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# Diagnosis and management of acquired aplastic anemia in childhood. Guidelines from the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association (AIEOP)

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ABSTRACT

Acquired aplastic anemia (AA) is a rare heterogeneous disorder characterized by pancytopenia and hypoplastic bone marrow. The incidence is 2–3 per million population per year in the Western world, but 3 times higher in East Asia. Survival in severe aplastic anemia (SAA) has improved significantly due to advances in hematopoietic stem cell transplantation (HSCT), immunosuppressive therapy, biologic agents, and supportive care. In SAA, HSCT from a matched sibling donor (MSD) is the first-line treatment. If a MSD is not available, options include immunosuppressive therapy (IST), matched unrelated donor, or haploidentical HSCT. The purpose of this guideline is to provide health care professionals with clear guidance on the diagnosis and management of

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pediatric patients with AA. A preliminary evidence-based document prepared by a group of pediatric hematologists of the Bone Marrow Failure Study Group of the Italian Association of Pediatric Hemato-Oncology (AIEOP) was discussed, modified and approved during a series of consensus conferences that started online during COVID 19 and continued in the following years, according to procedures previously validated by the AIEOP Board of Directors.

## 1. Introduction

Aplastic anemia (AA) is a rare bone marrow (BM) disease in which hematopoietic stem cells are damaged by an autoimmune attack [1,2]. In recent decades, the outcome of the disease has improved remarkably thanks to hematopoietic stem cell transplantation (HSCT) and immunosuppressive treatment (IST). Matched related donor (MRD) HSCT remains the first-line therapy for severe AA. In recent years several retrospective studies, have shown that matched unrelated donor (MUD) HSCT, particularly in young patients, provides results comparable to those achieved by MRD HSCT and superior to those obtained with immunosuppressive therapy (IST) [3–5].

The aim of this paper by the Marrow Failure Syndrome Group (MFSG) of AIEOP (Associazione Italiana Emato-Oncologia Pediatrica), is to provide updated recommendations for the diagnosis and treatment of pediatric AA based on the latest scientific evidence.

## 2. Design and methods

The design and methodology were the same as those used for the "Diagnosis and management of acquired aplastic anemia in childhood" of the AIEOP, published in 2015 [3], and are detailed in Supplementary document N.1 and N.2.

The present manuscript is structured to include short descriptive sections followed by recommendations approved by a panel of experts, all members of the AIEOP Bone Marrow Failure Study Group, in final consensus conferences initiated online during the COVID 19 pandemic in 2021 and continued in the following years.

The need for reviewing previous 2015 AIEOP guidelines [3] was suggested by a much stronger indication to perform first-line transplantation from a MUD and possibly from a haploidentical donor in patients who lack a matched sibling donor and have a high risk of infection, rather than using standard immunosuppressive therapy with hATG and cyclosporine.

Eltrombopag and other TPO mimetics in our 2015 guidelines were not taken in account whereas in the last years increasing evidence related to their use in adult and in children, in combination with ATG and CsA, have been provided and needed re-evaluation. Finally, the advent of new genetic tools has made the diagnosis and monitoring scenario quite different from that of 10 years ago.

### 2.1. Literature review and assessment of evidence

#### 2.1.1. Data source

Experts drew evidence from literature searching in the PubMed database from 2013 to 10/31/2023, and these guidelines are from our interpretation of the literature. Search terms included: adolescents, children, aplastic anemia, idiopathic, acquired, congenital, granulocyte-colony-stimulating factor, bone marrow transplantation, hematopoietic stem cell transplantation, myelodysplasia, G-CSF, G-CSF-receptor, paroxysmal nocturnal hemoglobinuria (PNH), immunosuppressive treatment, anti-thymocyte globulin, horse, rabbit, cyclosporine A, TPO-mimetics, Eltrombopag, Romiplostim, antibiotic treatment, anti-fungal treatment, prophylaxis, vaccinations, transfusion, chelation, pregnancy.

### 2.2. Consensus conference

When controlled, non-controlled studies and case report series (the basis for levels of evidence I through V) were not available, topics were considered expert opinion (EO), regardless of whether they were included in the published literature or represented the opinion of the expert panel. The strength of this consensus was quantified on a scale of 1 to 9, with 1 representing no consensus and 9 representing complete consensus regarding the appropriateness and necessity of the practice. A mean score was calculated for each statement. Mean scores of 1 to 3 indicated an inappropriate practice; mean scores of 3.01 to 7 indicated a practice of uncertain appropriateness; mean scores of 7.01 to 9 indicated an appropriate/necessary practice.

The degree of unanimity of opinions, which expresses the degree of consensus, was assessed according to the following criteria (see Supplementary document N.1 and N.2):

- **Level A** (strong agreement): if the variance for each statement was lower than the mean variance;
- **Level B** (moderate agreement): if the variance for each statement was $\leq$2SD of the mean variance;
- **Level C** (disagreement): if the variance for each statement was >2SD of the mean variance.

Based on the criteria detailed in Supplementary document N.1 and N.2, in the text of the manuscript, after each statement, the following symbols are reported: level of evidence in Roman numbers from I to V or EO if expert opinion; strength of consensus in Arabic numbers; level of consensus in capital letters from A to C.

We acknowledge that the degree of agreement may reflect the views of a homogeneous group of experts that may not fully coincide with the variability of practice across other European and non-European lower income and resourced countries.

## 3. Definition and classification

The term AA defines a disease characterized by peripheral blood (PB) pancytopenia due to a reduced or absent production of hematopoietic cells by the BM, without intrinsic or extrinsic atypical cell infiltration and without increase in reticulin fibers [4,5].

The incidence of AA in the western world is 2 new cases/year/million inhabitants, while it is two to three times higher in East Asia. The male-female ratio is 1:1 and there are two incidence peaks, one in young adults and the other one in the elderly [6,7]. The median age at diagnosis in the pediatric group is 8–9 years [8,9].

Most cases (70–80 %) are idiopathic (that is without a detectable cause) but, in some cases, drugs, chemical or infectious agents can be identified as a possible precipitating or triggering cause of bone marrow failure (BMF) (Table 1). A possible classification of acquired aplasia includes:

- Idiopathic or immune-mediated AA (not documented cause).
- Infectious causes (hepatitis viruses, EBV, CMV, Parvovirus B19, herpetic viruses, Adenovirus, HIV, Mycobacteria, etc.).
- Toxic exposure to radiation and/or chemical agents (Supplementary document N.3).

  Toxic exposure to radiation and/or chemical agents (Supplementary document N.3).
- Graft versus host disease (GvHD).
- AA with onset during pregnancy.
- AA associated to thymoma.

**Table 1**
AA classification based on severity.

| Moderate or non-severe (NSAA) | Severe | Very severe |
|---|---|---|
| • Hypocellular bone marrow with peripheral blood cytopenias not fulfilling criteria for severe or very severe aplastic anemia | • Markedly hypoplastic marrow (<25 % of normal cellularity) or<br>• Moderately hypoplastic marrow (25 %–50 % of normal cellularity with <30 % of remaining cells being hematopoietic)<br>• At least two of the following conditions:<br>a) Neutrophils <500/μl<br>b) Platelets <20.000/μl<br>c) Reticulocytes <20.000/μl[a] | • Like severe but with neutrophils <200/μl |

[a] If reticulocytes are counted manually. If an automated coulter is used, then reticulocytes need to be <60.000/μl because the instrument tends to overestimate lower values [20].

- Vitamin B12, folic acid, copper deficiency.
- AA in the course of an autoimmune diseases (SLE, ALPS, etc.).
- AA in the setting of paroxysmal nocturnal hemoglobinuria (AA/PNH).
- AA associated with immune dysfunction/dysregulations.

Some drugs such as antibiotics, antidiabetics, anticonvulsants and antidepressants appear to be involved in the pathogenesis of AA.

**It is usually extremely difficult to prove the etiological role of a given substance. However, if a drug is considered to have an etiological association with AA, discontinuation of the drug should be considered whenever possible (level of evidence EO; strength of consensus 8.7; level of consensus B).**

In 25–30 % of pediatric cases [10] an acquired AA may be mimicked by a constitutional/hereditary BMF or an immune dysregulation [9,11–15], and it may be very difficult to differentiate these entities. This "diagnostic challenge" will be discussed in detail later in this article.

AA can be differentiated in 3 categories according to severity [16–19] (Table 1).

Current knowledge suggests that idiopathic AA results from several mechanisms, sometimes acting in combination[2]. The most important is an autoimmune damage to the hematopoietic stem cell compartment triggered by an unknown antigen. During this process, which may be favored by genetic predisposition and reduced numbers of regulatory T cells [21], activated autoreactive T cell clones release inflammatory molecules, including *TNF*-alpha and interferon (IFN)-gamma, against the stem cell compartment, which is ultimately destroyed [22,23]. Intrinsic hematopoietic progenitor defects and dysfunction of the BM microenvironment may also contribute to disease development [1].

Telomere shortening is not considered a key pathogenic mechanism in idiopathic AA. However, the length of the telomeres at diagnosis of AA is considered a powerful predictor of the response to IST [24] and of the evolution into MDS/AML [25,26], perhaps through a mechanism of genomic instability [27]. In a recent machine learning study, short telomere length measurement was the top predictor for identifying inherited BMFs [28].

Clonal hematopoiesis is common in AA [29]. The most frequently reported somatic mutations are *BCOR/BCOR1*, *PIG-A*, while genetic alterations typically found in MDS/AML, such as *DNMT3A* and ASXL1, are less common [30]. However, since patients with mutated clones rarely evolve to MDS/AML, the predictive power of somatic mutations towards MDS/AML does not appear to be robustly proven and therefore their impact on therapeutic decisions in idiopathic AA is currently limited [31].

There is also a complex relationship between acquired AA and PNH, with the possibility of one form evolving into the other. Altered hematopoiesis is present in most patients with PNH, at diagnosis or during the course of the disease [32,33]. Current evidence suggests that PNH+ cells escape the immune-mediated attack on bone marrow stem cells and gain a selective advantage that allows them to survive, proliferate and expand [34]. In line with this, the presence of minor PNH+ clones has been associated with a better response to immunosuppressive therapy in some studies in adult patients [35–39]. This has not been consistently confirmed in pediatric AA patients [40–43].

## 4. Diagnosis

The diagnostic algorithm should aim to characterize and define the degree of aplasia, investigate other potential causes of pancytopenia with hypocellular marrow and define the differential diagnosis with neoplastic, constitutional, autoimmune/immune dysregulation forms (Tables 2a, 2b). Some tests are considered mandatory, and others are considered ancillary.

The medical history should focus on ethnicity, consanguinity, family history of hematologic disorders and/or solid neoplasms, infections and exposure to hematotoxic agents [5,20]. Clinical evaluation should include weight-growth status, search for microcephaly, facial dysmorphism, skeletal abnormalities, skin spots, nail dystrophy, premature graying, hypogonadism, oropharyngeal disease (especially *erythro*/leukoplakia) and other signs characteristic of the congenital forms [44]. Signs and symptoms of cytopenia and of liver, lung and CNS involvement should also be sought. Abdominal US scan is suggested for both size and parenchymal evaluation of the spleen and liver and for detection of renal/urinary tract malformations.

The full blood count in AA is usually characterized by normochromic, normocytic, or macrocytic anemia with reticulocytopenia, neutropenia and thrombocytopenia. In the early stages there may be isolated cytopenia, more commonly thrombocytopenia [20]. In peripheral blood smear no blasts are visible, and neutrophils may show toxic granulations. In general, morphologic abnormalities of monocytes, neutrophils and erythrocytes, typical of MDS, are not found in AA [20]. Immunologic work-up, including lymphocyte subset analysis, autoantibody search, immunoglobulin serum level, and antibody titers to vaccines, is aimed at detecting immune deficiency/dysregulations that may underlie BMF. BM aspiration does not provide accurate information on hematopoietic cellularity, as hypocellularity may be due to technical problems with aspiration, and rarely, if the aspiration falls in one of the islands of still-preserved hematopoiesis, cellularity may appear falsely normal. Instead, BM aspiration is useful for the detection of dysplastic and blast cells, which may aid in the differential diagnosis with MDS and hypocellular leukemias. BM trephine biopsy is the gold standard test for the diagnosis of AA [45]. The main differential diagnoses of AA in children are:

- **Hypocellular leukemia:** Approximately 2 % of all childhood acute lymphoblastic leukemias (ALL) are preceded by a transient aplastic phase and may present with hypocellular bone marrow. Acute myeloid leukemia (AML) may also present as AA, although the phenomenon is more frequent in adulthood [46]. BM trephine biopsy can support the diagnosis of acute leukemia by showing the increase of CD34+ cells on immunohistochemistry. Furthermore, the analysis through flow cytometry of both myeloid and lymphoid markers and the detection of clonal molecular markers address the correct diagnosis [46].
- **MDS with low blasts (cMDS-LB) and refractory cytopenia of childhood (RCC):** about 20 % of childhood MDS presents with hypocellular marrow. The most frequent form of MDS in pediatric age is refractory cytopenia of childhood (RCC), introduced as a provisional entity in the 2008 WHO classification and confirmed as

**Table 2a**
Mandatory diagnostic tests.

| Mandatory diagnostic tests | Information on |
|---|---|
| • Full blood count | • Diagnosis and definition of severity |
| • Reticulocyte count (with automatic coulter or manual) | • Diagnosis and definition of severity |
| • Peripheral blood smear | • Differential diagnosis |
| • Liver function tests | • Association with hepatitis |
| • Serology and viral genome research of hepatitis viruses (HAV, HBV, HCV, HDV, HEV, HGV), CMV, EBV, Parvovirus B19, HIV, HHV6. | • Association with viral hepatitis or other viral infection |
| • Bone marrow aspirate for morphology, immunophenotype, standard karyotype | • Diagnosis, differential diagnosis, prognosis |
| • BM and PB flow cytometry analysis of B and T lymphocytes, NK cells and monocytes. Monoclonal populations and/or blasts search, evaluation of abnormal maturation/differentiation patterns as a sign of dysplasia | • Differential diagnosis with myeloid neoplasms, PID/PIRD association with peculiar genetic variants. Association with lymphoma |
| • Bone marrow trephine biopsy with immuno-staining for CD34 and CD117 antigens and iron staining | • Diagnosis, differential diagnosis, prognosis |
| • Chromosomal fragility test (MMC or DEB). In case of doubtful result these tests should be done on fibroblasts to identify somatic mosaicism | • Differential diagnosis of FA |
| • Flow FISH analysis for TL measurement | • TL < 1st centile in lymphocytes is strongly indicative of TBD. Shortened telomere, usually above 1st centile in lymphocytes and granulocytes may be seen in AA because of increased cell turnover. However, TL between 1$^{st}$ and 10$^{th}$ percentile in lymphocytes indicates probable telomeropathy but can also be seen in other congenital BMFs (i.e DBA)<br>• Differential diagnosis with constitutional marrow failure syndromes: |
| • Sequencing of major genes associated with bone marrow failure and WES/NGS panels including genes involved in TBD, FA, DBA, SBDS, CAMT, SCN, *GATA2* deficiency, *SAMD9/SAMD9L, ETV6, MECOM* and other congenital marrow failures; DADA2, immune dysregulation syndromes/PID. WGS, if NGS/WES turns out negative and suspicion persists | 1. Consider TERC, as it is frequently associated (1-10%) with idiopathic AA with no somatic abnormalities.<br>2. If short telomeres are associated with stigmata of dyskeratosis, candidate genes are *DKC1, TINF2*.<br>3. If thrombocytopenia with absence of megakaryocytes, candidate gene is *c-Mpl*.<br>4. If monocytopenia, papillomavirus infections, lymphedema, candidate gene is *GATA2*.<br>5. If metabolic/pancreatic disorders, consider *SDS*.<br>6. If history of vascular disease/inflammation, consider *ADA2*. |
| • Flow cytometry (FLAER) for PNH clones | • Detection of PNH clones: diagnosis, differential diagnosis, prognosis |
| • Screening for autoantibodies (panel according to clinical presentation), including core and DNA antibodies. Double-negative T lymphocyte sub-populations, Tregs analyses, Ig, and vaccine titers. | • Association with autoimmune diseases, immunodeficiencies, immune dysregulation syndromes: diagnosis, differential diagnosis, prognosis |
| • Vitamin B12, folic acid, thyroid function assay | • Exclusion of vitamin deficiency or hypothyroidism |
| • Fibrinogen, ferritin | • Differential diagnosis with hemophagocytic syndrome |
| • Fecal pancreatic elastase, serum amylase and lipase | • Differential diagnosis with SDS |
| • Serum bilirubin, LDH, HbF assay | • Nonspecific indices. May increase in mild ineffective erythropoiesis. |
| • Chest x-ray | • Exclusion of infections or displacement of the mediastinum due to proliferative diseases |

**Table 2a** (*continued*)

| Mandatory diagnostic tests | Information on |
|---|---|
| • Abdominal ultrasound and echocardiogram | • Increased volume of spleen and/or lymph nodes (acute lymphoproliferation from hematological neoplasm or chronic benign lymphoproliferation due to autoimmune lymphoproliferative syndrome/ALPS). Organ malformation or malposition of internal organs (FA) |

**Table 2b**
Ancillary diagnostic tests.

| Ancillary diagnostic tests | Information on |
|---|---|
| • Bone marrow culture and stain for acid-alcohol resistant bacilli | • Presence of mycobacterial infections (especially atypical mycobacteria, less frequently TB) |
| • FISH analysis on BM for monosomy 7, trisomy 8, deletion of 5q, etc. | • Diagnosis, differential diagnosis, prognosis |
| • Clonogenic tests on BM (not standardized results, cannot be done in all centers) | • Differential diagnosis between BMF and MDS |
| • STIR or traditional MRI of skeletal segments (spine) | • Inhomogeneity of bone marrow content due to bone marrow replacement by adipose tissue (probable AA) |

such in the 2022 ICC (International Consensus Classification) review [47]. In the 5th edition of the World Health Organization (WHO) classification of hematolymphoid tumors, childhood MDS with low blasts (cMDS-LB) replaces the former term "refractory cytopenia of childhood" [48]. It includes two subtypes: childhood MDS with low blasts, hypocellular and childhood MDS with low blasts not otherwise specified (NOS). Both conditions include blast count of <5 % in bone marrow and < 2 % in peripheral blood; differential diagnosis with AA is difficult and controversial. RCC and cMDS-LB are forms of myelodysplasia with an hypocellular bone marrow in at least 80 % of cases and, despite the increasing molecular knowledge, close morphologic examination to evaluate the distribution, maturation, and presence of dysplasia in hematopoietic lineages are still required for identification [49]. Supplementary document N.4 shows the morphological and histological [49] alterations that differentiate SAA from RCC. Cytogenetic abnormalities (monosomy of chromosome 7, trisomy of chromosome 8 or 21, complex karyotype with ≥3 abnormalities) are found in about half of cases of hypocellular pediatric MDS. In general, cytogenetic studies in AA are normal, although an abnormal cytogenetic clone can be detected in about 10–12 % of patients. Sometimes these abnormalities may be transient, reflecting the oligoclonality of the stem cells. If insufficient material is obtained for cytogenetic analysis, interphase FISH analysis with centromeric probes specific for chromosomal regions most commonly involved in AA and MDS may be used [50,51].

**MDS with low blasts (cMDS-LB) and refractory cytopenia of childhood (RCC):** about 20 % of childhood MDS presents with hypocellular marrow. The most frequent form of MDS in pediatric age is refractory cytopenia of childhood (RCC), introduced as a provisional entity in the 2008 WHO classification and confirmed as such in the 2022 ICC (International Consensus Classification) review [47]. In the 5th edition of the World Health Organization (WHO) classification of hematolymphoid tumors, childhood MDS with low blasts (cMDS-LB) replaces the former term "refractory cytopenia of childhood" [48]. It includes two subtypes: childhood MDS with low blasts, hypocellular and childhood MDS with low blasts not otherwise specified (NOS). Both conditions include blast count of <5 % in bone marrow and < 2 % in peripheral blood; differential diagnosis with AA is difficult and controversial. RCC and cMDS-LB are forms of myelodysplasia with an hypocellular bone marrow in at least 80 % of

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- **Genetic and/or constitutional bone marrow failure syndromes.** These conditions present with cytopenia and hypocellular bone marrow and must be considered in the differential diagnosis of AA. They may also mask/predict hematological neoplasms and have recently been included in the ICC and WHO review of hematologic neoplasms with germline predisposition within the subgroup "associated with a constitutional disorder affecting multiple organ systems" (see Supplementary document N.5). Constitutional BMFs are associated with somatic signs and symptoms, however, some genetic forms may have a mild or normal phenotype (e.g. FA and some forms of TBD, cAMT, DBA, SDS) [52]. This occurrence is particularly well documented in case of patients with *TERT* or *TERC* mutations who may not show signs of classic DKC and may have a negative family history. They tend to have a hypocellular bone marrow, reduced numbers of CD34+ cells and hematopoietic progenitors, in the presence of normal or mildly abnormal (e.g., isolated macrocytosis) blood counts. An intrinsic tendency to develop solid and hematologic malignancies is present in the classical constitutional syndromes (e.g. FA), but also in recently described disorders such as those associated with *GATA2*, *RUNX1*, *DDX41*, *ANKRD26*, *SAMD9*, *SAMD9L*, *ETV6*, *SRP54*, *MECOM* mutations [53]. Indeed genetic background has recently proven as an important determinant on the outcome of patients undergoing HSCT, since those patients misdiagnosed as AA who were instead inherited bone marrow failure syndrome (IBMFS), had a far inferior survival after transplant [54]. For all these reasons, these genetic variants should be included as much as possible in the diagnostic work-up of AA in children.

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- **Autoimmune/immune dysregulation diseases and immunodeficiencies.** Immune system abnormalities should be considered in the differential diagnosis of AA and investigated with targeted screening. Signs of immune dysregulation may be present in "classic" constitutional AA and occasionally be predominant [55,56]. However, it is also known that autoimmunity due to immune dysregulation syndromes can affect bone marrow precursors thus generating BMF [57,58]. The diagnostic scenario is further complicated by some congenital disorders where both bone marrow failure and immune dysregulation are part of the pathophysiological process, creating an overlap between immunodeficiency and AA. For example, the proteins involved in chromosomal breakage syndromes alter both *VDJ* recombination of TCR and immunoglobulins and hematopoietic stem cell homeostasis [59]. In *GATA2* syndrome, deficiency of this transcription factor plays a key role in stem cell homeostasis, especially in myelo-monocyte precursors, resulting in BMF, monocytopenia and immunodeficiency [60,61].

  In a large cohort of 97 pediatric BMF patients, 17 % were found to carry pathogenic/likely pathogenic variants related to PID/PIRD genes including *GATA2*, *TACI* (CVID), *CARD11*, *CD40L*, *LIG4*, *PI3K*, *XLF*/Cernumnos and D*ADA2*. In addition, 69 % had clinical biochemical immune markers of immune-dysregulation [62] thus reinforcing the need for an accurate immunological survey in the diagnostic work up of BMF patients. *ADA2*, an enzyme produced by dendritic cells, is particularly expressed in the BM where it binds to specific T cell receptors exerting a cytokine-like growth activity. Its deficiency results in a clinical phenotype of immune dysregulation, inflammation, vasculopathy, and BMF mainly in the erythroid lineage [63,64].

Some studies show how a comprehensive and early molecular framework, which allows the exclusion of pathologies related to inborne marrow errors, can improve the outcome of patients, by choosing the most appropriate therapeutic approach and the most suitable conditioning regimen, if any, in case of need for hematopoietic stem cell transplantation [54,62].

In milder forms, however, it is possible to postpone some investigations (especially imaging) based on the information obtained from the anamnesis, hematochemical tests, molecular and cytofluorimetric investigations that are sent to frame these patients [65].

**The work-up for severe AA includes several biochemical, genetic, and instrumental tests identified as either mandatory or ancillary; they are listed in Tables 2a and 2b and may be performed, depending on the severity of the clinical picture, in a stepwise mode (level of evidence EO; strength of consensus 8.4; level of consensus B).**

## 5. Specific treatment

Treatment of pediatric patients with AA should be performed in specialized centers with proven expertise in the management of patients with bone marrow failure [56,66]. Until the diagnosis of AA and its severity are established, a limited observation period is recommended, during which only supportive therapy, but no steroids, should be provided. It is also recommended that the risk of bleeding and infection be minimized before starting treatment.

Specific treatment is based on restoration of hematopoiesis by HSCT or initiation of combined immunosuppressive therapy (IST). The treatment algorithm is shown in Fig. 1.

Non-severe forms (NSAA) may remain stable, evolve, or, more rarely, resolve spontaneously, and it is not possible to define a time limit on the likelihood of progression. There is no uniform position in literature on the treatment of NSAA. In fact, some authors suggest observation only

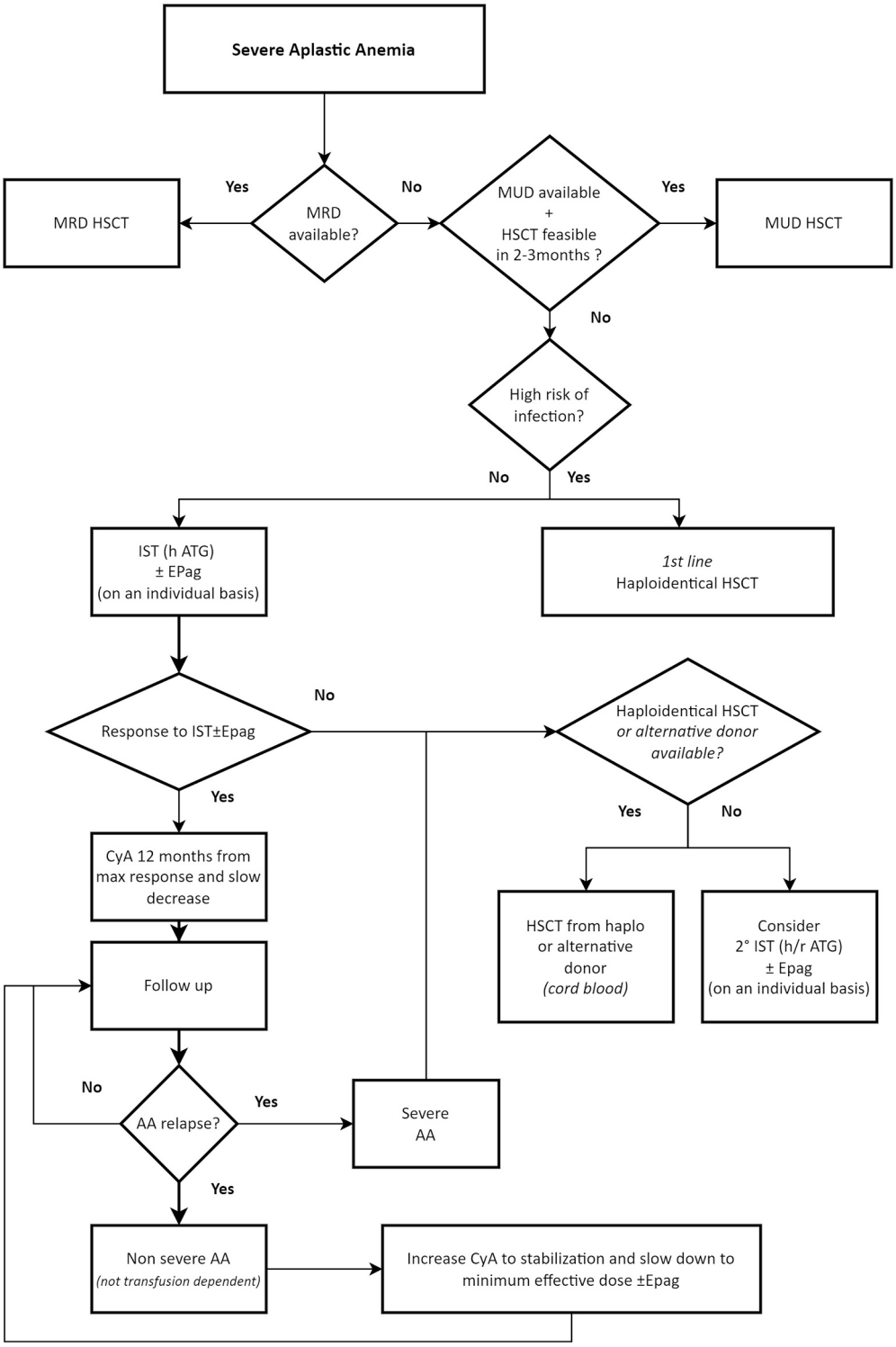


**Fig. 1.** Therapeutic algorithm in children with aplastic anemia.

whereas others propose to use IST or alternatives like eltrombopag or androgens [65,67].

In NSAA with bleeding, frequent transfusion requirements and high risk of infection, treatment is indicated as in severe aplastic anemia (IST and HSCT) [4].

### 5.1. Matched family donor HSCT

The probability of long-term survival after a MRD transplantation is 90–100 % [4,42,68–70].

**HLA typing is recommended at diagnosis for both patient and family members (level of evidence EO; strength of consensus 9; level of consensus A).**

**The first-line therapy for a pediatric patient with AA who requires treatment and has a compatible HLA family donor is MRD HSCT (level of evidence IV; strength of consensus 9; level of consensus A).**

There is clear evidence that bone marrow stem cells are a superior

source of cells than peripheral stem cells for overall survival (OS) and GvHD control [4,71–73].

**Bone marrow is the recommended source of stem cells (level of evidence IV; strength of consensus 8.9; level of consensus B).**

The most widely used and effective conditioning regimen is the combination of cyclophosphamide and rabbit ATG [5,56,74–79]. Good results are also achieved with a combination of fludarabine and cyclophosphamide associated to ATG or Alemtuzumab [80].

**The recommended conditioning regimen for MRD transplantation is the combination of cyclophosphamide 50 mg/kg for 4 days with rabbit ATG (Genzyme Tymoglobulin Product 2.5–3.75 mg/kg for 3 days or Grafalon product from Neovii Biotech) (level of evidence II; strength of consensus 8.4; level of consensus B).**

**An alternative regimen is the combination of fludarabine 30 mg/kg/day for 4 days + cyclophosphamide 30 mg/kg for 4 days (total dose 120 mg/kg) combined with ATG or Alemtuzumab (level of evidence IV; strength of consensus 8.1; level of consensus B).**

The most widely used and effective drugs for the GvHD prophylaxis are CSA and MTX [56,78,81–83], although there is a clear evidence that MTX can be omitted in patients receiving Alemtuzumab [84,85].

**The recommended GvHD prophylaxis regimen in patients receiving ATG is MTX/CSA. The MTX doses to be used are: a) 8 mg/m$^2$ on days +1, +3, +6, +11 or b) 15 mg/m$^2$ on day +1 followed by 10 mg/m$^2$ on days +3, +6, +11 or 10 mg/m$^2$ on days +1, +3, +6 (level of evidence II; strength of consensus 8.3; level of consensus B).**

**The recommended GvHD prophylaxis regimen in patients receiving Alemtuzumab is CSA alone (level of evidence II; strength of consensus 8.4; level of consensus B).**

**The recommended dose of intravenous CSA is 1.5 mg/kg every 12 h, starting at day −1. The blood level of CSA should be maintained at 150–250 ng/ml until 9–12 months after transplantation. Thereafter, in the absence of GvHD and under tight chimerism monitoring, the dose should be reduced until final discontinuation in approximately 3 months (level of evidence III; strength of consensus 8.4; level of consensus B).**

It seems that tacrolimus can replace CSA without affecting the final HSCT result [86].

**In case of intolerance, toxicity or allergy to CSA, tacrolimus is a valid alternative (level of evidence I; strength of consensus 8.3; level of consensus B).**

### 5.2. Matched unrelated donor HSCT

Thanks to the use of reduced-intensity conditioning regimens, increased resolution of HLA typing, and improved supportive therapies, there has been a significant improvement in the outcomes of MUD HSCT in SAA/VSAA. OS and event-free survival (EFS) are excellent, similar to those obtained with MRD HSCT, especially in patients younger than 20 years [69,87]. Retrospective studies on pediatric patients [69,88] confirmed similar OS and EFS in MUD and MRD transplants and better outcomes, including frequency of post HSCT malignancies of 0.7 %, compared to those obtained with IST, which carries a high rate of refractoriness (up to 50 %) and a greater risk of clonal evolution [89]. In 2015, a collaborative UK/EBMT study [90] compared the outcomes of 29 pediatric patients treated with MUD HSCT upfront with matched historical controls who received first-line MRD HSCT, IST or MUD after IST failure. The 2-year OS was comparable in the first 3 groups (96 % in the MUD, 91 % in the MRD and 94 % in the IST group), but the 2-year EFS was 92 % in the MUD cohort, 87 % in the MRD and 40 % in the IST cohort respectively. Cumulative incidence of Ac GvHD grade II–IV was 10 ± 6 % (with only one case of grade III/IV) mostly treated with topical steroid therapy. Frequency of chronic GVHD was 17.2 %, limited in all cases and restricted to skin, and required topical therapy only.

In two other large studies from the EBMT in children and adolescents (ages between 12 and 18 years) the 3-year EFS in patients receiving MUD HSCT after IST failure was 81 % [69] and 71 % [68] respectively. Choi et al. in 2017 [91] retrospectively compared the outcome of 19 pediatric patients with SAA who underwent first-line IST with that of 23 patients who underwent first-line HSCT from an alternative donor (19/23 where MUD HSCT). The failure free survival (FFS) of patients undergoing HSCT was significantly higher (91.3 %) than that observed in the IST group (30.7 %, $p < 0.001$). A retrospective Brazilian study of 106 pediatric patients with SAA treated with MRD or MUD HSCT showed no significant difference in the 4-year OS (82 % in MRD and 69 % in MUD, respectively, $p > 0.05$) [92]. Finally, a large (74 patients, median age 20 years) retrospective EBMT study confirmed a remarkably good outcome of MUD HSCT with a 2-year OS and GvHD-free relapse-free survival (GRFS) of 89 % and 83 % respectively [88].

While interpreting these results we acknowledge that these retrospective studies, albeit are the only currently available, often do not provide data on outcomes and complications in patients eligible for transplantation who are unable to undergo the procedure and either receive second-line treatment or delayed transplantation.

In addition, the applicability of MUD HSCT in frontline whenever MSD is not available, might have some potential limitation in lower income and lower resourced countries. All the above account for the moderate level (B) of consensus of the next two statements.

In this respect the need and the feasibility of higher level of evidence studies has been highlighted by a North American publication [93] and it is likely that a top level of evidence will come by the ongoing multicenter, randomized Phase III clinical trial (NCT05600426) comparing CsA + hATG with front-line MUD HSCT in newly diagnosed SAA patients aged ≤25 years [94].

However, all this considered, the panel reckoned that the evidence for MUD HSCT up-front, if MSD is not available, was supported by sufficient and consistent evidence to enable the two following statements.

**If an identical HLA family donor is not available, a donor search in international registries should be initiated early at the end of diagnostic work-up process of AA (level of evidence EO; strength of consensus 9; level of consensus B).**

**The first-line therapy for a pediatric AA patient who requires treatment and does not have a compatible HLA family donor is MUD transplantation from a 10/10 or 9/10 HLA-matched donor, which should be performed within 2 to 3 months of diagnosis (level of evidence III; strength of consensus 8.8; level of consensus B).**

The most effective conditioning regimen [95–97] is fludarabine combined with cyclophosphamide and ATG. Low-dose total body irradiation (TBI 200 cGy) may be added in multi-transfused patients to reduce the risk of rejection [98–101].

**The recommended conditioning regimen for patients with SAA undergoing allogeneic MUD transplantation is fludarabine 120 mg/m$^2$ (30 mg/m$^2$/day x 4) in combination with cyclophosphamide 120 mg/kg (30 mg/kg/day x 4) plus rabbit-ATG (Genzyme™) 2.5 mg/kg/day for 3 days, or rabbit-ATG (Grafalon™) 10 mg/kg/day for 3 days. Low-dose (200 cGy) TBI should be added in patients older than 14 years of age, multi-transfused (> 20 transfusions) or in case of partial HLA mismatch (1 or 2 Ag). If TBI is used, the dose of cyclophosphamide may be reduced to 100 mg/kg (level of evidence IV; strength of consensus 8.5; level of consensus B).**

**A valid alternative regimen is the combination of fludarabine, cyclophosphamide and alemtuzumab 0.2 mg/kg/day x 4–5 days (FCC regimen) (level of evidence IV; strength of consensus 8.1; level of consensus B).**

**CSA + short-term MTX are indicated for GvHD prophylaxis only when the FCA (fludarabine, cyclophosphamide and ATG) regimen is used. The recommended dose of intravenous CSA is 1.5 mg/kg every 12 h, to maintain a trough blood level of 150–250 ng/ml for up to 9–12 months after transplantation. Thereafter, in the absence of GvHD and under close chimerism monitoring, the dose may be tapered to final discontinuation in approximately 3 months.**

**The most used MTX doses are 10 mg/m$^2$ on day +1, followed by**

**8 mg/m$^2$ on days +3, +6, or 10 mg/m$^2$ for three doses (day +3, +6, +11) (level of evidence V; strength of consensus 8.2; level of consensus B).**

**If the FCC regimen is used, only CsA is recommended for GvHD (level of evidence III; strength of consensus 8.4; level of consensus B).**

### 5.3. Immunosuppressive treatment with or without eltrombopag

The improved outcomes of HSCT in pediatric AA, both in terms of OS and EFS compared to immunosuppressive therapy (IST), has led to a change in the strategy of therapeutic choice in favor of transplantation over IST. A recent meta-analysis [102] including some retrospective pediatric studies [69,91] showed that the quality of life, expressed in terms of EFS, is lower in patients receiving IST than in patients undergoing transplantation, including haploidentical transplantation.

**In patients who cannot undergo MRD or MUD HSCT (maximum of 1 mismatched HLA antigen) within 2 or 3 months of diagnosis, and do not have a high risk of infections, IST ± eltrombopag may be considered as a front-line treatment (level of evidence II; strength of consensus 8; level of consensus C).**

In a prospective randomized study [103] conducted in pediatric and adult patients, the hematologic response after treatment with rabbit ATG was significantly lower than that achieved with horse ATG (37 % vs 68 %). Survival in the rabbit ATG arm was also significantly lower (76 %) than that observed in the horse ATG arm (96 %). In a meta-analysis comparing the efficacy and safety of horse and rabbit serum [104], 13 studies were analyzed. Horse ATG was associated with a better overall response rate (ORR) at six months. Furthermore, when the meta-analysis was performed on 12 studies, one of which was excluded due to heterogeneity, early mortality at 3 months was higher in the rabbit ATG group, with deaths mainly due to infection and bleeding.

**The most effective ATG is horse ATG. The use of rabbit ATG (Thymoglobulin) should be limited to cases where horse ATG (ATGAM™) is unavailable (level of evidence II; strength of consensus 9; level of consensus B).**

**The recommended horse ATG dose is 40 mg/kg/day for 4 days, while that of rabbit ATG is 3.75 mg/kg/day for 5 days. The recommended dose of oral CsA is 5 mg/kg/day, maintaining baseline blood levels between 100 and 250 ng/ml (level of evidence II; strength of consensus 8.8; level of consensus B).**

**It is recommended that CsA be continued at the therapeutic dose for at least 12 months after the maximum response, with subsequent tapering (5–10 % of the dose each month) until discontinuation, not earlier than 24 months after maximum response (level of evidence IV; strength of consensus 8.9; level of consensus B).**

Because the hematological response to IST does not occur until 3 months, response should be assessed on day +120 from the start of treatment. Response must be evaluated by a complete blood count with reticulocytes, bone marrow aspirate, trephine bone marrow biopsy, karyotype and PNH clone search. Hematological response must be confirmed by at least two or three blood counts performed without concomitant use of G-CSF.

#### 5.3.1. Definition of complete response, partial response and non-response [105]

All of the following criteria must be met to define a Complete Response (CR):

- Hb > 10 g/dl
- Neutrophils >1.000/mmc
- PLT > 100.000/mmc
- No evidence of clonal evolution

All of the following criteria must be met to define Partial Response (PR):

- No longer meet the criteria for the diagnosis of SAA
- Transfusion independence (both red cells and platelets)
- Hb > 8 g/dl
- Neutrophils >500/mmc
- PLT > 20.000/mmc.

For the definition of Non-Response (NR), the patient must not meet any of the above criteria.

Eltrombopag is an agonist of the thrombopoietin (TPO) receptor class, the main endogenous regulator of platelet production, that is expressed on megakaryocyte and on hematopoietic stem cells. The rationale for its use in AA is based on its capacity to stimulate hematopoietic stem cell proliferation [106,107]. Many studies [31,108–112], mainly in adult patients, have demonstrated its efficacy in improving outcome when combined with standard IST. In November 2018 the US Food and Drug Administration (FDA) has expanded the label for eltrombopag to include first-line treatment for adults and children ≥2 years with SAA in combination with IST (FDA Promacta Prescribing Information 2015). In 2021 a retrospective study with historical control [113] analyzed 40 pediatric patients with SAA who received eltrombopag in addition to first-line IST. No statistically significant differences in overall response rate (ORR, that is PR + CR) or CR at 6 months were observed. The authors concluded that, contrary to the results in adults, in pediatric age the addition of eltrombopag to first-line IST did not improve the outcome of patients with SAA.

Another retrospective study of 57 pediatric patients showed no statistically significant difference in ORR and CR at 3 months between patients treated with IST and with IST + eltrombopag at the dose of 12.5–50 mg/day. However, at 6 months the CR was 17.9 % in the first group and 50 % in the second one ($p < 0.05$) [114]. A retrospective study evaluated 14 patients treated with IST and eltrombopag given at 75 mg daily in children older than 6 years and 2.5 mg/kg body weight/day in children aged 2 to 5 years. CR and ORR at 6 months were 64.3 % and 78.6 % respectively. In responders, the survival rate was 100 % and no relapse occurred [115]. Another retrospective study showed that at 6 and 12 months, in the IST only arm, ORR was 71 % and 100 % respectively whereas at the same times CR was 29 % and 58 %. When eltrombopag was added to IST response rate was similar. Although eltrombopag was well tolerated, its addition to classical IST did not result in a substantial advantage [116]. Only one prospective randomized trial compared classical IST (horse ATG + CyA) with classical IST + eltrombopag. Three-year OS and EFS, ORR at 4 months, PR, time to CR were not significantly different in the two arms. An advantage for the eltrombopag arm was only observed in CR and ORR for SAA patients [117].

Overall, it seems the addition of eltrombopag to horse ATG and CsA in front line treatment in children does not generate the same advantages observed in adult population.

Unfortunately, the mechanisms underlying the different response to eltrombopag associated to classical IST in adults and children, are still largely ununderstood.

**The addition of eltrombopag to IST in the frontline treatment of SAA in children, while not generating relevant adverse effect, does not appear to produce clear advantage over classical IST alone. Therefore, in pediatric patients, the addition of eltrombopag to the combination of hATG + CsA can be considered an available option (level of evidence IV; strength of consensus 8.3; level of consensus C).**

### 5.4. Haploidentical HSCT in front-line and refractory/relapsed patients

HLA-haploidentical family donor transplantation was initially used in children who did not have a fully matched sibling donor or a matched unrelated donor and who did not respond to first-line immunosuppressive therapy. This option was also used in patients who rejected a previous MUD transplant [72,118]. In recent years, numerous reports have been published on pediatric [119–126] and adult patients [127–132]

with SAA treated with HSCT from a HLA-haploidentical family donor. Lu et al. published a single-center retrospective analysis of 89 patients who underwent HSCT from a haploidentical family donor ($n = 41$) or from a MUD ($n = 48$) after failure of first-line IST [123]. The results were very similar in the two groups of patients, with a 3-year OS of 80.3 % vs 89.6 %, disease free survival (DFS) of 76.4 % vs 89.4 %, and GvHD-free failure-free survival of 79 % vs 71.6 % for haploidentical and MUD transplants, respectively.

As for front-line treatment there is an ongoing prospective study (NCT02833805) comparing Haplo vs MUD HSCT. Currently, even if high-level evidence studies supporting haploidentical HSCT as an alternative to MUD as first-line treatment are very limited, haploidentical HSCT is increasingly used in clinical practice both in children and adults [133] in malignant and non-malignant settings including AA, especially in China, with satisfactory results [134]. De Zern et al. [135] conducted a prospective phase 2 trial of reduced-intensity conditioning HLA-haploidentical HSCT and post-transplantation cyclophosphamide (PTCy)-based GvHD prophylaxis as front-line therapy for patients with SAA. The overall survival of 27 patients was 92 % (95 % CI, 83–100) at 1, 2, and 3 years. The first 7 patients received lower dose TBI (200 vs 400 cGy), but 3 of them experienced graft failure which led the investigators to increase the TBI dose to 400 cGy. All the 20 patients who received 400 cGy survived and had minimal GvHD. However, despite the clear short-term advantage in OS and GRFS, the long-term effects of 400 cGy TBI on fertility and late tumor incidence remain to be evaluated.

A recent US Haplo HSCT study on refractory/relapsed SAA patients showed an OS of 81 % and a graft failure-free survival of 77 % [136] thus confirming that this can be a valuable option also in advanced patients.

Cord transplantation has been reported to provide survival rates of 80–84 % at 2 years [137,138] and may be a treatment option for patients refractory to initial IST who do not have an HLA-identical or haploidentical family or unrelated HLA-matched donor.

The post-transplant cyclophosphamide (PTCY) regimen with PB as a stem cell source is increasingly used in the haplo setting, with very encouraging results in both treatment-naive and refractory patients [127,130,135].

Patients who do not respond to the first IST may respond to a second course of IST. In historical studies the possibility of response was 30–60 % [136,139–141]. A subsequent Japanese study prospectively compared 52 children who did not respond to the first cycle of rabbit ATG and either received a second cycle of rabbit ATG or underwent unrelated donor transplantation. Relapse-free survival was largely superior (83.9 %) in the transplant over the IST group (9.5 %) [142]. In case of failure after the second IST course, the probability of responding to a third course is very low.

Overall, albeit data related to Haplo HSCT outcomes appear more and more convincing, the non-uniform tendency to develop this type of relatively new type of transplant across panelists' centers, might account for the moderate level (B) of consensus on the following statement.

**Haploidentical HSCT may be considered as front-line treatment, preferably in the context of clinical trials, in case of patients at high risk of infection when a MRD donor is not available and a MUD HSCT does not appear feasible within 2–3 months (level of evidence IV; strength of consensus 8.5; level of consensus B).**

**In patients relapsing or not responding to a first course of IST and who do not either have a HLA identical family or a HLA matched unrelated donor (accepted 1/10 HLA mismatched antigen), further IST cycles do not appear to be appropriate and all available transplantation strategies should be carefully considered (level of evidence II; strength of consensus 8.7; level of consensus B). In this circumstance haploidentical transplantation should be considered prior to cord blood (level of evidence IV; strength of consensus 8.5; level of consensus B).**

**In patients relapsing or not responding to second course of IST and who do not either have a HLA identical family or a HLA matched unrelated donor (accepted 1/10 HLA mismatched antigen), HSCT from haploidentical donor should be prioritized over a third course of IST (level of evidence EO; strength of consensus 8.9; level of consensus B).**

### *5.5. Patients refractory to IST or relapsed after IST and with no transplant strategy available*

For patients who are ineligible for transplantation and do not respond to IST (refractory/relapsed), there are limited treatment options. Not many comparative studies exist to clearly establish the superiority of one over another strategy. Therefore, the choice of the best treatment for these patients should rely on major driving factors like patient's age and comorbidities, drug-availability [143].

**A second course of horse or rabbit ATG ± Eltrombopag can be considered for patients refractory to IST or relapsed after IST and with no transplant strategy available (level of evidence IV; strength of consensus 4.2; level of consensus C).**

Other options are:

Mycophenolate mofetil

Mycophenolate mofetil (MMF), an inhibitor of purine synthesis, is a selective, non-competitive and reversible inhibitor of the enzyme inosine-5′-monophosphate dehydrogenase, which is involved in the synthesis of DNA and RNA in T and B lymphocytes thus inhibiting their proliferation. Its use in the treatment of patients with SAA was evaluated in a prospective phase II trial conducted by the National Institutes of Health (NIH): 104 patients (aged 3–76 years, 26 % younger than 20 years) with newly diagnosed SAA were treated with horse ATG + CsA + MMF; the comparison with the historical court (horse ATG + CsA) showed no advantage in terms of response to treatment (62 % at 6 months) or prevention of relapse (37 %, despite maintenance with MMF) [140]. Therefore, MMF does not appear to be effective as an add-on to CsA.

**The use of MMF is not recommended in children (level of evidence II; strength of consensus 8.2; level of consensus B).**

Rapamycin/Sirolimus

Rapamycin/Sirolimus is an antibiotic molecule that inhibits mTOR, a multifunctional serine threonine kinase. Sirolimus binds the immunophylline FKBP12 forming a complex that is responsible for blocking IL-2-dependent T-cell activation and cell cycle progression of lymphocytes from G1 to S [144]. The addition of sirolimus to CsA seems not effective in first-line AA treatment [105], but, according to one report [145], may be helpful in case of nephrotoxicity, when CsA cannot be used.

**Sirolimus may be used as an alternative to cyclosporine in children only when CSA cannot be administered for any reason (level of evidence I; strength of consensus 8.1; level of consensus B).**

High doses of Cyclophosphamide with no stem cell rescue

In 2016, a cohort of 28 pediatric patients with SAA (22 naïve and 6 relapsed or refractory) were treated with CTX at a dose of 50 mg/kg/day for 4 consecutive days without subsequent infusion of hematopoietic stem cells [146]. OS was of 85 %, hematologic response 79 % (with 66 % CR), mortality 14 % (with deaths occurring only in relapsed/refractory patients), bacterial and fungal infection rate 86 % and 62 % respectively. A short-lived study [147] had explored the possibility of using a lower total dose (120 mg/kg), but the rate of fungal and bacterial infections was still too high. Ultimately, high-dose CTX does not appear to be an effective treatment option for AA, especially in pediatric age [4].

**High doses of CTX as monotherapy without HSCT are not recommended in children (level of evidence IV; strength of consensus 8.7; level of consensus B).**

Androgens

Recent studies suggest that the efficacy of androgens may be

linked to an up-regulating effect on telomerase and T-regulatory cells [148–151]. Calado et al. demonstrated that estradiol has a similar effect to androgens on TERT gene expression and telomerase enzymatic activity. Tamoxifen abolished the effects of both estradiol and androgens on telomerase function, and letrozole, an aromatase inhibitor, blocks the effects of androgens on telomerase activity. This evidence suggests that in bone marrow failure, androgens appear to up-regulate telomerase expression and activity primarily through aromatization and through estrogen receptor (ER) alpha [152].

It is possible that, in selected adult patients, AA therapy may also incorporate the use of androgens [4]. In pediatric age their use has been substantially abandoned.

**The use of androgens is not recommended in children with AA (level of evidence EO; strength of consensus 8.2; level of consensus B).**

Alemtuzumab

Alemtuzumab, a monoclonal antibody anti-CD52, was shown in small studies to have some effect on the full blood count of AA patients in different stages of the disease, although the results should be confirmed in larger trials and in scenarios involving patients in the same disease phase [153,154].

**The use of alemtuzumab may be considered in pediatric age only in patients who relapsed after IST and are ineligible for HSCT (level of evidence IV; strength of consensus 8.0; level of consensus B).**

Romiplostim

Romiplostim is a peptide with *c-MPL* agonist activity that acts directly on *c-MPL*-expressing cells. Compared to eltrombopag, romiplostim binds to a more external TPO receptor domain and stimulates also endogenous TPO production. The drug promotes the proliferation and differentiation of megakaryocytes and hematopoietic stem cells in the bone marrow, stimulating primarily mature precursors [155]. In adults, romiplostim has been shown to be effective in 80 % of patients with non-severe AA (NSAA) or refractory SAA when administered at doses up to 20 μg/kg per week [156,157]. Unfortunately in pediatric age only case series are reported [158,159],showing generally excellent response to treatment but on a very small number of patients.

**Due to the lack of studies in children, the use of romiplostim in pediatric AA cannot be recommended (level of evidence EO; strength of consensus 8.2; level of consensus C).**

### *5.6. Patients with graft rejection or failure after allogeneic hematopoietic stem cell transplantation*

Graft rejection (GR) and graft failure (GF) are among the most serious complications for pediatric patients with AA undergoing HSCT, since spontaneous autologous recovery is reported in only 4.2 % of patients [160]. Although a second transplant is considered a procedure with a high risk of mortality due to infectious complications and organ toxicity, this option offers a probability of long-term survival >60–70 % [161,162]. OS and FFS are not influenced by age, donor type, conditioning regimen and GVHD prophylaxis. Only an interval of >60 days between the first and second transplant improves FFS (88.9 % vs. 61.4 %; $P = 0.036$) [162].

**Second allogeneic stem cell transplantation from the same or a different donor is a possible option in case of graft rejection or graft failure after a first allogeneic transplant (level of evidence IV; strength of consensus 8.2; level of consensus C).**

**If a second transplant is chosen, it is necessary to reduce the period of aplasia and the related risk of infection (level of evidence IV; strength of consensus 8.6; level of consensus B). Peripheral blood after stimulation with G-CSF is the preferred source of stem cells for a second allogeneic transplant with the aim to ensure a rapid engraftment [163–165] (level of evidence IV; strength of consensus 7.9; level of consensus C).**

In the absence of controlled studies, it is likely that each center tends to rely on conditioning regimens with which it is familiar and comfortable. This may probably account for the low level of consensus of the next statement.

**The use of non-myeloablative conditioning, with moderate doses of fludarabine and cyclophosphamide and reduced dose of TBI (2–4 Gy) is recommended to reduce the toxicity related to a second transplant procedure [162] (level of evidence IV; strength of consensus 8.1; level of consensus C).**

## 6. Long term follow up

In an Italian single-center study and a subsequent multicenter study, the occurrence and expansion of and expansion of EPN clones in previously negative STI-treated pediatric patients was associated with associated with CSA escalation or disease recurrence [43]. A retrospective study of an exclusively pediatric population undergoing IST demonstrated an overall survival of 93 % at 5 years, but an event-free survival without further treatment of 64 %; 7 % of subjects had acquired cytogenetic abnormalities after diagnosis with a median interval of 25 months and a progression to MDS/ML of 1.9 %. In the same study, stem cell transplantation in refractory or relapsed cases showed a better EFS compared to second-line treatment [166].

**In patients responsive to IST, it is recommended that a bone marrow trephine biopsy with karyotyping (classical cytogenetics or FISH or array) be performed at 6 and 12 months after initiation of IST, and then annually for 5 years after achieving a stable response. After the first 5 years follow-up, the interval may be extended if no karyotype changes have occurred during follow-up assessments and peripheral counts are stable (level of evidence EO; strength of consensus 8.2; level of consensus C).**

Recurrence of PNH clones is a rare event, although it has been reported in subjects undergoing HSCT, even in the presence of stable chimerism.

**It is recommended to monitor PNH clones, by FLAER, every six months (if negative at onset) in the first 2 years and then annually. If a PNH clone appears at any moment monitoring should be done every 3 months, for the first 2 years, extending the interval if the clone is stable (level of evidence EO; strength of consensus 8.4; level of consensus B).**

**PNH clones are recommended to be monitored also in post-HSCT period. In case of mixed chimerism and in case of relapse, it is recommended to test hemolysis parameters (level of evidence EO; strength of consensus 8.4; level of consensus B).**

**Monitoring of chimerism after HSCT in patients with AA is recommended once a month during the first year, every 3 months in the second year and every 12 months from the third year onward (level of evidence EO; strength of consensus 8.5; level of consensus B).**

## 7. Supportive therapy

The Panel recognizes that the vast majority of statements in this section are EO. This is obviously due to the lack of even low-level evidence studies and highlights the fact that the recommendations are not fully consistent with the variability of practice in other European and non-European low-income and resource countries. It also highlights future research priorities in the field of aplastic anemia to fill this gap.

### *7.1. Transfusions*

**It is recommended to use RBC units that are Kell compatible [4] (level of evidence EO; strength of consensus 8.6; level of consensus B).**

**The most used criteria for platelets transfusion are ongoing bleeding regardless platelet count, platelets <10.000/μl, platelets**

**<20.000/μl with concomitant fever (Level of evidence EO; Strength of consensus 8.4; Level of consensus B).**

**Single-donor platelet concentrate obtained by platelet-apheresis is preferable to random concentrates from buffy coat pools to achieve a better transfusion yield (level of evidence EO; strength of consensus 8.6; level of consensus B).**

**It is preferable to choose platelet concentrate AB0 compatible to prevent hemolysis, increase yield and reduce the incidence of refractoriness [167] (level of evidence EO; strength of consensus 8.5; level of consensus B).**

**The use of granulocyte concentrate may only be indicated in case of neutropenia with life-threatening infection and should be reserved for those rare cases where the potential benefits outweigh the risks [4,168,169] (level of evidence V; strength of consensus 8.1; level of consensus C).**

**Blood products from related donors are contraindicated because they may sensitize the recipient to minor HLA or leukocyte antigens of the potential HSCT donor (level of evidence EO; strength of consensus 8.8; level of consensus B).**

**Red cell and platelet concentrates should be leuko-depleted to avoid engraftment of residual lymphocytes causing post-transfusion GVHD in the recipient, to reduce the impact of alloimmunization and to prevent CMV transmission [170,171] (level of evidence IV; strength of consensus 9; level of consensus A).**

**All blood products intended for CMV-negative patients who are candidates for HSCT should be CMV-negative (level of evidence V; strength of consensus 8.3; level of consensus C).**

**In the absence of CMV-negative blood products, blood components that have undergone leukodepletion with pre-storage filters are a valid alternative (level of evidence V; strength of consensus 8.7; level of consensus B).**

**Red cell should also be irradiated to prevent post- transfusion GVHD and to reduce alloimmunization. Platelet concentrates should be leukodepleted or irradiated according to local standards (level of evidence EO; strength of Consensus 9; level of Consensus A).**

**Irradiation of cellular blood products is indicated as long as the patient is immunosuppressed, i.e. as long as the lymphocytes are < 1000–1500/mmc, or as long as the patient is taking cyclosporine or other immunosuppressants [4,172] (level of evidence EO; strength of consensus 8.7; level of consensus B).**

### *7.2. Chelating treatment*

There are more reliable methods to assess parenchymal iron than ferritin level, such as LIC (liver iron concentration), which can currently be measured by non-invasive methods such as MRI (T2* or R2*) [173] or SQUID (superconducting quantum interference device). However, the low cost, ease of use and availability in all laboratories favor the widespread use of ferritin as a reference parameter for assessing iron overload. Ferritin levels >1000 ng/ml could be an indication for iron chelation therapy in transfusion-dependent patients [5,174]. The recommendation to start chelation therapy is particularly relevant in patients who are eligible for HSCT, where iron overload is associated with increased transplant-related mortality and poorer survival [175–178].

**For patients with ferritin levels higher than 1000 ng/ml iron chelation is recommended (level of evidence IV; strength of consensus 8.2; level of consensus B).**

Recent studies confirm the efficacy of deferasirox in treating iron overload [179]. Some reports have also suggested that deferasirox could improve hematopoiesis in a variable percentage between 40 and 48 % [180–184]. Deferiprone is not indicated in aplastic patients due to the known increased risk of agranulocytosis. Deferoxamine has been progressively less used for toxicity and unsatisfactory compliance.

**Deferasirox is considered the first-choice iron chelating agent (level of evidence IV; strength of consensus 8.5; level of consensus B).**

**Therapeutic phlebotomy is a valid therapeutic option in post-transplant patients with iron overload [4,185] (level of evidence EO; strength of consensus 8.1; level of consensus C).**

This therapeutic strategy is feasible in patients without severe anemia, with stable hematologic counts and who have no other ferrochelating treatment alternatives.

### *7.3. G-CSF during IST*

A multicenter prospective study of 192 patients with SAA treated with ATG + CSA with or without G-CSF showed no difference in OS, EFS, non-response and risk of relapse between the two groups. G-CSF appeared to identify those patients more likely to respond to IST, which were those who achieved ANC ≥ 500/mmc at day +30 in the G-CSF arm [186,187]. The use of G-CSF during IST appeared to reduce infectious episodes and hospital days during the first 3 months of therapy in some studies. In a study of an adult population, the hematologic response rate at 6 months was higher in the G-CSF+ group than in the G-CSF- group. No differences were observed in the incidence of infections and febrile episodes. There were no differences in survival or development of myelodysplastic syndrome between the G-CSF- and G-CSF+ groups [189].

**Continuous use of G-CSF is recommended in SAA and VSAA treated with IST, but it is not possible to define the duration of treatment or, in the event of a response, the minimum neutrophil cut-off to be achieved. Indeed, it seems that a neutrophil count ≥500/mmc on day +30 is associated with a better chance of response (level of evidence II; strength of consensus 7.8; level of consensus C).**

"On-demand" administration of G-CSF at the onset of a febrile episode in patients with chronic neutropenia significantly reduces the episode severity, sepsis mortality and the number and duration of hospitalization. Efficacy appears to increase with early initiation of G-CSF treatment [190].

**When continuous GCSF is not used or not available, on-demand use of G-CSF is recommended in case of febrile neutropenia during IST (level of evidence EO; strength of consensus 8.9; level of consensus B).**

### *7.4. Anti infection treatment*

Infections are the leading cause of death in patients with SAA. Early mortality, within 90 days of diagnosis, ranges from 1.9 % to 16.3 % and depends on several factors such as the severity of SAA (higher in very severe forms), the age of the patient (more likely in patients >20 years) and the interval between diagnosis and initiation of treatment (< or > 30 days). After 90 days from diagnosis, mortality can range from 3 to 10 % and is related to the quality of response to IST and to the need for HSCT. In a randomized EBMT trial, 55 % of the deaths were due to bacterial or fungal infections [186]. Similar findings were shown in other studies [191,192], showing that a relevant predictive factor for infection was the degree of aplasia [193].

The infectious risk in AA depends on the impairment of innate immunity due to neutropenia, which reduces the ability to defend against bacteria and fungi, on immunosuppressive therapy which induces profound T-depletion and on the frequent use of central venous catheters, which promote the entry of skin-borne pathogens. The use of antibiotics to treat recurrent infections can promote intestinal colonization by antibiotic-resistant bacteria, which can cause bacteremia and sepsis.

In patients with SAA (PMN < 500/mmc), treatment of fever follows the indications for empiric antibiotic therapy adopted for onco-hematologic patients, based on immediate initiation of broad-spectrum antibiotic therapy after framing hematologic and microbiologic investigations. Broad-spectrum coverage can be achieved with a

single antibiotic (monotherapy with a 4th-generation cephalosporin, piperacillin/tazobactam, or meropenem) or with multiple antibiotics (combination with one of the previous antibiotics with an aminoglycoside and/or a glycopeptide). The decision is modifiable based on knowledge of the prevailing local epidemiology, prevalence of antibiotic-resistant bacteria, patient colonization with resistant bacteria, degree of aplasia, and clinical stability.

In case of non-response to broad-spectrum antibiotic therapy, it is necessary to repeat hematological, microbiological (including galactomannan antigen test on bronchoalveolar lavage and/or serum) and imaging studies (such as lung CT, abdominal US) to identify the cause of fever. While awaiting for the diagnostic conclusions, it's possible to consider empiric antifungal coverage with liposomal amphotericin or an echinocandin or triazole such as voriconazole [194–196].

The duration of antibiotic therapy depends on the clinical response and the severity of the bone marrow aplasia.

#### 7.4.1. Prophylaxis

The use of antibiotic prophylaxis is controversial due to the emergence of resistant or multi-resistant bacteria. There is no specific evidence that antibacterial prophylaxis is effective in patients with bone marrow aplasia. However, the incidence of bacterial and fungal infections in patients with very severe bone marrow aplasia (PMN < 200/mmc), especially in the first 30–90 days after diagnosis, suggests a prophylaxis strategy like that sometimes used in acute leukemia. In addition, lymphopenia induced by immunosuppressive therapy based on CSA, ATG and steroids exposes the patient with SAA to the risk of Pneumocystis jirovecii pneumonia.

**Antibiotic prophylaxis may be considered in patients with VSAA (PMN < 200/mmc) in the first 30–90 days after ATG (level of evidence EO; strength of consensus 7.3; level of consensus C).**

**Antifungal prophylaxis is indicated for patients with VSAA (PMN < 200/mmc) in the first 30–90 days after ATG (level of evidence IV; strength of consensus 8.1; level of consensus B).**

**Prophylaxis against Pneumocystis jirovecii is indicated with oral co-trimoxazole or aerosolized pentamidine in the presence of CD4+ < 400/mmc or lymphocytes <1000/mmc (level of evidence IV; strength of consensus 8.4; level of consensus B).**

**Herpes simplex prophylaxis is an option for seropositive patients in the first 30–90 days after ATG (level of evidence EO; strength of consensus 8.1; level of consensus B).**

**EBV and CMV peripheral blood copies should be monitored weekly while on ATG (level of evidence EO; strength of consensus 8.1; level of consensus B).**

#### 7.4.2. Empirical treatment of bacterial and fungal infections

**Initial antibiotic therapy in a febrile child with AA should follow the principles of empirical therapy in onco-hematological patients: early initiation, broad spectrum, clinical and instrumental re-evaluation after 72–96 h of therapy (level of evidence EO; strength of consensus 8.9; level of consensus B).**

**Knowledge of the prevalent epidemiology of the center is fundamental to choose the empirical antibiotic regimen (level of evidence EO; strength of consensus 8.8; level of consensus B).**

**In patients with SAA or vSAA rectal swab testing for colonization with antibiotic-resistant organisms may lead to a more appropriate empirical antibiotic therapy in the setting of fever (level of evidence EO; strength of consensus 8.6; level of consensus B).**

**Modification of empirical antibiotic therapy, such as the addition (escalation) or the reduction of antibiotics (descalation), or change of molecule, should be considered after 72–96 h of treatment, based on the clinical response, or, in advance, based on microbiological data or on worsening of clinical parameters (level of evidence EO; strength of consensus 8.7; level of consensus B).**

**Empiric antifungal therapy may be considered in patients with SAA/VSAA who have persistent fever despite 96 h of adequate broad-spectrum antibiotic therapy and without a clear focus of infection (level of evidence EO; strength of consensus 8.4; level of consensus B).**

#### 7.4.3. Vaccinations

One of the major side effects of IST during AA is profound lymphocyte depletion resulting in the disappearance of vaccine immunity. To date, there are no conclusive data regarding the timing of immune reconstitution after IST and much of the data in the literature refer to patients undergoing chemotherapy for lymphoproliferative diseases. It is recommended, if possible, to complete the vaccination schedule prior to the start of IST or HSCT. Vaccinations should be given during the remission phase of the disease and most authors agree that an interval of 6–12 months after the end of therapy is sufficient to achieve adequate immunological recovery [197].

**In patients receiving IST (ATG) the early administration of any vaccine is not recommended, also in view of the risk of recurrence of AA after vaccination as described in some cases [4] (level of evidence EO; strength of consensus 8.0; level of consensus C).**

**Patients with stable remission of AA after IST for more than six months and who are on therapy with CsA doses <2.5 mg/kg/day may be vaccinated with inactivated/purified antigens despite a possible suboptimal immune response, after careful risk vs benefit assessment (level of evidence EO; strength of consensus 8.5; level of consensus B).**

**In patients undergoing HSCT, can be used the same indications as in HSCT protocols for other hematologic diseases (level of evidence EO; strength of consensus 8.6; level of consensus B).**

**Evaluation of specific antibody titers and T lymphocyte subsets/function, although not routinely recommended, may be performed in special cases prior to vaccination (level of evidence EO; strength of consensus 7.9; level of consensus C).**

As of today, there are no data on the safety and efficacy of vaccination against SARS-CoV2 in patients with AA, therefore reference is made to the interim indications IPINET/SIAIP for immunocompromised subjects and EBMT and EHA recommendations on covid 19 in AA and PNH (https://www.aip-it.org/index.php/vaccine-anti-covid-19-le-indications-of-the-scientific-committee-aip-odv, https://ehaweb.org/covid-19/eha-statement-on-covid-19-vaccines/recommendations-for-covid-19-vaccination-in-patients-with-non-malignant-hematologic-diseases/, https://www.ebmt.org/sites/default/files/2020/SAAWP-COVID-Recommendations).

### 7.5. Psychological support

Aplastic anemia affects the physical, psychological, and social aspects of patients' lives. Therefore, healthcare providers need to consider patients' physical reactions and psychological feelings to provide relevant medical guidance and multichannel social support that would improve their confidence and quality of life (QoL).

Liu et al. developed an analysis method that ultimately identified 3 themes and 9 sub-themes, including: physical symptoms (declining physical capacity, treatment-related symptoms, changes in body image), psychological symptoms (mood changes related to disease stage, changes in self-image, growth resulting from the disease experience), social burden (decline in career development, perceived burden on family, social stigma) [198].

Specific questionnaires designed to assess the psychosocial, relational, emotional, physical, and mental domains of AA patients, as well as disease-specific symptoms and complications, are available [199,200].

**The assessment of patients' QoL at all stages of the disease and the implementation of specific assessment questionnaires for AA are recommended (level of evidence IV; strength of consensus 8.4; level of consensus B).**

## 8. Pregnancy

There is no clear pathophysiological link between pregnancy and AA. The onset of AA during pregnancy is associated with a higher incidence of obstetric and neonatal complications (intrauterine growth retardation, prematurity, premature rupture of membranes, pre-eclampsia and neonatal sepsis) ranging from 12 to 33 % [201]. The possibility of clinical remission has also been described, especially in cases of onset during pregnancy. Some authors have suggested induction of labor in patients with a severe form, given the increased frequency of remission of AA after delivery [202]. There is also a high risk of 20 % of recurrence of AA in pregnant women with a previous partial or complete response to IST [203]. In a retrospective monocentric study of 15 pregnant women, platelet count <20.000/mmc, bone marrow cellularity <25 %, and AA onset at advanced gestational age (>34 weeks) were found to be negative prognostic factors for response to therapy and survival in an univariate analysis [204,205]. Data on the treatment of aplastic anemia during pregnancy are few and come only from case reports and retrospective studies. Information on the teratogenicity and tolerance of drugs is often derived from studies regarding patients affected by other more common hematologic disorders, who use the same drugs. These can be the reason for low level of consensus on the next statement.

**Transfusion support is the therapy of choice for pregnant women with AA. IST and HSCT are not recommended in pregnancy, while the use of CsA may be considered in exceptional cases [206] , after a careful risk-benefit analysis, and only in the presence of refractoriness to transfusions (level of evidence EO; strength of consensus 8.1; level of consensus C).**

**The use of G-CSF during pregnancy may be recommended for severe neutropenia (level of evidence IV; strength of consensus 8.2; level of consensus C).**

In a multicenter retrospective observational study, 17 pregnant women with ITP were treated with eltrombopag ($n = 8$) or romiplostim ($n = 7$). No maternal thromboembolic events or neonatal complications were observed in association with treatment and response was achieved in 77 % of cases [207].

**TPO receptor agonists in pregnancy can be considered after a careful risk-benefit assessment and only in the presence of transfusion refractoriness (level of evidence EO; strength of consensus 7.8; level of consensus C).**

The use of iron chelating agents in pregnancy is not recommended because of the lack of data on their effect on fetal development and the possible teratogenicity observed in in vivo studies in experimental animals. Two retrospective studies evaluated the inadvertent use of deferasirox and deferoxamine, respectively, in 6 and 9 thalassemic pregnant women in the first trimester of pregnancy, without detecting any obstetric or fetal complications, thus implicitly inferring that their use might be considered after a careful risk-benefit analysis [208,209].

**The use of iron-chelating agents is generally not recommended during pregnancy (level of evidence EO; strength of consensus 8.5; level of consensus B).**

## 9. Cryopreservation in patients undergoing bone marrow transplantation

HSCT is associated with relatively high rates of infertility in both men and women [210,211], related to the conditioning regimens, especially those based on the use of TBI and busulfan [210]. A retrospective study of 344 pediatric patients undergoing HSCT, showed an overall infertility rate of 75 %, (83 % in females and 69 % in males) [210]. In some cases, restoration of fertility was possible after an apparent phase of sterility [211].

**Based on the above findings cryopreservation of semen and oocytes should be considered for patients undergoing HSCT for aplastic anemia (level of evidence EO; strength of consensus 8.5; level of consensus B).**

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## CRediT authorship contribution statement

**A. Guarina:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **P. Farruggia:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **E. Mariani:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **P. Saracco:** Visualization, Validation, Methodology, Formal analysis, Data curation. **A. Barone:** Visualization, Validation, Methodology, Formal analysis, Data curation. **D. Onofrillo:** Visualization, Validation, Methodology, Formal analysis, Data curation. **S. Cesaro:** Visualization, Validation, Methodology, Formal analysis, Data curation. **R. Angarano:** Visualization, Validation, Methodology, Formal analysis, Data curation. **W. Barberi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **S. Bonanomi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **P. Corti:** Visualization, Validation, Methodology, Formal analysis, Data curation. **B. Crescenzi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **G. Dell'Orso:** Visualization, Validation, Methodology, Formal analysis, Data curation. **A. De Matteo:** Visualization, Validation, Methodology, Formal analysis, Data curation. **G. Giagnuolo:** Visualization, Validation, Methodology, Formal analysis, Data curation. **A.P. Iori:** Visualization, Validation, Methodology, Formal analysis, Data curation. **S. Ladogana:** Visualization, Validation, Methodology, Formal analysis, Data curation. **A. Lucarelli:** Visualization, Validation, Methodology, Formal analysis, Data curation. **M. Lupia:** Methodology, Data curation, Formal analysis, Validation, Visualization. **B. Martire:** Visualization, Validation, Methodology, Formal analysis, Data curation. **E. Mastrodicasa:** Visualization, Validation, Methodology, Formal analysis, Data curation. **E. Massaccesi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **L. Arcuri:** Visualization, Validation, Methodology, Formal analysis, Data curation. **M.C. Giarratana:** Visualization, Validation, Methodology, Formal analysis, Data curation. **G. Menna:** Visualization, Validation, Methodology, Formal analysis, Data curation. **M. Miano:** Visualization, Validation, Methodology, Formal analysis, Data curation. **L.D. Notarangelo:** Visualization, Validation, Methodology, Formal analysis, Data curation. **G. Palazzi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **E. Palmisani:** Visualization, Validation, Methodology, Formal analysis, Data curation. **S. Pestarino:** Visualization, Validation, Methodology, Formal analysis, Data curation. **F. Pierri:** Visualization, Validation, Methodology, Formal analysis, Data curation. **M. Pillon:** Visualization, Validation, Methodology, Formal analysis, Data curation. **U. Ramenghi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **G. Russo:** Visualization, Validation, Methodology, Formal analysis, Data curation. **F. Saettini:** Visualization, Validation, Methodology, Formal analysis, Data curation. **F. Timeus:** Visualization, Validation, Methodology, Formal analysis, Data curation. **F. Verzegnassi:** Visualization, Validation, Methodology, Formal analysis, Data curation. **M. Zecca:** Visualization, Validation, Methodology, Formal analysis, Data curation. **F. Fioredda:** Visualization, Validation, Methodology, Formal analysis, Data curation. **C. Dufour:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The following authors declared COI: C. Dufour, P. Farruggia, G. Palazzi, U. Ramenghi, G. Russo. All Other Authors declared no COI.

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