Clinical Policy Bulletin: Chelation Therapy

Number: 0234

Policy

I. Aetna considers the use of chelation therapy medically necessary in the treatment of any of the following diseases/disorders:

1. Aluminum overload in persons with end-stage renal failure; or
2. Biliary cirrhosis; or
3. Cooley's anemia (thalassemia major); or
4. Cystinuria; or
5. Diamond-Blackfan anemia; or
6. Heavy metal poisoning (e.g., arsenic, cadmium, copper, gold, iron, lead, mercury)*; or
7. Secondary hemochromatosis (i.e., due to iron overload from multiple transfusions including persons with IPSS Low- or Intermediate-1-risk myelodysplastic syndrome); or
8. Sickle cell anemia; or
10. Non transfusion-dependent thalassemic members with evidence of clinically important iron overload
11. Non anemic members with iron overload who cannot tolerate therapeutic phlebotomy

* Testing of whole blood lead level is the most sensitive and specific means in assessing lead toxicity. Urinary lead level, which is an index of plasma lead concentration rather than whole blood lead concentration, is not an accurate measure of blood lead levels since plasma lead fluctuates more rapidly than blood lead levels.

II. Aetna considers the use of chelation therapy experimental and investigational in the prevention and treatment of cancer, cardiovascular disease (including individuals who had a myocardial infarction), neurodegenerative diseases (e.g., Alzheimer's disease), peripheral vascular disease, zygomycosis, individuals at risk from drug-eluting stents, and other conditions (e.g., autism, attention deficit hyperactivity disorder, diabetic cataract, Lyme disease, and treatment of "mercury toxicity" from dental amalgam fillings). The safety and effectiveness of this treatment for these indications has not been established.

III. Aetna considers laboratory testing medically necessary for heavy metal poisoning (e.g., arsenic, cadmium, copper, gold, iron, mercury) for members with specific signs and symptoms of heavy metal toxicity and/or a history of likely exposure to heavy metals.
IV. Aetna does not consider screening for heavy metal poisoning medically necessary for members with only vague, ill-defined symptoms (e.g., dysphoria, fatigue, malaise, and vague pain) and no history of likely heavy metal exposure.

V. Aetna considers the dimercaptosuccinic acid (DMSA) or ethylenediaminetetraacetic (EDTA) provocative chelation/mobilization test experimental and investigational as a means of diagnosing lead toxicity because of insufficient evidence of its effectiveness.

See also CPB 0300 - Hair Analysis, and CPB 0553 - Lead Testing.

Background

Chelation therapy is an established treatment for heavy metal poisoning. Heavy metals, which can not be metabolized, persist in the body and exert their toxic effects by combining with one or more reactive groups (ligands) essential for normal physiological functions. Chelating agents, also known as heavy metal antagonists, form complexes with toxic heavy metals rendering them physiologically inactive and enhancing their excretion in the urine. Specific chelating agents include edetate calcium disodium (EDTA), deferoxamine (Desferal), dimercaprol (BAL in oil) and penicillamine (Cuprimine, Depen).

Dimercaprol was developed as an antidote to lewisite, an arsenic-based war gas and was designated British anti-Lewisite or BAL. It is used principally to treat arsenic, gold and mercury poisoning and in combination with edetate calcium disodium, to treat lead poisoning. The main therapeutic use of edetate calcium disodium is in the treatment of metal intoxication, especially lead intoxication. Mercury poisoning does not respond to this drug. Penicillamine is used for treating copper, mercury, lead and arsenic poisoning, and cystinuria. It is the drug of choice for Wilson's disease (hepato-licantular degeneration due to an excess of copper). Deferoxamine has a highly affinity for iron and is the drug of choice for acute or chronic iron intoxication.

Chelation therapy with appropriate chelating agents is established treatment for biliary cirrhosis, Cooley's anemia (thalassemia major), cystinuria, heavy metal (arsenic, cadmium, copper, gold, iron, mercury) poisoning, Wilson's disease, and sickle cell anemia, i.e., secondary hemachromatosis (iron overload from multiple transfusions).

The administration of the chelating agent calcium EDTA as a mobilization test (provocative chelation) to determine if chelation therapy is indicated is controversial. The provocative chelation test was developed to assess the total body lead burden and efficacy of chelation treatment. The tests involve obtaining a timed urine collection after administering a dose of calcium EDTA. In view of a paucity of relevant clinical outcome studies of provocative chelation, and in view of and animal studies suggesting that single doses of chelation might cause harm from mobilizing lead and redistributing to the central nervous system, the use of provocative chelation is not indicated.

Intravenous or oral chelation therapy is indicated in all children with acute lead intoxication, and in children with moderate to severe chronic lead intoxication (blood lead level of 45 mcg/dL or greater). For children with mild intoxication (blood level less than 45 mcg/dL), oral chelation (DMSA or D-penicillamine) is indicated for those with blood levels are between 20 and 44 mcg/dL). Chelation therapy is not necessary for children with blood levels of lead less than 20 mcg/dL.

For adults, intravenous or oral chelation therapy is recommended for those with acute lead toxicity, and for adults with blood lead levels greater than 80 mcg/dL. Chelation therapy is also indicated for adults with blood lead levels between 60 and 80 mcg/dL if they have lead-
related symptoms. In addition, chelation therapy may be considered in adults with blood lead levels between 40 and 60 mcg/dL, if they have continued symptoms and elevated blood lead levels after 2 weeks of removal from exposure.

Treatment with chelators should be considered in persons with acute symptoms arising from the central nervous system due to confirmed mercury poisoning (e.g., via measurement of mercury in air, blood, or urine). The normal range of mercury concentrations in whole blood is 0 to 10 mcg/L. Early signs and symptoms may occur with concentrations greater than 35 mcg/L. Clinically significant poisoning from mercury is unlikely if blood and urine concentrations are below 100 µg/L.

A concentration greater than or equal to 50 mcg/L or 100 mcg of arsenic/g creatinine in the absence of recent fish or shellfish intake strongly suggests arsenic poisoning. Chelation indicated in symptomatic arsenic poisoning and in all patients whose speciated urine arsenic level exceeds 200 mcg/L. Patients who are minimally symptomatic and have chronic arsenic poisoning may be removed from the source of their exposure without chelation therapy. Chelation can be accomplished with oral penicillamine; IV dimercaprol can be used for person who cannot take oral medications.

Chelation therapy with calcium EDTA may be indicated in acute cadmium toxicity. Blood levels of cadmium above 5 mcg/dL suggest acute cadmium toxicity. There is a lack of evidence of beneficial effects of chelating agents on cadmium toxicity after prolonged exposure. The literature on the influence of chelating agents on cadmium distribution and excretion is limited to animal studies, and is confined to the early period after acute cadmium exposure. Developing an effective chelation therapy for cadmium is difficult because cadmium is tightly bound to metallothionein in liver and kidney.

Gold is used in the treatment of rheumatoid arthritis (RA) and other rheumatic diseases. Chelation therapy may be used in persons with gold toxicity with severe reactions who are unresponsive to steroids. Moderate to high-dose steroid therapy may be beneficial in gold-induced thrombocytopenia, bone marrow toxicity, enterocolitis, and pulmonary infiltrates. Dimercaprol, penicillamine, N-acetylcysteine, and other chelating agents have been used to treat reactions unresponsive to glucocorticoids.

Chelation therapy may be indicated in copper toxicity. For copper toxicity due to ingesting grams of copper, prompt gastric lavage followed by daily intra-muscular injections of dimercaprol may prevent death. The oral chelating drug penicillamine binds copper, facilitating its excretion, and may promote excretion of copper absorbed from burned skin. Chronic oral chelation therapy may be necessary in persons with inherited chronic copper toxicity (Wilson's disease).

There is insufficient evidence to support the use of chelation therapy for prevention or treatment of cardiovascular disease. Chelation therapy for atherosclerosis involves the intravenous infusion of ethylene diaminetetraacetic acid, also known as edetate disodium, endrate or EDTA. It may involve as many as 20 to 40 infusions, each 3 to 4 hours long, administered 1 to 3 times weekly.

Used since the 1950s, the premise for EDTA chelation is the removal of calcium from the atherosclerotic lesion. Proponents claim that EDTA forms a chelated soluble complex with the calcium which is excreted in the urine. Calcium, however, is not a major constituent in the pathogenesis of atherosclerosis. The atherosclerotic lesion is highly cellular and contains smooth muscle, macrophages, lipid particles, and connective tissue. Within the lesion there are areas of necrotic debris, cholesterol crystal and calcification. Lesions are primarily fibrous overgrowths and calcium deposition is an insignificant part of the total lesion.
Proponents also champion EDTA as the original calcium-channel antagonist. However, there is no evidence that lowering serum, tissue and bone calcium with EDTA produces the same physiologic effects as the calcium-channel antagonists. These work by binding to calcium channel receptors to reduce calcium influx into the myofibril, therefore producing relaxation of smooth muscle without affecting the serum concentration of calcium.

Explanations for individual positive responses to chelation therapy include placebo effect (often seen in the controlled evaluation of therapies for angina pectoris), lifestyle changes and natural variations in the disease. There are case reports of symptomatic improvement with angiographically documented persistence of the lesion. Toxic effects may include death, renal failure, arrhythmias, tetany and hypocalcemia.

A systematic review of chelation therapy for cardiovascular disease (Villaruz et al, 2003) reached the following conclusions: "[a]t present, there is insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improving clinical outcomes of patients with atherosclerotic cardiovascular disease. This decision must be preceded by conducting randomized controlled trials that would include endpoints that show the effects of chelation therapy on longevity and quality of life among patients with atherosclerotic cardiovascular disease."

The American Heart Association (2002) has concluded that there is "no scientific evidence to demonstrate any benefit from this form of therapy."

A assessment of chelation therapy by the West Midlands Health Technology Assessment Collaboration (Cornock et al, 2002) concluded that "[c]urrently there is little objective evidence that CT [chelation therapy] is effective for CHD [coronary heart disease] or IC [intermittent claudication]."


A Canadian Cardiovascular Society consensus conference statement on heart failure (2006) concluded that "[c]helation therapy should not be used as heart failure therapy."

The American College of Cardiology (Hirsch et al, 2005) stated that "[c]helation (e.g., ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects." The Scottish Intercollegiate Guidelines Network (2006) explained: "[c]helation has been studied in only one robust trial of patients with intermittent claudication [citing van Rig et al, 1994], which showed no difference between experimental and placebo groups, leaving no evidence on which to base a recommendation. Adverse effects are potentially serious."

The American College of Physicians (Snow et al, 2004) concluded that chelation should not be used to prevent myocardial infarction (MI) or death or to reduce symptoms in patients with symptomatic chronic stable angina.

In August 2002, the National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) announced that they have launched the Trial to Assess Chelation Therapy (TACT), which is the first large-scale, multi-center study to find out if EDTA chelation therapy is safe and effective for people with coronary heart disease. This placebo-controlled, double-blind study will involve 2,372 participants aged 50 years and older with a history of MI. Recruitment for this study began in March 2003, and the study will take 5 years to complete.

In a randomized double-blind, placebo-controlled study (n = 47), Anderson et al (2003) reported that EDTA chelation therapy in combination with vitamins and minerals did not
provide additional benefits on abnormal vasomotor responses in patients with coronary artery disease optimally treated with proven therapies for atherosclerotic risk factors.

Rose and colleagues (2010) stated that iron chelation therapy improves survival in thalassemia major but its beneficial effects on survival in patients with myelodysplastic syndrome (MDS) remain uncertain. These researchers analyzed, by multi-variate analysis, survival and causes of deaths in 97 low or intermediate 1 International Prognostic Scoring System (IPSS) patients regularly transfused as outpatients, chelated or not, who were included during a month period and followed for 2.5 years. A total of 44 (45 %) of patients were not chelated and 53 (55 %) received chelation therapy, mainly with deferoxamine, for at least 6 months (median duration of chelation of 36 months, range of 6 to 131+ months). During the follow-up period, 66 of the 97 patients died, including 51 % and 73 % of chelated and non-chelated patients, respectively. Median overall survival was 53 months and 124 months in non-chelated and in chelated patients, respectively (p < 0.0003). Causes of death did not significantly differ between the 2 groups (p = 0.51). In multi-variate Cox analysis, adequate chelation was the strongest independent factor associated with better overall survival. The authors concluded that iron chelation therapy appears to improve survival in heavily transfused lower risk MDS. Moreover, they stated that prospective randomized studies are needed to confirm these findings, and to determine more precisely the mechanisms of this potential survival benefit.

Zhang et al (2011) noted that oxidative stress plays a critical role in cataractogenesis, the leading cause of blindness worldwide. Since transition metals generate reactive oxygen species (ROS) formation, metal chelation therapy has been proposed for treatment of cataracts. However, the effectiveness of most chelators is limited by low tissue penetrability. This study was the first to demonstrate that the topically applied di-valent metal chelator EDTA combined with the carrier and permeability enhancer methyl sulfonyl methane (MSM) ameliorates both oxidation-induced lens opacification and the associated toxic accumulation of protein-4-hydroxynonenal (HNE) adducts. Both in vitro (rat lens culture) and in vivo (diabetic rats), EDTA-MSM (i) significantly reduced lens opacification by about 40 to 50 %, (ii) significantly diminished lens epithelial cell proliferation and fiber cell swelling in early stages of cataract formation in vivo, and (iii) notably decreased the levels of protein-HNE adducts. The authors stated that these findings have important implications specifically for the treatment of cataract and generally for other diseases in which oxidative stress plays a key pathogenic role.

Although chelation therapy has been cited as a potential treatment for autism and attention deficit hyperactivity disorder (ADHD) (e.g., Curtis and Patel, 2008), there is insufficient evidence to support its use for these indications. Well-designed clinical trials are needed to ascertain the clinical value, if any, of chelation therapy for autism and ADHD.

In a systematic review on novel and emerging treatments for autism spectrum disorders (ASD), Rossignol (2009) stated that currently only 1 medication (risperidone) is Food and Drug Administration (FDA)-approved for the treatment of ASD; and the use of novel, unconventional, and off-label treatments is common, with up to 74 % of children with ASD using these treatments. The author performed a systematic literature search of electronic scientific databases to identify studies of novel and emerging treatments for ASD, including nutritional supplements, diets, medications, and non-biological treatments. A grade of recommendation ("Grade") was then assigned to each treatment using a validated evidence-based guideline as outlined in this review: "Grade A": Supported by at least 2 prospective randomized controlled trials (RCTs) or 1 systematic review; "Grade B": Supported by at least 1 prospective RCT or 2 non-randomized controlled trials; "Grade C": Supported by at least 1 non-randomized controlled trial or 2 case series; and "Grade D": Troublingly inconsistent or inconclusive studies or studies reporting no improvements. Potential adverse effects for each treatment were also reviewed. Grade A treatments for ASD included melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include
carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment (HBOT), immunomodulation and anti-inflammatory treatments, oxytocin, and vision therapy. Grade C treatments for ASD include carnosine, multi-vitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback. The author concluded that the reviewed treatments for ASD are commonly used, and some are supported by prospective RCTs. Promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the reviewed treatments are currently considered off-label for ASD (i.e., not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed.

Furthermore, in a review on autism, Levy et al (2009) stated that popular biologically based treatments include anti-infectives, chelation medications, gastrointestinal medications, HBOT, and immunoglobulins. Non-biologically based treatments include auditory integration therapy, chiropractic therapy, cranio-sacral manipulation, interactive metronome, and transcranial stimulation. However, few studies have addressed the safety and effectiveness of most of these treatments.

Chelation therapy has been shown to be useful in treatment of aluminum toxicity in renal failure. Hernandez and Johnson (1990) noted that aluminum (AL) toxicity, common among individuals with chronic renal failure, is associated with disabling osteomalacia, encephalopathy, and anemia. The control of AL intake has included standards to limit the amount of AL in the dialysis fluid in addition to the use of non-AL containing phosphate binders. Deferoxamine (DFO) mesylate, a heavy metal chelating agent, is used to remove AL from the tissues of dialysis patients. Chelation therapy has resulted in improvements of clinical symptoms and bone histology. Ocular, auditory, and infectious adverse effects have occurred with the use of DFO. Day and Ackrill (1993) stated that DFO now finds extensive use in the treatment and diagnosis of AL-related diseases in renal patients. Moreover, the American Academy of Pediatrics’ statement on AL toxicity in infants and children (1996) stated that intravenous DFO has been used successfully in treating AL toxicity in children.

Barata and colleagues (1996) reported that according to the recommendations proposed at the 1992 consensus conference on diagnosis and treatment of AL overload in end-stage renal failure patients, low-dose DFO treatment was applied for the first time in 41 acutely AL-intoxicated patients. DFO-related neurological/ophthalmological side-effects were observed in 9 of 11 patients with a post-DFO serum AL level greater than 300 μg/L and in 2 patients of 30 below this level after a single administration of a 5 mg/kg dose of the chelator in the conventional way (i.e., the last hour of a dialysis session). They were no longer observed after introducing an alternative DFO administration schedule (i.e., administration of the chelator 5 hours prior to the start of a hemodialysis session; group I: n = 14). A significant decrease in the serum AL levels as well as in the post-DFO serum AL increment (delta sAL) was observed during the first 6 months, course of low-dose DFO treatment in group I as well as group II (which consisted of patients receiving DFO in the conventional way; n = 27). Low-dose DFO treatment was accompanied by a significant increase in the mean +/- SD serum iPTH levels (group I: 174 +/- 245 up to 286 +/- 285 ng/L; group II: 206 +/- 272 up to 409 +/- 424 ng/L; p < 0.005) and the mean corpuscular volume (group I: 80 +/- 6.4 up to 85 +/- 3.7 fl, p < 0.005; group II: 76 +/- 5.0 up to 87 +/- 4.3 fl, (p < 0.0001). Serum ferritin levels significantly decreased in both groups. No further side-effects were observed during the DFO course. Patients in which DFO treatment could be stopped (i.e., subjects in which both serum AL and delta sAL were below 50 μg/L at two successive occasions) before the end of the 6 months’ treatment course had a significantly greater residual diuresis (700 +/- 682 ml/min versus 84 +/- 109 ml/24 hours). Also, residual diuresis was found to protect against AL intoxication as reflected by the values noted in group I versus those in group II. The authors concluded that the 5 mg/kg DFO treatment provides a safe and adequate therapy for
AI overload. In severely AI-intoxicated patients presenting post-DFO serum AI levels above 300 μg/L, DFO should be given once weekly 5 hours prior to high-extraction dialysis ensuring (i) maximal chelation of AI, (ii) limited exposure to circulating AI noxamine levels, and (iii) adequate removal of the latter compound.

Chappell (2007) stated that the recently reported increased risk of blood clots, resulting in MI and sudden death beginning 6 months after medicated stents were implanted in patients following percutaneous transluminal coronary angioplasty (PTCA), has left physicians pondering what course of action to take. The purpose of adding implanted medication to a stent is to prevent thrombin accumulation and re-stenosis. However, these stents may increase, rather than decrease, the risk. Although long-term treatment with clopidogrel plus aspirin for at least 12 months has been suggested as a preventive treatment, there is no evidence from randomized, controlled trials that this approach is effective for more than 6 months. Clopidogrel also increases the risk of major bleeding episodes. The author served as the primary investigator for a study that showed cardiovascular patients treated with EDTA chelation therapy had a lower rate of subsequent cardiac events, including MI and death, than those treated with cardiac medications, PTCA, or coronary artery bypass graft. The data also indicated chelation therapy might be effective in preventing thrombosis and cardiac events from stent implantation. There is evidence that EDTA chelation therapy might prevent hyper-coagulability resulting from the placement of stents, although not specifically medicated stents. Based on the limited data currently available, intravenous EDTA may be safe and effective for treating patients who have implanted medicated stents. The author noted that prospective clinical trials are needed, and EDTA should be included in those trials.

Whayne (2010) noted that a wide range of alternative medications with relevance or connection to cardiovascular (CV) disease have been considered. While many are worthless, others have definite benefit, and at least one, chelation therapy, is associated with definite harm, significant risk, no benefit, and enrichment of the practitioners who prescribe it. The issues concerning alternative therapies will likely never be studied with randomized clinical trials due to the lack of a profit motive on the part of pharmaceutical companies — only rarely do other institutions, such as the National Institutes of Health, support medicinal studies. Basic knowledge of alternative therapies is essential for the CV specialist and other practicing physicians and other practitioners, since at least a few of their patients will take these medications regardless of medical advice. The result is that a number of these alternative medications will then interact with conventional CV medications, many times unfavorably.

In a review on current and future treatments of zygomycosis, Rogers (2008) noted that zygomycosis is a frequently lethal invasive infection in high-risk patients such as the immunocompromised (especially hematopoietic stem cell transplant (HSCT) recipients) and patients with type 2 diabetes mellitus. However, zygomycosis has also been reported in individuals without known risk factors. Zygomycosis can present clinically as rhinocerebral, pulmonary or disseminated disease which progresses rapidly. The management of cases is based on early diagnosis, surgical debridement when possible and aggressive anti-fungal therapy. Based on clinical experience, but without the benefit of comparative studies, liposomal amphotericin B has become the therapeutic agent of choice. Posaconazole is a new orally administered triazole anti-fungal and the first member of this class to have comparable in vitro activity to amphotericin B against most zygomycetes. Studies of salvage therapy of zygomycosis with posaconazole have yielded promising results and there are additional case reports of successful outcomes using these and other anti-fungal drugs as combination therapy. Moreover, adjunctive approaches that are showing promise but with limited clinical experience are iron chelation and immunotherapy.

Bolognin et al (2009) stated that available evidence suggests a central role for transition biometals in the pathogenesis of neurodegenerative diseases (ND). It has become increasingly evident that biometals and non-physiological aluminum are often involved in
pathological onset and progression, either by affecting the conformation of specific proteins or by exacerbating local oxidative stress. The apparently critical role played by metal dishomeostasis in ND makes chelation therapy an attractive pharmacological option. However, classical metal chelation approaches, relying on potent metal ligands, turned out to be successful only in those rare cases where exceptional brain metal accumulation occurs due to specific defects in metal metabolism. In contrast, metal-targeted approaches using ligand of intermediate strength seem to be more appropriate in fighting the major ND, although their benefits are still questioned.

Hedge et al (2009) noted that a close association between brain metal dishomeostasis and the onset and/or progression of Alzheimer's disease (AD) has been established in a number of studies, although the underlying biochemical mechanisms remain obscure. This observation renders chelation therapy an attractive pharmacological option for the treatment of this disease. However, a number of requirements must be fulfilled in order to adapt chelation therapy to AD.

A Cochrane systematic evidence review found insufficient evidence for the use of chelation (metal protein attenuating compounds) in AD (Sampson et al, 2008). Metal protein attenuating compounds have great affinity for copper and zinc ions, preventing them from binding to beta amyloid, a protein strongly implicated in the development of AD. Chelation of these metal ions promotes dissolution of beta amyloid, thus presenting a potential therapeutic target for AD. The Cochrane systematic evidence review found 1 RCT (n = 36) of metal protein attenuating compounds in AD. That trial, of clioquinol (also known as PB1T1) showed no statistically significant difference in cognition between active treatment and placebo groups at 36 weeks. The authors concluded that there is no current evidence that treatment with clioquinol (PB1T1) has any significant effect on cognition (as measured by the ADAS-Cog scale) in patients with AD.

Garcia-Manero et al (2011) noted that myelodysplastic syndromes (MDS) are a very heterogeneous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML). Myelodysplastic syndromes occur more frequently in older male and in individuals with prior exposure to cytotoxic therapy. Diagnosis of MDS is based on morphological evidence of dysplasia upon visual examination of a bone marrow aspirate and biopsy. Information obtained from additional studies such as karyotype, flow cytometry, or molecular genetics is complementary but not diagnostic. Therapy is selected based on risk, transfusion needs, percent of bone marrow blasts and more recently cytogenetic profile. Goals of therapy are different in lower risk patients than in higher risk. In lower risk, the goal is to decrease transfusion needs and transformation to higher risk disease or AML. In higher risk, the goal is to prolong survival. Current available therapies include growth factor support, lenalidomide, hypomethylating agents, intensive chemotherapy, and allogeneic stem cell transplantation. The use of lenalidomide has significant clinical activity in patients with lower risk disease, anemia, and a chromosome 5 alteration. 5-azacitidine and decitabine have activity in higher risk MDS. 5-azacitidine has been shown to improve survival in higher risk MDS. Additional supportive care measures may include the use of prophylactic antibiotics and iron chelation. At the present time, there are no approved interventions for patients with progressive or refractory disease particularly after hypomethylating based therapy. Options include cytarabine-based therapy, transplantation, and participation on a clinical trial.

In the National Comprehensive Cancer Network's clinical practice guidelines on MDS, Greenberg et al (2011) stated that 4 drugs have recently been approved by the FDA for treating specific subtypes of myelodysplastic syndromes (MDS); (i) lenalidomide for MDS patients with del(5q) cytogenetic abnormalities; (ii) azacytidine and (iii) decitabine for treating patients with higher-risk or non-responsive MDS; and (iv) deferasirox for iron chelation of iron overloaded patients with MDS.
Dental amalgam is a widely used restorative material containing 50 % elemental mercury that emits mercury vapor. Available evidence indicates that this low-level mercury exposure in children with dental amalgam is not associated with adverse health outcomes (Bellinger et al, 2006; DeRouen et al, 2006; and Shenker et al, 2008). Moreover, when chelation therapy is used to treat individuals who attribute their health problems to mercury from dental amalgam, there appears to be a strong placebo effect (Grandjean et al, 1997).

In a randomized study, Bellinger et al (2006) compared the neuropsychological and renal function of children whose dental caries were restored using amalgam or mercury-free materials. A total of 534 children aged 6 to 10 years at baseline with no prior amalgam restorations and 2 or more posterior teeth with caries were randomly assigned to receive dental restoration of baseline and incident caries during a 5-year follow-up period using either amalgam (n = 267) or resin composite (n = 267) materials. The primary neuropsychological outcome was 5-year change in full-scale IQ scores. Secondary outcomes included tests of memory and visuomotor ability. Renal glomerular function was measured by creatinine-adjusted albumin in urine. Children had a mean of 15 tooth surfaces (median, 14) restored during the 5-year period (range of 0 to 55). Assignment to the amalgam group was associated with a significantly higher mean urinary mercury level (0.9 versus 0.6 microg/g of creatinine at year 5, p < 0.001). After adjusting for randomization stratum and other covariates, no statistically significant differences were found between children in the amalgam and composite groups in 5-year change in full-scale IQ score (3.1 versus 2.1, p = 0.21). The difference in treatment group change scores was 1.0 (95 % confidence interval: -0.6 to 2.5) full-scale IQ score point. No statistically significant differences were found for 4-year change in the general memory index (8.1 versus 7.2, p = 0.34), 4-year change in visuomotor composite (3.8 versus 3.7, p = 0.93), or year 5 urinary albumin (median, 7.5 versus 7.4 mg/g of creatinine, p = 0.61). The authors concluded that there were no statistically significant differences in adverse neuropsychological or renal effects observed over the 5-year period in children whose caries were restored using dental amalgam or composite materials. Although it is possible that very small IQ effects cannot be ruled out, these findings suggested that the health effects of amalgam restorations in children need not be the basis of treatment decisions when choosing restorative dental materials.

In a randomized clinical trial, DeRouen et al (2006) evaluated the safety of dental amalgam restorations in children. A total of 507 children in Lisbon, Portugal, aged 8 to 10 years with at least 1 carious lesion on a permanent tooth, no previous exposure to amalgam, urinary mercury level less than 10 microg/L, blood lead level less than 15 microg/dL, Comprehensive Test of Nonverbal Intelligence IQ greater than or equal to 67, and with no interfering health conditions were included in this study. Routine, standard-of-care dental treatment was provided, with one group receiving amalgam restorations for posterior lesions (n = 253) and the other group receiving resin composite restorations instead of amalgam (n = 254). Main outcome measures were neurobehavioral assessments of memory, attention/concentration, and motor/visuomotor domains, as well as nerve conduction velocities. During the 7-year trial period, children had a mean of 18.7 tooth surfaces (median, 16) restored in the amalgam group and 21.3 (median, 18) restored in the composite group. Baseline mean creatinine-adjusted urinary mercury levels were 1.8 microg/g in the amalgam group and 1.9 microg/g in the composite group, but during follow-up were 1.0 to 1.5 microg/g higher in the amalgam group than in the composite group (p < 0.001). There were no statistically significant differences in measures of memory, attention, visuomotor function, or nerve conduction velocities (average z scores were very similar, near zero) for the amalgam and composite groups over all 7 years of follow-up, with no statistically significant differences observed at any time point (P values from 0.29 to 0.91). Starting at 5 years after initial treatment, the need for additional restorative treatment was approximately 50 % higher in the composite group. The authors concluded that children who received dental restorative treatment with amalgam did not, on average, have statistically significant differences in neurobehavioral
assessments or in nerve conduction velocity when compared with children who received resin composite materials without amalgam. These findings, combined with the trend of higher treatment need later among those receiving composite, suggested that amalgam should remain a viable dental restorative option for children.

Shenker et al (2008) evaluated a subpopulation of the participants in the New England Children's Amalgam Trial for in-vitro manifestations of immunotoxic effects of dental amalgam. These investigators conducted a randomized clinical trial in which children requiring dental restorative treatment were randomly assigned to receive either amalgam for posterior restorations or resin-based composite restorations. They assessed 66 children, aged 6 to 10 years, for total white blood cell counts, specific lymphocyte (T-cell and B-cell) counts and lymphocyte, neutrophil and monocyte responsiveness across a 5-year period. Because of the small number of participants, the authors acknowledged that the study is exploratory in nature and has limited statistical power. The mean number of tooth surfaces restored during the 5-year period was 7.8 for the amalgam group and 10.1 for the composite group. In the amalgam group, there was a slight, but statistically insignificant, decline in responsiveness of T cells and monocytes at 5 to 7 days after treatment; these researchers consistently observed no differences at 6, 12 or 60 months. The authors concluded that these findings confirmed that treatment of children with amalgam restorations leads to increased, albeit low-level, exposure to mercury. In this exploratory analysis of immune function, amalgam exposure did not cause overt immune deficits, although small transient effects were observed 5 to 7 days after restoration placement. They stated that these findings suggested that immunotoxic effects of amalgam restorations are minimal and transient in children and most likely do not need to be of concern to practitioners considering the use of this restorative dental material.

Furthermore, an UpToDate review on "Epidemiology and toxicity of mercury" (Elinder, 2012) states that "The release of mercury from amalgam fillings is proportional to the number of fillings and the total amalgam surface area. It has been difficult to accurately estimate the release from amalgam fillings; however, an expert committee from the World Health Organization believes that the average exposure from dental amalgam is approximately 10 mcg/day. Measurements of urinary excretion of mercury have revealed that persons with a habit of tooth grinding release considerably more mercury from their dental fillings than those without this habit. Health studies have focused on identifying the early effects of mercury on the central nervous system. Overall, there is no evidence suggesting a link between exposure to mercury from amalgam fillings and degenerative changes of the nervous system. There is also little evidence to support the removal of existing fillings .... Treatment with chelators may be considered in patients with acute symptoms arising from the central nervous system due to confirmed mercury poisoning (e.g., via measurement of mercury in air, blood, or urine)".

Grandjean et al (1997) stated that treatment of patients who attribute their environmental illness to mercury from amalgam fillings is largely experimental. On the Symptom Check List, overall distress, and somatization, obsessive-compulsive, depression, and anxiety symptom dimensions, were increased in 50 consecutive patients examined, and Eysenck Personality Questionnaire scores suggested less extroversion and increased degree of emotional liability. Succimer (meso-2, 3-dimercaptoposuccinic acid) was given at a daily dose of 30 mg/kg for 5 days in a double-blind, randomized placebo-controlled trial. Urinary excretion of mercury and lead was considerably increased in the patients who received the chelator. Immediately after the treatment and 5 to 6 weeks later, most distress dimensions had improved considerably, but there was no difference between the succimer and placebo groups. The authors concluded that these findings suggested that some patients with environmental illness may substantially benefit from placebo.

Glotzer (1993) stated that 2,3-dimercaptoposuccinic acid (DMSA) is an orally active chelating agent used in the treatment of lead and other heavy metal poisonings. In animals, DMSA
Chelates lead from soft tissues, including the brain, without clinically evident adverse effects or histopathological changes. In lead-poisoned children and adults, DMSA significantly increases urinary lead excretion, and, at least transiently, reduces the blood lead concentration. The safety profile of DMSA in both children and adults is encouraging, with few clinically apparent or biochemical adverse effects reported. However, clinical experience with DMSA is limited, and is not sufficient to exclude the possibility that other more serious drug-related adverse events including hypersensitivity or idiosyncratic reactions may occur. No data currently exist to determine whether drug-enhanced lead excretion with DMSA (or any other chelating agent) is beneficial in reducing lead-related neurotoxicity. The efficacy of DMSA in reducing neuropsychological morbidity, and additional safety data, are key areas requiring additional study before DMSA can be clearly recommended as the chelating agent of choice for the treatment of lead-poisoned children.

An UpToDate review on “Adult lead poisoning” (Goldman and Hu, 2012) states that “Provocative chelation is a mobilization test that has been proposed to give an indirect measure of lead body burden and thereby determine if chelation therapy is indicated. Some medical practices assess lead poisoning by provocative chelation with DMSA or CaEDTA, comparing urinary excretion to reference ranges for non-challenged urine specimens. Studies have failed to establish a valid correlation between prior metal exposure and post-challenge test values. The American College of Medical Toxicology (ACMT) does not support provocative chelation”. Furthermore, an UpToDate review on “Childhood lead poisoning: Management” (Hurwitz and Lee, 2012) states that “CaNa2EDTA mobilization tests, once used as indicators of potential response to chelation therapy in children with moderate lead intoxication, are no longer used by most centers that treat childhood lead poisoning. They are thought to be unnecessary because most patients with BLL [blood lead levels] greater than 40 microgram/dL (1.93 micromol/L) have an adequate response. In addition, they are expensive and difficult to administer”.

A report of the Advisory Committee on Childhood Lead Poisoning Prevention of the Centers for Disease Control and Prevention (2012) states that “There is no medical foundation for relying on the following methods to diagnose over-exposure to lead: gingival lead lines, testing of neurophysiologic function; evaluation of renal function (except during chelation with EDTA); testing of hair, teeth, packed red cells, saliva or fingernails for lead; radiographic imaging of long bones, nor is provocative chelation prior to measurement of lead in urine testing recommended. The widely accepted sequelae of BLLs less than 45 μg/dL are cognitive and behavioral impairment. Chelation of children with BLLs greater than or equal to 20 and less than or equal to 45 μg/dL has not been shown to offer therapeutic benefit for these outcomes”.

In a double-blind, placebo-controlled, 2 × 2 factorial randomized trial, Lamas and colleagues (2013) examined if an EDTA-based chelation regimen reduces cardiovascular events. A total of 1,708 patients aged 50 years or older who had experienced a myocardial infarction (MI) at least 6 weeks prior and had serum creatinine levels of 2.0 mg/dL or less were included in this study. Participants were recruited at 134 U.S. and Canadian sites. Enrollment began in September 2003 and follow-up took place until October 2011 (median of 55 months). A total of 289 patients (17 % of total; n = 115 in the EDTA group and n = 174 in the placebo group) withdrew consent during the trial. Patients were randomized to receive 40 infusions of a 500-ml chelation solution (3 g of disodium EDTA, 7 g of ascorbate, B vitamins, electrolytes, procaine, and heparin) (n = 839) versus placebo (n = 869) and an oral vitamin-mineral regimen versus an oral placebo. Infusions were administered weekly for 30 weeks, followed by 10 infusions 2 to 8 weeks apart. Fifteen percent discontinued infusions (n = 38 [16 %] in the chelation group and n = 41 [15 %] in the placebo group) because of adverse events. The pre-specified primary end-point was a composite of total mortality, recurrent MI, stroke, coronary re-vascularization, or hospitalization for angina. This report described the intention-to-treat comparison of EDTA chelation versus placebo. To account
A primary end-point occurred in 222 (26%) of the chelation group and 261 (30%) of the placebo group (hazard ratio [HR], 0.82 [95% confidence interval [CI]: 0.69 to 0.99]; p = 0.035). There was no effect on total mortality (chelation: 87 deaths [10%]; placebo, 93 deaths [11%]; HR, 0.93 [95% CI: 0.70 to 1.25]; p = 0.64), but the study was not powered for this comparison. The effect of EDTA chelation on the components of the primary end-point other than death was of similar magnitude as its overall effect (MI: chelation, 6%; placebo, 8%; HR, 0.77 [95% CI: 0.54 to 1.11]; stroke: chelation, 1.2%; placebo, 1.5%; HR, 0.77 [95% CI: 0.34 to 1.76]; coronary revascularization: chelation, 15%; placebo, 18%; HR, 0.81 [95% CI: 0.64 to 1.02]; hospitalization for angina: chelation, 1.6%; placebo, 2.1%; HR, 0.72 [95% CI: 0.35 to 1.47]). Sensitivity analyses examining the effect of patient drop-out and treatment adherence did not alter the results. The authors concluded that among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of adverse cardiovascular outcomes, many of which were re-vascularization procedures. Moreover, they stated that these results provided evidence to guide further research; but were insufficient to support the routine use of chelation therapy for treatment of patients who had an MI.

Escolar et al (2014) examined the effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior MI. Patients received 40 infusions of EDTA chelation (n = 322) or placebo (n = 311); EDTA reduced the primary end-point (death, re-infarction, stroke, coronary re-vascularization, or hospitalization for angina; 25% versus 38%; hazard ratio, 0.59; 95% CI: 0.44 to 0.79; p < 0.001) over 5 years. The result remained significant after Bonferroni adjustment for multiple subgroups (99.4% CI: 0.39 to 0.88; adjusted p=0.002). All-cause mortality was reduced by EDTA chelation (10% versus 16%; HR, 0.57; 95% CI: 0.36 to 0.88; p = 0.011), as was the secondary end-point (cardiovascular death, re-infarction, or stroke; 11% versus 17%; HR, 0.60; 95% CI: 0.39 to 0.91; p = 0.017). However, after adjusting for multiple subgroups, those results were no longer significant. The number needed to treat to reduce 1 primary end-point over 5 years was 6.5 (95% CI: 4.4 to 12.7). There was no reduction in events in non-diabetes mellitus (n = 1.075; p = 0.877), resulting in a treatment by diabetes mellitus interaction (p = 0.004). The authors concluded that post-MI patients with diabetes mellitus aged greater than or equal to 50 demonstrated a marked reduction in cardiovascular events with EDTA chelation. They stated that these findings supported efforts to replicate these findings and define the mechanisms of benefit. However, they do not constitute sufficient evidence to indicate the routine use of chelation therapy for all post-MI patients with diabetes mellitus.

Vlachos and Muir (2010) stated that Diamond-Blackfan anemia (DBA) is characterized by red cell failure, the presence of congenital anomalies, and cancer predisposition. In addition to being an inherited bone marrow failure syndrome, DBA is also categorized as a ribosomopathy as, in more than 50% of cases, the syndrome appears to result from haplo-insufficiency of either a small or large subunit-associated ribosomal protein. Nonetheless, the exact mechanism by which haplo-insufficiency results in erythroid failure, as well as all the other clinical manifestations, remains uncertain. New knowledge regarding genetic and molecular mechanisms combined with robust clinical data from several international patient registries has provided important insights into the diagnosis of DBA and may, in the future, provide new treatments as well. Diagnostic criteria have been expanded to include patients with little or no clinical findings. Patient management is therefore centered on accurate diagnosis, appropriate use of transfusions and iron chelation, corticosteroids, hematopoietic stem cell transplantation, and a coordinated multi-disciplinary approach to these complex patients.
An UpToDate review on “Anemia in children due to decreased red blood cell production” (Sandoval, 2013) states that “The mainstays of therapy of DBA are corticosteroids and blood transfusion. However, spontaneous remissions have been reported in as many as 25 percent of patients. Overall, approximately 40 percent of individuals with DBA are steroid-dependent, 40 percent are transfusion-dependent, and 20 percent go into remission by age 25 years. In most cases the remission is stable …. Transfusion therapy is the mainstay of treatment for patients in whom steroid therapy is ineffective or in whom corticosteroid toxicity is prohibitive. To avoid red cell sensitization and transfusion reactions, complete red cell typing should be performed, and blood should be leuko-depleted. Patients are transfused to maintain Hgb levels compatible with normal activity (Hgb ≥ 8 g/dL), usually every four to six weeks. Immediate family members should not be used as blood donors, to avoid allosensitization which might jeopardize future hematopoietic cell transplantation. The major complication of transfusion therapy is hemosiderosis, which may result in significant morbidity and mortality. Iron chelation therapy should, therefore, be instituted in patients with evidence of significantly increased iron stores”.

Also, the CDC’s DBA Fact Sheet states that “In Diamond Blackfan anemia (DBA) the bone marrow (the center of the bones where blood cells are made) does not make enough red blood cells. One of the treatments for DBA is blood transfusion therapy. Blood transfusions temporarily increase the number of red blood cells. Some people need blood transfusions only now and then, such as when they are sick. Other people need regular blood transfusions over a long period of time. This is called chronic transfusion therapy. One of the risks of chronic transfusion therapy is getting too much iron in the body. Blood contains a lot of iron. Because the body has no natural way to get rid of iron, the iron in transfused blood builds up in the body, a condition called iron overload. Eventually, after dozens of transfusions, the iron will build up to toxic levels and can damage different organs in the body. The iron cannot be removed from the blood before transfusion, as it is a critical component of hemoglobin, a protein in red blood cells that carries oxygen. Fortunately, iron overload and organ damage can be prevented with chelation therapy …. There are currently 2 chelation drugs available in the United States: (i) deferoxamine (Desferal), and (ii) deferasirox (Exjade)”.


Delforge and colleagues (2014) noted that most patients with myelodysplastic syndromes (MDS) require transfusions at the risk of iron overload and associated organ damage, and death. Emerging evidence indicated that iron chelation therapy (ICT) could reduce mortality and improve survival in transfusion-dependent MDS patients, especially those classified as IPSS Low or Intermediate-1 (Low/Int-1). In a follow-up of a retrospective study, outcomes of 127 Low/Int-1 MDS patients from 28 centers in Belgium were analyzed. Statistical analysis stratified by duration (greater than or equal to 6 months versus less than 6 months) and quality of chelation (adequate versus weak). Crude chelation rate was 63 %, but 88 % among patients with serum ferritin greater than or equal to 1,000 μg/L. Of the 80 chelated patients, 70 % were chelated adequately mainly with deferasirox (26 %) or deferasirox following deferoxamine (39 %). Mortality was 70 % among non-chelated, 40 % among chelated, 32 % among patients chelated greater than or equal to 6 months, and 30 % among patients chelated adequately; with a trend toward reduced cardiac mortality in chelated patients. Overall, median overall survival (OS) was 10.2 years for chelated and 3.1 years for non-chelated patients (p < 0.001). For patients chelated greater than or equal to 6 months or patients classified as adequately chelated, median OS was 10.5 years. Mortality increased as a function of average monthly transfusion intensity (HR = 1.08, p = 0.04), but was lower in patients receiving adequate chelation or chelation greater than or equal to 6 months (HR = 0.24, p < 0.001). The authors concluded that 6 or more months of adequate ICT is associated with markedly better overall survival.
Angelucci and associates (2014) stated that in the absence of RCT data to support ICT in transfusion-dependent patients with MDS, continued evidence from large prospective clinical trials evaluating the efficacy and safety of iron chelation therapy in this patient population is warranted. The safety and efficacy of deferasirox was examined in a prospective, open-label, single-arm, multi-center trial of transfusion-dependent patients with IPSS Low- or Intermediate-1-risk MDS and evidence of transfusion-related iron overload. The effects of deferasirox therapy on hematological response and disease progression were also examined. Of 159 participants enrolled from 37 Italian centers, 152 received greater than or equal to 1 dose of deferasirox (initiated at 10 to 20 mg/kg/day and titrated as appropriate), and 68 completed the study. Of 84 patients who discontinued deferasirox therapy, 22 died during the trial, and 28 withdrew due to an adverse event (AE). Fourteen treatment-related grade 3 AEs occurred in 11 patients, whereas no grade 4 or 5 drug-related AEs were reported. Significant risks for drop-out were a higher serum ferritin level at baseline, a higher MDS-Specific Comorbidity Index, and a shorter diagnosis-enrollment interval. Median serum ferritin level fell from 1,966 ng/ml to 1,475 ng/ml (p < 0.0001). The cumulative incidence of transfusion independence, adjusted for death and disease progression, was 2.6 %, 12.3 %, and 15.5 % after 6, 9, and 12 months, respectively. The authors concluded that deferasirox therapy in transfusion-dependent patients with MDS was moderately well-tolerated and effectively lowered serum ferritin levels. Positive hematological responses were observed, and a subset of patients achieved transfusion independence.

Remacha et al (2014) evaluated the evolution of iron overload, assessed by serum ferritin (SF), in transfusion-dependent lower risk patients with MDS, as well as described the occurrence of organ complications, and analyzed its relationship with ICT. This observational retrospective study was conducted from March 2010 to March 2011 in 47 Spanish hospitals. A total of 263 patients with lower risk MDS (IPSS Low/Intermediate-1 risk or Spanish Prognostic Index [SPI] 0-1 risk), transfusion-dependent, and who had received greater than or equal to 10 packed red blood cells (PRBC) were included. At MDS diagnosis, patients received a mean of 2.8 ± 3.9 PRBC/month, and 8.7 % of patients showed SF greater than or equal to 1,000 μg/L. Over the course of the disease, patients received a mean of 83.4 ± 83.3 PRBC, and 36.1 % of patients presented SF greater than or equal to 2,500 μg/L. Cardiac, hepatic, endocrine, or arthropathy complications appeared/worsened in 20.2, 11.4, 9.9, and 3.8 % of patients, respectively. According to investigator, iron overload was a main cause of hepatic (70.0 %) and endocrine (26.9 %) complications. A total of 96 (36.5 %) patients received iron chelation therapy for greater than or equal to 6 months; deferasirox being the most frequent first chelation treatment (71.9 %). Chelation-treated patients showed longer overall survival (p < 0.001), leukemia-free survival (p = 0.007), and cardiac event-free survival (p = 0.017) than non-chelated patients. In multi-variable analyses, age (p = 0.011), IPSS (p < 0.001), and chelation treatment (p = 0.015) were predictors for overall survival; IPSS (p = 0.014) and transfusion frequency (p = 0.001) for leukemia-free survival; and chelation treatment (p = 0.040) and Sorror comorbidity index (p = 0.039) for cardiac event-free survival. The authors concluded that these results confirmed the potential survival benefit of ICT and provided additional evidence on the deleterious effect of iron overload in lower risk MDS patients.

The National Comprehensive Cancer Network’s clinical practice guideline on “Myelodysplastic syndromes.” (Version 1.2015) recommends “consideration of once-daily deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload (aiming for a target ferritin level less than 1,000 ng/ml) in the following IPSS Low- or Intermediate-1-risk patients: (i) patients who have received or are anticipated to receive greater than 20 RBC transfusions; (ii) patients for whom ongoing RBC transfusions are anticipated; and (iii) patients with serum ferritin greater than 2,500 ng/ml."
CPT Codes / HCPCS Codes / ICD-9 Codes

Chelation therapy:

Other CPT codes related to the CPB:

96365 - 96368  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)

HCPCS codes covered if selection criteria are met:

J0470  Injection, dimercaprol, per 100 mg
J0600  Injection, edetate calcium disodium, up to 1000 mg
J0895  Injection, deferoxamine mesylate, 500 mg
J3520  Edetate disodium, per 150 mg
M0300  IV chelation therapy (chemical endarterectomy)
S9355  Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-9 codes covered if selection criteria are met:

270.0  Disturbances of amino-acid transport [cystinuria]
275.02  Hemochromatoses due to repeated red blood cell transfusions
275.09  Other disorders of iron metabolism
275.1  Disorders of copper metabolism [Wilson's disease]
282.41  Sickle-cell thalassemia without crisis
282.42  Sickle-cell thalassemia with crisis
282.44  Beta thalassemia
282.60 - 282.69  Sickle-cell anemia
284.01  Constitutional red blood cell aplasia [Blackfan-Diamond syndrome]
571.6  Biliary cirrhosis
585.6  End stage renal disease [due to iron overload from multiple transfusions]
961.1  Poisoning by arsenical anti-infectives
961.2  Poisoning by heavy metal anti-infectives [not covered for treatment of (mercury toxicity) from dental amalgam filings]
964.0  Poisoning by iron and its compounds
965.69  Poisoning by other antirheumatics [gold salts]
984.0 - 984.9  Toxic effect of lead and its compounds (including fumes)
985.0 Toxic effect of mercury and its compounds [not covered for treatment of (mercury toxicity) from dental amalgam fillings]
985.1 Toxic effect of arsenic and its compounds
985.5 Toxic effect of cadmium and its compounds
985.8 Toxic effect of other specified metals

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>088.81</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>117.7</td>
<td>Zygomycosis (Phycomycosis or Mucormycosis)</td>
</tr>
<tr>
<td>140.0 - 209.36, 209.75</td>
<td>Malignant neoplasm</td>
</tr>
<tr>
<td>230.0 - 234.9</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>299.00 - 299.01</td>
<td>Autistic disorder</td>
</tr>
<tr>
<td>314.00 - 314.01</td>
<td>Attention deficit disorder</td>
</tr>
<tr>
<td>330.0 - 337.9</td>
<td>Hereditary and degenerative diseases of the central nervous system</td>
</tr>
<tr>
<td>366.41</td>
<td>Diabetic cataract</td>
</tr>
<tr>
<td>390 - 429.9</td>
<td>Rheumatic heart disease, hypertensive disease, ischemic heart disease, diseases of pulmonary circulation, and other forms of heart disease</td>
</tr>
<tr>
<td>440.20 - 440.29</td>
<td>Atherosclerosis of native arteries of the extremities</td>
</tr>
<tr>
<td>440.30 - 440.32</td>
<td>Atherosclerosis of bypass graft of the extremities</td>
</tr>
<tr>
<td>440.8</td>
<td>Atherosclerosis of other specified arteries</td>
</tr>
<tr>
<td>440.9</td>
<td>Generalized and unspecified atherosclerosis</td>
</tr>
<tr>
<td>443.0</td>
<td>Raynaud’s syndrome</td>
</tr>
<tr>
<td>443.1</td>
<td>Thromboangiitis obliterans (Buerger’s disease)</td>
</tr>
<tr>
<td>443.82 - 443.9</td>
<td>Other specified peripheral vascular diseases</td>
</tr>
<tr>
<td>780.79</td>
<td>Other malaise and fatigue</td>
</tr>
<tr>
<td>V07.8 - V07.9</td>
<td>Other and unspecified prophylactic measure [prevention of cardiovascular disease]</td>
</tr>
<tr>
<td>V45.82</td>
<td>Percutaneous transluminal coronary angioplasty status</td>
</tr>
</tbody>
</table>

Other ICD-9 codes related to the CPB:

V45.11 Renal dialysis status

Laboratory tests for heavy metal poisoning:

CPT codes covered if selection criteria are met:
Heavy metal (e.g., arsenic, barium, beryllium, bismuth, antimony, mercury); screen

quantitative, each

ICD-9 codes covered if selection criteria are met (not all-inclusive):

279.00 - 279.9 Disorders involving the immune mechanism
280.0 - 280.9 Iron deficiency anemias
307.52 Pica
312.9 Unspecified disturbance of conduct
315.00 - 315.9 Specific delays in development
389.00 - 389.9 Hearing loss
523.00 - 523.11 Gingivitis
527.7 Disturbances of salivary secretion
558.9 Other and unspecified noninfectious gastroenteritis and colitis
564.00 Constipation, unspecified
583.0 - 583.9 Nephritis and nephropathy, not specified as acute or chronic
593.9 Unspecified disorder of kidney and ureter
698.8 - 698.9 Other and unspecified pruritis
728.87 Muscle weakness (generalized)
780.01 Coma
780.02 Transient alteration of awareness
780.39 Other convulsions
780.93 Memory loss
781.0 Abnormal involuntary movements
781.3 Lack of coordination [ataxia]
782.0 Disturbance of skin sensation
782.1 Rash and other nonspecific skin eruption
782.2 Localized superficial swelling, mass, or lump
782.3 Edema
782.8 Changes in skin texture
783.0 Anorexia
783.21 Loss of weight
783.40 - 784.43 Lack of expected normal physiological development in childhood
784.0 Headache
787.01 - 787.03 Nausea and vomiting
787.91 Diarrhea
788.5 Oliguria and anuria
789.00 - 789.09 Abdominal pain
794.4 Nonspecific abnormal results of function studies of kidney
799.2 Nervousness
961.1 Poisoning by arsenical anti-infectives
961.2 Poisoning by heavy metal anti-infectives
964.0 Poisoning by iron and its compounds
965.69 Poisoning by other antirheumatics [gold salts]
976.4 Poisoning by keratolytics, keratoplastics, other hair treatment drugs and preparations
984.0 - 984.9 Toxic effect of lead and its compounds (including fumes)
985.0 Toxic effect of mercury and its compounds
985.1 Toxic effect of arsenic and its compounds
985.5 Toxic effect of cadmium and its compounds
985.8 Toxic effect of other specified metals
995.52 Child neglect (nutritional)
995.59 Other child abuse and neglect
E861.5 Accidental poisoning by lead paints
E866.0 Accidental poisoning by lead and its compounds and fumes
E904.0 Abandonment or neglect of infants and helpless persons
V15.86 Exposure to lead

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):
780.79 Other malaise and fatigue [lethargy]

Dimercaptosuccinic acid (DMSA) or ethylenediaminetetraacetic (EDTA) provocative chelation/mobilization test:
No specific code

ICD-9 codes not covered for indications listed in the CPB:
984.0 - 984.9 Toxic effect of lead and its compounds (including fumes)
The above policy is based on the following references:

neuropsychological and behavioral development of lead-exposed children after school
22. Smith HJ, Meremikwu M. Iron chelating agents for treating malaria. Cochrane
transfusional iron overload in people with transfusion-dependent thalassaemia.
24. Risher JF, Amler SN. Mercury exposure: Evaluation and intervention the inappropriate
use of chelating agents in the diagnosis and treatment of putative mercury poisoning.
25. Pittler MH, Ernst E. Complementary therapies for peripheral arterial disease:
27. Agency for Health Care Policy and Research (AHCPR). Hemoperfusion in conjunction
with deferoxamine for the treatment of aluminum toxicity or iron overload in patients
Rockville, MD; AHCPR; 1986;8:1-20.
29. No authors listed. Aluminum toxicity in infants and children. American Academy of
30. Barata JD, D’Haese PC, Pires C, et al. Low-dose (5 mg/kg) deferoxamine treatment
in acutely aluminium-intoxicated haemodialysis patients using two drug administration
32. Shrihari JS, Roy A, Prabhakaran D, Reddy KS. Role of EDTA chelation therapy in
33. Arthur HM, Patterson C, Stone JA. The role of complementary and alternative
therapies in cardiac rehabilitation: A systematic evaluation. Eur J Cardiovasc Prev
34. Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA). Efficacy,
effectiveness and security of the chelation therapy for the treatment of autistic
38. Chappell LT. Should EDTA chelation therapy be used instead of long-term clopidogrel
plus aspirin to treat patients at risk from drug-eluting stents? Altern Med Rev. 2007;12
(2):152-158.
Safety Monographs. International Program on Chemical Safety. WHO/IEG/94.2
40. Fischbein, A. Occupational and environmental exposure to lead. In: Environmental
and Occupational Medicine, Rom, WN (Ed), Philadelphia, Lippincott-Raven


71. Elinder C-G. Epidemiology and toxicity of mercury. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2012.
73. Hurwitz RL, Lee DA. Childhood lead poisoning: Management. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2012.
76. Sandoval C. Anemia in children due to decreased red blood cell production. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2013.


