

Table 8. 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 <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Diagnostic gold standard: MRI for liver and cardiac iron assessment <ul style="list-style-type: none"> 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 saturation³ 		
Goals and adjustment plan	<ul style="list-style-type: none"> Adjust therapy frequently, based on efficacy/toxicity (typically every 3-6 months) Optimal target values for iron overload⁴: <ul style="list-style-type: none"> MRI liver iron content <3mg/g⁵ dry weight; MRI heart T2* >20-35 msec⁶ Serial ferritin: <500ng/ml Reduction/stopping rules based on ferritin if MRI not available (not standard)³ <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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.