbiologist (assistance in the diagnosis of complications),
  - immunologist (initial assessment – follow-up),
  - doctor responsible for the use of labile blood products (treatment, follow-up)
  - dental surgeon (dental care),
  - stomatologist (stomatological follow-up),
  - gynaecologist (follow-up),
  - occupational health doctor (investigation at the workplace);

- the nurse (management of treatment and follow-up as decided on the basis of the patient’s condition);
- the psychologist if necessary (the law does not provide for reimbursement of the cost of this service)

2.3. Confirming the diagnosis

► Circumstances in which discovered

- discovered by chance on a haemogram prescribed in another medical context;
- discovered on a haemogram prescribed on account of clinical signs suggesting cytopenia: anaemic syndrome, infectious syndrome (associated with neutropenia), haemorrhagic syndrome (associated with thrombopenia).
Clinical examination

Patient interview and physical examination to check for signs suggestive of a general or dissociated bone marrow failure syndrome:

- anaemic syndrome;
- infectious syndrome (any fever even in isolation must be investigated);
- haemorrhagic syndrome.

A systematic check for signs of severity is necessary (Appendix 2):

- widespread purpura or mucosal purpura (blisters in the mouth), if accompanied by visceral bleeding;
- retinitis bleeding.

The clinical examination does not reveal any adenopathy, hepatomegaly or splenomegaly.

Additional examinations

The initial assessment includes:

- a haemogram

By definition, AA involves the three blood lines. Dissociated involvement is however possible in the early stages.

The haemogram indicates pancytopenia, defined as the combination of:

- aregenerative, normochromic, macrocytic or normocytic anaemia associated with a low level of reticulocytes indicating the central nature of the anaemia,
- neutropenia: polynuclear neutrophils $< 1.5 \times 10^9/l (< 1500/mm^3)$,
- thrombopenia: platelets $< 150 \times 10^9/l (< 150 000/mm^3)$;

- the blood smear indicates the absence of abnormal cells;

- determination of the blood group with complete erythrocyte phenotyping with a view to a possible transfusion;

- checking for irregular agglutinins;

- a myelogram:

Usually, the bone marrow smear is poor or barren. Most of the cells observed are lymphocytes or plasmocytes. There are no blast cells, no morphological abnormalities in the bone marrow cells, and no extrahaematopoietic cells.

If the bone marrow in a myelogram is poor, it is not possible to make a definite diagnosis;
- bone marrow karyotyping, which is necessary in all cases (differential diagnosis: myelodysplastic syndrome);
- lymphocyte karyotyping (blood) with a test for chromosome breakage to check for Fanconi disease, associated with the measurement of alphafoetoprotein and foetal haemoglobin levels. Essential in any case of AA in children, sometimes necessary in young adults, particularly in cases involving a dysmorphic syndrome, “café au lait” spots on the skin, or if the disorder is suspected on the basis of the family history.
- A bone marrow biopsy
  This is the examination that confirms the diagnosis of AA. The bone marrow is hypoplastic, with no tumoral infiltration and no myelofibrosis;
- tests for infection, as appropriate to the context;
- phenotyping by flow cytometry to test for a PNH clone;
- an immunological profile: study of lymphocyte sub-populations and determination of immunoglobulins;
- viral serology:
  ‣ testing for viral infection: viral serology for Parvovirus B19 and EBV,
  ‣ transfusion safety: viral serology for hepatitis A, B and C, HIV and CMV;
- measurement of the prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen concentration;
- exploration of liver function abnormalities: determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), free and conjugated bilirubin, and alkaline phosphatase;
- whenever transplantation could be considered: emergency HLA grouping of the patient and siblings;
- follow-up of treatment with ciclosporin
  Haemogram:
  ‣ investigation of liver function abnormalities (AST, ALT, γGT, alkaline phosphatase, total bilirubin),
  ‣ investigation of renal function abnormalities: serum electrolytes, urea, creatininaemia and calculation of creatinine clearance,
  ‣ investigation of a lipid profile abnormality (TC, HDL-C, TG, calculation of the plasma LDL-C concentration).

Additional examinations necessary for the diagnosis of constitutional AA (Fanconi disease and rarer diseases) vary considerably depending on the cause and can include highly specialised biological and genetic tests together with radiological investigations.
Assessing the degree of severity

Pancytopenia can be life-threatening. Diagnosis and treatment are more urgent in cases where pancytopenia is severe. Severity criteria for pancytopenia are:

- **Clinical criteria**
  
  Existence of clinical manifestations of poorly-tolerated anaemia, manifestations of infection or the existence of signs of severity of thrombopenia (widespread cutaneous purpura, haemorrhagic blisters in the mouth, retinal bleeding).

- **Biological criteria**
  
  **Severe aplasia** (Camitta Index):
  - bone marrow content < 25% or between 25 and 50% with less than 30% residual haematopoietic cells,
  - presence of 2 or 3 of the following criteria:
    - thrombopenia < 20 x 10⁹/l,
    - neutropenia < 0.5 x 10⁹/l,
    - reticulocytopenia < 20 x 10⁹/l;

  **Very severe aplasia** *(European Group for Blood and Marrow Transplantation)*:
  - criteria identical to those for severe aplasia but with neutropenia < 0.2 x 10⁹/l.

- The existence of aggravating factors (underlying terrain, age, associated immune deficiency).

Any signs of severity require management as a matter of urgency (Appendix 2) in a haematology or paediatrics unit.

Investigating the cause of aplasia

The interview with the patient sometimes provides initial aetiological guidance in checking or clarifying:

- acute onset of the syndrome or chronic nature of the symptoms of bone marrow failure;
- profession, terrain, occupational or accidental exposure to toxins;
- haematological history;
- history of neoplasia;
- medication taken recently or in the past;
- history of hepatic disorders or infection;
- clinical examination: phenotyping associated with a constitutional form.

Any general or dissociated AA must lead to checking for constitutional AA, particularly in young subjects.
General aplastic anaemia

Acquired AA

- The deficiency may be associated with:
  - Toxic agents:
    - medication: any medication is a priori suspect,
    - environmental or professional toxins;
  - viral infections (parvovirus B19...);
  - pregnancy.

- AA may indicate Marchifava-Micheli disease or paroxysmal nocturnal haemoglobinuria (PNH) (aplastic form)
  PNH is a rare acquired clonal disease of the haematopoietic stem cells which involves chronic haemolytic anaemia associated with episodes of haemoglobinuria, particularly at night. This disease can also take the form of pancytopenia with hypoplasia or AA.
  The course may be marked by severe venous and arterial thrombotic complications (in particular Budd-Chiari syndrome) and episodes of pain. Flow cytometry can confirm the diagnosis.

- Idiopathic apanasias are the most common (60% of cases)
  The diagnosis is made after having eliminated all known causes of AA.
  They are probably of an autoimmune nature. These chronic aplasias can develop into myelodysplasia and acute myeloid leukaemia.

Congenital aplastic anaemia

- Fanconi disease or anaemia (FA).

This is a rare disease (incidence estimated at 1/350 000 births) but it is the most frequent of the constitutional disorders that affect haematopoiesis. Transmission is recessive autosomal. The clinical expression of FA is heterogeneous and reflects the genetic heterogeneity of this disease. The classic picture involves short stature, malformation syndrome (facial dysmorphia with a triangular face and cephalic hypotrophy, absence or abnormalities of the thumbs, pigmentation of the skin and “café au lait” spots, height and weight retardation, abnormalities of the urinary tract (horseshoe kidneys), heart deformities, and bone deformities), and secondary pancytopenia becoming worse with age. The malformation syndrome is variable (Table 1) and is far from constant, its absence does not rule out the diagnosis.

The diagnosis is often easy on a clinical level at the haematological disorders stage. Their association with a triad including short stature, facial dysmorphia and skin irregularities is highly indicative of the condition.

In these children, alpha-foetoprotein elevation has been identified as a potentially useful biological marker of different types of AA.

On a diagnostic level, the formal test is the increase in the number of chromosome breakages induced by alkylating agents. FA cells are
hypersensitive to alkylating agents such as diepoxybutane (DEB), Caryolysine or mitomycin C (MMC). The test needs to be carried out in a reference laboratory. Karyotyping is carried out on blood lymphocytes. On the other hand, this test does not detect heterozygous subjects. The genes involved are identified by molecular biology.

The study of the cell cycle, also carried out on blood, by flow cytometry, is also of good diagnostic value.

Prenatal diagnosis is possible by karyotyping on a sample of foetal blood, amniotic fluid or chorial villosities, showing the increase in the number of chromosome breakages induced by alkylating agents. Identification of some of the genes involved makes it possible to consider prenatal diagnosis after the 14th week of gestation by a molecular study.

Progression to severe AA is very common but does not occur in all cases. There is a risk of progression to a myelodysplastic syndrome and then acute leukaemia, and to solid cancer tumours (ENT and hepatic).
**Table 1. Extrahaematological manifestations of Fanconi anaemia**

<table>
<thead>
<tr>
<th><strong>Height and weight retardation</strong></th>
<th>Practically constant.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>Hyperpigmentation. “Café au lait” spots. Localised areas of hypopigmentation</td>
</tr>
<tr>
<td><strong>Head and neck</strong></td>
<td>Facial dysmorphia. Microcephaly, hydrocephalus, short neck.</td>
</tr>
<tr>
<td><strong>Upper limbs</strong></td>
<td>Thumbs: missing, hypoplastic, supernumerary, bifid, rudimentary, short, positioned low or incorrectly on the hand. Radius: absent or hypoplastic, radial pulses absent or weak. Cubitus: dysplastic.</td>
</tr>
<tr>
<td><strong>Spine and ribs</strong></td>
<td>Spina bifida, scoliosis, abnormal ribs, sacrococcygeal sinus, aplasia of the coccyx, abnormal or supernumerary vertebrae.</td>
</tr>
<tr>
<td><strong>Genitals</strong></td>
<td>Boys: hypogonadism, cryptorchidism, hypospadias, testicles missing or atrophic, azoospermia, phimosis, urethral abnormalities, micropenis, delayed puberty. Girls: hypogonadism, bicornate uterus, aplasia of the uterus or vagina, atresia of the cervix, uterus, or vagina, hypoplastic ovaries, irregular cycles.</td>
</tr>
<tr>
<td><strong>Kidneys</strong></td>
<td>Kidney(s) ectopic or pelvic, abnormal, horseshoe, hypoplastic or dysplastic, hydronephrosis, duplication of the excretory ducts, renal duplication, incorrect position of the kidneys (rotation), reflux, hyperplastic kidneys, non-functional kidneys, abnormal renal artery.</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>Microphthalmia. Hypotelorism, strabismus, epicanthus, hypertelorism, ptosis, oblique eyes, cataract, astigmatism, blindness, epiphora, nystagmus, proptosis, small-sized iris.</td>
</tr>
<tr>
<td><strong>Ears</strong></td>
<td>Deafness (usually conductive), ears of abnormal shape, hypoplastic or malformed, in a low position, large in size, abnormalities of the middle ear, absence of an eardrum, atresia of the external auditory canal.</td>
</tr>
<tr>
<td><strong>Digestive tract</strong></td>
<td>Ogival palate, atresia of the oesophagus, duodenum, jejunum, anal imperforation, oesotracheal fistula, Meckel’s diverticulum, umbilical hernia, hypoplasia of the uvula, biliary tract abnormalities, megacolon, diastasis recti, Budd-Chiari syndrome, annular pancreas, colonic strictures.</td>
</tr>
<tr>
<td><strong>Heart and lungs</strong></td>
<td>Persistent ductus arteriosus, interventricular communication, stenosis of the pulmonary artery, aortic stenosis, coarctation of the aorta, pulmonary lobe missing, vascular deformities, aortic atheroma, inter-atrial communication, Fallot’s tetralogy, hypoplasia of the aorta, abnormal pulmonary venous return, cardiomyopathy, prolapse of the mitral valve, <em>situs inversus</em>.</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td>Intellectual retardation, hyperreflexia, facial paralysis, arterial deformities, stenosis of the internal carotid artery, pituitary gland missing or hypoplastic (or section of the pituitary stalk).</td>
</tr>
</tbody>
</table>
Other forms of constitutional AA

These are very rare.

— Dyskeratosis congenita.

Dyskeratosis congenita, or Zinsser-Cole-Egmann syndrome, is suggested by a diagnostic triad involving reticulate pigmentation of the skin, mucosal leukoplakia and ungual dystrophy. This is a multi-systemic disorder associated with the development of bone marrow failure, an immune deficiency, and an increased risk of neoplasia. Progression to bone marrow failure appears to occur in almost 90% of patients. Three methods of transmission have been reported. In the majority of families studied, transmission is X-linked (Xq28). Analysis of other families, on the other hand, indicates autosomal recessive or autosomal dominant transmission.

— Other constitutional aplastic anaemias.

Apart from FA and dyskeratosis congenita, the constitutional nature of AA is apparent in a number of children. However, this group appears to be very heterogeneous. Some of these cases of aplasia occur in syndromes which are very isolated on a clinical level and include a significant risk of progression to AA (Table 2).
### Table 2. Other constitutional aplastic anaemias

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Type of transmission</th>
<th>Clinical phenotype</th>
<th>Haematological disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubowitz</td>
<td>Autosomal recessive</td>
<td>Height and weight retardation&lt;br&gt;Microcephaly with moderate or no mental retardation&lt;br&gt;Eczema&lt;br&gt;Facial dysmorphia with hypertelorism and blepharophimosis</td>
<td>AA in 10% of patients&lt;br&gt;Risk of progression to leukaemia</td>
</tr>
<tr>
<td>Seckel</td>
<td>Autosomal recessive</td>
<td>“Bird-headed dwarfism”&lt;br&gt;Height and weight retardation&lt;br&gt;Microcephaly with marked mental retardation&lt;br&gt;Facial dysmorphia</td>
<td>AA in 25% of patients&lt;br&gt;Risk of progression to leukaemia</td>
</tr>
<tr>
<td>WT</td>
<td>Autosomal dominant</td>
<td>Similar to the picture of FA.</td>
<td>“High risk”&lt;br&gt;Risk of progression to leukaemia</td>
</tr>
<tr>
<td>IVIC</td>
<td>Autosomal dominant</td>
<td>Similar to the picture of FA:&lt;br&gt;Radial hypoplasia, absence of thumbs, anal imperforation, deafness, strabismus</td>
<td>Isolated thrombopenia</td>
</tr>
</tbody>
</table>

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2.4. Differential diagnosis

This is dominated by hypoplastic forms of myelodysplastic syndromes.

The diagnosis of acquired AA is an elimination diagnosis, which applies to only 10% of the cases of pancytopenia or bicytopenia encountered. A simple bone marrow aspiration must be interpreted with caution and the notion of bone marrow “cellularity” considered as ambiguous. Particularly in the early stages of progression and in subacute forms, areas of normal haematopoiesis can exist around fatty territories. It is also necessary to take account of the patient’s age in order to assess the bone marrow content at different puncture points. A difficult aspiration leading to dilution of the bone marrow fluid can be another trap. In this case, the smear is artificially enriched with polynuclear cells with a lower level of megakaryocytes. For all these reasons, the bone marrow study must systematically include one aspiration and one biopsy of good quality.

Myelodysplasia (MDS) with hypoplastic bone marrow and AA historically constitute, by definition, two different nosological entities, but the boundary between them is shifting. Some authors refer to a continuum between aplasias, cases of MDS with poor bone marrow, MDS with normal or rich bone marrow, and leukaemia. Furthermore, there are forms that move from one to the other, during progression in a single patient. There are cytological criteria for MDS when examining the blood and bone marrow, but these are not completely specific and delayed maturation, particularly in the erythroblast line, may be seen in AA. The presence of clonal abnormalities in cytogenetics is an argument in favour of myelodysplasia.
3. Therapeutic management of a patient with aplastic anaemia

3.1. Main objectives

The main objectives of medical treatment are:

- to improve survival in patients and to reduce the complications associated with AA (anaemia, infectious and haemorrhagic complications);
- to attenuate for as long as possible the impact of the symptoms on the personal, social and professional life of the patient and his close family and friends;
- to improve quality of life;
- to limit the adverse effects of treatment as far as possible.

3.2. Professionals involved

The professionals involved in the therapeutic management of patients with aplastic anaemia are:

- systematically:
  - the general practitioner and/or paediatrician (treatment and follow-up),
  - the haematologist (adult and paediatric) (treatment and follow-up);
- if necessary, depending on complications, specialists other than the haematologist: radiologists, microbiologists, doctors responsible for the use of labile blood products (LBPs), stomatologists, dental surgeons, gynaecologists;
- if necessary, recourse to paramedic health professionals:
  - nurse,
  - psychologist (the law does not provide for reimbursement of the cost of this service);
- if necessary, recourse to other professionals:
  - personal assistants,
  - home-help,
  - social worker.
3.3. Therapeutic education and lifestyle changes

Therapeutic education includes any action intended to help the patient (and his family and friends) to understand the disorder and its treatment, to contribute to the patient’s care, to take charge of his state of health and, as far as possible, to promote a return to normal activities.

Therapeutic education starts immediately the diagnosis is disclosed and is one of the dimensions of the work of various health professionals. Therapeutic education is intended to ensure that a patient with AA and those close to him have a proper understanding of the disorder. This education must make the patient, his family and carers aware of the existence of patient associations and of the benefit of contacting them. This involves providing information which may in particular cover the following points:

- the medicinal products prescribed long-term must be taken regularly and accompanied by a strict medical follow-up programme;
- following a bone-marrow transplant, for several months the patient must avoid places where there are a lot of people, such as public transport, shopping centres, cinemas… Strict standards of hygiene are required in order to limit the risk of infection and protection must be used during sexual relations. Furthermore, the subject must keep in contact with his doctor and advise him of the slightest sign that may suggest an infection (fever, pain, diarrhoea…);
- following the transplant, vaccinations must all be restarted within a period of 6 to 12 months. By taking these precautions, the transplant patient can, in principle, lead a normal life;
- these extreme initial precautions may gradually be relaxed, as the body readjusts to its environment and is functioning normally once again;
- finally, patients wanting a child must talk to the doctor, as medication may affect the foetus.

Rules of hygiene

Everyday hygiene is important in relation to food (avoid any products of dubious origin when eating out), but also avoid any situations that put the patient at risk (sport, violent blows which could cause bleeding). It is also necessary to wash the hands regularly, especially before eating, and to avoid visiting anyone with flu or any other infection known to be contagious. Furthermore, self-medication must be avoided and advice sought before taking any medicines. Finally, it is advisable not to smoke.
3.4. Treatments

For reasons of simplicity, guides for doctors generally refer to therapeutic classes without detailing all medicinal products indicated in the illness in question.

However, each medicinal product applies only in the precise context of its marketing authorisation (MA).

If, for evident reasons, this is not the case, and more generally for the off-label prescription of any product under the sole responsibility of the prescribing physician, the latter must specifically inform the patient of this situation.

► Symptomatic treatment

In patients with severe neutropenia, bacterial infections may soon prove to be fatal. This is therefore a therapeutic emergency and patients must be given broad-spectrum antibiotic therapy without delay. More specifically, patients with AA are particularly at risk of fungal infections (since the period of neutropenia, post-immunosuppression or post-transplantation of HSCs, may be particularly long). These fungal infections due to *Candida* or *Aspergillus* are currently one of the main causes of death in these patients.

Bleeding associated with thrombopenia, which is often deep-seated, constitutes another major cause of death. Anaemia is invariably present. Correction of thrombopenia and anaemia forms part of the essential symptomatic measures in the management of these patients in whom complete erythrocyte phenotyping must be carried out as soon as the diagnosis is made. However, if there is a clear need for transfusions in cases where anaemia is poorly tolerated or where there is a haemorrhagic syndrome, the transfusion policy for these patients may call for complex choices to be made. In fact, it is necessary at all costs to avoid transfusional allo-immunisation, which can compromise the subsequent results of HSC grafts or lead to irrecoverable situations in some patients receiving immunosuppression treatment (multiple allo-immunisations). To conclude, except in the context of an emergency, any indication for a transfusion in a patient with AA must take account of future transfusions for the patient (the rules of transfusions in cases of haemoglobin of less than 8 g/l and platelets of less than 20 g/l are less strictly applied).
Curative treatment

**Allogeneic HSC transplantation**

- Bone marrow transplant from an HLA-geno-identical sibling donor

The bone marrow must be the source of the cells to be transplanted. In fact, survival is significantly lower if stem cells from the blood are used.

A bone marrow transplant (BMT) is the only therapy that is actually curative in acquired AA.

There are three major problems with BMT treatment:
- the probability of having an HLA-identical sibling donor is only 25%;
- BMT can be considered, as a first-line treatment, only in young subjects (under 45-50 years of age);
- mortality associated with the transplant is still 10 to 30%, even in young subjects, with an HLA-geno-identical family donor.

A probability of survival in the order of 80-90% may be achieved in 2008. The risk of graft versus host disease and interstitial pneumonopathy has fallen, although the risk of the graft not taking or of its rejection remains relatively constant. The significant increase in survival is associated with a significant reduction in mortality in the first three months following the graft. This reduction can be attributed to haematological treatments (antibiotics, antivirals, transfusion policy, etc.) and in particular to the introduction of ciclosporin in the prophylaxis of graft versus host disease. On the other hand, there has been little change in late mortality (after 2 years), which still stands at 8 to 10%. This is due in particular to immunodepression associated with chronic graft versus host disease.

Favourable pre-graft criteria are: a short time between diagnosis and transplantation, a limited number of transfusions, and the absence of infection.

Consideration should be given to two points in particular:
- rejection of the graft or the graft not taking. This problem, which is relatively rare in BMT for leukaemia, is still a significant problem following BMT for AA. Its incidence (10-20%) has changed very little over time. Mortality rates are still high, second transplants in this situation achieving long-term survival in only about 1/3 of patients. The incidence of rejection/the graft not taking falls significantly if a) the transplant is rich (number of mononucleated cells) and not manipulated, 2) if the patient is not allo-immunised against major or minor histocompatibility antigens (hence the fundamental importance of an appropriate transfusion policy for these patients), and 3) if pre-transplant conditioning is sufficiently immunosuppressive.
In 2008, irradiation was abandoned on account of its carcinogenic potential. The reference conditioning method in AA is the association of Antithymocyte globulins (ATG) (15 mg/kg/d for 5 days) and cyclophosphamide (200 mg/kg), described by the Seattle group in 2008. It reduces the probability of rejection/the graft not taking to less than 5% (randomised trial comparing cyclophosphamide alone to cyclophosphamide + ALS). A recovery was achieved in almost 95% of patients with this conditioning, in patients not previously treated with immunosuppressants (experience of the reference centre);

- **graft versus host disease.** The incidence of severe acute graft versus host disease has fallen significantly since the introduction of ciclosporin: from approximately 40% in the eighties to approximately 15% in 2008. This is all the more common and severe in older patients, and takes account of the difference in survival observed in younger subjects (under 20 years old, probability of survival of approximately 90%) compared to older subjects (probability of survival in the order of 70%). A randomised trial comparing ciclosporin alone to ciclosporin + methotrexate indicated a significant reduction in GvHD in patients undergoing transplantation due to acquired AA.

- Bone marrow transplant from a non-HLA-identical sibling donor or an unrelated donor

As 75% of patients do not have an HLA-genome-identical donor, some teams have used “alternative” donors: non-HLA-A-identical siblings, or an unrelated donor. The results of this type of graft are not as good (probability of long-term survival not exceeding 40%) as those involving a BMT from an HLA-genome-identical sibling donor. These disappointing results, associated above all with a high incidence of graft versus host disease and a high rejection level, must however be studied in relation to the following parameters:

- these transplants have, logically, been carried out in most cases in patients resistant to or relapsing after immunosuppressant treatment;

- the current molecular biology screening criteria for donors make it possible to select donors whose compatibility with the recipient in the HLA system is clearly superior to that in the initial transplants.
Pharmacological treatments

- Antithymocyte globulins (ATG)

Antithymocyte globulins (ATG) was the first immunosuppressant therapy used in AA. Randomised studies have demonstrated the superiority of ATG compared to symptomatic treatment (transfusions and antibiotics). The dose of ATG typically used was 15 mg/kg/day for 5 days. This serum is from a horse or rabbit immunised with human lymphocytes from circulating blood (antilymphocyte globulins) or thymocytes (antithymocyte globulins). It is administered by the IV route as a 5-day course of treatment.

The mean time for achieving a haematological response (measured as the increase of polynuclear neutrophils) is still long with ATG, in the order of 3 months. The therapeutic response cannot generally be evaluated in less than this time. The variability of the response rates reported after ATG treatment can be explained by:

- the considerable variability, from one patient to another, of the extent of the response and the time in which this is achieved;
- the absence of a standard definition of response to treatment.

Fifty to 60% of patients have a haematological response to ATG. This response is largely a function of the severity of AA: 6-year survival after treatment with ALS (and corticosteroids) is in the order of 80% for non-severe forms, but only 40% for severe or very severe forms (< 200 polynuclear neutrophils). The most favourable results are obtained in children according to a study by the EBMT.

The side effects of ATG are the initial aggravation of leucopenia (a certain risk of infection justifying treatment in a specialist haematology unit) and thrombopenia, and serum sickness. The latter has practically disappeared since the concomitant administration of corticosteroids (1 to 2 mg/kg) with ATG. The administration of high doses of corticosteroids (> 2 mg/kg) does not increase the response rate, but significantly increases morbidity and mortality associated with corticosteroid therapy.

- Ciclosporin

Ciclosporin is a molecule that specifically blocks activation and proliferation of the T lymphocyte. The global response rate for ciclosporin alone (without ALS or androgens) is approximately 50%. As in the case of ATG the less severe the disorder the better the response to treatment (60% in non-severe forms, 34% in severe forms and only 25% for very severe forms).
Ciclosporin is used in association with ALS treatment at an initial dose of 5 to 10 mg/kg/day as two doses administered orally and adjusted according to residual blood ciclosporin levels, renal function and blood pressure. Ciclosporin alone is continued for 3 to 6 months, at which time its efficacy is evaluated. If it is efficacious, it is continued for at least a year. Its use calls for close monitoring of renal function and blood pressure. It can be responsible for joint pain, gingival hypertrophy (promoted by poor oral and dental hygiene and the use of certain dihydropyridines).

Immunosuppressants (ATG and ciclosporin) increase the risk of infections. Irrespective of immunosuppressant treatment, treated cases of AA in non-transplant patients may subsequently progress to:

- the secondary onset of a PNH clone, a phenomenon which can be associated with a relapse of AA;
- the onset of a myelodysplastic syndrome or acute leukaemia.

- Combined treatments
  
  - Combination of ATG + Ciclosporin
    
    This is the reference treatment for severe and non-severe cases of AA. The ATG + ciclosporin combination provides superior results compared to ATG alone. After 3 and 6 months, the response rate is 65% as compared to 39%, and 70% as compared to 46%. In the long term (follow-up for more than 10 years), relapse-free survival is higher with the ALS + ciclosporin combination, but global survival is identical thanks to rescue treatment with the combination of both drugs in the ALS only arm. These results have been confirmed, in particular by the Bethesda group, in the short and the long term. In the long term, a risk of relapse of approximately 35%, and ciclosporin dependency (preventing the withdrawal or reduction of the dose of the latter) in 30% of patients have been reported. Finally, in non-severe aplasia, superiority (in terms of disease-free survival) of the ATG + ciclosporin combination compared to ciclosporin alone has been demonstrated in a European study.

  - Combination of ATG + androgens
    
    The efficacy of the combination ALS + androgens combination is not superior to that of ALS alone.

    There are few indications for androgens alone in the treatment of the disease, apart from certain non-severe relapses.
• Haematopoietic growth factors
The isolated administration of growth factors such as G-CSF, IL1 or IL-3 has proven to be disappointing in the treatment of relapses in patients with AA. There is no role for the use of these growth factors alone, in the absence of immunosuppressant treatment, as a first-line treatment.

In 2008, the efficacy and safety of the combination of ALS + ciclosporin + G-CSF were discussed. According to a study by the EBMT, G-CSF could be associated with an increased risk of MDS/AML. Pending the results of a new trial by the EBMT concerning the combination of ALS + ciclosporin + G-CSF and other than in infectious situations that give cause for concern, the use of G-CSF is not recommended other than for the inclusion of patients in clinical trials.

• Cyclophosphamide
Cyclophosphamide has no role in the treatment of AA (randomised study comparing cyclophosphamide to ALS stopped early following the inclusion of 30 patients since fungal infection and death rates in the cyclophosphamide arm were significantly higher than those in the ALS arm).

• Mycophenolate Mofetil
In a phase II trial conducted by the NIH in the USA, the triple combination of ATG + ciclosporin + mycophenolate mofetil (MMF) did not prove to be superior to the classic association of ATG + ciclosporin. MMF did not prove to be efficacious in refractory patients in a phase II trial by the EBMT.

3.5. Indications for the various treatments

► Symptomatic treatment

• Treatment of anaemia by transfusion
  ▶ transfusion if Hb < 8 g/dl or more according to clinical tolerability and terrain.
- Transfusion of phenotyped erythrocyte concentrates compatible with the Rh (antigens RH1 to 5) and Kell (antigen K1) systems with leucocytes removed, CMV negative serology if the recipient’s serology is CMV negative or not determined.
- Systematically irradiated in the case of immunosuppressant treatment (very serious risk of transfusion-associated GVH disease).

- Prevention of iron overload with iron chelators to be discussed if ferritinaemia > 1 000 µg/l or if the patient has received more than 20 transfusions of red blood cells (long-term transfusion programme).

- Prevention and treatment of bleeding
  Transfusion of platelet concentrates in the event of signs of bleeding and or where platelets < 20 x 10⁹/l (see symptomatic treatment, page 21).

- Prevention and treatment of infectious complications
  Any fever in a patient with severe AA with neutropenia and PN < 0.5 x 10⁹/l calls for hospitalisation as a matter of urgency.

- Curative or preventive treatment of fungal infections.

➤ **Curative treatment**

**Treatment of acquired aplasias**

- Treatment of severe acquired aplasia
  - Bone marrow transplant

A transplant is highly indicated in a young patient with severe AA who has an HLA-identical intrafamilial donor. The transplant must be bone marrow and prophylaxis for graft versus host disease must consist of the combination of ciclosporin and methotrexate. Any variation in this regimen must be the subject of clinical trials (particularly in subjects over 40 years of age in order to reduce graft versus host disease and problems with the graft taking).

A bone marrow transplant can be considered in children and young adults, on a case-by-case basis, by specialist teams, from a related donor if a donor is available who is compatible on a molecular level for HLA-A, -B, -C, DRB1 & DQB1 (10/10 on an allelic level).
Allogeneic transplant from an unrelated donor (from the bone marrow donor database) is not a first-line treatment. Recent progress has led to some discussion regarding its role as a second-line treatment in children or young adults in whom properly-conducted immunosuppressant treatment has failed or who have relapsed following this treatment (ATG + ciclosporin).

- **Immunosuppressant treatments**

Two types of immunosuppressants are used in AA: ATG, and ciclosporin.

In 2008, the role of haematopoietic growth factors, androgens and MMF in the treatment of acquired AA was the subject of some discussion.

- **Granulocyte colony stimulating factors (G-CSF)**
  These are not a basic treatment. They can be prescribed for short-term treatment in the event of a severe infection. EPO is not generally of any benefit.

- **Androgen therapy**
  This has no role as a first-line treatment except in some non-severe forms in the elderly subject. It may be useful in refractory or partially-responding forms.

- **Mycophenolate mofetil (MMF) (Cellcept®)**
  This was evaluated in two phase II trials. In 2008, it has no role in the treatment of acquired aplasia.

- **Corticosteroids**
  As a general rule, they are prescribed only for a short period (15 days) in order to prevent the onset of serum sickness induced by ATG. They are not a basic treatment in any circumstances.

- **Bone marrow transplant or immunosuppressant treatment?**

Symptomatic measures (transfusions or antibiotic therapy) are emergency measures. The choice between immunosuppression and transplantation depends on:

1) whether or not a HLA geno-identical donor (a sibling) is available [25% probability];
2) the severity of the disease (severe or even very severe versus non-severe, according to international criteria);
3) the age of the patient [child versus young adult (40-45 years), versus adult].

Taking account of these remarks, the therapeutic options are as follows:
- bone marrow transplantation is the reference treatment for severe AA in the young subject (≤ 45 years old) who has an HLA-identical sibling donor;
- immunosuppressant treatment with ATG + ciclosporin (with or without G-CSF) for the most severe forms, is the first-line treatment for older patients or in patients (the majority) who do not have a sibling donor who is an identical match.

Studies comparing these two therapeutic regimens give results that are contradictory, favouring transplantation in some cases and immunosuppression in others. However, studies do not always include the same types of patients (younger patients with more severe disorders in series of transplanted patients; results less satisfactory for immunosuppression in children, etc.).

The risk of long-term complications with the two therapeutic options forms the basis for the choice of treatment.

- following immunosuppression, the risk of myelodysplasia or acute leukaemia is 9.6% and 6.6%, respectively, after 10 years. This risk of a secondary myeloid blood disorder is greater in older subjects and those who have had a splenectomy or have received a number of immunosuppressant treatments. Finally, Japanese studies have put forward the hypothesis that G-CSF prescribed at high doses and for many months increases this risk of myelodysplasia;
- following bone marrow transplantation, the risk of a secondary solid tumour is significantly higher than in the general population; their incidence is in the order of 5% after 10 years and is linked to the use of irradiation for conditioning, and to chronic graft versus host disease (especially when the latter has been treated with azathioprine);
- finally, with both types of treatment, there is a non-negligible risk of non-neoplastic complications, such as bone necrosis induced by corticosteroids.

The reference centre considers that the treatment of acquired AA, in a young patient (under 50 years of age), consists (in the absence of an HLA-geno-identical donor) of the combination of ATG + ciclosporin. There is no role as a first-line treatment for the use of MMF, androgens or cyclophosphamide.

The use of G-CSF, in the initial phase, must be restricted to patients with severe infections (this use is due to be revised once results of the EBMT study (which ended in April 2008) are available). The use of ATG in older patients must be discussed on a case-by-case basis according to the severity of the disease and the risks of infection faced by the patient.
• Treatment of moderate forms of aplastic anaemia

These moderate forms sometimes only require monitoring. The reference treatment for non-severe forms in the young subject (under 50 years of age) is the combination of ATG + ciclosporin. Older patients may be treated with ciclosporin alone, or with androgens.

**Specificity of aplasia/PNH syndrome**

Between 20 and 30% of cases of aplasia previously considered as idiopathic have a PNH clone detected by flow cytometry. Approximately 25% of haemolytic forms of PNH will progress to an aplastic form. The aplasia dominant in a clinical picture of an aplasia/PNH syndrome must be managed as an acquired aplasia by transplantation or immunosuppressant treatment. Only following the onset of a haemolytic form or thrombosis in the context of an aplastic/PNH syndrome is treatment with eculizumab indicated.

**Treatment of constitutional aplasia**

• Treatment and monitoring of Fanconi anaemia.

The symptomatic treatment of the various disorders justifies multidisciplinary management involving many paediatric specialists: haematologist, endocrinologist, surgeons (orthopaedic surgeon, urologist…).

**Symptomatic treatment**

- Transfusions must be given sparingly. Moderate anaemia is generally well tolerated. As for thrombopenia, the transfusion threshold depends more on the context than on the platelet count: it can sometimes fall to 10 000 in children not affected by bleeding, whose family is well-informed, and where a transfusion can be given without delay in the event of bleeding. Too many platelet transfusions lead to a risk of immunisation, which is high in such non-immunodepressed children, and leads to the onset of a refractory condition which does not respond to platelet transfusions. Vaccination against hepatitis B virus is given systematically;
- the benefit of the continuous administration of haematopoietic growth factors has not been demonstrated. G-CSF can be prescribed during treatment of a severe infection to achieve a transient increase in the number of polynuclear cells;
- treatment with androgens is regularly efficacious and can prevent the need for transfusions, or make it possible to stop transfusions in a child who has already received a transfusion. It is indicated while a bone marrow donor is being found, if no family donor is available. The initial dose is in the order of 0.5 mg/kg/day (norethandrolone); as a second stage, an attempt should be made to reduce the doses. The response time is 2 to 3 months. Haemoglobin rises first, followed by neutrophils, and then platelets. The response is often incomplete but can achieve a good quality of life without the need for transfusions. However, major toxicity occurs with this treatment: virilisation, ageing of the bones, hepatic adenomas.

Curative treatment
- Only bone marrow transplantation is curative and can prevent progression to leukaemia. The date that this is carried out depends on the age at onset of the haematological manifestations and the type of donor available. If the donor is an HLA-identical sibling (following a check for Fanconi anaemia), the transplant should be given as soon as the child’s cytopenia is sufficiently severe to justify transfusions (the number of transfusions given before the transplant has a negative impact on the prognosis). Conditioning of the transplant takes account of the sensitivity of these children to chemotherapy and ionising radiation (low doses of cyclophosphamide, limited irradiation, possible use of ATG in association);
- the results of geno-identical transplants are satisfactory with a probability of 2-year survival of 66% in a study by the IBMTR involving 150 children;
- the first cord blood transfusion carried out in 1989 was given to a child with FA. Geno-identical cord blood transfusions are now a validated therapeutic approach for this indication;
- the transplant decision is more difficult when the donor is unrelated, taking account of the initial results of these transplants. Nevertheless, there has been an improvement in the prognosis for these transplants recently thanks to a change in conditioning or even the selection of CD34 positive cells making it possible, de facto, to deplete T-lymphocytes;
- in 2008, clinical trials were conducted using gene therapy, which theoretically became possible following the identification of the genes in question.
Follow-up
- Initial follow-up primarily involves monitoring the development of the haematological disorder and management of the various extra-haematological disorders;
- psychological support for the child, and his parents, is also important;
- in the longer term, it is necessary to include the management of any complications or sequelae associated with the various treatments (androgens, transfusion, bone marrow transplant) and the detection of neoplasias, in particular in the upper digestive and respiratory tracts. This risk of cancer seems to be particularly high in transplant patients, with a projected incidence of 24% at 8 years. Apart from the role played by genetic abnormalities, the negative impact of the conditioning of the transplant (irradiation) and chronic graft versus host disease may also play a part.

- Dyskeratosis congenita
  - There is no specific treatment. Androgens can be efficacious in cases of bone marrow failure. The benefit of haematopoietic growth factors as a basic treatment has not been demonstrated. However, G-CSF can be useful as a one-off treatment in the event of a severe infection in a patient with neutropenia but with a certain degree of granulopoiesis conserved. Treatment is primarily symptomatic;
  - the only basic treatment for bone marrow failure is the allogeneic bone marrow transplant. This allows aplasia to be corrected, which indicates the normality of the bone marrow micro-environment. Nevertheless, the medium-term results of transplants have to date been poor on account of a particularly high incidence of post-transplant complications (lung disease, veno-occlusive disease of the liver, thrombotic microangiopathy), which may indicate the particular sensitivity of these patients to the conditioning techniques used (total body irradiation, busulfan). The benefit of using less toxic conditioning techniques has yet to be evaluated. The progression of the disease itself does in fact complicate the analysis of long-term progression in these patients, particularly on a pulmonary level;
  - bone marrow transplantation is not likely, a priori, to cure the bone marrow disorder or all the manifestations of the disease. These patients therefore require multidisciplinary management throughout their lives;
  - in 2008, gene therapy is still a highly theoretical approach.

- Other constitutional aplastic anaemias.

On account of their extreme rarity, their treatment is not codified but may involve the transplantation of haematopoietic stem cells.
► **Other treatments**

- Withdrawal of suspect pharmacological treatments.
- Correction of any adverse effects of treatments:
  - antihypertensive treatments;
  - oral and dental hygiene (prevention of gingival hypertrophy);
  - hydration with at least 2 litres a day in adults.
- Curative or preventive treatment for fungal infections.
4. Follow-up of a patient with aplastic anaemia

4.1. Objectives

- Evaluation of the tolerability of the treatment (checking for adverse effects).
- Adjustment of the treatment.
- Evaluation of compliance with the treatment.
- Evaluation of progression of the disease.
- Evaluation of the improvement in the patient’s knowledge concerning his illness.
- Continued education and support for the patient and his family, friends and carers.
- Investigation of the development of any comorbid conditions.

4.2. Professionals involved in follow-up

See Professionals involved in treatment. Other health professionals may be involved, depending on the onset of any complications directly linked to the progression of the disease.

4.3. Regularity and content of consultations

The AA patient must be followed up by the haematologist (adult and paediatric) and by the general practitioner, working in close collaboration. In patients who respond (not dependent on transfusions and PN over $10^9/l$), alternating monitoring by the haematologist and the general practitioner every 2 to 3 months can be considered.

► Post-transfusional follow-up

- Checking of the haemogram to establish the transfusion programme and assess the risk of infection;
- Monitoring iatrogenesis:
  - checking for allo-immunisation: RAI on the 10th day, RAI 1 month later;
  - testing for a transmissible infectious disease, viral serology in the fourth month (anti-HCV, anti-HIV1+2, anti-HBc antibodies, HBs antigen…) and ALAT determination;
  - testing for iron overload (ferritinaemia).
Monitoring of ciclosporin treatment

- Haemogram.
- Determination of serum magnesium level.
- Liver function (ASAT, ALAT, γGT, alkaline phosphatase, total bilirubin).
- Renal function: serum electrolytes, urea, creatinine and calculated creatinine clearance.
- Investigation of a lipid anomaly (TC, HDL-C, TG, calculated plasma concentration of LDL-C).

4.4. Additional examinations

In non-transplant patients, systematic myelogram approximately once a year with bone marrow karyotyping (in the years following initial treatment) as part of the post-ATG + ciclosporin follow-up (therapeutic response, monitoring for the onset of MDS).

- In patients treated with an iron chelator: monitoring appropriate to the chelator medication used.
Appendix 1. List of contributors to this guide

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Appendix 2. Action to be taken in an emergency

Events requiring emergency admission to hospital

- Fever which is not well tolerated, and a state of shock.
- Ulceronecrotic or antibiotic-resistant throat infection.
- Fever following the administration of medication.
- Fever which does not respond to antibiotics.
- Any fever associated with neutropenia of less than 500/mm$^3$.
- Petechial purpura with haemorrhagic syndrome.
- Thrombopenia of less than 10 000/mm$^3$, even if there is no haemorrhagic syndrome.
- Anaemia which is not well tolerated (cardiovascular and cerebral effects).

Assessing the tolerability of anaemia

In response to any anaemia, signs of severity should be investigated before a decision is taken regarding therapy, in particular a transfusion: more so than biological signs (haemoglobin level), these are certain functional signs (dyspnoea at slight effort, vertigo, poorly tolerated tachycardia, oedema, angina, signs of vascular insufficiency...); they depend on the severity of the anaemia but also on age, the speed of onset of the anaemia, the existence of previous illnesses, in particular cardiovascular disorders.

Action to be taken in a febrile patient with neutropenia

► In general practice
This is a diagnostic and therapeutic emergency requiring immediate management in a specialist environment.

► In a hospital
Establish the difference with expected aplasia, occurring in a patient who has undergone chemotherapy (telephone the department which administered the chemotherapy).
The clinical examination is repeated to look for sites of infection, signs of poor haemodynamic tolerability. The level is often very low (absence of polynuclear cells), and may give false reassurance.
Management consists of 3 parts: diagnosis, infection, monitoring

- **Diagnosis:**
  - Aetiological study: medication taken,
  - Myelogram,
  - Discontinue any non-essential pharmacological treatment;

- **Infection:**
  - **As an emergency:** antibiotic treatment started no later than 6 hours after the onset of fever, as soon as samples have been taken and without waiting for the results, using broad spectrum antibiotics, on a probabilistic basis, subsequently adjusted, given by the IV route at appropriate doses,
  - Preceded by haemocultures at close intervals, CBEU or any relevant microbiological sample,
  - Fitting of a venous shunt,
  - Chest X-ray,
  - Measurement of SaO$_2$ which may be low at an early stage,
  - Measures to isolate the patient.

- **Clinical and biological monitoring:**
  - Report to be sent to the Pharmacovigilance Centre in the case of drug-induced aplasia,
  - Issue to the patient of the list of medicinal products that are contraindicated.

### Assessing of the risk of haemorrhage in cases of thrombopenia

There is generally no risk of spontaneous haemorrhage as long as platelets are $> 30 \times 10^9/l$ except in the case of associated thrombotic disease (renal insufficiency, platelet aggregation inhibitors), associated anticoagulant treatment, or a lesion or process promoting bleeding (gastrointestinal lesions, poorly-controlled hypertension).

There is a latent risk of haemorrhage when platelets are $< 30 \times 10^9/l$;

- This risk is increased:
  - by associated thrombotic disease;
  - where anticoagulants or platelet aggregation inhibitors or NSAIDs are taken.

A platelet transfusion is indicated:
- in cases of patent bleeding (generalised purpura, cutaneous-mucosal bleeding);
- in cases of an associated infection;
- as preparation for an invasive procedure (bone marrow biopsy – endoscopy).
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