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GUIDELINE

BSH Guideline

Guidelines for the diagnosis and management of adult aplastic anaemia: A British Society for Haematology Guideline

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Summary

Pancytopenia with hypocellular bone marrow is the hallmark of aplastic anaemia (AA) and the diagnosis is confirmed after careful evaluation, following exclusion of alternate diagnosis including hypoplastic myelodysplastic syndromes. Emerging use of molecular cyto-genomics is helpful in delineating immune mediated AA from inherited bone marrow failures (IBMF). Camitta criteria is used to assess disease severity, which along with age and availability of human leucocyte antigen compatible donor are determinants for therapeutic decisions. Supportive care with blood and platelet transfusion support, along with anti-microbial prophylaxis and prompt management of opportunistic infections remain key throughout the disease course. The standard first-line treatment for newly diagnosed acquired severe/very severe AA patients is horse anti-thymocyte globulin and ciclosporin-based immunosuppressive therapy (IST) with eltrombopag or allogeneic haemopoietic stem cell transplant (HSCT) from a matched sibling donor. Unrelated donor HSCT in adults should be considered after lack of response to IST, and up front for young adults with severe infections and a readily available matched unrelated donor. Management of IBMF, AA in pregnancy and in elderly require special attention. In view of the rarity of AA and complexity of management, appropriate discussion in multidisciplinary meetings and involvement of expert centres is strongly recommended to improve patient outcomes.

KEYWORDS
aplastic anaemia, ATG, stem cell transplantation

METHODOLOGY

This guideline was compiled according to the BSH process at https://b-s-h.org.uk/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

LITERATURE REVIEW DETAILS

The guideline group was selected to be representative of UK-based aplastic anaemia (AA) medical experts. Recommendations are based on a literature search conducted on Medline (PubMed) covering articles published between 1 January 2010 and 15 May 2020, inclusive. A small number of key articles published prior to 2010 and after 2020 are also included. Filters were applied to include only English language papers, and human data in subjects aged 16 years and over only. The search included clinical trials and studies, as well as comparison and observation studies, alongside meta-analyses, review articles and guidelines. Search terms were 'aplastic anaemia' or 'aplastic anaemia', 'anti-thymocyte globulin', 'stem cell transplantation', 'bone marrow transplantation' and 'eltrombopag'. Case reports were included for the search term "('aplastic anaemia or aplastic anemia')" only. Papers that focused on 'anaemia' as an isolated term or 'paediatric aplastic anaemia' were excluded.

REVIEW OF THE MANUSCRIPT

Review of the manuscript was performed by the BSH Guidelines Committee and General Haematology Task Force, the BSH Guidelines Committee and the sounding board of BSH. It has also been reviewed by a patient representative, the Aplastic Anaemia Trust chairman and chief executive, but they do not necessarily approve or endorse the contents. The manuscript has also been reviewed by external global AA experts.

PURPOSE

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of adult patients with AA. The guidance may not be appropriate to every patient, and in all cases individual patient circumstances may dictate an alternative approach. A separate BSH guideline covers paediatric AA (Paediatric amendment to adult BSH Guidelines for aplastic anaemia, 2017).

DEFINITION, DISEASE SEVERITY AND CLINICAL PRESENTATION OF AA

Aplastic anaemia is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow (BM) in the absence of an abnormal infiltrate or marrow fibrosis. To diagnose AA, there must be at least two of the following, haemoglobin concentration (Hb) <100 g/L, platelet count $<50\times10^9$/L and neutrophil count $<1.5\times10^9$/L. Reticulocyte count is useful in delineating the severity of AA. The majority (70%–80%) of cases are idiopathic. The remainder mainly consist of inherited bone marrow failure (IBMF) syndromes. There is a biphasic distribution, with peaks at 10–25 years and over 60 years.[1] The incidence is 2–3 per million per year in Europe, but higher in East Asia.[2,3]

Criteria used to assess severity

- Severe AA (SAA): Marrow cellularity <25% (or 25%–50% with <30% residual haematopoietic cells), plus at least two of: (a) neutrophil count $<0.5\times10^9$/L; (b) platelet count $<20\times10^9$/L; (c) reticulocyte count $<60\times10^9$/L (using an automated reticulocyte count)
- Very severe AA (VSAA): As for SAA but neutrophils $<0.2\times10^9$/L
- Non-severe AA (NSAA): AA not fulfilling the criteria for SAA or VSAA

Patients commonly present with symptoms of anaemia and thrombocytopenia. Serious infection is a less frequent symptom early in the course of the disease. A preceding history of jaundice may suggest a posthepatitic AA.[4] While most cases are idiopathic, a careful drug, occupational exposure and family history should be obtained. Any putative drugs should be discontinued and the patient should not be re-challenged. If a possible drug association is suspected, this must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) using the Yellow Card Scheme (http://yellowcard.gov.uk). There is usually no hepatosplenomegaly or lymphadenopathy (except during infection). Table 1 highlights some clinical features that suggest constitutional AA.

Key Recommendations for Definition, Severity and Presentation

- **The severity of AA should be assessed according to the Camitta criteria (1C).**
- **Most cases of AA are idiopathic, nevertheless a careful drug history must be taken and any putative causative drug should be discontinued and reported to the MHRA using the Yellow Card Scheme (1C).**

TABLE 1 Features of the inherited bone marrow failure syndromes.

	FA	DC	SDS	DBA	CDA	CAMT	SCN	New[a]
Inheritance pattern	AR, XLR	XLR, AR	AR	AD	AR	AR	AD	AR
		AD	AD	XLR	AD	AD	AR	AD
Extra-haematopoietic abnormalities[b]	Yes	Yes	Yes	Yes	Rare	Yes	Rare	Yes
Bone marrow failure	AA (90%)	AA (80%)	AA (20%)	RCA[c]	Dysery[d]	Meg[e]	Neut[f]	Yes
Short telomeres	Yes	Yes[g]	Yes	No	No	No	?	?
Malignancy	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Chromosome instability	Yes	Yes	Yes	?	?	No	?	Yes
Genes identified	22	16	4	21	5	4	7	25+

Abbreviations: CAMT, congenital amegakaryocytic thrombocytopenia and syndromic thrombocytopenia; CDA, congenital dyserythropoietic anaemia; DBA, Diamond–Blackfan anaemia; DC, dyskeratosis congenita; FA, Fanconi anaemia; SCN, severe congenital neutropenia; SDS, Shwachman–Diamond syndrome.

[a]This category includes new and overlapping syndromes such as *GATA2*, *MECOM* and *SAMD9*/*SAMD9L*-associated disease (AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; AA, aplastic anaemia).

[b]The extra-haematopoietic abnormalities in these syndromes can be overlapping, for example short stature and skeletal defects are observed in FA, DC, SDS and DBA; skin pigmentation abnormalities are common in both DC and FA. Some extra-haematopoietic abnormalities may be syndrome-specific such as pancreatic insufficiency in SDS; nail dystrophy, lung fibrosis, cirrhosis in DC; lymphoedema, immunodeficiency, sensorineural deafness and lung disease in GATA2 deficiency.[5]

[c]RCA: red cell aplasia, although some patients can develop global bone marrow failure.

[d]Dysery, usually dyserythropoiesis.

[e]Meg, low megakaryocytes typically but can progress to global bone marrow failure.

[f]Neut, usually low neutrophils.

[g]Yes, usually very short.

- **A multidisciplinary team (MDT) meeting approach is recommended to collate relevant results and develop a treatment plan. Consideration should be given to seeking expert advice on the diagnosis and management of patients where there is uncertainty, or when an IBMF syndrome is being considered (2B).**

INVESTIGATIONS REQUIRED FOR THE DIAGNOSIS OF AA

Idiopathic AA is a diagnosis of exclusion. Consequently, the diagnostic evaluation must exclude alternative aetiologies of BMF. The 'empty' BM on histology of AA is characteristic and a prerequisite for the diagnosis, but there is increasing recognition that inherited BMF syndromes are commoner than previously recognised even in adults. The following investigations (Table 2) are required to confirm the diagnosis, and:

(i) exclude other causes of pancytopenia and a hypocellular BM;
(ii) exclude inherited BMF syndrome;
(iii) screen for an underlying cause; and
(iv) document coexisting abnormal cytogenetic and paroxysmal nocturnal haemoglobinuria (PNH) clones.

Table 2 summarises investigations for diagnosis and further evaluation of AA.

Both a BM aspirate and trephine biopsy are required for the diagnosis of AA, and key BM findings are summarised in Table 3. Investigations in Table 2 should exclude alternate causes of pancytopenia with a hypocellular BM, which are listed in Table 4.

Hypocellular myelodysplastic syndrome

Most cases of myelodysplastic syndrome (MDS) have a normocellular or hypercellular BM; however, 10%–20% of cases have decreased cellularity.[15] The World Health Organization (WHO) classification of myeloid neoplasms terms this hypoplastic MDS (h-MDS)[17] recently recognised as a diagnostic and coded subtype of MDS.[18] Hypocellular MDS may be difficult to distinguish from NSAA. Acquired somatic mutations, like *DNMT3A*, *ASXL1*, *PIGA* and *BCOR/BCORL1*, can be present at low variant allele frequency in approximately 20%–30% of idiopathic AA.[11,19] Integrating cytohistological and genetic features led to criteria (the hg-score) to define h-MDS.[15] Patients can be divided into two distinct groups, one with clinical and genetic features highly consistent with a myeloid neoplasm and one with features more consistent with non-neoplastic BMF (Table 5). The two groups have significantly different risks of blast progression and overall survival (OS). In some patients with cytopenia and a hypocellular BM, conventional diagnostic work up and hg-score are not diagnostic for AA or h-MDS, and a provisional diagnosis of 'hypoplastic idiopathic cytopenia of uncertain significance (hypoplastic ICUS)' is appropriate. Additionally, quantitative CD34 enumeration can help in discriminating h-MDS from AA.[20] 'High-risk' mutations (e.g. *RUNX1*) and cytogenetic abnormalities (e.g. chromosome 7) during the course of AA can help identify patients at risk of transformation to MDS.[21,22] As somatic mutations at diagnosis or during treatment are not uncommon in AA, these should be interpreted with caution. Presence of mutations does not necessarily indicate transformation to MDS, and hence physicians should not interpret the presence of mutations in isolation, especially to make therapeutic choices that is in recommending HSCT.

TABLE 2 Summary for the diagnosis and further investigation of aplastic anaemia.

Tests	Key changes
1. Full blood count	Pancytopenia. Usually the haemoglobin concentration and neutrophil and platelet counts are uniformly depressed. In the early stages, isolated cytopenia, particularly thrombocytopenia, may occur. Lymphocyte counts are usually preserved. The presence of monocytopenia needs further investigation to exclude hairy cell leukaemia or inherited bone marrow failure due to the *GATA2* mutation (Emberger/MonoMac syndrome; see section on "Inherited AA")
2. Reticulocyte count	Reticulocytopenia: automated reticulocyte counting will overestimate the count compared with the levels set in the Camitta criteria[1] for defining disease severity, which were defined on manual counts. This criterion has now been modified from manual percentages to absolute reticulocyte levels $<60 \times 10^9$/L as assessed by automated technologies[6]
3. Blood film examination	Frequent macrocytosis and anisopoikilocytosis. Neutrophils may show toxic granulation. Platelets are mainly small in size. Exclude the presence of dysplastic neutrophils, abnormal platelets, blasts or other abnormal cells
4. Hb F%	Hb F; measure pretransfusion. Note that the level is often elevated in constitutional syndromes
5. Peripheral blood chromosomal breakage analysis: diepoxybutane Test (DEB Test)	For possible Fanconi anaemia if <50 years, but it would also be indicated to screen older patients if Fanconi anaemia is clinically suspected, as anecdotal cases have been diagnosed in the fifth decade. Screen all patients who are transplant candidates and siblings of Fanconi anaemia patients
6. Flow cytometry for GPI-anchored proteins to detect PNH clone (6-colour methodology including fluorescent aerolysin—FLAER)[7]	See the "PNH and AA" section for a full description
8. Vitamin B12 and folate	Documented vitamin B12 or folate deficiency should be corrected before a final diagnosis of aplastic anaemia is confirmed. Bone marrow aplasia due to vitamin deficiency is exceedingly rare
9. Liver function tests	Liver function tests should be performed to detect antecedent/ongoing hepatitis
10. Viral studies: hepatitis A/B/C/E, EBV, CMV, HIV and parvovirus B19	AA due to hepatitis is rare; it usually occurs 2–3 months after an acute episode of hepatitis and is more common in young males. In posthepatitic aplastic anaemia, the serology is often negative for the known hepatitis viruses. CMV should be assessed if HSCT is being considered. HIV more commonly causes isolated cytopenias but is a very rare cause of AA.[8,9] Parvovirus B19 is usually associated with pure red aplasia but has very rarely been reported with AA[10]
11. Anti-nuclear antibody and anti-double stranded DNA	Pancytopenia in systemic lupus erythematosus may be (i) autoimmune with a cellular bone marrow, (ii) associated with myelofibrosis or (iii) rarely associated with a hypocellular marrow
12. Chest X-ray and other radiology	It is useful at presentation to exclude infection and for comparison with subsequent films. X-rays of the hands, forearms and feet may be indicated if an IBMFS is suspected. A high-resolution CT scan of the chest (prone) looking for lung fibrosis is indicated for suspected constitutional bone marrow failure syndrome
13. Abdominal ultrasound scan and echocardiogram	An enlarged spleen and/or lymph nodes raise the possibility of a neoplastic haematological disorder as the cause of the pancytopenia. In younger patients, abnormal or anatomically displaced kidneys are features of Fanconi anaemia
14. Genetic tests on peripheral blood or bone marrow	Next-generation sequencing gene panels • Acquired somatic mutations, typical of myeloid neoplasms, to help distinguish AA from hypocellular MDS and for early detection of clonal evolution to MDS/AML.[11] Somatic mutations are present in 20%–30% of cases of idiopathic AA, especially during the disease course, with increasing frequency. The presence of mutations does not necessarily indicate transformation to MDS, and hence physicians should not interpret the presence of mutations in isolation, especially to make therapeutic choices that is in recommending HSCT In selected cases based on age and family history: • Telomere gene complex mutations • Other inherited bone marrow failure syndromes
15. Emerging diagnostic tests: Peripheral blood leucocyte telomere length	Useful for disease screening for telomere gene mutations in classic dyskeratosis congenita; less specific in adult-onset AA with *TERC*/*TERT* mutations; short telomeres may also occur in acquired AA with reduced stem cell reserve[12]

Abbreviations: AA, aplastic anaemia; AML, acute myeloid leukaemia; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein–Barr virus; GPI, glycerophosphatidylinositol; Hb F, fetal haemoglobin; HIV, human immunodeficiency virus; HSCT, haemopoietic stem cell transplant; IBMFS, inherited bone marrow failure syndrome; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria.

TABLE 3 Bone marrow features of aplastic anaemia.

Bone marrow aspirate	Difficulty obtaining fragments may indicate marrow fibrosis or infiltration and should raise the suspicion of a diagnosis other than AA. In AA, fragments and trails are hypocellular, with prominent fat spaces and variable numbers of residual haemopoietic cells. Erythropoiesis is reduced or absent; dyserythropoiesis is very common, often marked and does not distinguish MDS from AA. Megakaryocytes and granulocytic cells are markedly reduced or absent. Dysplastic megakaryocytes and granulocytic cells are not seen in AA. Lymphocytes, macrophages, plasma cells and mast cells often appear prominent. The mast cells will have a normal phenotype. In the early stages of disease, there may be increased macrophages with some haemophagocytosis and background eosinophilic staining representing interstitial oedema
Cytogenetic, FISH and single nucleotide polymorphism array karyotyping analysis	Karyotyping may fail in very hypocellular marrows with insufficient metaphases. In this situation, perform FISH analysis for chromosomes 5, 7, 8 and 13 It was previously assumed that the presence of an abnormal cytogenetic clone indicated a diagnosis of MDS and not AA. However, it is now evident that abnormal cytogenetic clones [such as del(13q), trisomy 8, among others], which may be transient, are present in up to 12% of patients with otherwise typical AA at diagnosis. Although in children, monosomy 7 may indicate the likelihood of MDS, in adults, monosomy 7 can also be seen in AA. Abnormal cytogenetic clones may arise during the course of the disease, and the appearance of a new cytogenetic abnormality provides evidence of clonal evolution[13] Single nucleotide polymorphism array karyotyping may alternatively be used; whole genome scanning can be used to detect unbalanced chromosomal defects[14]
Bone marrow trephine biopsy	A good-quality trephine biopsy specimen of at least 2 cm is essential to assess the overall cellularity and morphology of residual haemopoietic cells and to exclude an abnormal infiltrate. Care should be taken to avoid tangential biopsies, as subcortical marrow is normally hypocellular. The cellularity could also be misleadingly low in patients who had pelvic radiotherapy In most cases, the biopsy specimen is hypocellular throughout; sometimes hypocellularity is patchy with both hypocellular and residual cellular areas. In such cases, an overall average cellularity of <30% should be ascertained after excluding lymphocytes and plasma cells. Focal hyperplasia of erythroid or granulocytic cells at a similar stage of maturation may be observed. Small lymphoid aggregates may occur, particularly in the acute phase of the disease or when AA is associated with systemic autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus. Increased reticulin staining, dysplastic megakaryocytes (best assessed by immunohistochemistry) and blasts are not seen in AA; their presence either indicates a hypoplastic MDS or evolution to MDS or leukaemia[15]

Abbreviations: AA, aplastic anaemia; FISH, fluorescence in situ hybridisation; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria.

A MDT meeting approach is recommended to collate relevant results and plan treatment. Consideration should be given to seeking expert advice on diagnosis and management of patients where there is uncertainty.

Key Recommendations for the Investigation of Adult AA

- **An adequate BM aspirate and trephine biopsy of good length (>1.5 cm) should be taken for diagnosis, and investigations must exclude other causes of pancytopenia with a hypocellular marrow (1C).**
- **AA should be differentiated from hypoplastic MDS by integrating cytohistological and genetic features (2C).**

PNH AND AA

Approximately, 50%–60% of patients with AA have a PNH clone; PNH testing should be performed by flow cytometry.[23] Analysis of glycosylphosphatidylinositol (GPI)-anchored proteins is a sensitive and quantitative test for PNH-enabling detection of small PNH clones. Small PNH clones are associated with AA and other BMF syndromes.[24] Monitoring for clonal change is essential; patients should be screened for PNH at diagnosis of AA. If positive, test 3 monthly for 1 year, then annually if a PNH clone remains stable. If screen is negative, test in 6 months, then annually. Screening should be undertaken more frequently if the clone is increasing or patients develop symptoms/signs of haemolysis. A significant PNH clone is often associated with clinical or laboratory evidence of haemolysis, or thrombosis, requiring consideration for anti-complement treatment.[24]

PNH clones, especially if large and present in all cell lineages, make the diagnosis of inherited AA unlikely. Although PNH clones can be detected in 40% of acquired AA, the absence of a PNH clone does not rule out immune-mediated AA.[25] The presence of a PNH clone does not directly influence AA treatment decisions; patients should receive treatment as per guidelines, including the decision for haemopoietic stem cell transplantation (HSCT).[26,27] HSCT for the sole indication of PNH is not appropriate in the United Kingdom. Patients with a significant PNH clone receiving immunosuppressive therapy (IST), should be closely monitored for haemolysis. Conversely, AA may later emerge in patients with haemolytic or thrombotic PNH. New PNH patients should be referred to one of the two specialised nationally commissioned PNH centres, St James's University Hospital, Leeds and King's College Hospital, London, for assessment of PNH complications and consideration for anti-complement therapy (https://pnhserviceuk.co.uk). Haematologists should feel free to contact the PNH centres at any time for individual patient advice (Table 6).

TABLE 4 Other causes of pancytopenia and a hypocellular bone marrow.

Associated with PNH (AA/PNH)	Variable cellularity depending on the phase of the disease and the transition from PNH to AA. Test peripheral blood immunophenotyping for GPI-linked molecules in red and white cell populations
Hypoplastic (MDS/AML)	It may be challenging to distinguish from AA. The following features are not found in AA: dysplastic cells of the granulocytic and megakaryocytic lineages; blasts in the blood; marrow aspirate or trephine biopsy specimen[16]; or increased reticulin in the trephine biopsy specimen. The presence of ALIP is more indicative of MDS than AA, though small collections of immature granulocytic cells may be seen in the bone marrow in AA when regeneration occurs. ALIP must not be confused with dysplastic pro-erythroblast islands and can be easily differentiated on immunohistochemistry. Dyserythropoiesis is very common in aplastic anaemia and does not distinguish MDS from AA
Hodgkin lymphoma or non-Hodgkin lymphoma	Can present with pancytopenia and a patchy hypocellular bone marrow with limited areas of lymphoid infiltration, which can easily be missed in small samples. The bone marrow biopsy should be examined carefully for foci of lymphoma cells or fibrosis, which may be seen in only a small part of the specimen. Lymphocytes are often prominent in AA, and immunophenotypic marker studies and gene rearrangement studies will help to exclude a diagnosis of lymphoma. Additional features, such as splenomegaly, make AA very unlikely
Anorexia nervosa or prolonged starvation	May be associated with pancytopenia. The bone marrow may show hypocellularity, gelatinous transformation (serous degeneration/atrophy), loss of fat cells as well as haemopoietic cells, and an increased background substance that stains a pale pink on a haematoxylin and eosin stain. The pink background substance may also be seen on a May–Grünwald–Giemsa stained aspirate and Alcian Blue can confirm the mucopolysaccharide
ITP	Occasionally, AA presents with isolated thrombocytopenia, and pancytopenia develops later. Such patients can initially be misdiagnosed as ITP, but bone marrow examination in aplastic anaemia shows hypocellularity with reduced or absent megakaryocytes, which is not commonly seen in ITP, although rarely ITP is associated with reduced megakaryocytes
GATA2 deficiency—MonoMac (Monocytopenia with susceptibility to Mycobacteria)	This diagnosis may be considered in hypoplastic marrows with absent peripheral blood monocytes or severe monocytopenia[5]

Abbreviations: AA, aplastic anaemia; ALIPs, abnormal localisation of immature precursors; AML, acute myeloid leukaemia; GPI, glycerophosphatidylinositol; ITP, immune thrombocytopenia; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal haemoglobinuria.

TABLE 5 Integrated cyto-histological/genetic score for differentiating h-MDS from AA (Adapted from Ref. [15]).

Cyto-histological/genetic variables	Score
Requisite criteria	
Bone marrow blasts AND/OR CD34+ cells ≥5%	2
Bone marrow blasts AND/OR CD34+ cells 2%–4%	1
Fibrosis grade 2–3/3	1
Dysmegakaryopoiesis	1
Co-criteria	
Ring sideroblasts ≥15%	2
Ring sideroblasts 5%–14%	1
Severe dysgranulopoiesis	1

Abbreviations: AA, aplastic anaemia; h-MDS, hypoplastic-myelodysplastic syndrome.

TABLE 6 Indications for treatment in PNH.[a]

Indications for complement inhibition	Laboratory or imaging definitions
PNH-related thrombosis	
Complications associated with haemolysis	Pulmonary hypertension Renal failure
Pregnancy and for 3 months postpartum	If PNH clone is greater than 20% (PNH clone requires increased monitoring in pregnancy)
Haemolytic PNH	LDH > 1.5 × ULN and anaemia or agreement with Joint Service MDT
Exceptional cases by agreement at PNH Joint MDT	

Abbreviations: MDT, multidisciplinary team; PNH, paroxysmal nocturnal haemoglobinuria; ULN, upper limit of normal.

[a]https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-parox-haem-serv.pdf.

Key Recommendations for PNH and AA

- **All AA patients should be screened for PNH using flow cytometry on peripheral blood to detect deficiency of GPI-anchored proteins, such as CD14, CD16 and CD24 as well as the FLAER reagent for white blood cells and CD55 and CD59 for red cell analysis (2A).**
- **Patients should be screened for PNH at diagnosis of AA. If negative, test in 6 months and then move to annual unless symptoms/signs develop. If the PNH screen is, or becomes, positive test 3 monthly for the first year and only reduce the frequency if the proportion of the PNH cells has remained stable (2C).**
- **Small PNH clones can be detected in up to 50% of patients with AA, usually without evidence of haemolysis; large clones are clinically significant and may result in haemolysis as well as increased thrombotic risk ('haemolytic PNH') (2A).**

- **The presence of a PNH clone in AA does not directly influence the choice of treatment, but helps exclude inherited forms of AA (3A).**
- **New PNH patients should be referred to the PNH National Service to be monitored for PNH complications and assessed for anti-complement therapy (1C).**

INHERITED AA

A number of inherited/genetic disorders are characterised by BMF/AA usually in association with one or more somatic abnormalities[28,29] (Table 1). The BMF typically presents in childhood but this may also be in adulthood, even mid/late adulthood.

The syndromes frequently associated with generalised BMF/AA are Fanconi anaemia (FA), telomere biology disorders like dyskeratosis congenita (DC) and ribosomopathies.[30,31] These can sometimes present with AA alone as their initial manifestation. These syndromes are genetically heterogeneous; 22 FA genes and 16 DC genes have been identified. The FA genes are principally important in DNA repair, the DC genes in telomere maintenance. Based on the DNA repair defect a diagnostic test—'chromosomal breakage test' (using diepoxybutane or mitomycin C) is available for FA. Patients with DC usually have very short telomeres and this measurement (using flow cytometric fluorescence in situ hybridisation [FISH] or multiplex quantitative polymerase chain reaction [PCR]) can be useful in the assessment of DC. Genetic testing for known DC genes (representing ~75% of cases) is possible in specialised centres.

In addition, there are several other genetic syndromes that can be associated with AA/cytopenias.[32] This includes Shwachman–Diamond syndrome—SDS[33] (mutations in *SBDS*), congenital amegakaryocytic thrombocytopenia—CAMT[34] (mutations in *MPL*) and GATA2 deficiency (e.g. Emberger syndrome, MonoMAC)[35,36] as well as many newly characterised entities (e.g. those due to mutations in *ERCC6L2*, *MECOM*, *SAMD9* and *SAMD9L*[32]).

Rare cases of inherited AA first present in adulthood, and it is important to recognise these as their management differs from that of idiopathic AA. Where there are sufficient characteristic abnormalities, a diagnosis may be straightforward (e.g. mucocutaneous features in DC). Where the presentation is only with AA and with minimal non-haematological abnormalities, inherited BMF should be considered, and testing for known BMF syndromes should be undertaken using next-generation sequencing as some genetic defects have variable penetrance. MDS at young age or high susceptibility to chemotherapy or squamous cell carcinoma at young age and cytopenias are classical situation where inherited disorder testing is useful. Genetic testing for a constitutional disorder is available in the United Kingdom (as a targeted gene panel, for example R91 cytopenia panel, R92 rare anaemia panel, R229 for FA) or will be available in the near future (whole genome sequencing) (https://www.england.nhs.uk/publication/national-genomic-test-directories). In patients initially classified as having 'idiopathic AA' and who fail to respond to anti-thymocyte globulin (ATG), investigations for inherited forms of AA should be re-appraised.

Genetic counselling for inherited/constitutional AA

A careful family history and examination may identify an inherited form of AA. Early age of onset is more likely to have a genetic susceptibility. Consent for genetic testing for constitutional disorders should be taken both for diagnostic and predictive genetic testing and a record of the discussion should be kept in the patient's notes (https://www.england.nhs.uk/publication/nhs-genomic-medicine-service-record-of-discussion-form/). Accurate molecular diagnosis informs the management of the patient (e.g. pulmonary fibrosis in patients with DC, lymphoedema and immunodeficiency in patients with *GATA2* mutation). It also enables genetic testing of relatives, following genetic counselling, to determine the risk of them developing the same disorder (predictive testing) and allows prenatal diagnosis for future pregnancies for couples with an affected child.[28,37]

Main pitfalls are:

- Identification of variants of unknown significance that may require testing by further family members to clarify—this may lead to increased anxiety in the family and relatives should be carefully counselled before testing.
- Predictive genetic testing in relatives for genes that confer susceptibility to AA—it is difficult to quantify that risk, and there are no clear guidelines for the surveillance of the relatives.

Key Recommendations for Inherited AA

- **Chromosomal breakage analysis of peripheral blood lymphocytes following exposure to diepoxybutane (DEB) to test for FA should be performed (1B).**
- **A comprehensive assessment should be performed, including family history, abdominal ultrasound, echocardiogram, high-resolution CT scan of the chest and pulmonary function tests and evaluation for other extra-haematopoietic abnormalities (such as cirrhosis, pulmonary fibrosis or renal anomalies); the presence of these will support a diagnosis of constitutional rather than idiopathic BMF (1B).**
- **The presence of a PNH clone, especially if large and detected in all lineages, helps exclude inherited AA (2B).**
- **Genetic testing for the identification of a constitutional disorder in affected individuals allows surveillance for associated abnormalities, accurate testing for the same pathogenic variants in close relatives to predict their risks and prenatal diagnosis for future pregnancies (1B).**

- **Consent must be taken for diagnostic and predictive genetic testing for constitutional disorders (2B).**
- **Variants of unknown significance identified by genetic testing for constitutional disorders may require further investigations or family studies (2B).**
- **Assessment of risk and surveillance of relatives who have inherited the susceptibility is difficult for some constitutional genetic disorders (3A).**

SUPPORTIVE CARE

Blood product support

Restrictive red cell transfusion thresholds of 70–80 g/L haemoglobin concentration (80 g/L for those with cardiovascular disease) are recommended for adult hospitalised stable patients, although robust randomised trial data are lacking for AA.[38] Decisions for red cell transfusion in AA should be based on individual transfusion plans, taking into consideration symptoms of anaemia, patient age and comorbidities.[39] Phenotype-matched blood (for Rh and Kell) should be considered to reduce the risk of alloimmunisation.[40]

The strength of the relationship between the severity of thrombocytopenia and bleeding risk is unclear in chronic thrombocytopenia.[1,41–43] However, bleeding related to severe thrombocytopenia is a cause of death in AA.[3,44] General recommendations for platelet transfusions should be followed as per BSH guidelines.[45] During hospitalisation for specific treatment and acute events, prophylactic platelet transfusions should be given to stable AA patients on active therapy for a platelet count $<10\times10^9$/L. During treatment with ATG, worsening thrombocytopenia is due to increased platelet consumption in the presence of cross-reacting antibodies in ATG binding to platelets, and clinicians may apply a higher threshold (20×10^9/L).[1,46,47] For asymptomatic patients with chronic thrombocytopenia, prophylactic platelets are not recommended, but this requires an assessment of clinical bleeding risk. Although tranexamic acid in patients undergoing intensive chemotherapy suggests no benefit,[48] it may be considered in AA patients. For patients who develop platelet refractoriness due to human leucocyte antigen (HLA) alloimmunisation, HLA-matched platelets would be appropriate, including HLA epitope-matched platelets for highly sensitised patients when HLA-matched platelets using serological matching are not available.[45,49,50]

Irradiated granulocytes should be considered in patients with a life-threatening infection related to severe neutropenia,[1] and anecdotally, they may be life-saving, although data on efficacy and safety remains limited; clinicians are encouraged to contribute to a national registry.[51]

Additional considerations

Recommendations for irradiation are addressed in recent BSH guidelines.[52] For recommendations regarding cytomegalovirus (CMV)-selected blood components, see the Advisory Committee on Safety of Blood, Tissues and Organs (SaBTO; SaBTO Annual Report, 2011/12)[53] and the European Society for Blood and Marrow Transplantation (EBMT; EBMT Handbook 7th Edition, 2019) recommendations.

Iron chelation therapy

Patients receiving regular blood transfusions will inevitably develop iron overload. Although evidence is accumulating for the benefit of iron chelation therapy in MDS patients with transfusion-related iron overload,[54] there is a paucity of data in AA. The 1-year Evaluation of Patients' Iron Chelation with Exjade study[55] showed chelation with deferasirox was safe and could reduce the ferritin level. Impaired renal function is observed with deferasirox, so it should be used with caution in AA in combination with ciclosporin. Deferasirox is licensed for use in transfusion-dependent anaemia as a second-line therapy when desferrioxamine is inadequate or contra-indicated. Deferiprone is efficacious but not recommended in neutropenic patients.[56] For those responding to immunosuppression or after a successful HSCT, venesection is recommended for iron overload.

Infection in AA: Prevention and treatment options

Infections, due to prolonged and persistent neutropenia, remain the major cause of death in AA.[57] Survival of non-responders to ATG has markedly improved, and this has occurred in conjunction with decreased infection-related mortality and a decreased frequency of invasive fungal infections.[58]

Prevention of infections

Severely neutropenic hospitalised AA patients should ideally be nursed in isolation.[59] Prophylactic antibiotics, such as quinolones (e.g. ciprofloxacin), should be initiated, according to the National Institute for Health and Care Excellence (NICE).[60] A mould (*Aspergillus*)-active azole (e.g. itraconazole/posaconazole), should be used as prophylaxis. Antiviral prophylaxis (e.g. aciclovir/valaciclovir) should be used during and after ATG and with ciclosporin. During ATG therapy, subclinical reactivation of CMV and Epstein–Barr virus is common, but clinical viral disease is extremely rare, especially after horse ATG.[61] It is not UK practice to give *Pneumocystis jirovecii* prophylaxis with ATG or ciclosporin.

Treatment of infections

Clinicians should follow local and NICE guidance.[62] Empirical anti-fungal therapy should be initiated early for patients with clinically suspected invasive fungal infections.

Haemopoietic growth factors

Erythropoietin and granulocyte colony-stimulating factor (G-CSF) are invariably ineffective in AA patients.[63] In SAA and VSAA, G-CSF given along with ATG and ciclosporin does not improve long-term outcomes and complications.[64] The thrombopoietin (TPO) receptor agonist, eltrombopag, is discussed later.

Vaccinations in AA

There are case reports of AA developing postvaccination and of recovered AA patients relapsing following vaccine administration. The evidence is limited and based also on an appreciation that a viral insult is likely to be an important trigger in the pathogenesis of AA.[65–67]

In the setting of the Coronavirus disease 19 (COVID-19) pandemic, current American Society of Hematology (ASH) COVID-19 and AA guidance (https://www.hematology.org/covid-19/covid-19-and-aplastic-anemia) is that the risk versus benefit would favour vaccine administration, particularly in those with additional risks for severe COVID-19 disease (age, obesity and other comorbidities associated with increased risk). No data on efficacy in immunosuppressed patients have been made available to date for any of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccines in development.

Those patients within 6 months of ATG/ciclosporin (CSA) initiation are unlikely to mount an appropriate immune response to a vaccine. Those AA patients remaining on CSA for more than 6–12 months post-ATG treatment may respond to a vaccine. Vaccinations may be given after thoroughly considering and balancing risk versus benefit.

Post-transplantation AA patients should follow standard post-transplantation guidelines for vaccine administration. These will be updated regarding SARS-CoV-2 vaccines when efficacy data become available, extrapolating from recommendations for other vaccines (https://bsbmtct.org/bsbmtct-and-covid/; https://www.ebmt.org/covid-19-and-bmt; https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines).

Psychological support

Aplastic anaemia is a complex, often life-threatening and chronic disease, which places significant adjustment-related demands on patients/families at all stages of the disease pathway—from diagnosis (including 'genetic' elements, potentially) through treatment and coping with post-treatment complications or relapse. There is a patient support group in the United Kingdom for AA patients, the Aplastic Anaemia Trust (AAT) (http://www.theaat.org.uk, email: support@theaat.org.uk), which offers information and support to patients and families affected by AA, including children. The psychological impact of illness should be routinely borne in mind by treating teams, as some patients may require formal psychotherapy or counselling support. There is variability in the provision of this across the United Kingdom, with some centres having access to psychology services internally and others having to refer externally.

Key Recommendations for Supportive Care

- **There is insufficient evidence on which to base a recommendation for red cell transfusion support for AA patients. Although not evidence based, for stable hospitalised patients, a restrictive transfusion strategy (70–80 g/L haemoglobin concentration and 80 g/L for those with cardiovascular disease) can be considered, while for outpatients, individual transfusion plans based on patients' symptoms and comorbidities can be adopted in line with the limited data in MDS (2C).**
- **Prophylactic platelet transfusions should be offered for AA patients undergoing active treatment if the platelet count is $<10\times10^9$/L (1B). This threshold may be increased in the presence of additional risk factors (administration of ATG) (2C).**
- **For AA patients with chronic severe thrombocytopenia, in the absence of ongoing bleeding, prophylactic platelet transfusion might be avoided (2B/C).**
- **The need for iron chelation should be decided on an individual patient basis. Patients with iron overload after a successful haemopoietic stem cell transplantation (HSCT) should undergo venesection (1B).**
- **AA patients who are severely neutropenic should be given prophylactic antibiotics and anti-fungal therapy according to local policies (2B).**
- **AA patients receiving IST should also receive prophylactic anti-viral agents, although routine prophylaxis against *Pneumocystis jirovecii* is not necessary (2C).**
- **Psychological support should be provided (2C).**

FIRST-LINE TREATMENT OF ACQUIRED AA

Severe/very severe AA

Standard treatment for newly diagnosed acquired SAA patients is ATG-based IST with eltrombopag or allogeneic HSCT from a matched sibling donor (MSD)[1,68–70] (Figure 1).

With improved survival after HSCT, the upper age limit for up-front MSD HSCT has steadily increased, according to comorbidities and fitness for HSCT.[68,71–75] Up-front matched unrelated donor (MUD) HSCT may be considered as an option for young adults with SAA/VSAA who lack a MSD, who urgently need a transplant to achieve early neutrophil engraftment on account of severe/life-threatening sepsis, and where multiple MUDs are readily available and

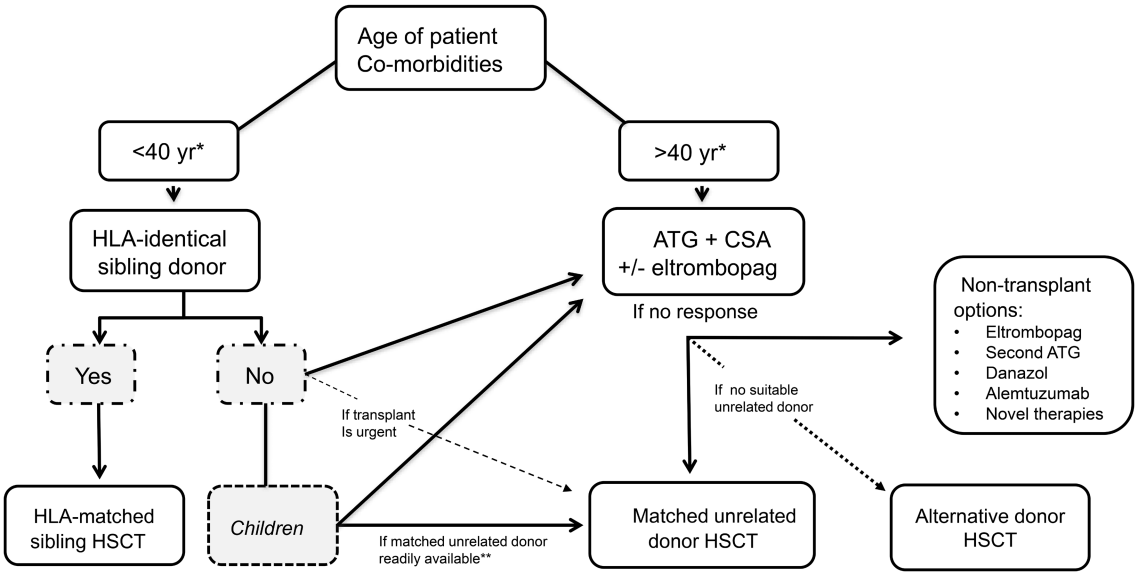

FIGURE 1 Treatment of acquired severe aplastic anaemia. *For patients aged between 40 and 50 years, an individual patient assessment based on comorbidities, performance status, expertise of transplant centre and rapid availability of sibling donor can be made to help decide whether to treat with first line IST or MSD HSCT. **Within 8 weeks. IST, immunosuppressive therapy; MSD, matched sibling donor.

one is recruited to donate in a very short time frame. This reflects a similar approach in children,[76–78] although randomised controlled trials comparing IST with MUD are not yet available.[79]

ATG with CSA is currently first-line therapy for SAA or VSAA in the absence of an HLA-matched sibling and for older SAA/VSAA patients. See below regarding the addition of eltrombopag to ATG and CSA.

Patients aged >60 years must be carefully assessed for fitness to receive ATG.[80,81]

Non-severe AA (moderate AA)

Because patients with constitutional BMF present more often with NSAA than SAA/VSAA, it is especially important to exclude constitutional AA or hypocellular MDS prior to treatment planning.[82] Treatment guidelines are less well defined, and fewer prospective randomised trials have been performed than for SAA/VSAA. Many patients require no treatment. Indications for treatment are transfusion dependency, progression to SAA and where patient lifestyle dictates. Based on the only prospective randomised trial in NSAA, the combination of ATG and CSA results in similar OS but better failure-free survival and a faster and better response (74% vs. 46%, respectively), compared to CSA alone.[82] Danazol is another option, but there are limited data on efficacy[83] and supply issues (see "Treatment of AA in the Elderly"), and response to danazol should trigger re-consideration of possible underlying constitutional AA. The use of eltrombopag for NSAA is not approved.[84]

IMMUNOSUPPRESSIVE THERAPY

Indications

ATG with CSA is indicated as first-line therapy for:

- NSAA who are transfusion dependent, bleeding, encountering infections or for lifestyle (activities).

ATG with CSA and eltrombopag is indicated as first-line therapy for:

- SAA/VSAA in the absence of a MSD.
- SAA/VSAA with a MSD and >40 years of age (patients aged between 40 and 50 years with MSD could be considered for HSCT depending on performance status and comorbidities, in addition to centre expertise) (Figure 1).

Standard first-line IST

- Horse ATG is the preferred source. A prospective randomised study from the National Institute of Health (NIH) and a prospective EBMT study showed significantly better response at 3 and 6 months and survival with horse ATG compared to rabbit ATG for first-line IST.[46,85] Large retrospective studies/meta-analyses confirm the advantages of horse ATG.[86–89]
- The EBMT phase III study comparing first-line ATG and CSA with or without eltrombopag for SAA/VSA (RACE; ClinicalTrials.gov number, NCT02099747) showed a significant increase in complete response (CR) with

eltrombopag.[70] The addition of eltrombopag increased the CR at 3 months (22% vs. 10%), the overall response at 6 months (68% vs. 41%) and the shorter median time to response (3 vs. 8.8 months) as compared to standard IST. No increase in serious adverse events was evident on addition of eltrombopag. Although 2-year OS was similar between the two arms, long-term data is required to ascertain ciclosporin and eltrombopag dependence, late relapses and clonal evolution. Pending regulatory approval, ATG with CSA and eltrombopag should be recommended as first-line IST.

- Prednisolone is used with ATG for the sole purpose to abrogate infusion-related side effects and prevent serum sickness.
- There is no indication for routine use of G-CSF with ATG + CSA, as this confers no additional benefit in terms of response or survival.[90]
- There is no upper age limit for ATG, but there is increased mortality from infection and bleeding and cardiovascular side effects in patients aged >60 years treated with ATG, specifically dysrhythmias (tachycardia and bradycardia), myocardial ischaemia and cardiac failure.[81]

Administration of ATG

The recommended protocol currently used at King's College Hospital is available in Supporting Information. ATG must be given as an inpatient and only be used in centres that are familiar with using the drug. Prior to starting ATG:

- The patient should be clinically stable and, ideally, afebrile.
- Platelet count increment studies should be performed to exclude platelet refractoriness. During ATG, give platelets to achieve a platelet count $>20 \times 10^9$/L.
- Prophylactic anti-viral, antibiotic and anti-fungal drugs should be administered according to local policy and NICE guidance.

The dose of horse ATG (ATGAM®) is 40 mg/kg/day for 4 days. Dilute each dose of ATGAM in 1000 mL of sodium chloride (0.9%). Precede with the test dose by running the first infusion slowly at 5 mL/h for the first hour of the infusion (see Supporting Information, ATG protocol, for further details). CSA is commenced on Day 1 of ATG at a dose of 5 mg/kg/day to achieve trough blood levels of 150–200 μg/L. Although the practice in the United Kingdom is to keep levels between 150 and 200 μg/L, higher therapeutic levels between 200 and 400 μg/L are used in many countries, but renal toxicity should be carefully monitored. CSA should be continued while the blood count rises. A slow tapering of the drug (25 mg every 2–3 months) can be started after at least a further 12 months of therapy.[91] Be aware of the interaction of CSA with posaconazole to maintain therapeutic CSA levels (see ATG protocol, Supporting Information). Eltrombopag is administered orally at a dose of 150 mg per day from Day 14 through 6 months or through 3 months in patients who have achieved a CR at 3 months.

Early side effects of ATG include fever, rash, rigors, hypo/hypertension, fluid retention, rarely acute pulmonary oedema/adult respiratory distress syndrome and anaphylaxis. Serum sickness can occur Days 7–14 from the start of ATG, most commonly with arthralgia, myalgia, rash and fever. See King's protocol above for more details and treatment of side effects. Long-term clonal evolution after ATG comprises MDS/AML is 15%–25% at 10 years[13] although a lower incidence of 8% at 10 years was reported in a recent EBMT study,[64] solid tumours in 5%–11% at 10 years and haemolytic PNH in 10% at 10 years.[1,92]

A second course of ATG may be indicated for failure to respond or relapse after a first course and failure to respond to eltrombopag, and if the patient is ineligible for MUD HSCT[47,93,94] (Figure 1). Response to a second course is 35% and 60% following non-response and relapse respectively.[95] For a second course, rabbit ATG is usually given, but as it produces more profound lymphodepletion than horse ATG, the risk of infection is higher. A second course of horse ATG is an alternative, but is associated with more immediate and late (serum sickness) side effects.

Outcomes

Response to ATG (as defined in Table 7) is delayed, starting after an average of 3–4 months. For SAA, the 6-month response rate is 50%–70%, and it is lower in VSAA (23%).[3,68] Fifteen-year OS is age dependent: 89% for age <20 years, 81% for 20–39 years, 55% for 40–60 years and 32% for

TABLE 7 Criteria for response to IST in AA.[93]

Response criteria following IST in severe AA	
None	Still fulfil severe disease criteria
Partial	Transfusion independent No longer meet criteria for severe disease
Complete	Haemoglobin concentration normal for age and gender Neutrophils $>1.5 \times 10^9$/L Platelets $>150 \times 10^9$/L
Response criteria following IST for non-severe AA	
None	Blood counts are worse, or do not meet criteria below
Partial	Transfusion independence (if previously dependent) *or* doubling or normalisation of at least one cell line *or* increase of baseline • Haemoglobin concentration of >30 g/L (if initially <60) • Neutrophils of $>0.5 \times 10^9$/L (if initially <0.5) • Platelets of $>20 \times 10^9$/L (if initially <20)
Complete	Same criteria as for severe disease

Abbreviations: AA, aplastic anaemia; IST, immunosuppressive therapy.

>60 years.[90] For NSAA, the response rate is 74% with ATG + CSA[3] compared to 46% using CSA alone.[96] As the response rates to second ATG are lower, especially in refractory AA, alternate strategies, including HSCT should be considered in patients with good performance status and a low comorbidity index. Additionally, as long-term event-free survival after ATG is low (20%–30%) due to late events in 50% of patients, HSCT should be considered in transplant-eligible young patients.

TPO receptor agonist: Eltrombopag

Eltrombopag, an oral peptide small molecule TPO mimetic, has shown 40% haematological improvement, including trilineage responses, in refractory and relapsed AA.[97–99] The response rates are lower, around 20%–30% in real-world settings, especially in elderly patients. Unlike immune thrombocytopenia, higher doses (150 mg) over a prolonged duration (16–24 weeks) are required to induce responses, and a proportion of robust responders could safely discontinue treatment. Eltrombopag is well tolerated, but early cytogenetic evolution, especially monosomy 7, is seen in 18% of patients, particularly in non-responders.[100] A BM examination to exclude an abnormal cytogenetic clone typical of MDS/AA is strongly recommended prior to treatment and at regular intervals during therapy. Eltrombopag should be avoided in patients with cytogenetic abnormalities, especially monosomy 7. Eltrombopag has been Food and Drug Administration (FDA)-approved and licensed by the European Medicines Agency (EMA) for SAA refractory to IST or patients heavily pretreated and unsuitable for HSCT. Although early-phase clinical trials show the efficacy of high doses of romiplostin in refractory AA, its use is not approved and is not routine practice.[101–104]

Eltrombopag combined with ATG and ciclosporin, as first-line treatment for SAA and VSAA, was associated with a markedly improved CR in a single-arm study[83,105] and also in the recently published pivotal randomised controlled RACE trial.[70] The addition of eltrombopag to ATG and ciclosporin in SAA/VSAA has been approved by the US FDA and several regulatory authorities globally. European approvals are required before routine use of eltrombopag in an up-front setting in the UK.

Other immune suppressive drugs that have been used in AA

It is recommended that expert advice be sought when considering the use of other immunosuppressive drugs, such as alemtuzumab.[106] Mycophenolate mofetil, sirolimus, corticosteroids and cyclophosphamide are not recommended in the treatment of AA (Table 8).

Key Recommendations for IST and Eltrombopag

- **The current standard first-line IST is horse ATG (hATG-ATGAM) combined with ciclosporin (CSA), Grade 1A, but pending regulatory approval, hATG-ATGAM with CSA and eltrombopag should be recommended instead for SAA/VSAA (1B).**
- **IST is recommended as first-line therapy for non-severe AA patients requiring treatment (see indications in the text), severe AA (SAA) or very severe AA (VSAA) patients aged <40 years who lack a MSD and older SAA/VSAA patients (1A).**
- **A second course of ATG may be indicated following failure to respond to a first course (if the patient is ineligible for a MUD HSCT) or following relapse after a first course (1A).**

TABLE 8 Other immunosuppressive drugs that have been used in AA.

Alemtuzumab	• Effective in around 35% and 55% of patients with refractory and relapsed AA respectively • Not recommended as first-line IST, as a response rate of only 19% was reported from the prospective NIH study[106] • May be considered as an option for refractory/relapsed AA, (i) when a second course of ATG is not possible, (ii) in the presence of renal impairment, as it is effective as monotherapy without the addition of CSA or (iii) if the patient is ineligible for a HSCT • Given as a total dose of 100 mg; given as a subcutaneous dose of 10, 30, 30 and 30 over 4 days • Relapses are frequent, although patients may respond again to a further course. All patients should receive adequate prophylaxis, including against *Pneumocystis jirovecii* • Patients being considered for alemtuzumab should be referred to a tertiary centre, treated as part of the established EBMT protocol and reported to the EBMT registry
Mycophenolate mofetil and sirolimus	• There is no indication for the addition of other immunosuppressive drugs such as mycophenolate mofetil or sirolimus, either in addition to ATG or in isolation, as there is no evidence that they are effective in AA • In combination with ATG + CSA, they do not increase the response rate, survival or reduce relapse compared to ATG + CSA[47]
Cyclophosphamide	• The use of high-dose or even 'moderate' dose cyclophosphamide as treatment for AA is not recommended due to prolonged cytopenia, despite a high failure-free survival[107] • Although response occurs in around 50% of patients with refractory AA, its predictable prolonged duration of neutropenia results in a high incidence of severe fungal infections and mortality[47,93,108–110]

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; CSA, ciclosporin; EBMT, European Bone Marrow Transplantation; HSCT, haemopoietic stem cell transplant; NIH, National Institutes of Health.

- **ATG is an immunosuppressive drug and should only be administered in centres familiar with its use; the drug must only be given to inpatients (1B).**
- **The use of high- or moderate-dose cyclophosphamide (without stem cell support) is not recommended in AA (1A).**
- **Eltrombopag is licensed by EMA for SAA refractory to IST or patients heavily pretreated and unsuitable for HSCT. It should be used with meticulous long-term monitoring for clonal evolution (2B).**

HSCT IN AA

Current indications for HSCT in adults

Current indications for HSCT are based on the EBMT Severe Aplastic Anaemia Working Party (SAAWP) guidelines.[111] Patients should be managed in Joint Accreditation Committee ISCT-Europe and EBMT (JACIE)-accredited centres.[112] HLA-typing should be performed at diagnosis to facilitate rapid identification of suitable related donors and unrelated donor searches where required. Early referral to the transplant centre is advocated to facilitate appropriate decision-making in relation to HSCT versus other therapies.

HLA-matched sibling donor

Up-front HSCT from a MSD is indicated for SAA in young and adult patients aged <40 years who have a MSD. EBMT data show similar outcomes for patients aged 40–50 to those aged 30–40 years.[111] However, comorbidities should be carefully assessed to determine fitness for up-front transplantation instead of IST for patients aged 40–50 years.[75]

HLA-matched unrelated donor

MUD HSCT is indicated for SAA after failure to respond to one course of IST. There is no strict upper age limit, but this should be discussed on an individual patient basis and according to comorbidities at the respective transplant centre. The donor should be 10/10 matched based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1) antigens. Recent evidence demonstrating high OS rates in well-matched MUD HSCT creates a case for offering this up front to selected young, otherwise fit patients with the aim of offering a cure. Use of up-front HSCT resulting in rapid neutrophil recovery in young adult patients is advocated where early infection is present, as there may not be time to wait for IST to be effective. Fludarabine, low-dose cyclophosphamide and ATG with low-dose total body irradiation (TBI) are widely used.[113,114] Alternatively, the development of irradiation- and methotrexate (MTX)-free conditioning protocols limit organ toxicity, and rates of graft-versus-host disease (GVHD) are low with an alemtuzumab-based approach.[115,116]

Alternative donor: Cord blood and haploidentical

Alternative donor HSCT using either cord blood or a haploidentical family donor, a 9/10 MUD may be considered, among other treatment options, after failure to respond to IST and in the absence of a MSD or a suitably matched MUD.[117,118] All donors should be screened for donor-directed HLA antibodies, which are associated with a very high risk of graft rejection. Improved survival with haploidentical approaches using post-transplant cyclophosphamide, when MSD and MUD are lacking, may be preferred over cord blood due to considerations such as stem cell dose, cost and centre expertise.[119,120] Haploidentical HSCT is being increasingly used in relapsed/refractory AA in the absence of MUD, with encouraging outcomes and survival rates. Haplo donors are easily available and have also expanded the donor options for all ethnicities.

Syngeneic donor

Where a syngeneic donor is available, HSCT should be considered in all patients, regardless of age, as long-term OS exceeds 90% with ATG conditioning and the use of peripheral blood-derived stem cells.[57,121]

Older patients

Outcomes in older patients, including those over 70 years, have improved,[72,74,122] but the presence of comorbidities impacts on outcome. A conditioning protocol that minimises GVHD is advocated.

Pretransplant work up

An MDT approach is essential to (1) confirm the diagnosis and exclude or document clonal evolution; (2) assess comorbidities; (3) select the donor, conditioning regimen and stem cell dose and source; (4) address fertility issues; (5) inform the transfusion laboratory of the potential transplant and review transfusion requirements; and (6) offer psychological input[123] to meet relevant JACIE standards[97] (Table 9).

Conditioning regimens

Choice of conditioning regimens depends on (i) patient age, (ii) type of donor and (iii) centre preference for choice of antibody (see Table 10; Figure 2). To reduce the risk of late graft failure, postgraft immunosuppression with CSA is continued for 9 months, followed by 3 months of tapering, with blood CSA trough levels maintained at high levels, ideally >250 μg/L. Stem cell source depends on the conditioning regimen used: BM is recommended for ATG-based regimens; peripheral blood stem cells or BM can be

TABLE 9 Pretransplant work up.

Confirm diagnosis and exclude/document clonal evolution	• Perform a reassessment BM aspirate, trephine biopsy specimen and cytogenetic analysis (and FISH for chromosomes 5, 7, 8 and 13 if cytogenetic analysis fails) to confirm the diagnosis is still AA and to exclude other causes of pancytopenia, such as hypocellular MDS (see "Investigations required for the diagnosis of AA" section) • Repeat flow cytometry to document whether or not there is a PNH clone • Exclude a constitutional form of AA (see "Investigations required for the diagnosis of AA" section, emerging diagnostics), for example FA or DC, not only in children but also in adults. Late-onset FA or DC may present without the classical somatic abnormalities and instead may be associated with, for example, pulmonary fibrosis or cirrhosis, which may both impact on transplant outcomes.[121] Conditioning regimens are different from those used in acquired AA, which are likely to be fatal in undiagnosed constitutional AA. Sibling donors for patients with a confirmed or suspected constitutional AA should be screened comprehensively with available genomic testing prior to being used as donors • Consider referral for opinion/advice to a centre with AA expertise and access to integrated diagnostic laboratories, including molecular genetic techniques to help differentiate AA from MDS and to exclude constitutional AA
Assess comorbidities	• Follow standard guidelines for all patients undergoing allogeneic HSCT and document the Haematopoietic Cell Transplant Comorbidity Index (HCT-CI) or equivalent • As AA patients are likely to be multitransfused at the time of HSCT, assess for iron overload with serum ferritin and, if available, a T2* MRI scan for assessment of cardiac and liver iron can be considered (see "Blood product support" section for patients with AA) • Perform a serum HLA antibody screen to assess for HLA antibodies. This is to (i) ensure adequate platelet count increments and (ii) select the appropriate donor for patients being considered for mismatched HSCT, whether using cord blood, haploidentical or a 9/10-matched unrelated donor
Select donor, conditioning regimen, stem cell source and dose	• Choice of donor and type of conditioning regimen is usually straightforward but not always, so give consideration to discussion with a centre with AA expertise • Compared to HSCT for haematological malignancies, a higher stem cell dose is required in order to reduce the risk of graft failure. For MSD and MUD HSCT, a minimum of 3×10^6 CD34-positive cells/kg [or 3×10^8 total nucleated cells (TNC)/kg] is required. For cord blood HSCT, a minimum of 4×10^7 TNC/kg is recommended, thus usually necessitating a double cord infusion.[117] There is no consensus on cell dose for haploidentical HSCT, but a proposed algorithm for donor selection to optimise the cell dose includes using, if possible, a young and male family donor[124] • For ATG-based conditioning regimens, BM is the preferred stem cell source.[125] For alemtuzumab-based regimens, either BM or PBSC may be used, as a higher stem cell dose facilitates rapid engraftment and reduces the risk of graft failure, and the use of alemtuzumab limits the development of GVHD. The use of PBSC to increase the stem cell dose is being explored in the EBMT SAAWP protocol for haploidentical HSCT[119,120]
Address fertility issues	• AA patients receiving high-dose cyclophosphamide (CY) as part of the conditioning regimen are likely to retain their fertility post-HSCT.[126] Less long-term data are available using fludarabine with lower-dose CY regimens, although cases of successful pregnancy have been reported. The effect of low-dose total body irradiation (TBI) (2 Gy) is another factor • For patients of childbearing age, a referral to an assisted conception unit for discussions on fertility should be offered. Men should be offered sperm storage. Women should have the opportunity to discuss with an assisted conception unit specialist the latest results of egg/embryo cryopreservation so they can decide if they wish to proceed with this • However, if the patient has ongoing systemic sepsis and needs an urgent HSCT, the procedure of gonadal hyperstimulation may be too dangerous. In addition, in the presence of a significant PNH clone, the risk of venous thrombosis is further increased by the state of gonadal hyperstimulation, and in this situation, expert advice from one of the two national UK PNH centres should be sought regarding the use of eculizumab
Offer psychological support	• To meet relevant JACIE standards

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; BM, bone marrow; CSA, ciclosporin; CY, cyclophosphamide; DC, dyskeratosis congenital; EBMT, European Bone Marrow Transplantation; FA, Fanconi anaemia; HSCT, haemopoietic stem cell transplant; IBMFS, inherited bone marrow failure syndrome; MDS, myelodysplastic syndrome; MSD, matched sibling donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; PNH, paroxysmal nocturnal haemoglobinuria; TBI, total body irradiation.

used for alemtuzumab-based regimens.[74,127,128] The choice of using Campath or ATG is dependent on the availability of the drug and also on the local expertise/experience of the transplant centre in managing complications related to the specific serotherapies. TBI (2 Gy) is also not required with alemtuzumab in the setting of a 10/10 HLA-compatible sibling or unrelated donor, while low-dose TBI reduces graft failure and aids engraftment for older patients (>30 years) in the setting of MUD while using ATG as serotherapy.

How successful is HSCT for AA?

For adult HSCT, survival is age dependent, but between the ages of 30 and 50 years, OS is 70%–90%.[68] Survival has improved in recent years, particularly for MUD and haploidentical HSCT. The potential for cure with HSCT versus IST and the potential for longer-term clonal evolution should be discussed with patients when making decisions in regard to first-line therapy.

Haploidentical HSCT has been increasingly used in HSCT. Although numbers remain small, OS estimates range from

TABLE 10 Conditioning regimens used in HSCT for severe AA (see also Figure 2).

Matched sibling donor	• For patients aged <30 years, high-dose CY (200 mg/kg) with ATG or alemtuzumab. Postgraft immune suppression with CSA and 'short' course MTX if using ATG, or CSA alone if using alemtuzumab • For patients aged >30 years, fludarabine 30 mg/m^2 × 4, CY 300 mg/m^2 × 4 and ATG ('FCATG') or alemtuzumab ('FCC'). Postgraft immune suppression as for patients aged <30 years • If there are concerns about using high-dose CY in individual patients, then the excellent outcomes with FCC in an unrelated setting suggest this may be an alternate and acceptable regimen regardless of age • Postgraft CSA is usually continued for 9 months with tapering of dose over 3 months, to reduce late graft failure • There is no indication for using radiation as part of the conditioning regimen • Stem cell source: BM for ATG-based regimens; PBSC or BM for alemtuzumab-based regimens • Even in the setting of COVID-19, fresh stem cells are recommended due to concerns about stem cell loss and the risk of graft failure following the thawing of cryopreserved cells
Unrelated donor	• For 10/10-matched MUD HSCT, for adults, the choice is either (i) the EBMT protocol of FCATG with 2 Gy TBI or (ii) FCC without TBI • For 9/10-matched MUD HSCT, either FCATG +2 Gy TBI or FCC + 2 Gy TBI • Stem cell source: BM for ATG-based regimens; PBSC or BM for alemtuzumab-based regimens • Even in the setting of COVID-19, fresh stem cells are recommended due to concerns about stem cell loss and the risk of graft failure following the thawing of cryopreserved cells
Cord blood	• There is no consensus but it is recommended that the EBMT-adopted French protocol be followed, using fludarabine, CY 120 mg/kg, ATG, TBI 2 Gy, with one dose of rituximab on day +5, total nucleated cell dose infused >4 × 10^7/kg and not less than 4 out of 6 HLA mis-matched cord units[117]
Haploidentical family	• There is no consensus[117] but it is recommended that the current EBMT SAAWP protocol be followed, using non-myeloablative conditioning (CY 14.5 mg/kg × 2, fludarabine 30 mg/m^2 × 4, TBI 2 Gy) with postgraft high dose CY (50 mg/kg on days +3 and +4) with tacrolimus and MMF postgraft. Either BM or PBSC can be used, but a high stem cell dose is essential[119,120]
Syngeneic	• Conditioning prior to stem cell infusion is recommended, using high-dose CY and probably also ATG. There may be a good rationale for using PBSC in preference to BM, as the use of PBSC is associated with a lower risk of graft failure in the setting of syngeneic HSCT[57]
Second HSCT for graft failure	• There is no consensus, but the following FATG conditioning is commonly used: fludarabine 30 mg/m^2 × 5, ATG and CSA as postgraft immunosuppression

Abbreviations: AA, aplastic anaemia; ATG, anti-thymocyte globulin; BM, bone marrow; CSA, ciclosporin; CY, cyclophosphamide; EBMT, European Bone Marrow Transplantation; FCC, fludarabine, cyclophosphamide, alemtuzumab (Campath); HSCT, haemopoietic stem cell transplant; MMF, mycophenolate mofetil; MSD, matched sibling donor; MUD, matched unrelated donor; MTX, methotrexate; PBSC, peripheral blood stem cells; TBI, total body irradiation.

78%[120] to >90%[119] for patients receiving haploidentical HSCT that includes the use of post-transplant cyclophosphamide.[129]

Specific issues relating to AA HSCT regarding early post-transplant management and management of late effects are summarised in Table 11.

COVID-19

The emergence of SARS-CoV-2 in late 2019 illustrated the need for a considered approach to decision-making for HSCT in the context of a pandemic (NICE, EBMT and BSBMTCT guidance). For SAA patients, delay may be considered in less urgent cases. Eltrombopag can be considered as a bridge to transplant or IST to enable definite therapy to be performed when the pandemic has abated and infection control may be more assured (https://www.england.nhs.uk/coronavirus/publication/eltrombopag-as-bridging-therapy-to-haematopoietic-stem-cell-transplant-in-severe-or-very-severe-aplastic-anaemia-during-the-covid19-pandemic-in-adults/).

Key Recommendations for HSCT

- **All patients being considered for HSCT should be evaluated in a MDT setting, and consideration should be given to discussion of the case with a centre that has expertise in AA regarding the indications for HSCT and the choice of conditioning regimen (1C).**
- **All patients who are potential HSCT candidates should undergo HLA-typing at diagnosis, followed by related or unrelated donor searches as appropriate to assess the availability of potential donors (1B).**
- **A careful reassessment should be made to confirm the precise diagnosis and exclude clonal evolution to MDS or PNH, as this will influence the choice of conditioning. It is also vital not to miss constitutional AA so as to avoid (i) serious (and potentially lethal) toxicity from the transplant and (ii) inappropriate selection of a family donor (1C).**
- **The haematopoietic cell transplant comorbidity index or equivalent assessment should be documented (2B).**
- **Alternatives to HSCT, including IST, should be actively considered in the management plan (1B).**
- **Up-front MSD HSCT for young and adult patients aged <40 years is the treatment of choice for severe AA, but patients aged between 40 and 50 years need to be carefully assessed for comorbidities prior to consideration for transplantation (1B).**
- **Unrelated donor HSCT in adults should be considered after a lack of response to one course of IST and up front for young adults with severe infections and a readily available MUD (1B).**

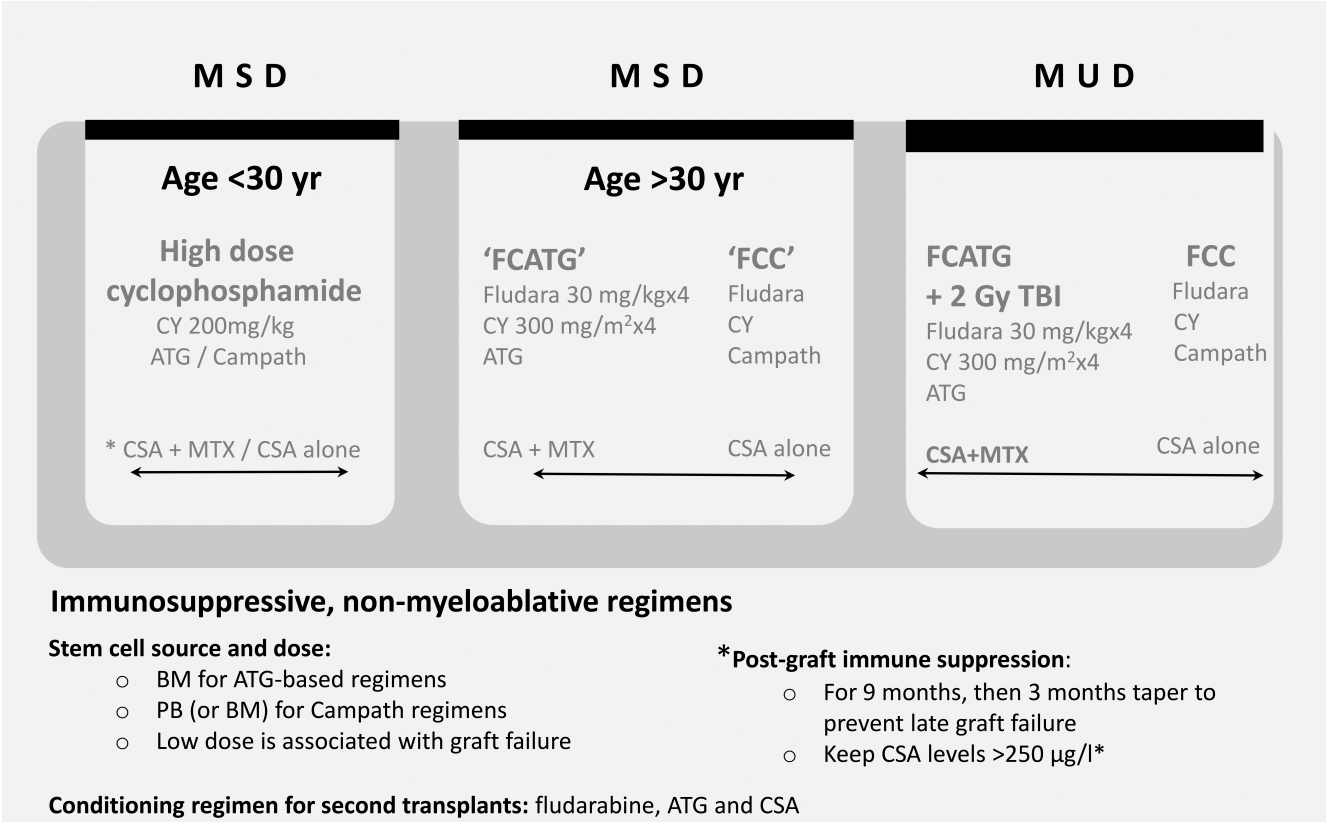

FIGURE 2 Transplant conditioning regimens in aplastic anaemia. Campath, alemtuzumab; CSA, ciclosporin; CY, cyclophosphamide; MSD, HLA matched sibling; MTX, methotrexate. *If renal function is compromised, a 'half dose' CSA and 'half dose' mycophenolate mofetil regimen can be used instead.

TABLE 11 Management of early issues and late complications post-HSCT for severe AA.

Early post-transplant management	• Postgraft CSA is continued for 9 months, followed by tapering to 12 months, to reduce the risk of late graft failure • Blood CSA trough levels need to be maintained at higher levels, >250 µg/L, than used in haematological malignancies. If renal function is compromised, a 'half dose' CSA and 'half dose' MMF regimen can be used instead • Regular monitoring of unfractionated and lineage-specific CD3 (T-cell) chimerism in peripheral blood and bone marrow is recommended to detect early graft failure. Progressive mixed chimerism predicts a high risk of graft rejection. Stable mixed T-cell chimerism in the presence of full donor myeloid chimerism is common when using FCC regimen
Management of late effects	• Late effects monitoring should follow international guidelines, and these include routine surveillance for secondary malignancy, endocrine, metabolic, bone (including avascular necrosis) and cardiovascular risks[130] • The risk of second malignancy in AA HSCT is reduced by avoiding irradiation and by the absence of chronic GVHD • Iron overload is common and is most easily addressed by regular venesections once patients are fully engrafted post-transplant • In transplanted AA patients, re-vaccination should proceed as per standard allogeneic HSCT practice

Abbreviations: AA, aplastic anaemia; CSA, ciclosporin; CY, cyclophosphamide; FCC, fludarabine, cyclophosphamide, alemtuzumab (Campath); GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant; MMF, mycophenolate mofetil.

- **Alternative donor HSCT is an option for patients who lack a suitably matched donor; a haploidentical family donor is preferable to cord blood HSCT, using a reduced-intensity regimen with post-transplant high-dose cyclophosphamide (2B).**
- **Patients should be treated in a JACIE-accredited centre, meeting all quality standards for HSCT (2B).**

TREATMENT OF AA IN THE ELDERLY

Treatment of elderly patients (>60 years) with AA is more complex than in younger patients due to comorbidity and treatment toxicity, and assessment of quality of life is especially relevant.[131] It is important to exclude hypocellular

MDS, which is far more common than AA in this age group. Response rates to treatment are age independent; however, assessment of individual comorbidity is essential to guide treatment decisions.[132]

IST is the treatment of choice. There is no place for allogeneic HSCT as first-line therapy, although it should be considered in selected patients unresponsive to first-line immunosuppression.[72,74] In NSAA, treatment with ATG and CSA results in a more rapid, CR than CSA alone.[96] Patients must be assessed carefully before treatment, as the risks of infection, bleeding, heart failure and arrhythmias with ATG are higher. Outpatient-based alternative treatments include CSA alone, and patients must be carefully monitored for nephrotoxicity and hypertension. Second-/third-line options include eltrombopag or oxymetholone/danazol.[133] Danazol has now been discontinued in the UK, but hospital pharmacies can obtain unlicensed imports from various companies listed in the Department of Health and Social Care guidance 29 May 2020. When considering eltrombopag, patients require prior assessment for the risk of clonal evolution. Danazol has fewer masculinising side effects than oxymetholone. Careful monitoring is required for nephrotoxicity, hepatic tumours, mood changes, cardiac failure, prostatic enlargement and raised blood lipids. Single-agent alemtuzumab may be used in refractory/relapsed AA, but medical fitness needs very careful assessment prior to considering this.[106] Patients who are ineligible or who decline above therapies should be offered the best supportive care.

Key Recommendations for Treatment of AA in the Elderly

- **Elderly patients with AA should be individually assessed and their specific wishes respected, as quality of life is paramount in this patient group (1C).**
- **IST is considered the treatment of choice. ATG and ciclosporin result in a more rapid recovery of blood counts, but alternatively, ciclosporin alone, eltrombopag or anabolic steroids (oxymetholone/danazol) can be considered (1B).**
- **Patients unfit for, who decline or who are intolerant of IST should be offered the best supportive care (1C).**

MANAGEMENT OF AA IN PREGNANCY

AA can develop, progress or relapse during pregnancy and it needs obstetricians, anaesthetists and haematologists to work together for the best outcome for the mother and baby.[134] Mild anaemia and thrombocytopenia of advancing pregnancy should be differentiated from AA, and iron, folic acid or vitamin B12 deficiency should be excluded. Cytopenias worsen in a third of patients, with 14% needing transfusions during pregnancy/at delivery. The mode of delivery should be determined on obstetric grounds. Normal blood counts before conception do not guarantee freedom from the relapse of AA during pregnancy. In contrast, pregnancy does not trigger AA relapse following a successful HSCT. The presence of a PNH clone can be associated with placental insufficiency, thrombosis and miscarriage. Treatment with eculizumab can abrogate the risk of thrombosis and haemolysis.[135] Early discussion with a PNH specialist centre is recommended.

Supportive care is the mainstay of treatment. The platelet count should preferably be maintained at $>20\times10^9$/L (expert opinion). Better-matched blood products and supportive care have improved maternal and fetal outcomes.[136] The risk of alloimmunisation and platelet refractoriness is high. CSA is safe during pregnancy[1,137] and is recommended for those needing transfusions. ATG, HSCT, androgens or eltrombopag are not recommended during pregnancy.

Key Recommendations for Management of AA in Pregnancy

- **Supportive care remains the mainstay of treatment for AA in pregnancy, aiming to maintain the platelet count above 20×10^9/L with platelet transfusions (3A).**
- **Ciclosporin is safe in pregnancy if needed (2C).**

AUTHOR CONTRIBUTIONS

JM and AK chaired the guidelines group and coordinated the manuscript drafts. All authors were involved in formulation, writing and approval of the guidelines. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interest to the BSH and Task Force Chairs, which may be viewed on request. The members of the writing group have no conflicts of interest to declare.

DISCLAIMER

While the advice and information in this guidance is believed to be true and accurate at the time of going to press,

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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