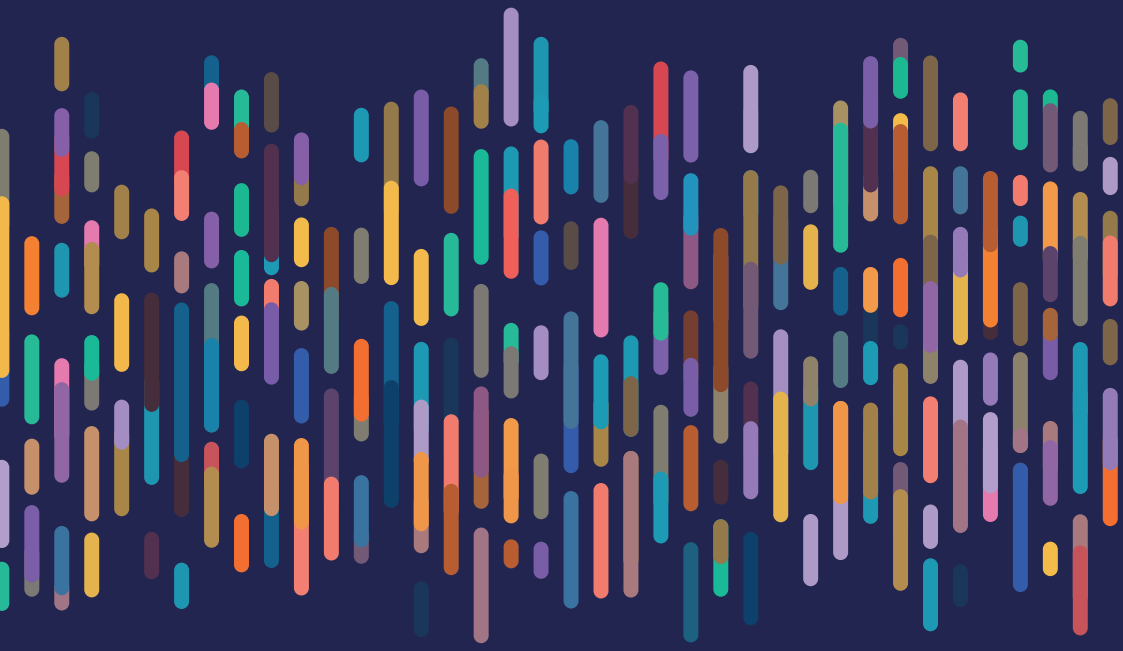
dbas UK

THE UK'S **DIAMOND BLACKFAN ANAEMIA SYNDROME** CHARITY



2024 Guidelines

For people with DBAS

THE UK'S **DIAMOND BLACKFAN ANAEMIA SYNDROME** CHARITY

Diagnosis, Treatment And Surveillance Of Diamond Blackfan Anemia (DBA) Syndrome: International Consensus Statement

Diamond Blackfan anaemia (DBA) is a rare, clinically and genetically heterogeneous inherited bone marrow failure syndrome

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 DBA (EuroDBA) consortium and the DBA Registry of North America (DBAR) the objective was to revise and replace the previous 2008 guidelines

DEFINITION OF THE SYNDROME

DBA has historically been defined as a macrocytic anemia with reticulocytopenia and a paucity of bone marrow (BM) erythroid precursors, presenting at less than one year of age. However, we acknowledge that variable phenotypes exist within and among DBA genotypes, and some individuals with DBA-associated gene mutations paradoxically lack anemia, and the diagnosis may occur in adulthood. Therefore, we adopt the term "Diamond Blackfan anemia (DBA) syndrome",

Treatment options

Red blood cell transfusions

Our panel unanimously agreed that restrictive transfusion strategies (with a "transfusion trigger" at Hb 6-7/dL) as applied in other fields **are harmful to patients with DBA syndrome**. Many patients will require life-long RBC transfusions to maintain Hb levels sufficient for normal growth, development, and quality of life. We agreed that the therapeutic nadir (pre-transfusion) Hb should be maintained at **≥9-10/dL** life-long

Oral steroids

Corticosteroids (steroids) have been successfully used in treating DBA syndrome for >70 years. The standard are equally potent oral prednisone or prednisolone.

Treatment-independence (formerly "remission").

Approximately 20% of patients previously treated with steroids or transfusions may become "treatment- independent", able to discontinue all therapy for anemia

Chelation therapy

Iron overload in DBA syndrome

Transfusion-associated iron overload and cancer are the leading causes of death in non-transplanted patients. **Serum ferritin is not a reliable indicator of iron overload in DBA syndrome.**

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 chronically transfused patients.

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. Three drugs are available

Hematopoietic stem cell transplantation

HSCT represents the only option for hematopoietic cure, preventing long-term side effects of steroids and transfusion/chelation in DBA syndrome.

Age at HSCT

Since studies have shown that the OS in patients transplanted before the age of 10 years is superior to that seen in older patients,70,93,94 HSCT should be performed preferentially below the age of 10 years.

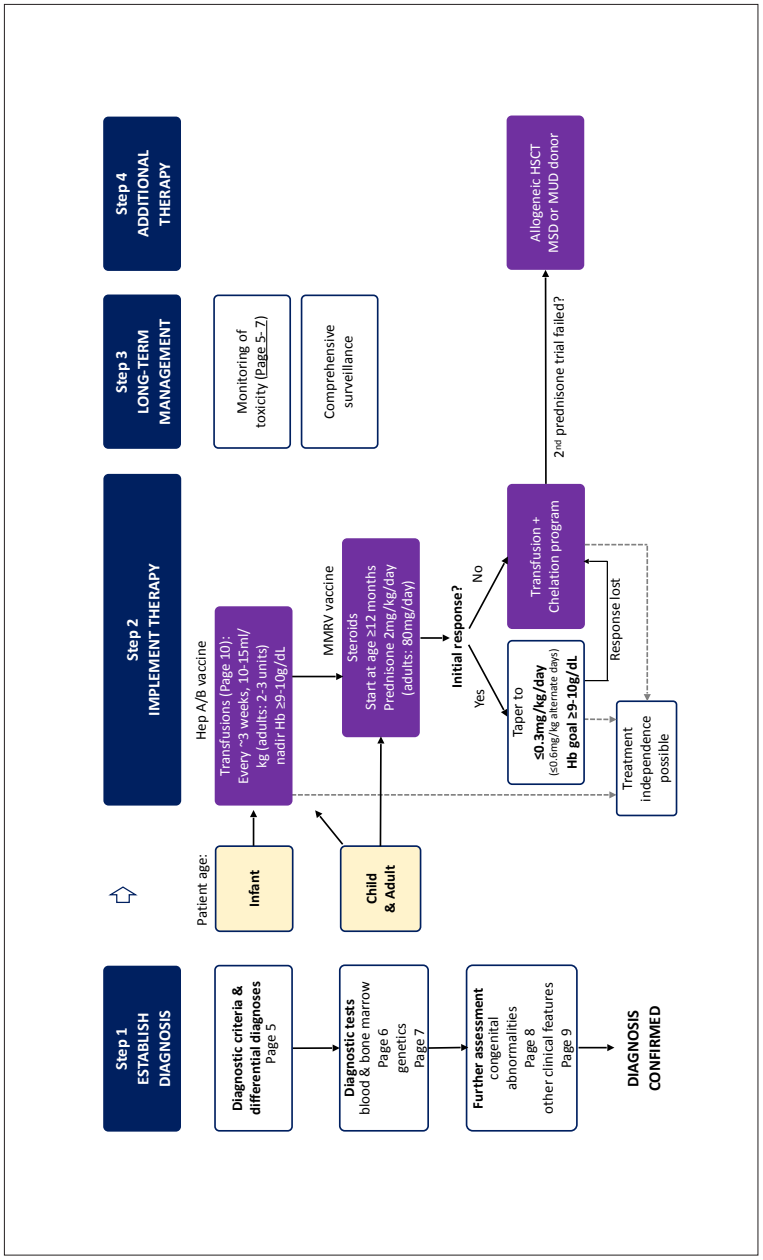
Other treatments for anemia

The amino acid L-leucine has been shown to induce erythroid response and linear growth in some transfusion- dependent patients with DBA syndrome.

Cancer Risk And Surveillance

There is a significantly increased cancer risk in patients with DBA syndrome

Approach to diagnosis, therapy, and long-term management of patients with DBA syndrome



Diagnostic criteria and differential diagnoses of DBA syndrome

DIAGNOSTIC CRITERIA		
• **Pathogenic or likely pathogenic mutation in a DBA syndrome gene** **OR** • **Hematologic features consistent with DBA:** macrocytic anemia[1] with reticulocytopenia and BM erythroblastopenia; absence of dysplasia, dyserythropoiesis[2], and sideroblasts AND: Exclusion of known differential diagnoses (below)		
TYPICAL FINDINGS (NOT MANDATORY FOR DIAGNOSIS) [3]		
• Age at onset less than 1 year • Elevated eADA activity (prior first transfusion; in non-transfused patients and/or parents) • Elevated HbF (reliably assessed in patients > 6 months of age) • Positive family history or unexplained history of anemia during infancy or childhood • Congenital abnormalities • Abnormal rRNA processing in patient cells [4]		
DIFFERENTIAL DIAGNOSES		
ACQUIRED	Transient erythroblastopenia of childhood	• Onset usually > 1 year of age • Normal MCV, eADA, HbF • Negative family history and no congenital abnormalities • Transient course: erythroid recovery in days to weeks
	Viruses: Specific to red cell lineage (Parvovirus B19) Non-specific (HIV, CMV, EBV and others)	• Positive PCR and/or serology • Normal eADA and HbF • Normal MCV (except Parvovirus B19) • Negative family history and no congenital abnormalities • Concomitant immune deficiency or chronic hemolysis
	Myelodysplastic syndrome [5], specifically with 5q deletion (acquired RPS14 haploinsufficiency)	• Typical BM findings (morphology, histology, karyotype, FISH, MDS-related somatic mutations) • Normal eADA
	Drugs Autoimmunity (SLE, acquired PRCA) Lymphoproliferative diseases Malignancy: CLL[5], LGL[5], acute leukemias and some solid tumors	• Typical BM and immunologic findings • Normal eADA • No congenital abnormalities • Features of malignancy
	Thymoma with concomitant PRCA[5]	• Typical imaging (chest x-ray, CT or MRI) • No congenital abnormalities • Mostly in adults, unlikely in children
GENETIC	IBMFS (specifically FA, SDS, DC)[6] Pearson syndrome Congenital sideroblastic anemia Congenital dyserythropoietic anemia	• Classical clinical presentation, laboratory findings • BM morphology consistent with respective condition • MCV and HbF can be elevated, eADA normal • Syndrome-specific diagnostic findings and genetics
	ADA2 deficiency	• Onset at any age, vasculopathy often absent • Low B cells and hypogammaglobulinemia • Normal eADA and HbF; MCV can be high • Low ADA2 enzyme activity and *ADA2* mutations • Typically, no congenital abnormalities
	Erythropoietin dysfunction	• Homozygous *EPO* R150Q mutation

[1] Additional cytopenia can be encountered (neutropenia more often than thrombocytopenia), transient thrombocytosis in infants.
[2] Except for cases with *GATA1* mutations.
[3] Highly suggestive of DBA syndrome; however not specific enough to make the diagnosis.
[4] Research test in specialized labs only; useful in cases with ambiguous or uninformative genetics.
[5] Typically presenting in adults.
[6] These IBMFS typically demonstrate multi-lineage 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.

Abbreviations: BM; bone marrow; eADA, erythrocyte adenosine deaminase; HbF, fetal hemoglobin; SLE, systemic lupus erythematosus; PRCA, pure red cell aplasia; CLL, chronic lymphocytic leukemia; LGL, large granular lymphocytic leukemia; CT, computer tomography; MRI, magnetic resonance imaging; IBMFS, inherited bone marrow failure syndromes; FA, Fanconi anemia; SDS, Shwachman Diamond syndrome; DC, dyskeratosis congenita.

Recommended diagnostic tests in patients with suspected DBA syndrome

Essential diagnostic tests	• CBC (including differential, red cell indices and reticulocyte count) • eADA and HbF [1] • BM morphology/cellularity at initial manifestation or prior to starting steroids • Parvovirus B19 PCR and/or serology in BM or blood • DBA genetic testing • Evaluation for congenital abnormalities: physical examination, echocardiography, abdominal ultrasound; additional imaging as indicated[2]
Additional baseline evaluations (all patients)	• Laboratory parameters: ferritin, LDH, bilirubin, transaminases, creatinine, vitamin B12/MMA, folate • DAT (direct Coombs test), blood group antigens, RBC antibodies to guide transfusion management • Immunoglobulin levels (>6 months of age) and lymphocyte immunophenotyping • HLA typing of patient and family members[3]
Further tests in selected patients	• BM cytogenetics and BM biopsy[4] • Suspicion of IBMFS: chromosome breakage (Fanconi anemia), telomere length (dyskeratosis congenita), fecal elastase (Shwachman Diamond syndrome), mitochondrial DNA genetics (Pearson syndrome), ADA2 genetics or enzyme activity (ADA2 deficiency), genetics for other IBMFS[5] • Erythropoietin (EPO) level[6]

[1] Prior to first transfusion or ≥6 weeks (or as far away as possible) after last transfusion, HbF reliably assessed in patients >6 months of age.
[2] Neuro-imaging, hand x-ray and other imaging studies as clinically indicated.
[3] Not required for diagnosis, but essential for long-term therapeutic planning.
[4] In patients with suspicion of MDS or leukemia.
[5] In patients with clinical suspicion of respective syndromes.
[6] In suspected renal dysfunction; note, EPO levels are elevated in patients with DBA syndrome.

Abbreviations: CBC, complete blood counts; ADA, erythrocyte adenosine deaminase; HbF, fetal hemoglobin; BM; bone marrow; MMA, methylmalonic acid; DAT (direct antiglobulin test); IBMFS, inherited BM failure syndromes.

Recommendations for transfusion support

GENERAL PRINCIPLES	
Indications and timing	**Therapeutic considerations**
• Any patient with severe anemia • Patient within 12 months of life • Patient not responding to steroids or experiencing significant side effects • Patient responding to steroids and experiencing acute Hb drop (e.g., due to viral illness) • Patient on steroid holiday (to improve growth during adolescence) • Pregnant patient with anemia	General: • Hepatitis B vaccination • RBC antigen typing and repeat RBC antibody screening Hb goal prior transfusion (nadir Hb): • **≥9-10g/dL** or a higher level at which the patient is asymptomatic, independent of age Transfusion process: • [1]Volume: 10-15ml/kg (children), ~2-3 RBC units (adults) • [2]Interval: every 3 (2-4) weeks
ADVERSE EFFECTS AND CLINICAL PROBLEMS	
Iron overload	Start early chelation
Clinically significant anemia, especially days before transfusion	Increase transfusion volume or decrease transfusion interval, "catch-up" transfusion
Blood-transmitted pathogens	Hepatitis B vaccine Virus testing (HIV, Hepatitis B and C) at least yearly
Higher transfusion requirements	Rule out alloimmunization and hypersplenism (rare in DBA syndrome), hemorrhage

[1] Higher transfusion volumes occasionally required across all ages (i.e., ~20ml/kg).
[2] Interval may be longer in patients with some erythropoiesis who maintain Hb ≥9-10g/dL for longer period of time.

Recommendations for steroid treatment

GENERAL PRINCIPLES	
Indications and timing	**Therapeutic considerations**
First trial: • Patient with chronic transfusions: Start ≥12 months old. Possible start at 15-18 months in children with failure to thrive. Earlier start (~9 months) if unable to provide safe venous access or safe transfusions Second trial: • In previous non-responders (1-2 years after first unsuccessful trial), recommended before planned HSCT Additional trials: Not recommended	**Before:** • Live viral vaccines (1st dose MMRV) given optimally ≥ 3 weeks before first steroid trial **Dosing:** • Drug: Oral prednisone or prednisolone (equal potency) • Start dose: 2mg/kg per day in children (max 80mg); 80mg per day in adults • When to start: one day or ~10-14 days after last transfusion • Initial response assessment: reticulocytes and Hb at day 10-14 **Tapering principles and stopping rule:** • Initial response: start taper after 2 weeks but not later than 4 weeks: reduce by 0.5mg/kg every ~2 weeks. • From 0.5mg/kg slow taper to arrive at maximum maintenance dose (0.3mg/kg per day or 0.6mg/kg alternate days) • Further passive/active taper to reach minimally effective dose • Non-response after 4 weeks: stop initial dose without unnecessarily extending therapy **Definitions of steroid response:** • Initial response: significant reticulocytosis (≥50-100x10^9/L) and stable/increasing Hb (expected within 2-4 weeks). • Long-term response: maximum maintenance dose resulting in Hb ≥9g/dl without transfusions
CLINICAL SCENARIOS AND MANAGEMENT	
Loss of efficacy	• Acute Hb drop (e.g., viral illness): single RBC transfusion • Persistent Hb drop: consider increasing dose; if dose too high, declare non-response and switch to RBC transfusions
Estrogen-containing oral contraception	• May limit steroid response
Pregnancy, systemic disease (including cancer)	• Discontinue steroids and switch to RBC transfusions
Preadolescence/adolescence	• Consider steroid holiday (1-3 years) to improve growth
Immunosuppression, lymphopenia with risk of opportunistic infections	• Taper/discontinue steroids if clinically relevant infection • Avoid live vaccines during initial high dose steroids
Classic side effects: hypertension, diabetes, adrenal insufficiency, and others	• Monitoring toxicity with endocrinologist • Annual eye exam (cataracts?) • Annual bone densitometry scan (osteopenia?)
SUPPORTIVE CARE	
Vitamin D and calcium supplementation	• All patients on long-term steroids
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 (2mg/kg). Adapt to local standard

Abbreviations: HSCT, hematopoietic stem cell transplantation; Hb, hemoglobin; MMRV, mumps, measles, rubella, varicella; RBC, red blood cells

Recommendations for chelation therapy

	DEFEROXAMINE, DESFERRIOXAMINE (DFO)	DEFERASIROX (DFX)	DEFERIPRONE (DFP)
Indications	First line: DFO or DFX (off label in children <2 years old[1]) Second line: switch between or combine both • Start after 10 transfusions or evidence of iron load (transferrin saturation >60%, serial ferritin >500ng/ml) • Infant with DBA: wait until after first failed steroid trial, then start with low dose and close monitoring		Third line in patients with cardiac iron overload or failure /intolerance to other chelators First line in patients with severe cardiac iron overload or cardiac failure (in combination with DFO)
Formulation	Subcutaneous (SQ) or intravenous (IV): 500mg/vial or 2 g/vial	a) film-coated oral tablet or granules (90, 180, 360mg); b) dispersible oral tablet (125, 250, 500mg)	Oral tablet: 500mg, 1g Oral syrup: 100mg/ml
Dose	30-60mg/kg/day (max 30mg/kg/day in children <3 years), as (10-)12h SQ infusion 5-7 days/week or 24h continuous IV infusion	a) 14-28 mg/kg/day b) 20-40 mg/kg/day once daily	75mg/kg/d, 3 times daily Combination with DFO is standard, with DFX possible
Benefits	Longest experience, liver>heart iron removal	Most effective in liver iron removal	Most effective in heart iron removal
Relevant side effects	Ototoxic, skeletal abnormalities	Renal, hepatic, and gastrointestinal toxicity	Agranulocytosis[2], zinc deficiency, arthralgia
Monitoring of iron overload	• **Diagnostic gold standard: 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 HSCT) ○ Follow up: annual MRI liver iron (more or less often according to iron status). Annual MRI heart iron (more frequently if cardiac iron load present) • Serial ferritin levels and transferrin saturation[3]		
Goals and adjustment plan	• Adjust therapy frequently, based on efficacy/toxicity (typically every 3-6 months) • Optimal target values for iron overload[4]: ○ MRI liver iron content <3mg/g[5] dry weight; MRI heart T2* >20-35 msec[6] ○ Serial ferritin: <500ng/ml • Reduction/stopping rules based on ferritin if MRI not available (not standard)[3] ○ Ferritin 500-1000ng/ml: consider dose reduction ○ Ferritin 300-500ng/ml: dose reduction or temporary pause required ○ Ferritin <300ng/ml: temporary pause required • Patients with low ferritin (<500ng/ml), but high liver iron by MRI (>5mg/g dry weight): consider chelation at lower dose and with intensified monitoring for toxicity		
Toxicity monitoring	• DFO and DFX: Annual audiometry (sensineuronal hearing loss?) • DFX: Annual eye exam (cataracts?) • DFX: Monitor for renal (creatinine increase in serum, Fanconi syndrome: phosphate loss, protein in urine), and hepatic injury (transaminitis), gastrointestinal symptoms • Pancreatic iron overload: regularly assess endocrine pancreatic function by fasting glucose, oral glucose tolerance test, fructosamine (instead Hba1c) • Consider hemochromatosis gene testing in patients with rapid/severe iron overload		

[1] Approval status in most countries: DFO first line >3 years old, DFX in 2-6 years old when DFO cannot be used.
[2] DFP prescription should come from an experienced provider. Patient/primary care team must receive emergency protocol for agranulocytosis and fever (immediate drug cessation, antibiotics, G-CSF if needed).
[3] 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.
[4] There is a risk of chelator toxicity if treatment is continued too aggressively when MRI liver iron content is <3mg/g, or when serial ferritin is below 500ng/ml (in case MRI measurement is not available).
[5] Unit conversion: mg/g x 18 = µmol/g
[6] Some panel members suggest a more restrictive threshold of >25 msec.

Recommendations for allogeneic hematopoietic stem cell transplantation

General	• Assessment of iron overload (MRI liver/heart) before planning HSCT • Iron overload: chelation prior HSCT, consider phlebotomies post HSCT
Age	• In general, before the age of 10 years in chronically transfused patients • If possible, preferably at the pre-school age (~2–5 years) to minimize risk of toxicities • In individual patients, HSCT for transfusion dependence can be considered after the age of 10 years (low transfusion burden, optimal iron balance, adequate organ function) • In adults, HSCT is generally not advised solely for the avoidance of transfusion dependence[1]
Indications	**Listed in order of increasing urgency and clinical necessity:** • Chronic transfusions in patients not responding to steroids • Chronic transfusions in patient with non-manageable iron overload (significant toxicity or chelator failure) • Chronic transfusions in patient with alloimmunization to RBC • Severe immunodeficiency and/or multilineage cytopenia • MDS/AML
Donor choice	**Donors listed with most optimal first:** • MSD: after exclusion of DBA syndrome in potential donor (genetic testing, CBC, eADA) • MUD: 10/10 HLA match based on molecular testing • MMUD and MMFD[2]: only in the absence of alternative therapies (patients with MDS/AML) 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 mobilized peripheral blood stem cells
GVHD prophylaxis	• Standard GVHD prophylaxis i.e., calcineurin inhibitor plus MTX or MMF and serotherapy (also for MSD)

[1] to be considered on a case-by-case basis for transfusion-dependent young adults in good health, after weighing the risks and benefits.
[2] includes haplo-donors.

Abbreviations: HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; MMUD, HLA-mismatched unrelated donor; MMFD, HLA-mismatched family donor; CBC, complete blood counts; eADA, erythrocyte adenosine deaminase; MTX, methotrexate; MMF, mycophenolate mofetil.

Common Congenital Abnormalities Associated With DBA Syndrome

ORGAN SYSTEM	Frequency, median (range)	FINDINGS
Any type	54.4% (40.6-71.8)	(Including short stature, small for gestational age/intrauterine growth retardation)
Craniofacial and neck	21.6% (14.5-25) *Cleft palate: 4.26% (3.5-5.8)*	Hypertelorism, microcephaly, micrognathia (Pierre-Robin), microtia, broad flat nasal bridge, epicanthus, cleft lip, cleft palate, shorted/webbed neck, Sprengel deformity, Klippel-Feil deformity, low set ears, prominent ears, low hair line, ptosis, mandibulofacial dysostosis (Treacher-Collins syndrome phenocopy)
Cardiac	11.6% (6.9-15)	Ventricular septal defect, atrial septal defect, coarctation of the aorta, tetralogy of Fallot, bicuspid aortic valve, pulmonary stenosis, anomalous venous return, other complex cardiac defects
Thumb and skeletal	18.5% (17.9-19) *Thumbs: 7.6% (6-9.2)*	Thumb (absent, atypical, duplex, bifid, triphalangeal), flat thenar eminence, polydactyly, syndactyly, absence of radial artery, acetabular dysplasia, pectus excavatum
Urogenital	10.7% (6.3-19.5)	Absent or horseshoe kidney, duplicated collecting systems, hypospadias, inguinal hernias
Ophthalmological	Rare	Congenital glaucoma or cataracts, strabismus
Skin	Rare	Café au lait spots, congenital nevi, hemangioma, dermatofibroma
Neurodevelopmental	3% (1.3-4.6)	Learning difficulties, mild to severe developmental delay

Data on frequency are from DBA syndrome registry papers cited in the manuscript.

Summary of clinical features in patients with DBA syndrome

	INTRINSIC (DISEASE RELATED)	THERAPY RELATED
Hematologic	Macrocytic anemia with reticulocytopenia Leukopenia, neutropenia Thrombocytopenia Thrombocytosis (infants) Hypocellular marrow (mostly in adults, sometimes in children)	Alloimmunization with subsequent increased transfusion requirement Agranulocytosis (DFP)
Immunologic	Lymphocytopenia Decreased B-cell numbers Hypogammaglobulinemia Recurrent infections	Port catheter infections Transfusion-related pathogens Viral infections (steroids) Lymphocytopenia (steroids) Infections: campylobacter and other bacteria (associated with iron overload), yersiniosis, mucor mycosis (exacerbated by DFX)
Endocrinologic	Intrauterine growth restriction Failure to thrive Short stature Congenital abnormalities	>50% patients experience endocrine problems related to steroids and iron overload: • Adrenal insufficiency • Sex hormone insufficiency • Growth hormone dysfunction • Hypogonadism • Thyroid and parathyroid problems • Pancreatic insufficiency, diabetes mellitus
Orthopedic	Short stature Congenital abnormalities Osteosarcoma (osteogenic sarcoma)	Osteopenia and bone fractures (steroids)
Hepatic, Urogenital, Cardiac	Congenital abnormalities	Liver toxicity (DFX) Liver cirrhosis (iron) Cardiomyopathy with arrhythmias (iron) Nephrotoxicity, phosphate loss (DFX) Urinary stones (DFX, DFO)
Gastrointestinal	Colitis	Diarrhea, esophagitis, nausea (DFX)
Otolaryngologic, ophthalmologic	Congenital abnormalities	Cataract (steroids, DFX) Ototoxicity (DFO)
Neurologic and psychosocial	Developmental delay	High psychosocial burden from chronic illness
Oncologic	Cancer risk: MDS, osteosarcoma, colorectal cancer, and other cancers	Increased risk after HSCT
Obstetric	High risk pregnancies	Infertility (iron overload, HSCT)

Abbreviations: DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; HSCT, hematopoietic stem cell transplantation.

Comprehensive long-term surveillance in children and adults with DBA syndrome

Clinical scenario	Surveillance recommendations
HEMATOLOGY	
Any patient (including therapy-independent) Monitor changes in blood counts (Hb, other blood lineages): viral infection, drug induced, MDS/AML	• CBC and reticulocyte count at regular intervals (once yearly if therapy-independent) • Bone marrow aspirate if: more severe anemia without explanation, unexpected reticulocytosis, worsening of neutropenia or thrombocytopenia, abnormal cells

Patient receiving steroids
 	
Monitor efficacy (Hb and reticulocyte count) and treatment toxicity (see also **Table 4**)
 	
Involve endocrinology
	• CBC every ~3-4 months in stable patients
	• LFTs, creatinine, vitamin D levels regularly
	• Vitamin D and calcium supplementation as needed
	• Proton pump inhibitors (or H2 antagonists) during initial high dose prednisone therapy, or when symptomatic
	• Disclose that estrogen-containing oral contraceptives might weaken steroid effect
	• Steroid toxicity requires repeat endocrine evaluation
	  o At least yearly testing for diabetes/ metabolic syndrome, bone health (densitometry scan), eye exam (cataract exclusion)
	  o Bisphosphonates as therapy option in patients with significant osteoporosis
	  o Joint/bone pain must be investigated being mindful of steroid-induced avascular necrosis and risk of osteogenic sarcoma (MRI may be warranted)

Patients on transfusions and chelation
 	
Monitor efficacy (nadir Hb before transfusion) and toxicity (see also **Table 3 and 5**)
 	
Patients with poor iron balance
	• Before every transfusion: CBC with reticulocyte counts, RBC antibodies (if possible)
	• Ferritin and transferrin saturation trend (i.e., every 1-3 months before transfusion)
	• Routine transaminases, creatinine, electrolytes (phosphate if on DFX) virus serology (hepatitis B/C)
	• Annual MRI evaluation or more often according to iron status:
	  o Liver iron content (LIC) by T2* or R2
	  o Heart iron by T2*
	• Echocardiography, ECG evaluation every 1 to 3 years according to iron status. Consider Holter monitor for patients with cardiac iron overload. Intensify chelation; consider DFP
	• Pancreas and pituary glands: specific endocrine tests: fructosamine (instead of HbA1c in transfused patients), TSH, PTH
	• Growth hormone replacement when indicated
	• Consultation for medically assisted reproduction
	• Dose adjustments and combination of two chelators are frequently required, emphasize importance of medication adherence, facilitate networking with patient groups

Patients on DFO Monitor for toxicity: hearing loss, osteopenia, renal lithiasis	• Bone densitometry (every 1 to 3 years) • Regular audiogram and eye exam (at least annually or more often with dose changes) • Regular renal ultrasound surveillance

	• Higher risk of toxicity is present in patients with low ferritin
Patients on DFX: monitor for toxicity: renal (glomerular or tubular damage including Fanconi syndrome), hepatic toxicity, transaminitis, gastrointestinal issues	• Frequent evaluation of liver and kidney parameters. Patients with toxicity: decrease dose • Regular renal ultrasound surveillance • Audiogram and eye exam (yearly) • Higher risk of toxicity is possibly present in patients with low ferritin
Patients on DFP: screening for neutropenia/agranulocytosis	• Weekly CBC at treatment initiation and during any fever episode, monitor counts often and discontinue DFP for any sign of unusual or progressive neutropenia • Patient information & education (drug passport for emergencies with established plan)
For transplanted patients	• Standard surveillance recommendations. • Higher cancer risk in DBA syndrome patients must be taken into account
IMMUNOLOGY / INFECTIONS	
Hypogammaglobulinemia, Lymphopenia, recurrent infections	• Ig G, A, M levels and lymphocyte subsets (regularly if indicated) • Antibody responses, discuss immunizations and immunoglobulin treatment • For severe T-cell lymphopenia: consider pneumocystis jirovecii pneumonia prophylaxis • Additional prophylaxis and diagnostics according to local standard
Transfusion-related pathogens	• Virus testing at least once yearly (hepatitis B/C, HIV)
Vaccinations	• No restrictions on vaccines: Hepatitis B vaccine especially in patients receiving transfusions; live vaccines: first dose ideally before start prednisone, following doses after steroid reduction. • Patient with significant hypogammaglobulinemia: measure specific vaccine antibody titers
ONCOLOGY	
Solid tumors, MDS/AML	• Patient education, healthy lifestyle (avoid smoking, alcohol, toxins, unprotected sun exposure) • HPV vaccination • Patient adherence to screening procedures as in the general population • Colonoscopy beginning age 20 years, every 5 years or more often if clinically indicated • Bone marrow analysis: consider as baseline in adolescents/ young adults before transitioning to adult care, otherwise in any patient with significant unexplained cytopenia or rise in reticulocytes • Unexplained joint/bone pain: risk of osteogenic sarcoma (low threshold for x-ray / imaging)
FAMILY PLANNING, PREGNANCY	
Genetic risk (transmission)	• Patient education and genetic counselling • Discuss medically assisted reproduction for individuals asking for prenatal or pre-implantation diagnostics (according to national legal regulations)
Pregnancies in DBA syndrome: high risk obstetric care required	• Intensification of chelation prior planned pregnancy to optimize iron balance • Blood support frequently needed to maintain Hb >10.0-10.5 g/dL during pregnancy • Screening for fetal anemia • Detailed recommendations reviewed elsewhere (reference 136)

DIAGNOSIS, TREATMENT AND SURVEILLANCE OF DIAMOND BLACKFAN ANEMIA (DBA) SYNDROME: INTERNATIONAL CONSENSUS STATEMENT

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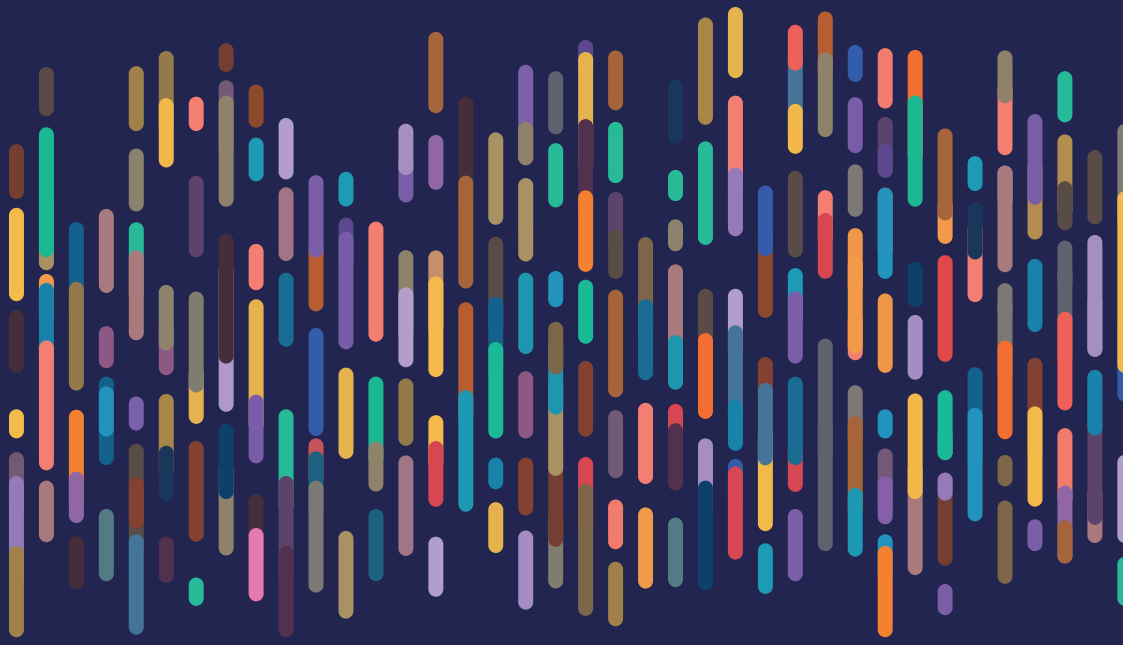

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