Title: Chelation Therapy for Off-Label Uses

**Professional**
Original Effective Date: October 29, 2009
Revision Date(s): November 19, 2012; March 31, 2014, August 19, 2016
Current Effective Date: August 19, 2016

**Institutional**
Original Effective Date: October 29, 2009
Revision Date(s): December 19, 2012; March 31, 2014, August 19, 2016
Current Effective Date: August 19, 2016

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<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<tr>
<td>• With Alzheimer disease, cardiovascular disease, autism, diabetes, multiple sclerosis, or arthritis</td>
<td>• Chelation therapy</td>
<td>• Standard medical care</td>
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<tr>
<td></td>
<td></td>
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<td>• Change in disease status</td>
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DESCRIPTION
Chelation therapy, an established treatment for treating heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of other applications including treatment of atherosclerosis, Alzheimer’s disease, and autism.

Background
Chelation therapy is an established treatment for the removal of metal toxins by converting them to a chemically inert form that can be excreted in the urine. Chelation therapy comprises intravenous or oral administration of chelating agents that remove metal ions such as lead, aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body (see Appendix Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, desferroxamine (not approved by the Food and Drug Administration [FDA]) is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning (Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.)

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer’s disease, which is associated with the disequilibrium of cerebral metals. Unlike traditional systemic chelators that bind and remove metals from tissues systemically, MPACs have subtle effects on metal homeostasis and abnormal metal interactions. In animal models of Alzheimer’s disease, they promote the solubilization and clearance of β-amyloid by binding its metal-ion complex, and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt 2 putative pathogenic processes of Alzheimer’s disease. However, no MPACs have received FDA approval for the treatment of Alzheimer’s disease.

Chelation therapy has also been discussed as a treatment for other indications including atherosclerosis and autism. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved calcium-EDTA (Versenate) for lowering blood lead levels among both pediatric and adult patients with lead poisoning. Succimer is approved for the treatment of lead poisoning in pediatric patients only. FDA approved disodium-EDTA for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, FDA withdrew approval of disodium-EDTA due to safety concerns, and recommended that other forms of chelation therapy be used.

Several iron chelating agents are FDA approved:
- Deferoxamine for subcutaneous, intramuscular, or intravenous injections was approved to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia.
Deferasirox, approved in 2005, is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients aged 2 years and older. Under the accelerated approval program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia.

In 2011, FDA approved the iron chelator, deferiprone (Ferriprox®), for treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form for oral use.

In a June 2014 warning to consumers, FDA advised that FDA-approved chelating agents are available by prescription only. There are no FDA-approved over-the-counter chelation products.

**POLICY**

Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration) are considered *experimental / investigational*, including, but not limited to:

1. Alzheimer’s disease
2. arthritis (includes rheumatoid arthritis)
3. atherosclerosis (e.g., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
4. autism
5. diabetes
6. multiple sclerosis

Policy Guidelines

1. A number of indications for chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:
   a. extreme conditions of metal toxicity
   b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)
   c. Wilson disease (hepatolenticular degeneration)
   d. lead poisoning
   e. control of ventricular arrhythmias or heart block associated with digitalis toxicity
   f. emergency treatment of hypercalcemia
2. For items 1 e and 1 f, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. FDA removed the approval for NaEDTA as chelation therapy due to
safety concerns and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

3. Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1.

**RATIONALE**
The evidence review was updated with literature searches using MEDLINE. Most recently the literature review covered the period through December 10, 2015.

Chelation therapy is an established treatment for metal toxicity and transfusional hemosiderosis. These uses are not covered in this evidence review. Literature searches have focused on the use of chelation therapy for off-label conditions including, but not limited to, Alzheimer disease, atherosclerosis, autism, diabetes, and other conditions (eg, multiple sclerosis, arthritis).

**Alzheimer Disease**
A 2008 Cochrane review evaluated metal protein attenuating compounds (MPACs) for treating Alzheimer disease. The review identified 1 placebo-controlled randomized trial. This study, by Richie et al, was published in 2003. Patients were treated with PBT1, an MPAC also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier. The Food and Drug Administration withdrew clioquinol for oral use in 1970 because of its association with subacute myelo-optic neuropathy. Richie administered oral clioquinol to 16 Alzheimer disease patients in doses increasing to 375 mg twice daily and compared this group with 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer Disease Assessment Scale–Cognitive (ADAS-Cog). One patient in the treatment group developed impairments in visual acuity and color vision during weeks 31 to 36 of treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. A 2012 update of this review included trials through December 2011. Only the Lannfelt et al trial, discussed next, was identified.

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt et al (2008) completed a double-blind, placebo-controlled randomized trial of 78 Alzheimer disease patients who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29). There was no statistically significant difference in ADAS-Cog or Mini-Mental Status Examination scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis, transient ischemic event) were reported in the placebo arm.

Ongoing investigations in chelation therapy for the treatment of Alzheimer disease and other neurodegenerative diseases include linking a carbohydrate moiety to drug molecules to enhance drug delivery across the blood-brain barrier; this strategy may solve the potential problem of premature and indiscriminate metal binding. In addition, multifunction drugs that not only bind metal but also have significant antioxidant capacity are in development.

**Section Summary: Alzheimer Disease**
There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published randomized controlled trials (RCTs) did not find that the treatment was superior to placebo for improving health outcomes.
Cardiovascular Disease

Atherosclerosis
In 2002, Villarruz et al published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease. Five placebo-controlled randomized trials were identified, none of which reported mortality, nonfatal events, or cerebrovascular events. Four (n=250 patients) of the 5 studies found no significant benefit of EDTA chelation therapy on reported outcomes, including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study (n=10 patients) was stopped early due to benefit, but relevant outcome data were unavailable. The Cochrane reviewers concluded that evidence was insufficient to draw conclusions about the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were needed.

Among published RCTs, Knudtson et al (2002) randomized 84 patients with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo. Treatment was administered for 3 hours twice weekly for 15 weeks and then monthly for 3 months. Outcome measures included change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the 2 groups. Another double-blind, placebo-controlled randomized trial of EDTA chelation showed no difference between groups in short- or long-term improvement in vasomotor response. Two small RCTs from the 1990s also reported no benefit of chelation therapy as a treatment for peripheral arterial disease.

Section Summary: Atherosclerosis
Several RCTs of chelation therapy for treating atherosclerosis generally have reported intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs that report health outcomes are needed to establish treatment efficacy.

Myocardial Infarction
In 2013, Lamas et al published results of the multicenter, 2×2 factorial, randomized, double-blind Trial to Assess Chelation Therapy (TACT). TACT included 1708 patients, ages 50 years or older, who had a history of myocardial infarction (MI) at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to receive 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Patients also received oral high-dose vitamin plus mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. Primary end point was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years. The threshold for statistical significance was adjusted for multiple interim analyses to a p value of 0.036. A total of 361 (43%) patients in the chelation group and 464 (57%) patients in the placebo group discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary end point were 33% (95% confidence interval [CI], 29% to 37%) in the chelation group and 39% (95% CI, 35% to 42%) in the control group, a statistically significant difference (log-rank test, p=0.035). The most common individual clinical end point was coronary revascularization, which occurred in 130 (16%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=0.08). The next most frequent end point was death, which occurred in 87 (10%) patients in the chelation group and 93 (11%) patients in the placebo group (p=0.64). No individual component of the primary outcome differed statistically between groups; however, the study was
not powered to detect differences in individual components. Four severe adverse events definitely or possibly related to study therapy occurred, 2 each in the treatment and control groups, including 1 death in each group. Quality-of-life outcomes (reported in 2014) did not differ between groups at 2-year follow-up.\textsuperscript{15}

Another 2014 follow-up publication reported results of the 4 treatment groups in the $2 \times 2$ factorial design (double-active group [disodium EDTA infusions with oral high-dose vitamins; $n=421$ patients], active infusions with placebo vitamins [$n=418$ patients], placebo infusions with active vitamins [$n=432$ patients], double placebo [$n=437$ patients]).\textsuperscript{16} The proportion of patients who discontinued treatment, withdrew consent, or were lost to follow-up per treatment group was not reported. Five-year Kaplan-Meier estimates for the primary composite end point were 32\%, 34\%, 37\%, and 40\%, respectively. The reduction in primary end point by double-active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74; 95\% CI, 0.57 to 0.95). In 633 patients with diabetes ($\approx$36\% of each treatment group), the primary end point reduction in the double-active group compared with the double placebo group was more pronounced (HR=0.49; 95\% CI, 0.33 to 0.75).

The study is limited by the high number of withdrawals, with differential withdrawals between groups. The primary end point included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary end point barely met the significance threshold; if more patients had remained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the original (2013) publication, 60\% of patients were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in a population that was not generalizable to that seen in general clinical care.\textsuperscript{17} Editorialists commenting on the subsequent (2014) publication suggested that further research is warranted to replicate the findings.\textsuperscript{18}

This substudy has the same limitations as the parent study previously described, namely, high and differential withdrawal and heterogeneous composite end point. Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

**Section Summary: Myocardial Infarction**
One RCT with limitations, including high dropout with differential dropout between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes mellitus. However, this trial was not of high quality and, therefore, results may be biased. More high-quality trials are needed to corroborate whether chelation therapy improves outcomes in patients with prior MI.

**Autism**
Based on symptoms similarities between mercury poisoning and autism spectrum disorder, Bernard et al (2001) hypothesized a link between environmental mercury and autism.\textsuperscript{19} This theory was rejected by Nelson and Bauman (2003), who found that many characteristics of mercury poisoning, such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children.\textsuperscript{20} A 2007 meta-analysis by Ng et al concluded that there was no association between mercury poisoning and autism.\textsuperscript{21}
In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and identified no controlled studies. The author stated that case series suggested a potential role for chelation in treating some autistic people with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

Section Summary: Autism
There is a lack of controlled studies on how chelation therapy effects health outcomes in patients with autism.

Diabetes
Cardiovascular Disease in Patients With Diabetes
A 2009 trial by Cooper et al in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes. Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area in the active treatment group than in the placebo group (-10.6 g/m² vs -0.1 g/m², p=0.01). The study was limited by small sample size and high dropout rate.

Escolar et al (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. In TACT, there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes: Among 538 (31% of the trial sample) self-reported diabetic patients, those randomized to EDTA had a 39% reduced risk of the primary composite outcome compared with placebo (HR=0.61; 95% CI, 0.45 to 0.83; log rank test, p=0.02); among 1170 nondiabetic patients, risk of the primary outcome did not differ statistically between treatment groups (HR=0.96; 95% CI, 0.77 to 1.20; log rank test, p=0.73). For the subsequent subgroup analysis, the definition of diabetes mellitus was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose of 126 mg/dL or more at trial entry. Of 1708 patients in TACT, 633 (37%) had diabetes mellitus by this definition: 322 were randomized to EDTA and 311 to placebo. Compared with all other trial participants, this subgroup of diabetic patients had higher body mass index, fasting blood glucose, and prevalence of heart failure, stroke, hypertension, peripheral artery disease, and hypercholesterolemia. Within this subgroup, baseline characteristics were similar between treatment groups. With approximately 5 years of follow-up, the primary composite end point occurred in 25% of the EDTA group and 38% of the placebo group (HR=0.59; 99.4% CI, 0.39 to 0.88 [adjusted for multiple subgroups]; log-rank test, p=0.002). In adjusted analysis of the individual components of the primary end point, there were no statistically significant differences between treatment groups. Thirty-six adverse events attributable to study drug that led to trial withdrawal, 16 in the EDTA group and 20 in the placebo group.

Diabetic Nephropathy
Chen et al (2012) conducted a single-blind RCT of chelation therapy effects on the progression of diabetic nephropathy in Chinese patients with high-normal lead levels. Fifty patients with diabetes, high-normal body lead burden (80-6000 µg), and serum creatinine 3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 µg/dL in the treatment group and 7.1 µg/dL in the control group; baseline mean body lead burden was 151 µg in the treatment group and 142 µg in the control group. According to the U.S. Occupational and Health Safety Administration, maximum acceptable blood lead level in adults is 40 µg/dL. Patients were
randomized to 3 months of calcium disodium EDTA or placebo. During 24 months of treatment follow-up, patients in the chelation group received additional chelation treatments as needed (ie, for serum creatinine level above pretreatment levels or body lead burden >60 μg), and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate (eGFR). Mean (SD) yearly rate of decrease in eGFR was 5.6 (5.0) mL/min/173 m² in the chelation group and 9.2 (3.6) mL/min/173 m² in the control group, a statistically significant difference (p=0.04). Secondary end point was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) patients in the treatment group and 17 (68%) in the control group attained the secondary end point, a statistically significant difference (p=0.02). There were no reported adverse effects of chelation therapy during the 27-month trial period.

Section Summary: Diabetes
Two small RCTs with limitations represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small, single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients that report health outcomes, such as cardiovascular events, end-stage renal disease, and mortality, are needed.

Other Potential Indications
No RCTs or other controlled trials that evaluated safety and efficacy of chelation therapy for other conditions, such as multiple sclerosis or arthritis, were identified. Iron chelation therapy is being investigated for Parkinson disease and endotoxemia.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov identified the following ongoing and unpublished trials that might influence this review, listed in Table 1.

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<th>NCT No.</th>
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<td>NCT01627938</td>
<td>A Phase II Proof of Concept Study Evaluating the Reduction of Mitoxantrone-induced Cardiotoxicity and Neurological Outcome in the Combined Use of Mitoxantrone and Dexrazoxane (Cardioxane®) in Multiple Sclerosis (MSCardioPro)</td>
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<td>NCT01741532</td>
<td>A Randomized, Double-blind, Placebo-controlled Trial of Deferiprone in Patients With Pantothenate Kinase-associated Neurodegeneration (PKAN)</td>
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<td>Study of Deferoxamine Mesylate in Intracerebral Hemorrhage</td>
<td>294</td>
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Summary of Evidence
The evidence for chelation therapy in individuals who have Alzheimer disease, cardiovascular disease, autism, diabetes, multiple sclerosis, or arthritis includes a small number of randomized controlled trials (RCTs) and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One RCT, the Trial to Assess Chelation Therapy (TACT), reported that chelation therapy reduced cardiovascular events in patients with a previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations, including high dropout rates, and therefore conclusions are not definitive. For other conditions, the available RCTs do not report improvements in health outcomes with chelation therapy and the case series are not adequate evidence to determine efficacy. The evidence is insufficient to determine the effect of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Physicians et al
In 2012, the American College of Physicians (ACP), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, and Society of Thoracic Surgeons published a clinical practice guideline on management of stable ischemic heart disease (IHD).30 The guideline recommended that “chelation therapy should not be used with the intent of improving symptoms or reducing cardiovascular risk in patients with stable IHD. (Grade: strong recommendation; low-quality evidence).” However, citing the Trial to Assess Chelation Therapy,14 a 2014 focused update of this guideline included a revised recommendation on chelation therapy, stating that the “usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable IHD.”31 The recommendation was upgraded from class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies).

American College of Cardiology et al
In 2005, the American College of Cardiology, AHA, and other medical societies stated that chelation “is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.)”32 In 2013, ACCF and AHA compiled previous ACC/AHA and ACCF/AHA recommendations issued in 200532 and 201133 on the management of peripheral artery disease.34 The recommendation against chelation therapy remained unchanged.
American College of Physicians
A 2004 clinical practice guideline from ACP\textsuperscript{35} stated that chelation “should not be used to prevent myocardial infarction or death or to reduce symptoms in patients with symptomatic chronic stable angina. (Level of evidence B: Based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.)”

Canadian Cardiovascular Society
Evidence-based, consensus guidelines from the Canadian Cardiovascular Society in 2014 included a conditional recommendation (based on moderate quality evidence) that chelation therapy should not be used to attempt to improve angina or exercise tolerance in patients with stable ischemic heart disease.\textsuperscript{36}

National Institute for Health and Care Excellence

U.S. Preventive Services Task Force Recommendations
Not applicable.

CODING

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<td>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</td>
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Contains Public Information
**Diagnoses**
Experimental / Investigational for all diagnoses related to this medical policy.

### REVISIONS

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<td>▪ Added to A 4 &quot;and due to nontransfusion-dependent thalassemia (NDTD)&quot; to read, &quot;4. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NDTD)&quot;</td>
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<td>▪ Removed ICD-9 Diagnoses Codes: 427.9, 440.0-440.9</td>
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<td>▪ Added ICD-10 Diagnoses Codes</td>
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<td>08-19-2016</td>
<td>Published 07-20-2016. Effective 08-19-2016</td>
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<td>▪ Removed the following from the Policy language and restated the FDA approved indications in Policy Guidelines:</td>
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<td>&quot;Chelation therapy may be considered medically necessary in the treatment of each of the following conditions:</td>
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<tr>
<td></td>
<td>1. extreme conditions of metal toxicity</td>
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<td>2. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT) (NDTD)</td>
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<td>5. control of ventricular arrhythmias or heart block associated with digitalis toxicity</td>
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<td>6. emergency treatment of hypercalcemia</td>
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<td>▪ In policy statement removed &quot;Other&quot; and added &quot;Off-label&quot; and &quot;(see Policy Guidelines section for uses approved by the Food and Drug Administration)&quot; to read &quot;Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration) are considered experimental / investigational, including, but not limited to:&quot;</td>
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<td>▪ Removed Off-label indication &quot;hypoglycemia&quot;</td>
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Administered (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:

a. extreme conditions of metal toxicity
b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)
c. Wilson disease (hepatolenticular degeneration)
d. lead poisoning
e. control of ventricular arrhythmias or heart block associated with digitalis toxicity
f. emergency treatment of hypercalcemia

2. For items 1 e and 1 f, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

3. Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1.

Rationale section updated

In Coding section:
- CPT Code Correction: Replaced 96375 with 96374
- Removed ICD codes and replaced with the phrase "Experimental / Investigational for all diagnoses related to this medical policy."

References updated

Added "Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals"

REFERENCES


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blind, randomised, placebo-controlled trial. Lancet Neurol. Sep 2008;7(9):779-786. PMID 18672400
18. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: When evidence conflicts with beliefs. Am Heart J. Jul 2014;168(1):4-5. PMID 24952853


35. Snow V, Barry P, Fihn SD, et al. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from


APPENDIX

Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1. Reference standards for bismuth, chromium, and manganese were not identified and are not included in the table.

Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Toxic Levels (Normal Levels Where Indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>24-h urine: ≥50 μg/L urine or 100 μg/g creatinine</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Proteinuria and/or ≥15 μg/g creatinine</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Normative excretion: 0.1-1.2 μg/L (serum), 0.1-2.2 μg/L (urine)</td>
</tr>
<tr>
<td>Copper</td>
<td>Normative excretion: 25 μg/24 h (urine)</td>
</tr>
<tr>
<td>Iron</td>
<td>• Nontoxic: &lt;300 μg/dL</td>
</tr>
<tr>
<td></td>
<td>• Severe: &gt;500 μg/dL</td>
</tr>
<tr>
<td></td>
<td><strong>Pediatric</strong></td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lead</td>
<td>• Symptoms or blood lead level ≥45 μg/dL (blood)</td>
</tr>
<tr>
<td></td>
<td>• CDC level of concern: 5 μg/dL</td>
</tr>
<tr>
<td>Mercury</td>
<td>Background exposure normative limits: 1-8 μg/L (whole blood); 4-5 μg/L (urine)^a</td>
</tr>
<tr>
<td>Nickel</td>
<td>• Excessive exposure: ≥8 μg/L (blood)</td>
</tr>
<tr>
<td>Selenium</td>
<td>• Mild toxicity: &gt;1 mg/L (serum)</td>
</tr>
<tr>
<td></td>
<td>• Serious toxicity: &gt;2 mg/L</td>
</tr>
<tr>
<td>Silver</td>
<td>Asymptomatic workers have mean levels of 11 μg/L (serum) and 2.6 μg/L (spot urine)</td>
</tr>
<tr>
<td>Thallium</td>
<td>24-hour urine thallium &gt;5 μg/L</td>
</tr>
<tr>
<td>Zinc</td>
<td>Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)</td>
</tr>
</tbody>
</table>

CDC: Centers for Disease Control and Prevention.

^a Hair analysis is useful to assess mercury exposure in epidemiologic studies. However, hair analysis in individual patients must be interpreted with consideration of the patient’s history, signs, and symptoms, and possible alternative explanations. Measurement of blood and urine mercury levels can exclude exogenous contamination; therefore, blood or urine mercury levels may be more robust measures of exposure in individual patients.45