Diagnosis, treatment, and surveillance of Diamond-Blackfan anaemia syndrome: international consensus statement

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Lancet Haematol 2024; 11: e368–82

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Diamond-Blackfan anaemia (DBA), first described over 80 years ago, is a congenital disorder of erythropoiesis with a predilection for birth defects and cancer. Despite scientific advances, this chronic, debilitating, and life-limiting disorder continues to cause a substantial physical, psychological, and financial toll on patients and their families. The highly complex medical needs of affected patients require specialised expertise and multidisciplinary care. However, gaps remain in effectively bridging scientific discoveries to clinical practice and disseminating the latest knowledge and best practices to providers. Following the publication of the first international consensus in 2008, advances in our understanding of the genetics, natural history, and clinical management of DBA have strongly supported the need for new consensus recommendations. In 2014 in Freiburg, Germany, a panel of 53 experts including clinicians, diagnosticians, and researchers from 27 countries convened. With support from patient advocates, the panel met repeatedly over subsequent years, engaging in ongoing discussions. These meetings led to the development of new consensus recommendations in 2024, replacing the previous guidelines. To account for the diverse phenotypes including presentation without anaemia, the panel agreed to adopt the term DBA syndrome. We propose new simplified diagnostic criteria, describe the genetics of DBA syndrome and its phenocopies, and introduce major changes in therapeutic standards. These changes include lowering the prednisone maintenance dose to maximum 0·3 mg/kg per day, raising the pre-transfusion haemoglobin to 9–10 g/dL independent of age, recommending early aggressive chelation, broadening indications for haematopoietic stem-cell transplantation, and recommending systematic clinical surveillance including early colorectal cancer screening. In summary, the current practice guidelines standardise the diagnostics, treatment, and long-term surveillance of patients with DBA syndrome of all ages worldwide.

Introduction

Diamond-Blackfan anaemia (DBA) is a rare, clinically and genetically heterogeneous inherited bone marrow failure syndrome.[1,2] Because of its rarity, advances in clinical care must extend to settings where the disorder is only infrequently encountered. In 2008, our first clinical consensus was developed to review the criteria for diagnosis and evaluate the available treatment options.[3] Advances in clinically relevant research (including discovery of new DBA-associated genes, new advances in iron burden assessment, and new knowledge on the epidemiology of cancers) and disparities in management and surveillance across centres strongly supported the need for a new set of recommendations. The present guidelines were developed to standardise the diagnostic process and management and to improve long-term outcomes for patients with DBA worldwide. These guidelines are not an absolute standard applicable to all clinical scenarios and resources. However, resource limitations should not reduce efforts to deliver the best possible care.

Methods

An international panel of 53 representatives from 27 countries, recognised as key opinion leaders in DBA diagnosis and management, was appointed by the leaders of the European Diamond Blackfan Anemia Consortium and the Diamond Blackfan Anemia Registry of North America (appendix p 1). The objective was to revise and replace the previous 2008 guidelines (appendix p 2). Panel composition, search strategy, and evidence level grading are outlined in the appendix (p 3). We sourced all publications on PubMed up to June 30, 2022, with the relevant search terms (including but not limited to Diamond Blackfan anemia, congenital hypoplastic anemia, congenital anemia, pure red cell aplasia, bone marrow failure, congenital abnormalities, hematopoietic stem-cell transplantation, transfusion, steroids, prednisone, chelators, deferoxamine, deferasirox, deferiprone, iron overload, liver iron content, heart iron, MRI, cancer risk, colorectal cancer, osteosarcoma, MDS, AML, cancer screening, toxicity, long-term management, surveillance) and made use of unpublished observations and updates from participating experts, particularly those from national registries. Because no level A or B evidence (data from randomised trials, meta-analyses, or large non-randomised studies) exists for DBA, the panel relied on level C evidence (expert consensus statement, retrospective analyses, and registry data), including published work, unpublished updates from registries,[4–17] and participant expertise and experience. We used a modified Delphi technique involving iterative voting on key topics

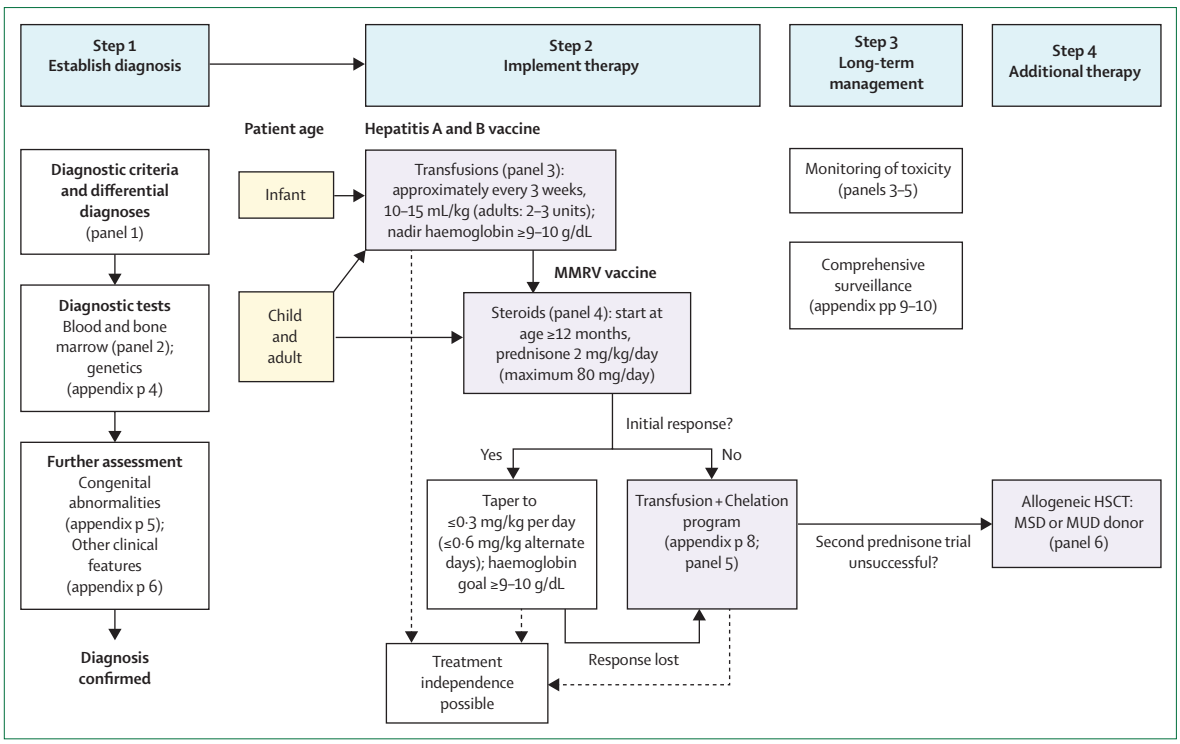

Figure: **Approach to diagnosis, therapy, and long-term management of patients with DBA syndrome**
DBA=Diamond-Blackfan anaemia. MMRV=mumps, measles, rubella, and varicella. HSCT=haematopoietic stem-cell transplantation. MSD=human leukocyte antigen-matched sibling donor. MUD=human leukocyte antigen-matched unrelated donor.

identified from expert judgments and available data until at least 85% consensus was reached.[18] Items on which the panel did not reach consensus were left with multiple options, as detailed. An outline of the contents of this Review is shown in the figure.

Definition of the syndrome

DBA has historically been defined as a macrocytic anaemia with reticulocytopenia and a paucity of bone marrow erythroid precursors, presenting in children younger than 1 year.[19] However, we acknowledge that: variable phenotypes exist within and among DBA genotypes; some individuals with DBA-associated gene mutations paradoxically do not have anaemia; and the diagnosis could occur in adulthood.[20–22] Therefore, we adopt the term DBA syndrome, which encompasses classic DBA, with an incidence of approximately 5–10 cases per million live births and an equal sex ratio, and a broader range of phenotypes. Most patients present with a reticulocytopenic (hyporegenerative) anaemia with or without additional findings. However, a variety of phenotypes might be encountered with or without anaemia or other cytopenias, B-cell lymphopenia, congenital anomalies, or cancer. For example, congenital heart disease can manifest in individuals with ribosomal protein gene mutations without anaemia.[21] We restrict the genetic nosology to genes encoding either small (*RPS* genes) or large (*RPL* genes) subunit-associated ribosomal proteins or their chaperones resulting in ribosomal protein haploinsufficiency (ribosomopathy), the erythroid transcription factor gene *GATA1*,[23] and gain-of-function mutations in *TP53*.[24,25] Phenocopies with different pathophysiology are mentioned but remain distinct from DBA syndrome.[24,26–29]

Clinical presentation

The haematological presentation of DBA syndrome was initially termed congenital hypoplastic anaemia, a description preferred by Dr Louis Diamond, an American paediatrician, when he initially reported the first case series of patients with this syndrome.[1,19] Classically, macrocytic anaemia and reticulocytopenia present initially, with 90% of patients becoming symptomatic in the first year of life (median age 3 months).[30] However, anaemia can manifest in utero as hydrops fetalis[31,32] or in adults older than 60 years, when DBA syndrome could be misdiagnosed as acquired pure red cell aplasia or myelodysplastic syndrome.[30] There is a shift towards an older age at diagnosis due to an improved index of suspicion in adults. In an unpublished UK DBA syndrome analysis, only 111 (76%) of 146 patients presented with anaemia in infancy. Other haematopoietic abnormalities at diagnosis, including thrombocytosis (only in infants), thrombocytopenia, or neutropenia are generally clinically insignificant. A study of 38 children found that

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21 (55%) had thrombocytosis, whereas 12 (32%) had thrombocytopenia, with three (8%) also exhibiting leukopenia.[33] Patients with a *RPL35A* genotype often present with severe neutropenia and immunodeficiency.[34] Impaired cellular and humoral immunity is observed, with up to 55% (59/107) of patients showing quantitative deficits in serum immunoglobulins or lymphocytes arising independently of steroid treatment or underlying genotype.[35] Patients with a *GATA1* mutation might present with thrombocytopenia and neutropenia,[23] with some patients showing dyserythropoiesis and dysmegakaryopoiesis, representing a distinct disease subset.[36] Haemolysis, hepatomegaly, or splenomegaly are not characteristic. In patients with anaemia, diagnostic bone marrow evaluation shows absent or diminished erythroid activity with left shifted erythroid precursors, rarely progressing beyond the pronormoblast stage, with normal erythroid morphology. Dyserythropoietic features (outside of *GATA1*), ring sideroblasts, or vacuoles are not observed, and other lineages do not show morphological abnormalities at presentation. Although initially normocellular, the bone marrow often becomes increasingly

Panel 1: **Diagnostic criteria and differential diagnoses of DBA syndrome**

Diagnostic criteria

- Pathogenic or likely pathogenic mutation in a Diamond-Blackfan anaemia (DBA) syndrome gene (appendix p 4); or
- Haematological features consistent with DBA syndrome: macrocytic anaemia* with reticulocytopenia and bone marrow erythroblastopenia; absence of dysplasia, dyserythropoiesis†, and sideroblasts; and exclusion of known differential diagnoses (see below)

Typical findings (not mandatory for diagnosis)‡

- Patients are younger than 1 year at onset of disease
- Elevated eADA activity (before first transfusion, in patients who have not received a transfusion, or in parents of patients)
- Elevated HbF (reliably assessed in patients older than 6 months)
- Positive family history or unexplained history of anaemia during infancy or childhood
- Congenital abnormalities (appendix p 5)
- Abnormal rRNA processing in patient cells§

Differential diagnoses: acquired

Transient erythoblastopenia of childhood

- Patients are usually older than 1 year at onset of disease
- Normal MCV, eADA, and HbF
- Negative family history and no congenital abnormalities
- Transient course: erythroid recovery in days to weeks

Viruses specific to red-cell lineage (human parvovirus B19) or non-specific viruses (eg, HIV, cytomegalovirus, and Epstein-Barr virus)

- Positive PCR or serology, or both
- Normal eADA and HbF
- Normal MCV (except parvovirus B19)
- Negative family history and no congenital abnormalities
- Concomitant immune deficiency or chronic haemolysis

Myelodysplastic syndrome¶, specifically with 5q deletion (acquired RPS14 haploinsufficiency)

- Typical bone marrow findings (morphology, histology, karyotype, fluorescent in situ hybridisation, myelodysplastic syndrome-related somatic mutations)
- Normal eADA

Drugs; autoimmunity (systemic lupus erythematosus, acquired pure red cell aplasia); lymphoproliferative diseases; and malignancies such as chronic lymphocytic leukaemia¶, large granular lymphocytic leukaemia¶, acute leukaemias, and some solid tumours

- Typical bone marrow and immunological findings
- Normal eADA
- No congenital abnormalities
- Features of malignancy

Thymoma with concomitant pure red cell aplasia¶

- Typical imaging (chest x-ray, CT, or MRI)
- No congenital abnormalities
- Mostly in adults, unlikely in children

Differential diagnoses: hereditary

Inherited bone marrow failure syndromes (specifically Fanconi anaemia, Shwachman-Diamond syndrome, and dyskeratosis congenita)||; Pearson syndrome; congenital sideroblastic anaemia; and congenital dyserythropoietic anaemia

- Classical clinical presentation and laboratory findings
- Bone marrow morphology consistent with respective condition
- MCV and HbF can be elevated and eADA is normal
- Syndrome-specific diagnostic findings and genetics

ADA2 deficiency

- Onset at any age, vasculopathy often absent
- Low B cells and hypogammaglobulinaemia
- Normal eADA and HbF, and MCV can be high
- Low ADA2 enzyme activity and *ADA2* mutations
- Typically, no congenital abnormalities

Erythropoietin dysfunction

- Homozygous *EPO* p.R150Q mutation

ADA2=adenosine deaminase 2. eADA=erythrocyte adenosine deaminase. HbF=fetal haemoglobin. MCV=mean corpuscular volume. *Additional cytopenia can be encountered (neutropenia more often than thrombocytopenia), as well as transient thrombocytosis in infants. †Except for patients with *GATA1* mutations. ‡Highly suggestive of DBA syndrome, but not specific enough to make the diagnosis. §Research test in specialised labs only; useful in patients with ambiguous or uninformative genetics. ¶Typically presenting in adults. ||These inherited bone marrow failure syndromes typically show multilineage cytopenia and often present with other disease-specific abnormalities affecting multiple organ systems; such distinguishing features can help differentiate these conditions from DBA syndrome, which initially characteristically manifests with isolated erythroid hypoplasia.

hypocellular with age, as shown in steroid-refractory patients, of whom 75% (21/28) developed moderate to severe bone marrow hypoplasia over time, with 39% (11/28) and 29% (8/27) of those patients developing neutropenia and thrombocytopenia, respectively.[37] Our unpublished experience supports the findings of hypocellular bone marrow in the majority of patients with DBA syndrome over time. However, severe hypocellularity and pancytopenia as seen in patients with severe aplastic anaemia are not a feature of DBA syndrome. Increased haematological toxicity (eg, delayed count recovery) has been reported in patients receiving radiotherapy or chemotherapy.[38]

Establishing the diagnosis

Diagnosis involves assessing patient history, clinical evaluation, laboratory testing of peripheral blood and bone marrow, and genetic analysis. To capture variable presentations, we agreed on streamlined diagnostic criteria requiring only one of the following: a pathogenic or likely pathogenic mutation in a DBA syndrome-associated gene; or haematological features consistent with DBA syndrome, after exclusion of other known differential diagnoses (panel 1). The presence of a pathogenic or likely pathogenic variant according to the criteria established by joint classification from the American College of Medical Genetics (ACMG) and Genomics and the Association for Molecular Pathology (AMP)[39] is sufficient for diagnosis and allows for inclusion of patients with DBA syndrome who are currently asymptomatic. Establishing a diagnosis on the basis of genetics alone has limitations because current gene panels may not include newly discovered genes and some genetic variants are difficult to interpret. Additionally, 20–30% of cases have an unknown genetic origin. Therefore, DBA syndrome can also be diagnosed by the presence of characteristic haematological features in peripheral blood and blood marrow after excluding other differential diagnoses (panel 1). Other common findings such as elevated erythrocyte adenosine deaminase (eADA) activity[40] and rRNA processing defect[41,42] are not required for diagnosis. Recommended diagnostic tests agreed on by our panel are shown in panel 2. In addition to essential tests, further initial evaluations are recommended in all patients to fully characterise the clinical phenotype and guide management. Although a diagnosis can be made based on haematological features alone after excluding other conditions, genetic testing should be done promptly. Patients diagnosed via genetics alone (eg, infants with typical manifestations or those with a positive family history and segregation of the mutation) should undergo confirmatory bone marrow evaluation, although this is typically deferred in infants until before they start steroid treatment. DBA syndrome should also be considered in those with family history, macrocytosis, DBA syndrome-associated congenital anomalies and cancers, or excessive chemotherapy-associated haematopoietic toxicity, regardless of anaemia.

Genetics

The genes and genetic phenocopies associated with DBA syndrome are shown in the appendix (p 4). Currently, published data indicate 70–80% of patients with DBA syndrome have an identifiable genetic defect. We defined two genetic categories of DBA syndrome: (1) ribosomopathy: mutations in genes directly involved in ribosome biogenesis, including 11 *RPS* and 13 *RPL* genes,

Panel 2: Recommended diagnostic tests in patients with suspected DBA syndrome

Essential diagnostic tests

- Complete blood counts (including differential, red cell indices, and reticulocyte count)
- Erythrocyte adenosine deaminase and fetal haemoglobin*
- Bone marrow morphology and cellularity at initial manifestation or before starting steroids
- Parvovirus B19 PCR in bone marrow or blood, or both, and parvovirus B19 serology
- Diamond-Blackfan anaemia (DBA) syndrome genetic testing (appendix p 4)
- Evaluation for congenital abnormalities: physical examination, echocardiography, abdominal ultrasound, and additional imaging as indicated†

Additional baseline evaluations (all patients)

- Laboratory parameters: ferritin, lactate dehydrogenase, bilirubin, transaminases, creatinine, vitamin B12, methylmalonic acid, and folate
- Direct antiglobulin test (direct Coombs test), blood group antigens, and red blood cell antibodies to guide transfusion management
- Immunoglobulin concentrations (age >6 months) and lymphocyte immunophenotyping
- Human leukocyte antigen typing of patient and family members‡

Further tests in some patients

- Bone marrow cytogenetics and bone marrow biopsy§
- Suspicion of inherited bone marrow failure syndromes: chromosome breakage (Fanconi anaemia), telomere length (dyskeratosis congenita), faecal elastase (Shwachman-Diamond syndrome), mitochondrial DNA genetics (Pearson syndrome), ADA2 genetics or enzyme activity (ADA2 deficiency), and genetics for other inherited bone marrow failure syndromes¶
- Erythropoietin concentration||

*Before first transfusion or ≥6 weeks (or as long as possible) after last transfusion, fetal haemoglobin reliably assessed in patients >6 months of age. †Neuroimaging, hand x-ray, and other imaging studies as clinically indicated. ‡Not required for diagnosis, but essential for long-term therapeutic planning. §In patients with suspicion of myelodysplastic syndrome or leukaemia. ¶In patients with clinical suspicion of respective syndromes. ||In suspected renal dysfunction; erythropoietin concentrations are elevated in patients with DBA syndrome.

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See **Online** for appendix

and the ribosome protein chaperones *TSR2* (*RPS26* chaperone) and *HEATR3* (nuclear import of *RPL5*); and (2) other: *GATA1* and *TP53* with gain-of-function mutations (unlike the loss-of-function mutations found in Li-Fraumeni syndrome) because these diseases can manifest with hyporegenerative anaemia and have altered pathways directly connected to DBA-ribosomopathy. Additionally, seven ribosome protein candidate genes require functional validation. We excluded erythropoietin (*EPO*) mutation[26] and ADA2 deficiency as distinct phenocopies with different mechanisms and associated clinical features from DBA syndrome.[43,44] The majority of the 28 DBA syndrome-associated genes are autosomal dominant, with eight genes affecting 50–65% of cases (*RPS19* [approximately 25%], *RPL5* [7–10%], *RPL11* [approximately 5%], *RPS26* [3–6%], *RPS10* [3–6%], *RPS24* [2–4%], *RPL35A* [2–4%], and *RPS17* [1–3%]). X-linked inheritance is seen with *GATA1* and *TSR2* and autosomal recessive inheritance with *HEATR3*. DBA syndrome is de novo or sporadic in two-thirds and familial in one-third of cases, with variable expressivity and penetrance within families.[4,20,45,46]

Most genetic alterations affect ribosome protein genes and are frequently due to single nucleotide variants at the start codon, nonsense mutations, indels or splice-site mutations inducing nonsense-mediated transcript decay, or genomic deletions (individual exons, whole gene, or multigenic deletions). Missense coding changes are less frequently implicated and appear enriched in *RPS* genes.[17] Whereas nonsense mutations in ribosome protein genes almost always result in DBA syndrome,[47] missense variants can be challenging to interpret and could require additional validation (eg, rRNA processing studies or animal models).[48]

The panel recommends genetic analysis for every patient with suspected DBA syndrome. Due to variable penetrance, family studies should also be pursued after identifying a pathogenic variant in the proband. Testing laboratories offer either stepwise or all-in-one testing to identify mutations; exon or gene deletions; or contiguous gene microdeletions using gene panel, genomic array, whole exome, or whole genome sequencing.[49,50] Genetic testing can lead to a revised diagnosis distinct from DBA syndrome (eg, ADA2 deficiency or Shwachman-Diamond syndrome), thus some panelists prefer simultaneous testing for DBA syndrome genes, phenocopies, and other inherited bone marrow failure syndrome genes. Variant interpretation should follow guidelines developed by the ACMG and AMP.[39] The ClinGen consortium establishes disease-specific variant specification rules; similarly standardised, DBA syndrome-specific rules are needed to enable accurate and uniform variant interpretation.

Congenital abnormalities

More than half of patients with DBA syndrome have a congenital abnormality, including craniofacial dysmorphisms (cleft lip or palate, or both, and others), cardiac, radial ray (thumb), urogenital, and eye malformations (appendix p 5).[4,45,51–53] More than one anomaly occurs in approximately 25% of patients.[7] Careful physical examination and imaging are vital, because subtle anomalies might not be apparent on initial evaluation, leading to delayed detection and management of consequential defects. Clinical expressivity varies within kindreds. Patients with large genomic deletions often have complex malformations and developmental delay.[34]

Most congenital anomalies are genotype-non-specific with only few established associations, including abnormal thumbs in *RPL5* or *RPL11*; cleft lip or palate, or both, in *RPL5*, *RPL11*, or *RPS26* genotypes.[17,54,55] More than one anomaly more frequently occurs with *RPL5* or *RPL11* mutations than with an *RPS19* mutation.[55] Congenital anomalies overall are more frequent with *RPL* than *RPS* genotypes.[17,47] Short stature is common, but confounded by steroid use, chronic anaemia, and iron overload.[56] In the past 5 years, severe colitis emerged as a new association in DBA syndrome.[57–60] Many issues are intrinsic to the disease, but some could be related to therapy (appendix p 6).

Differential diagnoses

Differential diagnoses include acquired or genetic conditions resulting in isolated erythroid failure (panel 1). Steroid treatment should be avoided in the absence of a DBA syndrome diagnosis. Transient erythroblastopenia of childhood, although rare,[61] remains the leading differential diagnosis. Viral infections could inhibit erythropoiesis, with parvovirus B19, due to its tropism for the erythroid CFU-E progenitor, specifically causing suppression of erythropoiesis (appendix p 7).[62] Most diagnostic tests can wait until after a life-saving red blood cell (RBC) transfusion except measuring eADA activity (done pre-transfusion).[63] The mechanism underlying elevated eADA activity in DBA syndrome remains unclear. However, eADA testing helps differentiate DBA syndrome from other anaemias or inherited bone marrow failure syndromes, with 84% sensitivity and 95% specificity.[64] Substantially elevated eADA strongly suggests DBA syndrome, but normal eADA does not rule it out, particularly in patients with *GATA1* mutations.[65] If genetics is inconclusive, other hereditary conditions that mimic DBA syndrome should be excluded (panel 1).[28,66] ADA2 deficiency is a common phenocopy (accounting for 6% of patients who are genetically undiagnosed in the German DBA registry).[29] An important differential in adults is acquired *RPS14*-haploinsufficient 5q deletion associated with pure red cell aplasia and macrocytosis.[67]

Therapy recommendations

The primary goals of therapy are to ensure an acceptable haemoglobin concentration, generally defined as at least 9–10 g/dL (≥90–100 g/L), and to enable adequate

growth and development in children, and good quality of life in adults. However, the haemoglobin goal must be individualised to ensure asymptomatic status. Advances are being made in the development of new therapies. However, as of 2024, the three therapeutic options remain: RBC transfusions with iron chelation, corticosteroid therapy, and allogeneic haematopoietic stem-cell transplantation (HSCT). Supplementation with folate, other vitamins, or other trace elements is not indicated. Birth defects should be surgically treated as much as possible.

RBC transfusions

Our panel unanimously agreed that restrictive transfusion strategies (with a transfusion trigger at haemoglobin concentrations of 6–7 g/dL) as applied in other fields are harmful to patients with DBA syndrome. Many patients will require lifelong RBC transfusions to maintain haemoglobin concentrations sufficient for normal growth, development, and quality of life. We agreed that the therapeutic nadir (pre-transfusion) haemoglobin concentration should be maintained at at least 9–10 g/dL for the patient's whole life (panel 3). Maintaining this therapeutic nadir usually requires 10–15 mL/kg packed RBC in children or 2–3 RBC units in adults, administered approximately every 3 weeks, although some patients need higher volumes (approximately 20 mL/kg) or so-called catch-up transfusions. A higher haemoglobin nadir might be needed for good quality of life with regard to school, work, social life, and exercise tolerance. Every patient treated with transfusions should be vaccinated against hepatitis B and regularly monitored for hepatitis B, hepatitis C, and HIV. RBC antigen typing by serological or molecular methods and RBC leukoreduction should be done per local standards. Although allo-immunisation is not common in DBA syndrome, some panelists prefer repeating extended RBC antibody screening before each transfusion, with crossmatching as needed. Patients developing atypically high transfusion needs should undergo testing to rule out increased RBC destruction or blood loss.

Oral steroids

Corticosteroids (steroids) have been successfully used in treating DBA syndrome for more than 70 years. The standard used corticosteroids are equally potent oral prednisone or prednisolone.[68] The panel agreed on six points with regard to therapeutic indications, timing, and considerations (panel 4). First, steroids can be initiated in any transfusion-dependent patient, after 1 year of age, and optimally after administration of the first live vaccines (measles, mumps, rubella, and varicella vaccines) and a diagnostic bone marrow evaluation. Second, the initial prednisone dose is 2 mg/kg per day (maximum 80 mg per day) in children or 80 mg/day in adults, given once daily in the morning or divided into two equal doses. The panel strongly opposed the use of higher doses. There was no consensus on when to initiate prednisone in relation to the last transfusion: starting concurrently (eg, 1 day after), or delaying approximately 10–14 days after transfusion are both acceptable approaches. Extending the initial dose beyond 4 weeks is strongly discouraged due to there being harmful side-effects without added benefit. Third, to assess for initial response, reticulocytes and haemoglobin are measured 10–14 days after starting steroids. If a substantial reticulocytosis ($\geq 50–100 \times 10^9$ cells per L) is observed and haemoglobin is stable or increasing, tapering should start within 2–4 weeks, decreasing by 0·5 mg/kg per day approximately every 2 weeks until reaching 0·5 mg/kg per day. Thereafter tapering should proceed over months to find the lowest effective maintenance dose. The panel agreed the maximum long-term maintenance dose should not exceed 0·3 mg/kg per day or 0·6 mg/kg on alternate days. Based on experience and published evidence from other conditions, alternate-day dosing seems equally effective to daily dosing.[69] A more restrictive threshold for maximum maintenance dose of 0·2 mg/kg per day was suggested by some panelists, without consensus. Experience with adult patients is limited, but the panel agreed the maintenance dose in adults should not exceed 10–15 mg/day.[68] There was no consensus on the optimal approach for further tapering to a minimally effective

***Panel 3:* Recommendations for transfusion support**

Indications and timing

- Any patient with severe anaemia
- Patient younger than 12 months
- Patient not responding to steroids or experiencing substantial side-effects
- Patient responding to steroids and showing acute haemoglobin drop (eg, due to viral illness)
- Patient on steroid holiday (to improve growth during adolescence)
- Pregnant patient with anaemia

General principles

- Hepatitis B vaccination
- Red blood cell antigen typing, and repeat red blood cell antibody screening
- Haemoglobin goal before transfusion (nadir haemoglobin): ≥9–10 g/dL or a higher concentration at which the patient is asymptomatic, independent of age
- Transfusion process: volume* is 10–15 mL/kg in children and approximately 2–3 red blood cell units in adults, and the interval† is every 3 (2–4) weeks

Adverse effects and clinical problems with therapeutic considerations

- Iron overload: start early chelation (appendix p 8)
- Clinically significant anaemia, especially days before transfusion: increase transfusion volume or decrease transfusion interval, or catch-up transfusion
- Blood-transmitted pathogens: hepatitis B vaccine, virus testing (HIV, hepatitis B, and hepatitis C) at least yearly
- Higher transfusion requirements: rule out alloimmunisation, hypersplenism (rare in Diamond-Blackfan anaemia syndrome), and haemorrhage

*Higher transfusion volumes occasionally required across all ages (ie, approximately 20 mL/kg). †Interval can be longer in patients with some erythropoiesis who maintain haemoglobin concentrations ≥9–10 g/dL for a longer period.

Panel 4: **Recommendations for steroid treatment**

Indications and timing

- First trial
  - In patient with chronic transfusions
  - Start steroid treatment when patient is 12 months or older, possible start at 15–18 months in children with failure to thrive, and earlier start (age approximately 9 months) if unable to provide safe venous access or safe transfusions
- Second trial
  - In patients who previously did not respond to steroids (1–2 years after first unsuccessful trial), recommended before planned allogeneic haematopoietic stem-cell transplantation
- Additional trials are not recommended

Therapeutic considerations

- Before steroid treatment
  - Live viral vaccines (first dose measles, mumps, rubella, and varicella vaccines) given optimally at least 3 weeks before first steroid trial
- Dosing
  - Drug: oral prednisone or prednisolone (equal potency)
  - Starting dose: 2 mg/kg per day in children (max 80 mg) and 80 mg per day in adults
  - When to start: 1 day or approximately 10–14 days after last transfusion
  - Initial response assessment: reticulocytes and haemoglobin at day 10–14
- Tapering principles and stopping rule
  - Initial response: start taper after 2 weeks but not later than 4 weeks, and reduce by 0·5 mg/kg approximately every 2 weeks.
  - From 0·5 mg/kg slow taper to arrive at maximum maintenance dose (0·3 mg/kg per day or 0·6 mg/kg on alternate days)
  - Further passive or active taper to reach minimally effective dose
  - No response at 4 weeks after starting therapy: stop initial dose without unnecessarily extending therapy
- Definitions of steroid response
  - Initial response: substantial reticulocytosis (≥50–100 × 10^9 cells per L) and stable or increasing haemoglobin (expected within 2–4 weeks).
  - Long-term response: dose not exceeding maximum maintenance dose (0·3 mg/kg per day or 0·6 mg/kg on alternate days) resulting in haemoglobin concentration of at least 9 g/dL without transfusions

Clinical scenarios and management

- Loss of efficacy
  - Acute haemoglobin drop (eg, viral illness): single red blood cell transfusion
  - Persistent haemoglobin drop: consider increasing dose, and if dose is too high, declare non-response and switch to red blood cell transfusions
- Oestrogen-containing oral contraception could inhibit steroid response
- Pregnancy or systemic disease (including cancer): discontinue steroids and switch to red blood cell transfusions
- Pre-adolescence or adolescence: consider steroid holiday (1–3 years) to improve growth
- Immunosuppression or lymphopenia with risk of opportunistic infections: taper or discontinue steroids if clinically relevant infection and avoid live vaccines during initial high dose steroids
- Classic side-effects (eg, hypertension, diabetes, and adrenal insufficiency): monitor toxicity with endocrinologist, annual eye exam (to screen for cataracts), annual bone densitometry scan (to screen for osteopenia)

Supportive care with indications

- Vitamin D and calcium supplementation: all patients on continuous steroid treatment
- Proton pump inhibitors or H2 antagonists: during initial high dose of steroids or if symptomatic
- *Pneumocystis jirovecii* pneumonia prophylaxis: no consensus reached on antibiotic prophylaxis during initial high-dose steroids (2 mg/kg), adapt to local standard

dose sufficient for haemoglobin concentrations of at least 9 g/dL. Some providers prefer active weaning, with gradual dose reduction to the minimally effective dose, with haemoglobin monitoring. Others do passive weaning, allowing the patient to outgrow the dose while closely monitoring linear growth and side-effects. Importantly, many patients require minuscule doses (eg, 0·05 mg/kg per day) for continued response. If the response is lost during weaning, the dose should be immediately increased to the previous dose at which the haemoglobin response was at least 9 g/dL. Not increasing the dose immediately could result in a total loss of response, requiring the process be restarted at 2 mg/kg per day. If the haemoglobin concentration cannot be sustained at or above 9 g/dL with 0·3 mg/kg per day or less, steroids should be discontinued. If a patient does not respond to 2 mg/kg per day of prednisone within 4 weeks, the drug must be discontinued promptly. However, there was no consensus whether to recommend gradual tapering or abrupt stopping, so providers should adhere to the local standard. An endocrinologist should be involved for monitoring of adrenal insufficiency during tapering and long-term maintenance therapy. Fourth, initial prednisone responsiveness (panel 4) is seen in approximately 60–80% of patients.[7,11,45] Over time patients might lose responsiveness or prednisone must be discontinued due to unacceptable side-effects. Across age

groups, approximately 30–40% of patients remain on steroids indefinitely, while maintaining a durable response.[45,70] A patient who is not responsive to steroids is defined as a patient who cannot reach haemoglobin concentrations of at least 9 g/dL after 4 weeks of 2 mg/kg per day of prednisone, or a patient who requires more than 0·3 mg/kg per day to maintain a haemoglobin concentration of at least 9 g/dL. Fifth, some patients could benefit from a temporary pause in steroid administration for 1–3 years during or before puberty to optimise growth. Based on their clinical experience, the panel agreed that the majority of patients regain steroid responsiveness after a so-called steroid holiday, although definitive evidence is deficient. Sixth, in patients who do not respond to steroid treatment, a second trial (>1–2 years later) is a reasonable option, especially before a planned HSCT. Toxicity monitoring and supportive care recommendations are outlined in panel 4.

Treatment-independence (formerly remission)

Approximately 20% of patients previously treated with steroids or transfusions can become treatment-independent (ie, able to discontinue all therapy for anaemia). For example, a report from the French registry showed that of 219 patients with treated DBA syndrome, 46 (21%) patients, of whom 42 previously had durable steroid response, and four had previously required long term transfusion support, attained treatment-independence.[4] Although treatment-independence often persists long term, over years to decades[71], anaemia can return and emerging registry data suggests that the risk of associated cancers persists. Thus, the term clinical remission should be avoided. All patients require life-long surveillance because neither steroid response nor genetics predict treatment independence.

Chelation therapy

Iron overload in DBA syndrome

Transfusion-associated iron overload and cancer are the leading causes of death in patients who do not undergo HSCT.[72] Increased iron absorption is not expected; RBC transfusions are the main source of iron. Without adequate chelation, even modest transfusion volumes lead to substantial iron accumulation and organ dysfunction, especially in the liver, heart, and endocrine glands. Iron overload develops early during chronic transfusions[73] and the non-transferrin bound iron (NTBI)—present when transferrin saturation exceeds 60–70%—plays a key role in tissue iron deposition. NTBI concentrations are increased in patients with DBA syndrome who have received transfusions compared with patients with thalassaemia or sickle cell disease treated with chronic transfusions,[74] probably because iron is not used in RBC production. Consequently, patients with DBA syndrome develop iron overload more rapidly than patients with thalassaemia. Furthermore, patients with DBA syndrome frequently develop cardiac complications.[75] Early pancreatic iron loading is also more prominent in patients with DBA syndrome than in patients with other transfusion-dependent anaemias.[76]

Evaluation of iron overload

Serum ferritin is not a reliable indicator of iron overload in DBA syndrome. Besides the low accuracy of measuring total iron burden, serum ferritin can be affected by factors such as inflammation.[77] High ferritin together with elevated transferrin saturation can confirm initial iron overload before starting chelators (appendix p 8). Liver iron concentration (LIC), measured by MRI using T2* or R2 (FerriScan, Resonance Health, Burswood, WA, Australia) methods accurately reflects total body iron

Panel 5: **Recommendations for monitoring and adjustment of chelation**

Monitoring of iron overload

- The diagnostic gold standard is MRI for liver and cardiac iron assessment
  - Start by age 5 years at the latest (earlier if possible, especially when evidence of high iron load and when planning allogeneic hematopoietic stem-cell transplantation)
  - Follow up with annual MRI liver iron (more frequently if required according to iron status) and annual MRI heart iron (more frequently if cardiac iron load present)
- Serial monitoring of ferritin concentration and transferrin saturation*

Goals and adjustment plan

- Adjust therapy frequently on the basis of efficacy and toxicity (typically every 3–6 months)
- The optimal target values for iron overload† are:
  - MRI liver iron content <3 mg/g‡ dry weight
  - MRI heart T2* >20 ms§
  - Serial ferritin: <500 ng/mL
- If MRI is not available (not standard) reduction or stopping rules based on ferritin are
  - If ferritin 500–1000 ng/mL, consider dose reduction
  - If ferritin 300–500 ng/mL, reduce dose or temporarily pause therapy
  - If ferritin <300 ng/mL, temporarily pause therapy
- For patients with low ferritin (<500 ng/mL), but high liver iron by MRI (>5 mg/g dry weight), consider chelation at lower dose and with intensified monitoring for toxicity

Toxicity monitoring

- Deferoxamine and deferasirox: perform audiometry exam to screen for hearing loss and ophthalmic exam to screen for cataracts and retinal disorders (at baseline and then yearly)
- Deferasirox: monitor for renal injury (creatinine increase in serum, phosphate loss indicating Fanconi syndrome, and protein in urine), hepatic injury (transaminitis), and gastrointestinal symptoms
- Deferiprone: assess complete blood counts to monitor for neutropenia
- Since pancreatic iron overload can cause pancreatic insufficiency, regularly assess endocrine pancreatic function by fasting glucose, oral glucose tolerance test, and fructosamine (instead of Hba1c in transfused patients)
- Consider hemochromatosis gene testing in patients with rapid or severe iron overload

*Ferritin and transferrin saturation have limited value in chelation monitoring. Ferritin often inaccurately reflects true iron burden in DBA syndrome (elevated levels may be observed despite low iron burden, while some patients with severe iron overload by MRI can have deceptively low ferritin). Given potential discordance with true tissue iron, these biomarkers alone are inferior to MRI for quantifying actual iron. MRI should be strongly advocated as the standard method for optimal chelation management. †There is a risk of chelator toxicity if treatment is continued too aggressively when MRI liver iron content is <3 mg/g, or when serial ferritin is below 500 ng/mL (in case MRI measurement is not available). ‡Unit conversion: mg/g × 18=µmol/g. §Some panel members suggest a more restrictive threshold of >25 ms.

burden[78] and should be strongly advocated as the standard for chelation guidance (panel 5). The target LIC for patients with DBA syndrome who are transfusion-dependent is as close as possible to normal (ie, lower than 3 mg iron per g dry weight).[79] Cardiac iron measurement using MRI T2* has been shown to be highly sensitive and reproducible.[80] In healthy volunteers, a mean T2* value of more than 40 ms has been considered normal.[81] Cardiac T2* less than 20 ms is associated with decreased cardiac function and a worse overall survival, whereas T2* values of less than 10 ms show clear association with an imminent risk of heart failure.[82] Emerging data support that T2* values above 35 ms indicate no relevant cardiac iron load and reflects little risk for heart dysfunction.[83,84] Thus, the panel recommended that the cardiac T2* should remain as close to normal as possible, with an acceptable T2* value of more than 20 ms. Many of the panelists argued to aim for a stricter T2* value of more than 25 ms. Hemosiderosis of the pancreas and the pituitary gland is predictive of the development of endocrinopathies. However, pancreatic and pituitary iron loading is difficult to measure due to the size, shape, and location of these organs.

The panel recommends initiating MRI-based liver and cardiac iron assessment as early as feasible, by age 5 years at the latest, and repeating yearly (or more often if needed) in all patients who receive chronic transfusions. Although MRI can be performed without sedation starting at around age 5 years, earlier evaluation under procedural sedation should be considered to allow for early detection and monitoring of iron burden in young children who are transfusion-dependent.

Treatment of iron overload

The goal of iron chelation therapy is to eliminate enough iron to reduce the harmful effects of excess iron from transfusions, control NTBI, and achieve neutral or negative total body iron balance (panel 5). Three drugs are available (appendix p 8).

Deferoxamine, also known as desferrioxamine, (referred to as deferoxamine throughout) is a parenteral chelator with a half-life of 20 min, requiring extended (usually subcutaneous) administration over 10–12 h, 5–7 days per week for effective iron chelation. Growth retardation and bone changes occur in young children with thalassaemia receiving higher deferoxamine doses. Although such data do not exist for DBA syndrome, the panel agreed that deferoxamine should be given at a lower dose (≤30 mg/kg) in patients younger than 3 years. Ototoxicity (sensineuronal hearing loss or tinnitus) is a serious side-effect of deferoxamine that is probably related to individual susceptibility because there are no reliable predictive variables.[85] Despite good compliance, some patients still develop cardiac iron loading. Intensive chelation with 24 h per day of intravenous deferoxamine can effectively reduce high cardiac iron, often in conjunction with another chelator.

Deferasirox is an oral chelator with a half-life of 8–16 h, allowing once-daily dosing. Deferasirox has shown linear dose-dependent effects on iron excretion, accomplished primarily through the biliary tract. The efficacy of deferasirox in causing a substantial reduction of iron load was shown across a wide range of patients with transfusion-dependent anaemias.[86] The most common adverse events are dose-dependent, transient, and of mild to moderate severity, including gastrointestinal symptoms (eg, nausea, vomiting, ulcers, and diarrhea), transient skin rash, increase in creatinine and transaminases, and ototoxicity. Severe toxicity has been reported (ie, gastrointestinal bleeding, nephrotoxicity including reversible Fanconi syndrome,[87] and hepatic failure).[88]

Deferiprone is an oral chelator with a half-life of 2–3 h showing high efficacy in removing excess cardiac iron. Common but less severe side-effects include gastrointestinal symptoms, arthralgia, zinc deficiency, and fluctuating transaminase concentrations.[89] Agranulocytosis is the most serious adverse event, occurring in 1% of patients with haemoglobinopathies, and approximately 10% of patients with DBA syndrome.[90] An analysis from France reported in 2022 showed that three (13%) of 23 patients with DBA syndrome treated with deferiprone developed non-fatal agranulocytosis that resolved after deferiprone discontinuation.[91] The panel agreed that deferiprone as primary chelation is indicated as first-line therapy in DBA syndrome for severe cardiac iron overload or cardiac failure,[92] or third-line therapy with persistent cardiac iron loading or iron loading with failure or toxicity of other chelators (appendix p 8). Patient education, monitoring of neutrophil counts, and an emergency plan for agranulocytosis are necessary.

Practical considerations

Published data on chelation in DBA syndrome are scarce. The panel agreed that early initiation of chelation is essential for long-term success. First-line therapy in transfusion-dependent patients with DBA syndrome should include either deferoxamine or deferasirox as the initial chelator. Second-line therapy involves switching from one first-line agent to the other (appendix p 8). Deferiprone is reserved for specific patient populations, as outlined in the previous paragraph. Generally, chelation is initiated after approximately ten transfusions or evidence of iron load (ferritin >500 ng/mL, transferrin saturation >60%, or elevated LIC), which in children typically coincides with the first unsuccessful steroid trial. Reduced chelator dose should be given when initiating therapy in children under labeled age limits (age 3 years for deferoxamine and age 2 years for deferasirox), as routinely practiced across expert centres. In patients younger than 3 years, the dose of deferoxamine should not exceed 30 mg/kg per day. In older children and adults, 50–60 mg/kg per day of deferoxamine can

effectively control iron overload. Importantly, chelation therapy in patients with DBA syndrome who are transfusion-dependent must be given continuously. The panel highlighted that a combination of two chelators is a standard approach often required in DBA syndrome. Examples are: deferoxamine for 5 days per week at night (approximately 12 hours) and deferasirox for 2 remaining days; or a more intensified regime with deferoxamine 7 days per week at night and deferasirox during the day. Panel members unanimously emphasised that patients with DBA syndrome who receive chronic transfusions require early, aggressive chelation and iron overload monitoring by liver and heart MRI as the gold standard. Chelator toxicity risk is higher when iron burden is low. Thus, doses should be lowered promptly to prevent overchelation toxicity. Patients with high tissue iron but low ferritin pose a challenge, requiring cautious low-dose chelation and close toxicity monitoring (panel 5). There is also risk of overchelation toxicity if the decrease in ferritin occurs too rapidly. Because iron overload often persists in patients becoming steroid-responsive or therapy-independent, or after HSCT, ongoing monitoring and chelation or phlebotomy (only after HSCT) could be indicated.

Allogeneic HSCT

Allogeneic HSCT represents the only option for haematopoietic cure, preventing long-term side-effects of steroids and transfusion or chelation in DBA syndrome. In our previous consensus,[3] HSCT from human leukocyte antigen (HLA)-matched sibling donors (MSD) was considered for patients who are transfusion-dependent, whereas unrelated-donor HSCT was reserved only for severe multilineage cytopenia or progression to myelodysplastic syndrome, or acute myeloid leukaemia due to previously poor overall survival after unrelated-donor HSCT.[7] However, data since 2000 show statistically significant improvements in overall survival, with rates as high as 85% for HLA-matched unrelated-donor (MUD) transplantation in the modern era.[70,93,94] Similarly improved alternative donor results come from China,[95] Austria,[96] and the Netherlands.[13] A large analysis from Germany and France found comparable 5-year overall for MSD (91%) or MUD (92%) transplantation, with a similar graft-versus-host disease-free survival at 89% or 83%, respectively.[94] Given these improvements, the panel recommends HSCT from MSD or 10/10 HLA MUD for children who are transfusion-dependent (panel 6).

Considerations before HSCT

Iron overload is one of the major risk factors for an unfavourable HSCT outcome. Therefore, chelation should be optimised before HSCT. Although there are no data clearly indicating that high iron load (measured by LIC) portends poorer survival after HSCT in DBA syndrome, the panel agreed that LIC values should be optimally lowered before HSCT to be as close as possible to the 3 mg/g threshold and not exceed 7 mg/g. These assumptions rely on expert opinion due to the absence of controlled studies. Evaluation of liver fibrosis or cirrhosis might be indicated in patients with very high LIC. Infertility remains a relevant late effect following HSCT, thus families should be counselled accordingly. Cryopreservation of sperm or stimulated oocytes or ovarian tissue should be routinely offered in patients who have undergone puberty. By contrast, cryopreservation of

***Panel 6:* Recommendations for allogeneic HSCT**

General

- Assessment of iron overload (liver and heart MRI) before planning haematopoietic stem-cell transplantation (HSCT)
- Iron overload: chelation before HSCT and consider phlebotomies after HSCT

Age

- In general, before age 10 years in patients who receive chronic transfusions
- If possible, preferably at the pre-school age (age 2–5 years) to minimise risk of toxicities
- In individual patients, HSCT for transfusion dependence can be considered after age 10 years (low transfusion burden, optimal iron balance, and adequate organ function)
- In adults, HSCT is generally not advised solely for the avoidance of transfusion dependence*

Indications, in order of increasing urgency and clinical necessity

- Chronic transfusions in patients not responding to steroids
- Chronic transfusions in patients with non-manageable iron overload (chelator failure or severe toxicity)
- Chronic transfusions in patient with alloimmunisation to red blood cells
- Severe immunodeficiency or multilineage cytopenia, or both
- Myelodysplastic syndrome or acute myelogenous leukaemia

Donor choice, in order from most to least optimal

- Human leukocyte antigen (HLA)-matched sibling donor, after exclusion of Diamond-Blackfan anaemia syndrome in potential donor (genetic testing, complete blood counts, and erythrocyte adenosine deaminase)
- Matched unrelated donor: 10/10 HLA match based on molecular testing
- HLA-mismatched unrelated donor and HLA-mismatched family donor†: only in the absence of alternative therapies (patients with myelodysplastic syndrome or acute myelogenous leukaemia) or in context of clinical trials

Conditioning regimen

- Myeloablative (busulfan or treosulfan) regimen combined with fludarabine
- Consider addition of thiotepa
- Avoid irradiation

Stem-cell source

- Bone marrow (any donor)
- Cord blood (healthy sibling donor)
- Avoid unmanipulated mobilised peripheral blood stem cells

Graft-versus-host disease prophylaxis

- Standard graft-versus-host disease prophylaxis (ie, calcineurin inhibitor plus methotrexate or mycophenolate mofetil and serotherapy [also for HLA-matched sibling donors])

HLA=human leukocyte antigen. HSCT=haematopoietic stem-cell transplantation. *To be considered on a case-by-case basis for transfusion-dependent young adults in good health who are transfusion-dependent, after weighing the risks and benefits. †Includes haplo-donors.

gonadal tissue from prepubertal patients remains experimental.

Age at HSCT

Considering studies have shown that the overall survival in patients who receive transplantation before age 10 years is superior to that seen in older patients,[70,93,94] HSCT should be performed preferentially before age 10 years, because in this patient group the morbidity from therapy-related complications is lower than for older patients. These potential adverse factors include iron overload, liver or kidney damage from chelation, and infections from underlying immunodeficiency. For patients who are 10 years or older, HSCT could be considered for transfusion dependence after individual evaluation (ie, short transfusion history, limited iron overload, and no organ dysfunction). Adults should generally not undergo HSCT only for transfusion dependence; however, exceptions can be considered after discussing the patient's specific situation, including iron overload, health status, and donor options.

Indications and type of donor

MSD or MUD donors with a 10/10 HLA match can be considered in patients younger than 10 years who are transfusion-dependent and unable to maintain adequate haemoglobin on a tolerable steroid dose. For clinically significant pancytopenia, immunodeficiency with frequent severe infections, alloimmunisation, severe toxicity or intolerance to chelators, myelodysplastic syndrome, or acute myeloid leukaemia, HSCT from the most suitable donor should be considered. In patients who respond to low-dose steroids without relevant toxicity, HSCT should generally not be considered because the risks could outweigh the benefits. However, each patient should be assessed and counselled individually. Sibling donors, even if clinically asymptomatic, require testing for the presence of the genetic mutation identified in the patient.

Preparative regimen

Important considerations for the type of conditioning regimen are the acute toxicity and late effects, including infertility and a possibly increased malignancy risk. Regimens utilising total body irradiation should be avoided. We recommend myeloablative conditioning with treosulfan or busulfan in combination with fludarabine.[97] The addition of thiotepa might be considered based on the published literature regarding the use of thiotepa in the preparatory regimen for thalassaemia, which is a relatively similar disease to DBA syndrome.[98] Reduced intensity regimens should be currently restricted to clinical trials pending more data to establish sufficient evidence for safety and efficacy.

Stem-cell source and graft-versus-host disease prophylaxis

Acute and chronic graft-versus-host disease substantially contribute to HSCT toxicity. Because patients with DBA syndrome do not benefit from graft-versus-host disease effect as reported in leukaemia, bone marrow remains the first choice for MSD or MUD transplantation. Results following MSD cord blood HSCT are excellent and a good choice for all indications. Unmanipulated peripheral blood stem cells should be avoided. Graft-versus-host disease prophylaxis in MUD and MSD settings includes serotherapy with a calcineurin inhibitor and methotrexate or mycophenolate.

Considerations following HSCT

DBA syndrome-specific cancer risk could be increased after HSCT.[72] Therefore, in addition to standard post-transplantation follow-up, physicians must closely monitor for subsequent cancers. Recommendations from the European Blood and Marrow Transplantation group provide excellent guidance.[99]

Other treatments for anaemia

The amino acid leucine has been shown to induce erythroid response and linear growth in some patients with DBA syndrome who are transfusion dependent.[100] Although not defined as standard of care, a few panelists use leucine routinely. Studies with leucine for steroid-responsive DBA syndrome are underway. Other drugs like sotatercept, immunosuppressive therapy (rituximab or cyclosporine), and haematopoietic growth factors such as erythropoietin have been shown to be ineffective and are not recommended for anaemia outside of clinical trials.[3]

Cancer risk and surveillance

There is a significantly increased cancer risk in patients with DBA syndrome.[101,102] Shimamura and Alter[30] described 15 patients with myelodysplastic syndrome or acute myeloid leukaemia and 19 patients with solid tumours among 970 patients with DBA syndrome. Of the 19 solid tumours, six were osteogenic sarcoma. In 2012, the Diamond Blackfan Anemia Registry reported a quantitative assessment of cancer risk, firmly establishing DBA syndrome as a cancer-predisposition syndrome.[103] The update from 2018 identified an overall five times increase of observed-to-expected ratio for all cancers, with colon cancer and osteogenic sarcoma as the most prevalent with observed-to-expected ratios of 45 and 42, respectively.[72] The risk of acute myeloid leukaemia (observed-to-expected ratio 29) and myelodysplastic syndrome (observed-to-expected ratio 350) was also increased. A 2020 report on 62 patients from the Czech and Slovak Diamond Blackfan anemia registry identified three patients with myelodysplastic syndrome (ages 25–29 years), 2 patients with breast cancer, and a patient each with colorectal cancer, diffuse large B-cell lymphoma, and multiple myeloma (ages 28–70 years).[14] In the same year, the Italian registry reported one patient with myelodysplastic syndrome (age 4 years) and a patient each with gastric cancer,

thyroid cancer, non-Hodgkin lymphoma, and osteosarcoma (ages 11–48 years). This registry also reported two patients with osteosarcoma and one patient with a cardiac Purkinje cell tumour after HSCT (ages 19, 18, and 9 years).[16] Because improvements in management allow patients to live longer, the number of malignancies in the Diamond Blackfan Anemia Registry cohort continuously increases, allowing better risk characterisation.[104] The short post-HSCT cancer latency in some patients suggests that respective tumours are DBA syndrome-related, rather than therapy-related. Various malignancies (eg, breast cancer, testicular cancer, skin cancers such as melanoma or squamous cell carcinoma, and Wilms tumour) indicate general susceptibility.[14,16,72,103] There is no known genotype-cancer association, except for *GATA1*-mutations associated with myelodysplastic syndrome with monosomy 7.[16,103]

Our panel reached consensus to recommend colorectal cancer screening in patients with DBA syndrome starting at age 20 years (with follow-up every 5 years if initially normal), supported by increased prevalence of early onset colorectal cancer in DBA syndrome.[105] For patients with abnormal findings, national guidelines for follow-up intervals are recommended.[106] There was no consensus on post-HSCT colonoscopy timing, but starting before age 20 years is reasonable. Data are still scarce, and prospective studies are warranted, particularly in patients after HSCT.

Haematological surveillance includes complete blood counts every 3–4 months, with substantial change triggering a bone marrow examination for acute myeloid leukaemia and myelodysplastic syndrome. Bone marrow examination should be considered in any patient before transition to adult care to assess for baseline changes. Broad screening such as whole-body MRI is currently not recommended. Imaging should be readily performed for any bone pain, joint pain, or injury given osteosarcoma risk. Specific cancer screening such as mammography should follow national preventive standards.

Long-term management and surveillance

Recommendations are discussed in detail in the appendix (pp 9–11). Major paediatric care goals include optimising growth and development while monitoring for hormone issues, steroid toxicity, iron overload, and considering HSCT after initial steroid failure. Key adult care priorities are transition from paediatric care, adjusting anaemia therapy, and monitoring for various clinically significant malignant and non-malignant complications that contribute to excess mortality. Other priorities include genetic counselling for family planning, high-risk pregnancy management, colon cancer screening, and comprehensive supportive care. Organisations for patients with DBA syndrome (appendix p 12) are key resources for health literacy.

Furthermore, DBA syndrome could be diagnosed in adults, particularly in family members. Rather than silent carrier, a term used in the past, individuals with no symptoms should be referred to as patients with DBA syndrome currently without phenotype because presentations including cancers can arise later in life.

Conclusions

In the 16 years since our first consensus, major advances have emerged in understanding DBA syndrome pathology, genetics, and treatment. These updated international recommendations synthesise extensive accumulated knowledge to further improve care of children and adults with DBA syndrome.

Contributors

MWW and TML contributed to initial conceptualisation and funding acquisition. MWW, AV, JEF, JML, and TML contributed to the identification of key opinion leaders, data curation and validation, formal analysis, development of panel and tables, manuscript writing, and access and verification of the underlying data reported. All authors contributed to the literature search, participation in selection of discussion items and iterative voting, manuscript writing, review, editing, and approval of the final manuscript.

Declaration of interests

AK declares honoraria from chiesi and Novartis and a research grant from Novaris. AK is on the advisory board of Chiesi and Novartis. FML declares honoraria from Chiesi and is on the advisory board of Chiesi. LK is on the advisory board of Agios, Amgen, Bayer, and Novartis. All other authors declare no competing interests.

Acknowledgments

This work was funded by Diamond-Blackfan Anemia Foundation USA; Diamond-Blackfan Anemia Charity UK; Fritz-Thyssen Stiftung and Eva-Uth Stiftung, Germany (support for in-person meetings); R01HL079571 to JML and AV; and R01HL150194 to JEF. We thank patient group representatives, physicians, and scientists facilitating the discussion (appendix pp 1, 12).

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