Anthem

Clinical UM Guideline

Subject: Chelation Therapy
Guideline #: CG-MED-90
Status: Reviewed

Publish Date: 06/28/2023
Last Review Date: 05/11/2023

Description

This document addresses the uses of chelation therapy. Chelation therapy uses naturally occurring or chemically designed molecules to reduce potentially dangerous levels of heavy metals within the body. Chelation therapy is routinely performed for cases of iron overload, lead poisoning, copper toxicity, and other heavy metal conditions. This document is not applicable to agents used for the treatment of drug overdose or toxicities.

Clinical Indications

Medically Necessary:

Chelation therapy is considered **medically necessary** treatment for individuals with relevant clinical findings suggestive of heavy metal toxicity and a probable exposure history in **any** of the following conditions when confirmed by laboratory testing*:

1. Individuals with disorders of iron metabolism (for example, primary or secondary hemochromatosis);**or**
2. Lead overload in cases of acute or long-term lead exposure;**or**
3. Individuals with disorders of copper metabolism (for example, Wilson's disease);**or**
4. Arsenic, mercury, iron, copper, or gold poisoning when long-term exposure and toxicity has been confirmed;**or**
5. Aluminum overload in individuals on chronic hemodialysis.

***Note:** Laboratory testing to confirm heavy metal toxicity should include blood or plasma specimens. In the case of suspected arsenic or mercury toxicity, it may be more appropriate to confirm diagnosis through a non-challenged urinalysis.

Not Medically Necessary:

Chelation therapy is considered **not medically necessary** for the treatment of all other conditions, including but not limited to, when the medically necessary criteria above have not been met.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS	
J0470	Injection, dimercaprol, per 100 mg [BAL in oil]
J0600	Injection, edetate calcium disodium up to 1,000 mg
J0895	Injection, deferoxamine mesylate, 500 mg [Desferal]
J3520	Edetate disodium, per 150 mg
M0300	IV chelation therapy
S9355	Home infusion therapy, chelation therapy; administrative services, care coordination, and all necessary supplies and equipment, per diem

ICD-10 Diagnosis	
D56.0-D56.9	Thalassemia
D57.00-D57.819	Sickle-cell disorders
D61.01-D61.9	Other aplastic anemias and other bone marrow failure syndromes
D64.0-D64.3	Sideroblastic anemias (hereditary, secondary, other)
E83.00-E83.09	Disorders of copper metabolism [includes Wilson's disease]
E83.10-E83.19	Disorders of iron metabolism [includes hemochromatosis]
N18.6	End stage renal disease
T45.4X1S	Poisoning by iron and its compounds, accidental (unintentional); sequela
T45.4X2S	Poisoning by iron and its compounds, intentional self-harm; sequela
T45.4X3S	Poisoning by iron and its compounds, assault; sequela
T45.4X4S	Poisoning by iron and its compounds, undetermined; sequela
T45.4X5S	Adverse effect of iron and its compounds, sequela
T56.0X1A-T56.0X4S	Toxic effect of lead and its compounds
T56.1X1S	Toxic effect of mercury and its compounds, accidental (unintentional); sequela
T56.1X2S	Toxic effect of mercury and its compounds, intentional self-harm; sequela
T56.1X3S	Toxic effect of mercury and its compounds, assault; sequela
T56.1X4S	Toxic effect of mercury and its compounds, undetermined; sequela
T56.4X1S	Toxic effect of copper and its compounds, accidental (unintentional); sequela
T56.4X2S	Toxic effect of copper and its compounds, intentional self-harm; sequela
T56.4X3S	Toxic effect of copper and its compounds, assault; sequela
T56.4X4S	Toxic effect of copper and its compounds, undetermined; sequela
T56.891S	Toxic effect of other metals, accidental (unintentional); sequela [gold]
T56.892S	Toxic effect of other metals, intentional self-harm; sequela [gold]
T56.893S	Toxic effect of other metals, assault; sequela [gold]

T56.894S	Toxic effect of other metals, undetermined; sequela [gold]
T57.0X1S	Toxic effect of arsenic and its compounds, accidental (unintentional); sequela
T57.0X2S	Toxic effect of arsenic and its compounds, intentional self-harm; sequela
T57.0X3S	Toxic effect of arsenic and its compounds, assault; sequela
T57.0X4S	Toxic effect of arsenic and its compounds, undetermined; sequela
Z77.010	Contact with and (suspected) exposure to arsenic
Z77.011	Contact with and (suspected) exposure to lead
Z99.2	Dependence on renal dialysis

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

Chelation therapy involves the administration of drugs that bind heavy metal ions such as lead, arsenic, iron, and mercury in the blood stream preventing their interaction with vital organs, such as the brain and kidneys. Drugs used in the administration of chelation therapy are known as chelating agents. The abnormal presence of metals in the blood stream can be the result of environmental exposure, including ingestion of contaminated water and food or inhalation of tainted air. One common cause of lead exposure is in older buildings (built before 1978) in which lead based-paints have been used and not abated. Occupational exposure may occur in industrial processes such as ore smelting and mining, as well as chemical production. Some medical conditions may result in the accumulation of iron in the blood, leading to health problems. Chelation therapy reduces the accumulation of essential heavy metals, such as iron and copper or nonessential metals, such as lead and aluminum. Once the chelation agent has bound with metal ion, the combined substance is more easily excreted by the body through the urinary and GI systems. Specific chelating agents are used to bind specific heavy metals.

Chelation therapy has been proposed as a treatment for the removal of heavy metal ions to reduce cellular oxidative damage caused by the production of hydroxyl radicals. This therapy is under investigation for the treatment of numerous non-overload conditions including, but not limited to, cardiovascular disease, reperfusion injury during coronary angioplasty or cardiopulmonary bypass surgery, anthracycline-associated cardiac damage, Alzheimer's disease, Parkinson's disease, autism spectrum disorders (ASD), and rheumatoid arthritis.

Chelation agents, also have potential toxicity. Chelation agents have been known to bind elements in the body which are necessary for regular functioning, including zinc and calcium. Large doses of vitamins usually accompany the use of chelation agents to lessen these types of side effects. When there is life threatening heavy metal toxicity necessitating treatment with high doses of chelating agents, treatment in the hospital may be needed to monitor for possible side effects. Under less urgent circumstances, chelating agents may be administered on an outpatient basis.

Chelation therapy has been well established to provide substantial clinical benefit for conditions where heavy metal overload has been accurately diagnosed (Angelucci, 2020; Botzenhardt, 2017; Cid, 2014; Delforge, 2014; Franchini, 2000; Guha Mazumder, 2001; Liu, 2020; Maggio, 2020 Mainous, 2014; Rogan, 2001; Shimizu, 1999; Waters, 2001; Yang, 2019; Zeidan, 2019). The diagnostic workup must consider the individual's history, an appropriate choice of testing methods, and the use of accurate and specific reference values (NCCN, 2021). With specific regard to urine testing, the diagnosis and use of chelation therapy should not be performed based on post-challenge urine testing. In post-challenge or post-provoked urine testing, the individual is first given a chelating agent followed by urine testing for heavy metals.

With appropriate heavy metal toxicity diagnosis, several studies published in the peer-reviewed medical literature have established that chelation therapy can be useful in binding toxic metal ions and facilitating their excretion through the liver or kidneys, and mitigating the morbidity associated with heavy metal toxicity such as end organ damage and impaired neurologic functioning.

Chelation therapy has been investigated as a treatment of a wide variety of diseases and conditions, including Alzheimer's disease (Sampson, 2014), Parkinson's (Devos, 2014), autism spectrum disorders (James, 2015), and diabetes (Escolar, 2014). The scientific evidence supporting the clinical utility of such methods is insufficient to recommend the use of chelation therapy. A meta-analysis by Ng and colleagues (2007) evaluated chronic mercury exposure in children and adolescents. The authors concluded that there was "no evidence to support the association between mercury poisoning and autism" and "there is a lack of data in the literature about the effect of chelation therapy in children with neuro-developmental disabilities." The causal role of heavy metal overload in these conditions, as well as the clinical benefit of chelation therapy is still being investigated.

Dental amalgams have been investigated as a cause of increased blood levels of mercury, potentially associated with a number of diseases and disorders such as chronic fatigue syndrome and Alzheimer's disease. In 2009, the American Dental Association's (ADA) Council on Scientific Affairs reviewed the scientific literature on amalgam and stated: "The scientific evidence supports the position that amalgam is a valuable, viable and safe choice for dental patients." The Journal of the American Dental Association (JADA) reported that researchers found "no significant association of Alzheimer's Disease with the number, surface area or history of having dental amalgam restorations" and "no statistically significant differences in brain mercury levels between subjects with Alzheimer's disease and control subjects." The ADA's position has been reaffirmed by the U.S. FDA Center for Devices and Radiological Health in 2002, 2006 and 2009. The ADA's 2010 amalgam safety update cites that "studies continue to support the position that dental amalgam is a safe restorative option for both children and adults."

Chelation therapy has been proposed as a treatment of coronary artery disease (CAD), based in part on the hypothesis that chelation could remove atherosclerotic calcium deposits or provide an antioxidant benefit (Dans, 2003; Lamas, 2013, 2014). One small placebo-controlled randomized study of 84 individuals with atherosclerotic heart disease did not report any advantage of chelation therapy, as measured by time to ischemia, at 27 weeks of follow-up (Anderson, 2003; Knudtson, 2002). The use of chelation therapy in lieu of established therapies, the lack of adequate prior research to verify its effectiveness and clinical utility, and the overall impact of CAD prompted the National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) to sponsor a large-scale clinical study. The 5-year Trial to Assess Chelation Therapy (TACT) in CAD began recruiting individuals in March of 2003. This multicenter, randomized, double-blind study enrolled more than 1600 participants aged 50 or older who had a history of heart attack. The study tested whether chelation therapy or high-dose vitamin therapy are effective for the treatment of CAD. The primary study endpoint of this trial was a composite of heart attack, stroke, hospitalization for angina, coronary revascularization, and death. The study also evaluated cardiac deaths, nonfatal heart attacks, health-related quality of life (HR-QOL), and cost effectiveness, among other factors. Final results indicated that among stable individuals with a history of heart attack, an intravenous chelation regimen with disodium ethylenediaminetetraacetic acid (EDTA), when compared with placebo, modestly reduced the risk of negative cardiovascular outcomes, particularly revascularization procedures. Study authors emphasized that these results are insufficient to support the routine use of chelation therapy for treatment of individuals who have previously suffered from a heart attack.

Lead Overload

Lead overload is the most common form of heavy metal toxicity and the most common methods of domestic lead exposure resulting from children consuming contaminated paint chips, ingesting contaminated food or water, and breathing in lead dust. Commercial and industrial exposures are most frequently seen in mining and ore processing, recycling, and manufacturing industries.

The Centers for Disease Control and Prevention (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) published their Medical Management Guidelines for Lead in 2014. They state the following:

> There is no antidote for lead. Treatment of lead poisoning consists of removal from the source of exposure.
>
> Chelation therapy should be considered for treatment of severe symptoms or markedly elevated blood lead levels. Chelation therapy is controversial in cases of asymptomatic and mildly symptomatic intoxication and should never be given prophylactically or during ongoing lead exposure. Once initiated, chelation therapy should be continued until symptoms improve and acceptable blood lead levels are achieved.
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> Adults: In the presence of severe encephalopathy or when blood lead levels exceed 100 µg/dL, chelation should start with dimercaprol (BAL) followed in 4 hours by another dose of BAL and either succimer (if oral administration is tolerated) or CaNa2-EDTA (if intravenous infusion is required). BAL treatment is phased out while treatment with one of the other chelating agents is continued (typically for 5 days), followed by decreased or interrupted dosing because continued chelator usage is associated with decreasing amounts of urinary lead excretion (Dart et al. 2004).
>
> Children: Use of chelators is not recommended for blood lead levels less than 25 µg/dL. At blood lead levels between 25 and 45 µg/dL, oral chelators may be of benefit if elevated blood levels persist following environmental intervention. Children with blood lead levels between 45 and 70 µg/dL should undergo chelation, usually with oral succimer; those with encephalopathy or with blood lead levels in excess of 70 µg/dL should be admitted to the hospital for parenteral therapy with BAL and EDTA. Therapy begins with BAL intramuscularly every 4 hours, establishment of adequate urinary output (hydration as needed), followed by CaNa2-EDTA continuous infusion. CaNa2-EDTA may be administered intramuscularly in divided doses every 4 hours. This combined therapy is continued for 5 days while liver and renal functions and blood lead levels are monitored. If blood lead levels rebound after 2 days without chelation therapy, a second course of therapy may be necessary (Dart et al. 2004).

The Pediatric Environmental Health Specialty Units and the American Academy of Pediatrics (PEHSU and AAP, 2021) provides the following statement regarding blood lead testing:

> Lead Level > 44 µg/dL
> Emergently admit all symptomatic children to a hospital; if there is evidence of significant central nervous system pathology, consider pediatric intensive care unit admission. If asymptomatic, consider hospitalization and/or chelation therapy (managed with the assistance of an experienced provider). Chelation in the context of ongoing exposure is ineffective and may result in increasing lead levels in the central nervous system. Factors that may influence management include the status of the home with respect to lead hazards, ability to isolate the lead source, family social situation, and chronicity of the exposure. An elevated blood zinc-chelated protoporphyrin level (ZPP) can confirm either an iron-deficiency anemia as a comorbidity in the lead-poisoned child or, if there is no iron deficiency present, a more chronic lead exposure. Contact your regional PEHSU or Poison Control Center (PCC) (1-800- 222-1222) for assistance.

Finally, the CDC's Childhood Lead Poisoning Prevention website (2022) includes their recommended actions based on blood lead level. They state chelation is not recommended for blood lead levels <45 mcg/dL and that chelation therapy is recommended for blood lead levels ≥45 µg/dL.

Definitions

Autism Spectrum Disorder (ASD): A collection of associated developmental disorders that affect the parts of the brain associated with social interaction and verbal and non-verbal communication.

Primary hemochromatosis: A rare genetic disease that results in the overabundance of iron in the liver, brain, heart, and kidneys, causing liver dysfunction, diabetes, changes in skin pigmentation, heart problems, arthritis, and testicular atrophy.

Secondary hemochromatosis: A type of hemochromatosis which is usually the result of another condition or disease that causes the overabundance of iron. This disease and condition may include anemias, chronic liver diseases, and the requirement of blood transfusions.

Sickle cell disease: An inherited genetic disorder that causes red blood cells to take on a characteristic crescent or sickle-like shape with decreased ability to carry oxygen.

Sideroblastic anemia: A condition in which there is excess iron in the bone cells.

Thalassemia intermedia: A genetic form of anemia in which there is an abnormality in the oxygen carrying portion of red blood cells.

Wilson's disease: An inherited (autosomal recessive) disorder where excessive quantities of copper build up in the body, particularly in the liver and central nervous system.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion, References, and Websites sections.
New	05/12/2022	MPTAC review. Initial document development. Moved content of MED.00127 Chelation Therapy to new clinical utilization management guideline document with the same title.

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services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.