



Name of Policy:**Treatment of Hyperhidrosis**

Policy #: 086

Category: Therapy

Latest Review Date: June 2014

Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Hyperhidrosis, or excessive sweating, can lead to impairments in psychologic and social functioning. Various treatments for hyperhidrosis are available, such as topical agents, oral medications, botulinum toxin, and surgical procedures.

Hyperhidrosis may be defined as excessive sweating, beyond a level required to maintain normal body temperature in response to heat exposure or exercise. Hyperhidrosis can be classified as either primary or secondary. Primary hyperhidrosis is idiopathic in nature, typically involving the hands (palmar), feet (plantar), or axillae. Secondary hyperhidrosis can result from a variety of drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or underlying diseases/conditions, such as febrile diseases, diabetes mellitus, or menopause.

Secondary hyperhidrosis is usually generalized or craniofacial sweating. Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. This trigeminovascular reflex typically occurs symmetrically on scalp or face and predominately over forehead, lips, and nose. Secondary facial gustatory sweating, in contrast, is usually asymmetrical and occurs independently of the nature of the ingested food. This phenomenon frequently occurs after injury or surgery in the region of the parotid gland. Frey syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve. After injury, these fibers regenerate, and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in gustatory sweating and facial flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial in nature. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the Minor starch iodine test, which is a simple qualitative measure to identify specific sites of involvement.

A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands. Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment of menopausal symptoms.

Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals; symptoms of botulism include cessation of sweating. Therefore, intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and focal primary hyperhidrosis, most frequently involving the axillae or palms. The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches.

Surgical treatment options include removal of the eccrine glands and/or interruption of the sympathetic nerves. Eccrine sweat glands produce an aqueous secretion, the overproduction of

which is primarily responsible for hyperhidrosis. These glands are innervated by the sympathetic nervous system. Surgical removal has been performed in patients with severe isolated axillary hyperhidrosis.

Various surgical techniques of sympathectomy may also be tried. The second (T2) and third (T3) thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglion controls axillary hyperhidrosis, and the first (T1) thoracic ganglion controls facial hyperhidrosis. Thoracic sympathectomy has been investigated as a potentially curative procedure, primarily for combined palmar and axillary hyperhidrosis that is unresponsive to nonsurgical treatments. While accepted as an effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner's syndrome, compensatory sweating on the trunk generally occurs in a majority of patients, with different degrees of severity. Medical researchers have investigated whether certain approaches, eg, T3 versus T4 sympathectomy, result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this adverse effect. In addition, with lumbar sympathectomy for plantar hyperhidrosis, there has been concern about the risk of postoperative sexual dysfunction in both men and women.

The outcome of different surgical and medical treatment modalities is best assessed by using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the Hyperhidrosis Disease Severity Scale (HDSS) has been found to have a good correlation to other assessment tools and to be practical in the clinical setting.

Policy:

Primary Focal Hyperhidrosis

Primary focal hyperhidrosis is defined as excessive sweating induced by sympathetic hyperactivity in selected areas that is not associated with an underlying disease process. The most common locations are underarms (axillary hyperhidrosis), palms (palmar hyperhidrosis), soles (plantar hyperhidrosis) or face (craniofacial hyperhidrosis).

The following **treatments for hyperhidrosis meet** Blue Cross and Blue Shield of Alabama coverage when there is documentation of functional impairment or medical complications related to the hyperhidrosis. The specific treatments and additional criteria for coverage are listed below by body area.

Focal Regions

Axillary

The following treatments for the **axillary meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- Aluminum chloride 20% solution;
- Botulinum (intradermal injection) for severe primary axillary hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older;

- Endoscopic transthoracic sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum type A, individually or in combination) has failed

The following treatments for the **axillary do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**:

- Axillary liposuction
- Iontophoresis
- Microwave

Palmar

The following treatments for the **palmar meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- Aluminum chloride 20% solution;
- Botulinum (intradermal injection) for severe primary palmar hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older;
- Endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride or botulinum type A, individually and in combination) has failed

The following treatments of hyperhidrosis of the **palmar focal region do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**:

- Iontophoresis
- Microwave
- Radiofrequency ablation

Plantar

Treatment of hyperhidrosis of the **plantar focal region meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- Aluminum chloride 20% solution.

The following treatments for the **plantar focal region do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**:

- Botulinum
- Iontophoresis
- Lumbar sympathectomy
- Microwave

Craniofacial

The following treatments for the **craniofacial focal region meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- Aluminum chloride 20% solution;
- Endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride) has failed

The following treatments for the **craniofacial** focal region **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**:

- Botulinum
- Iontophoresis
- Microwave

Secondary Hyperhidrosis

Secondary hyperhidrosis is excessive sweating that can be generalized or craniofacial sweating and may occur as a result of olfactory or gustatory stimuli, neurologic lesions, intrathoracic neoplasms, Raynaud's disease and Frey's syndrome.

Secondary Gustatory Hyperhidrosis

The following treatments **meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for the treatment of severe gustatory hyperhidrosis**:

- Aluminum chloride 20% solution
- Surgical options (i.e., tympanic neurectomy), if conservative treatment has failed.

The following treatments **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational** as a **treatment for severe gustatory hyperhidrosis** including, but not limited to:

- Botulinum toxins are considered **investigational** for treatment of gustatory hyperhidrosis.
- Iontophoresis

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Most recently literature was reviewed through March 14, 2014. The following is a summary of the key literature to date.

Aluminum chloride

Aluminum chloride is a common component of over-the-counter antiperspirants, although a prescription product is available (Drysol). Although the mechanism is unclear, aluminum chloride is associated with atrophy of the secretory cells seen in eccrine sweat glands. Aluminum chloride is predominantly used to treat axillary hyperhidrosis and not palmar or volar hyperhidrosis.

Iontophoresis

Iontophoresis is a technique that involves the use of an electric current to introduce various ions through the skin.

The mechanism of action is not precisely known, but is thought to be related to plugging of the sweat gland pores. The typical device consists of trays containing electrodes. Prior to using, the trays are filled with tap water, the patient inserts the hands or feet or positions the device in the axilla, and the current is turned on. Patients are treated for approximately 20 minutes, with treatments every two to three days for five to ten sessions before an effect is observed. Maintenance therapy may be applied every two weeks after initial therapy.

Iontophoresis in conjunction with tap water or anticholinergic agents is a long-standing treatment of palmar or plantar and more recently axillary idiopathic hyperhidrosis, with a reported success rate of up to 85%. However, the published literature regarding iontophoresis as a treatment of hyperhidrosis is sparse. A 2003 TEC Assessment on iontophoresis concluded that evidence was insufficient to determine whether the effects of iontophoresis for the treatment of hyperhidrosis exceed those of placebo or an alternate treatment. The TEC Assessment investigators identified only three small studies (n=10, 11, 18, respectively), all of which were conducted in patients with palmar hyperhidrosis.

Since the 2003 TEC Assessment, no randomized controlled trials (RCTs) evaluating tap water iontophoresis for treating hyperhidrosis have been published. Subsequent case series include a 2013 study from Ireland with 28 patients. Patients received a minimum of nine treatments over 21 days in a clinical setting. Twenty of the 25 patients (80%) for whom data were available after hospital administration of tap water iontophoresis reported a moderate or great amount of improvement in symptoms and a moderate or great improvement in quality of life (according to a Disease Life Quality Index). In addition, a 2014 retrospective case series from Turkey included 21 pediatric patients under age 18. Most of the patients (n=16) had palmoplantar hyperhidrosis. Nineteen patients completed the course of 21 tap water iontophoresis sessions. Among study completers, the mean self-report treatment effectiveness score rated on a 0 to 10 visual analog scale (VAS) was 6.36 at the end of treatment. Seventeen of 19 patients (89.5%) reported a 50% or more decrease in sweating at the end of treatment.

There is insufficient evidence, consisting of only small case series, that iontophoresis is an effective treatment of hyperhidrosis. Controlled trials are needed to determine whether iontophoresis improves the net health outcome in patients with hyperhidrosis.

Botulinum toxin type A

A considerable body of published literature addresses botulinum toxin injection of the treatment of axillary and palmar hyperhidrosis and substantiates the efficacy of this treatment. Studies include multiple randomized placebo-controlled trials evaluating Botox, a botulinum toxin type A product. In addition, another botulinum toxin A product, Dysport, has been evaluated in RCTs for treatment of axillary hyperhidrosis and palmar hyperhidrosis. Moreover, a small RCT published in 2007 compared Botox and Dysport and found similar levels of efficacy and safety with the two products.

One of the larger RCTs was published in 2007. This study was an industry-sponsored multicenter double-blind, placebo-controlled efficacy and safety study of botulinum toxin type A in patients with persistent bilateral primary axillary hyperhidrosis. Enrollment criteria included a resting sweat production of at least 50 mg/axilla in five minutes and a rating of 3 or 4 (underarm sweating barely tolerable or intolerable, and frequently or always interferes with daily activities) on the Hyperhidrosis Disease Severity Scale (HDSS). A total of 322 patients were randomized to receive 50 U, or 75 U of Botox or placebo. Retreatment after four weeks was allowed in patients with at least 50 mg of sweat (per axilla) over five minutes and an HDSS score of 3 or 4. Following the first injection, 75% of subjects in the Botox groups showed at least a two-point improvement in the HDSS, compared with 25% of subjects in the placebo group. Sweat production decreased by 87% (75 U), 82% (50 U), and 33% (vehicle). (Similar results were obtained in patients requiring a second treatment.) The median duration of effect was 197, 205, and 96 days (75 U, 50 U, and vehicle, respectively). Seventy-eight percent of subjects (252) completed the 52-week study; 96 of 110 (87%) in the 75-U group, 83 of 104 (80%) in the 50-U group, and 73 of 108 (68%) in the control group. Intent-to-treat analysis at 52 weeks showed a responder rate (greater than two-point improvement on the HDSS) for 54 (49%) subjects in the 75-U group, 57 (55%) in the 50-U group, and six (6%) in the placebo group. Injection-site pain was reported in about 10% of all groups, with a mean duration of 2.4 days (ten-day maximum).

No placebo-controlled RCTs were identified evaluating the safety and efficacy of the newest formulation of botulinum toxin A, Xeomin. Two double-blind randomized trials have compared Xeomin to Botox. In 2014, Campanati et al included 25 patients with moderate to severe primary palmar hyperhidrosis resistant to aluminum chloride or iontophoresis. Patients received injections of Xeomin in a randomly selected hand and Botox in the other hand. The botulinum toxin was given at a fixed dosage per cm² of the hand. There were no statistically significant differences in outcomes between groups. This included changes in the HDSS and the extent of sweating assessed using the Minor test. Previously, in 2010, Dresser et al published an RCT including 46 patients with bilateral axillary hyperhidrosis and a previously stable Botox treatment for at least two years. Patients received 50 MU of Botox in one randomly selected axilla and 50 MU Xeomin in the other axilla. All patients completed the study. According to patient self-report in structured interviews, there were no between-group differences in therapeutic effect including onset latency, extent and duration and no differences in injection site

pain. Moreover, clinical examination did not identify any differences between the two sides in the diffuse sweating pattern.

There is less evidence in support of botulinum toxin type A for treating plantar hyperhidrosis. No RCTs or large uncontrolled studies were identified; most published studies are case reports or small case series.

The evidence evaluating botulinum toxin A use for gustatory hyperhidrosis as a result of Frey syndrome includes non-controlled or nonrandomized studies, all showing favorable treatment outcomes. The patient inclusion criteria were variable across the studies and case reports; ages varied (16 to 87 years); patients had undergone varied types of parotid surgery (ie, bilateral, partial); not all studies documented gustatory sweating with Minor starch test as part of the patient screening.

Multiple RCTs support the efficacy and safety of botulinum toxin A for treating severe axillary and palmar hyperhidrosis. There is a lack of RCTs on use of botulinum toxin A for plantar hyperhidrosis and gustatory hyperhidrosis.

Botulinum toxin type B

There was one placebo-controlled randomized trial on botulinum toxin B (Myobloc) for treating primary axillary hyperhidrosis and one on palmar hyperhidrosis. Both studies were by Baumann et al and were published in 2005; neither discussed whether patients had failed previous treatments for hyperhidrosis. The study on axillary hyperhidrosis included 20 subjects; they received subcutaneous injections of Myobloc (2500 U or 0.5 mL per axilla) (n=15) or placebo (n=5). Patients who received placebo were offered Myobloc at subsequent injections. One patient in the placebo group did not return for follow-up and another responded to placebo and did not return for a subsequent Myobloc injection. Data were available on Myobloc efficacy for the remaining 18 participants (15 in the initial Myobloc group and three crossovers). There was a statistically significant improvement in axillary hyperhidrosis according to patient and physician subjective assessment from baseline (before receiving an active injection) to Day 30. Details on the efficacy outcomes were not reported. The mean length of time to return to baseline levels of sweating in these 18 patients was 151 days (range, 66-243 days). Sixteen participants reported 61 adverse events over the course of the study. Five of 61 adverse events (8.2%) were determined to be definitely related to the study; four axillary bruising events and one instance of pain at the injection site. Eleven adverse events (18%) were determined to be probably related to study treatment; dry eyes (n=3), dry mouth (n=5) and indigestion (n=3). Flu-like symptoms were reported by six of 20 patients (30%); however, the study period coincided with flu season. Note that the authors did not compare the active treatment and placebo groups in their analysis.

The RCT on Myobloc for treatment of palmar hyperhidrosis included 20 participants with excessive palmar sweating. Fifteen participants received injections of Myobloc (50,000 U per palm) and five received placebo. Nonresponders were offered an injection of Myobloc at day 30. At day 30, the two quality-of-life measures were significantly higher in the Myobloc group compared with the control group. However, there was not a statistically significant difference in efficacy in the physician analysis of the palmar iodine starch test at day 30 (p=0.56). No further details were provided on the efficacy outcome measures just described. The mean duration of

action according to self-report in 17 patients (15 in the initial treatment group and two who crossed-over from the placebo group) was 3.8 months (range, 2.3-4.9 months). Participants were asked about specific adverse events. Eighteen of twenty (90%) reported dry mouth/throat, twelve (60%) reported indigestion, twelve (60%) reported excessively dry hands, twelve (60%) reported muscle weakness, and ten (50%) reported decreased grip strength. Both studies by Baumann et al were limited by a small sample sizes and limited or no comparative data.

A small randomized trial by Frasson et al in Italy that compared botulinum toxin type A and type B for treating axillary hyperhidrosis was published in 2011. This study included ten patients with idiopathic focal axillary hyperhidrosis that was unresponsive to other nonsurgical treatments. Patients received 50 U botulinum toxin A in one axilla and 2500 U botulinum toxin B in the contralateral axilla. Gravimetry was performed at baseline and follow-up as an objective measurement of sweat production. In addition, the sweat area was photographed. At each follow-up point, the decrease in sweat weight from baseline was significantly greater on the botulinum toxin B side compared with the botulinum toxin A side. For example, after one month, the sweat weight in five minutes was 13% of the baseline value on the botulinum toxin A side and 4% of the baseline value on the botulinum toxin B side ($p=0.049$). By six months, the sweat weight returned to 91% of baseline on the botulinum toxin A side and 56% of baseline weight on the botulinum toxin B side ($p=0.02$). Findings were similar for sweating area. All patients tolerated injections of botulinum toxin types A and B well, and none reported systemic adverse effects. The authors commented that this study used a higher dosage of botulinum toxin B than previous studies.

A 2013 RCT by Ibrahim et al compared botulinum toxin B and suction-curettage in 20 patients with primary axillary hyperhidrosis. Patients received one treatment in one axilla and the other treatment in the contralateral axilla. The primary outcomes were reduction in the sweat rate in resting and exercise-induced states at three months. The mean percent reduction in the resting sweat rate at three months was 72.1% in the botulinum toxin group and 60.4% in the suction-curettage group; the difference between groups was not statistically significant, $p=0.29$). Similarly, the exercise-induced sweat rate did not differ between groups at three months. The mean percent reduction was 73.8% in the botulinum toxin group and 58.8% in the suction-curettage group, $p=0.10$. Scores on the validated four-point HDSS, however, did differ significantly between groups at three months and favored botulinum toxin B treatment. The difference in the decrease in HDSS scores between the botulinum toxin and suction-curettage groups at three months was 0.80 points, $p=0.0002$. Although findings of this single small trial are not conclusive, study findings suggest that botulinum toxin B may be at least as effective as suction-curettage for treatment of primary axillary hyperhidrosis.

There are few RCTs evaluating botulinum toxin type B for treating hyperhidrosis. One small placebo-controlled RCT did not clearly demonstrate the efficacy of botulinum toxin type B in patients with palmar hyperhidrosis. Two RCTs support the efficacy of this treatment for patients with axillary hyperhidrosis. An additional RCT in patients with axillary hyperhidrosis compared botulinum toxin type B with suction-curettage and found that botulinum toxin type B resulted in outcomes that did not differ significantly from suction-curettage.

Microwave treatment

A 2012 RCT evaluated a microwave device for treating hyperhidrosis. This device applies microwave energy to superficial skin structures with the intent of inducing thermolysis of the eccrine and apocrine sweat glands. This industry-sponsored double-blind study randomized 120 adults with primary axillary hyperhidrosis in a 2:1 ratio to active (n=81) or sham (n=39) treatment. Treatment consisted of two sessions, separated by approximately two weeks. Patients who responded adequately after one session or declined further treatment did not need to undergo the second session, and a third procedure was allowed within 30 days for participants who still had a high level of sweating after two sessions. All patients in the sham group had two sessions. In the active treatment group, eleven subjects (9%) had only one session and ten (8%) had a third procedure. The primary efficacy end point was a score of one (underarm sweating never noticeable) or two (underarm sweating tolerable) on the HDSS at the 30-day follow-up; HDSS score at six months was a secondary outcome. A total of 101/120 (84%) completed the study. At 30 days, 89% of the active treatment group and 54% of the sham group had an HDSS score of 1 or 2; $p<0.001$. At 6 months, 67% of the active treatment group and 44% of the sham group had an HDSS score of 1 or 2; the difference between groups remained statistically significant, $p=0.02$. Unblinding occurred at six months. Twelve-month data were available for the active treatment group only; 69% reported an HDSS score of 1 or 2. There were 45 procedure-related adverse events in 23 (28%) of the active treatment group and five (13%) of the sham group. The most frequently reported adverse event was altered sensation; no serious adverse events were reported. Compensatory sweating was reported by two subjects in each group and had a mean duration of 52 days. The authors noted that study data provided an opportunity to identify areas for improvement of the treatment protocol including waiting longer between treatments and using a higher dose of energy at the second session.

A 2012 industry-sponsored case series reported on 31 patients with primary axillary hyperhidrosis who were treated with microwave therapy using the miraDry system. All patients had an HDSS score of 3 or 4 at baseline. The primary efficacy outcome, the proportion of patients whose HDSS decreased to 1 or 2 was 28 (90%) at six months and 12 months after treatment. Longer-term skin-related adverse effects (that all resolved over time) were altered sensation in the skin of the axillae (65% of patients, median duration, 37 days) and palpable bumps under the skin of the axillae (71% of patients, median duration, 41 days).

One RCT and case series provide insufficient evidence that microwave treatment improves the health outcome for primary focal hyperhidrosis. The RCT reported short-term benefit of microwave treatment in reducing hyperhidrosis, but also reports a high rate of skin-related adverse effects such as pain and altered sensation. Additional controlled studies with long-term follow-up in the treatment and control groups, a longer period of blinding, and a consistent treatment protocol are needed to confirm the efficacy of this treatment and to better define the risk/benefit ratio.

Radiofrequency ablation

A 2013 study evaluated radiofrequency ablation (RFA) as a treatment option for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment. The study was conducted in Turkey and retrospectively reviewed outcomes after RFA (n=48) or transthoracic sympathectomy (n=46). Patients were not randomized to treatment group. After the mean of 15-

month follow-up, palmar hydrosis was absent in 36 patients (75%) in the RFA group and 44 patients (96%) in the surgery group. The difference in outcomes was statistically significant between groups, favoring the surgical intervention ($p<0.01$). Six patients in each group reported moderate or severe compensatory sweating ($p=0.78$).

One nonrandomized comparative study represents insufficient evidence on RFA as a treatment of hyperhidrosis. In this single available study, RFA was found to be inferior to surgical sympathectomy.

Surgical interventions

Tympanic neurectomy for gustatory hyperhidrosis

Review articles by Clayman et al and de Bree et al describe the various medical and surgical treatments for Frey syndrome. Tympanic neurectomy is described as a treatment for Frey syndrome, with satisfactory control reported in 82% of patients. In addition, this surgical treatment is generally definitive without a need for repeated interventions.

Sweat gland excision for primary focal hyperhidrosis

Surgery may involve removal of the subcutaneous sweat glands without removal of any skin, limited excision of skin, and removal of surrounding subcutaneous sweat glands, or a more radical excision of skin and subcutaneous tissue en bloc. Depending on the completeness of surgical excision, the treatment is effective in 50% to 95% of patients.

Transthoracic sympathectomy for primary focal hyperhidrosis

Several RCTs and one meta-analysis have compared different approaches with surgery; there were no sham-controlled RCTs. In 2011, Deng et al published a meta-analysis of data from RCTs and observational studies published to 2010 evaluating thoracoscopic sympathectomy for patients with palmar hyperhidrosis. The authors pooled outcome data from different approaches to sympathectomy, ie, single-ganglia blockage (T2, T3, T4), and multiganglia blockage (T2-3, T2-4, T3-4). (Note: T refers to rib.) Based on these analyses, they concluded that T3 (eleven studies) and T3-4 (two studies) had the “best” clinical efficacy ie, postoperative resolution of symptoms. The T3 approach resulted in a 97.9% pooled efficacy rate, and the T3-4 approach resulted in a 100% pooled efficacy rate. In the studies for which data were available, the pooled rate of postoperative compensatory sweating was 40% after T3 surgery. Data on compensatory sweating after T3-4 surgery was only available from one study with 60 patients; a pooled analysis could not be performed.

Subsequent RCTs have also compared levels of sympathectomy. For example, a 2011 study by Baumgartner et al included 121 patients with disabling palmoplantar hyperhidrosis. Patients were randomized to receive bilateral sympathectomy over T2 ($n=61$ patients) or T3 ($n=60$ patients). Six of 121 (5%) patients, three in each group, were considered treatment failures ie, had recurrent palmar sweating to a bothersome level. There were no significant differences between groups in the reported subjective change in plantar or axillary sweating after surgery. At six months, the mean level of compensatory sweating (0 to 10 severity scale) was 4.7 (standard deviation [SD]=2.7) for the T2 group and 3.8 (SD=2.8) for the T3 group ($p=\text{not significant}$). Similarly, at one year, the mean severity rating of compensatory sweating was 4.7 (SD=2.5) in the T2 group and 3.7 (SD=2.8) in the T3 group; $p=0.09$.

A trial by Ishy et al in Brazil compared surgery at the T3 and T4 levels and a trial by Yuncu et al in Turkey compared surgery at the T3 and T3-4 levels. Ishy et al included 20 patients with palmar hyperhidrosis. All patients experienced complete bilateral remission of palmary sweating after one year of follow-up. The level of compensatory sweating did not differ significantly between groups at one week, one month, or six months, but at one year, there was a significantly higher rate in the T3 compared with the T4 group (20/20, 100% in the T3 group and 15/20, 75% in the T4 group, $p=0.47$). Yuncu et al included 60 patients with axillary hyperhidrosis; 17 were assigned to T3-4 surgery and 43 to T3 surgery. There were no significant differences between groups in postoperative satisfaction. At the one-year follow-up, the incidence of compensatory sweating was lower in the T3 group (79%) than the T3-4 group (100%).

There is also a large amount of data from case series on transthoracic sympathectomy for treating primary focal hyperhidrosis. Case series generally report high success rates for palmar and axillary hyperhidrosis, although there are potential adverse effects, most commonly compensatory sweating.

For example, in 2010, Wait et al published a retrospective analysis of prospectively collected data on patients who underwent bilateral thoracoscopic sympathectomy for hyperhidrosis. Data were available on 322 of 348 (93%) of patients who underwent surgery. Patients' previous use of nonsurgical hyperhidrosis treatments was not reported. Complete resolution of symptoms was reported by 300 of 301 (99.7%) with palmar hyperhidrosis, 136 of 186 (73%) with axillary hyperhidrosis, 27 of 30 (90%) with craniofacial hyperhidrosis, and 19 of 197 (9.6%) with plantar hyperhidrosis. Compensatory sweating was reported by a total of 201 of 322 (62%) patients. The compensatory sweating was severe in 20 (6.2%) of patients and mild or moderate in 181 (56.2%) of patients. It is worth noting that thoracoscopic sympathectomy was performed in some cases of plantar hyperhidrosis, with a low rate of success. In addition, when reporting rates of compensatory sweating, the authors did not distinguish between mild and moderate levels of symptoms, although these could have different clinical implications for the patient.

In 2011, Smidfelt and Drott in Sweden reported on long-term outcomes after transthoracic sympathectomy. Of 3,015 patients who had been treated with endoscopic thoracic sympathectomy for hyperhidrosis and/or facial blushing, 1,700 (56%) responded to a written survey after a mean of 14.6 (SD=2.4) years. A total of 85.1% of respondents reported that they had a satisfactory and lasting effect of the surgery. Sweating and/or blushing recurred and was considered a problem in 8.1%, and 6.9% reported no initial effect or a poor effect. Compensatory sweating was considered troublesome by 299 (17.6%), annoying by 409 (24.1%), severe by 367 (21.6%), and incapacitating by 190 (11.2%). Nearly half of the patients who underwent surgery did not respond to the survey; their outcomes may have been different from those of study respondents.

A 2013 series reported on complications after thoracic sympathectomy in 1,731 patients with palmar, axillary, or craniofacial hyperhidrosis. Thirty days after surgery, 1,531 (88.4%) of patients reported compensatory sweating. Among the 1,531 patients, compensatory sweating

was mild in 473 (31%), moderate in 642 (42%), and severe in 416 (27%). Gustatory sweating was reported by 334 of the 1,731 (19%) patients.

RCTs and a meta-analysis of RCTs support the efficacy of transthoracic sympathectomy at various levels for palmar and axillary hyperhidrosis. These data are complemented by case series which have found high efficacy rates, but also high rates of compensatory sweating for these conditions. There is insufficient evidence in support of transthoracic sympathectomy for treating plantar hyperhidrosis; case series found lower rates of efficacy for plantar compared with axillary or palmar hyperhidrosis, and there are concerns for adverse effects in sexual functioning. There are insufficient data to conclude that any particular approach to surgery results in lower rates of compensatory sweating.

Endoscopic lumbar sympathectomy for primary plantar hyperhidrosis

No RCTs were identified but several case series were identified. A 2009 series by Rieger et al from Austria evaluated surgery results in 90 patients (59 men, 31 women with severe plantar hyperhidrosis). Thirty-seven patients (41%) had only plantar hyperhidrosis, and 53 (59%) had plantar and palmar hyperhidrosis. All patients had previously used other treatments including topical aluminum chloride therapy. There were a total of 178 procedures, 90 on the right-side and 88 on the left side. The technique involved resecting a segment of the sympathetic trunk between the third and fourth lumbar bodies together with the ganglia (L3 and/or L4). After a mean follow-up of 24 months (range, 3-45), hyperhidrosis was eliminated in 87 of 90 patients (97%). Postoperative neuralgia occurred in 38 (42%) patients between the seventh and eighth day. The pain lasted less than four weeks in eleven patients, one to three months in 19 patients, four to twelve months in five patients, and more than twelve months in three patients. Three men reported temporary sexual symptoms; one was incapable of ejaculation for two months. None of the women reported postoperative sexual dysfunction.

In 2010, Reisfeld reported on results of a U.S.-based study from a specialized hyperhidrosis clinic in which bilateral endoscopic lumbar sympathectomy was performed in 63 patients with focal plantar hyperhidrosis. There were 13 (21%) male patients and 50 (79%) female patients. A clamping method was used in which clamps were placed at L3 (46.6%), L4 (52.4%), and L2 in one case. There was a learning curve with this procedure, and five early cases had to be converted to an open procedure. Fifty-six (89%) of the patients had previously undergone some form of thoracic sympathectomy, and all had tried conservative measures. After a mean follow-up of seven months, all patients considered their plantar hyperhidrosis symptoms to be “cured” or “improved;” 97% reported “cure.” All of the patients with previous thoracic sympathectomy had some degree of compensatory sweating. After lumbar sympathectomy, 51 of the 56 patients (91%) reported that their compensatory sweating was unchanged. In the seven patients who did not have a previous thoracic sympathectomy, one reported mild and six reported moderate compensatory sweating. The authors stated that no sexual problems were reported by the male patients, and they did not discuss possible sexual problems among the female patients.

It is worth noting, that in contrast to earlier concerns about this procedure being associated with risks of permanent sexual dysfunction in men and women, the recent case series did not find any instances of permanent sexual dysfunction. A 2004 review from a multispecialty working group on hyperhidrosis stated that lumbar sympathectomy is not recommended for plantar

hyperhidrosis because of associated sexual dysfunction; this article did not cite any data documenting sexual dysfunction. To date, there are very few studies on endoscopic lumbar sympathectomy for focal plantar hyperhidrosis and no comparative studies.

There are insufficient data supporting the safety and efficacy of lumbar sympathectomy for treating primary plantar hyperhidrosis.

Summary

There is insufficient evidence on the efficacy and safety of iontophoresis or microwave treatment for treating hyperhidrosis and on radiofrequency ablation for palmar hyperhidrosis. There is evidence from randomized trials that botulinum toxin improves the net health outcome for patients with axillary hyperhidrosis and evidence that botulinum toxin A products improve the net health outcome for palmar hyperhidrosis. Due to the limited number of studies and high rates of adverse effects, there is insufficient evidence that botulinum toxin B improves the net health outcome for patients with primary palmar hyperhidrosis. There is insufficient evidence on the efficacy of any botulinum toxin products for other types of primary hyperhidrosis, including plantar and secondary hyperhidrosis.

Regarding surgical treatments for hyperhidrosis, data from randomized controlled trials and observational studies show high rates of efficacy of endoscopic transthoracic sympathectomy for primary focal hyperhidrosis, with the exception of plantar hyperhidrosis. There are, however, high rates of compensatory hyperhidrosis which must be considered in the treatment decision. There are insufficient data to draw conclusions on the efficacy of endoscopic lumbar sympathectomy in patients with primary plantar hyperhidrosis.

Practice Guidelines and Position Statements

In 2011, an expert consensus statement on the surgical treatment of hyperhidrosis was published by a task force of the Society of Thoracic Surgeons. The document states that endoscopic thoracic sympathectomy is the treatment of choice for patients with primary hyperhidrosis. They further recommend the following treatment strategies (with R referring to rib and the number to which rib):

- R3 interruption for palmar hyperhidrosis; an R4 interruption is also reasonable. The authors note a slightly higher rate of compensatory sweating with an R3 but R3 is also more effective at treating hyperhidrosis.
- R4 or R5 interruption for palmar-axillary, palmar-axillary-plantar or axillary hyperhidrosis alone; R5 interruption is also an option for axillary hyperhidrosis alone.
- R3 interruption for craniofacial hyperhidrosis without blushing; an R2 and R3 procedure is an option but may lead to a higher rate of compensatory sweating, and also increases the risk of Horner's syndrome.

The National Institute for Health and Care Excellence issued guidance in 2014 stating that there is sufficient evidence of the efficacy and safety of endoscopic thoracic sympathectomy (ETS) for primary facial blushing to support the use of the procedure.

In 2008, the American Academy of Neurology (AAN) created guidelines for use of botulinum neurotoxin for the treatment of autonomic disorders and pain. These guidelines include the following recommendations for botulinum toxin injection as a treatment of hyperhidrosis:

- Should be offered as a treatment option to patients with axillary hyperhidrosis (Level A).
- Should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B).
- May be considered for gustatory sweating (Level C).

Key Words:

Botulinum toxin, treatment of hyperhidrosis, Endoscopic sympathectomy, Gustatory hyperhidrosis, Hyperhidrosis, Iontophoresis, Sweating, excessive, Sympathectomy, thoracic, Thoracoscopic sympathectomy, miraDry System, Microwave Treatment for Hyperhidroses

Approved by Governing Bodies:

Drysol™ (aluminum chloride [hexahydrate] 20% topical solution, Person and Covey, Inc.) is approved by the U.S. Food and Drug Administration (FDA) to be used as an aid in the management of hyperhidrosis (axillae, palmar, plantar, and craniofacial); it is available by prescription.

In 2004 the FDA approved botulinum toxin type A (Botox®) to treat primary axillary hyperhidrosis (severe underarm sweating) that cannot be managed by topical agents. In 2009, this product was renamed to OnabotulinumtoxinA. Other FDA-approved botulinum toxin products include:

2000: RimabotulinumtoxinB, marketed as Myobloc® (Solstice Neurosciences)

2009: AbobotulinumtoxinA, marketed as Dysport® (Medicis Pharmaceutical Corporation, Scottsdale, AZ)

2010: IncobotulinumtoxinA, marketed as Xeomin® (Merz Pharmaceuticals)

None of these other botulinum toxin products are indicated for treatment of hyperhidrosis.

On July 31, 2009, the FDA approved the following revisions to the prescribing information of botulinum toxin products:

- “A *Boxed Warning* highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a *Medication Guide* to help patients understand the risk and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products.”

In January 2011, the miraDry® System (Miramar Labs, Inc.; Sunnydale, CA) was cleared by the FDA through the 510(k) process for treating primary axillary hyperhidrosis. This is a microwave

device designed to heat tissue at the dermal-hypodermal interface, the location of the sweat glands. Treatment consists of two sessions of approximately one hour in duration. Sessions occur in a physician's office and local anesthetic is used. (FDA Product Code: NEY)

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational and will be reviewed for medical necessity

Coding:

CPT codes:	64650	Chemodenervation of eccrine glands; both axillae (Effective 01/01/2006)
	64653	; other area(s) (e.g., scalp, face, neck), per day (Effective 01/01/2006)
	97033	Application of modality to one or more areas; iontophoresis, each 15 minutes
	32664	Thoracoscopy, surgical; with thoracic sympathectomy
HCPCS:	J0585	Injection, Onabotulinumtoxina, 1 unit (Effective 01/01/2006)
	E1399	Durable medical equipment, miscellaneous (Effective 01/01/2006)
	J0587	Injection, Rimabotulinumtoxinb, 100 units (Effective 01/01/2006)

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Medical Policy Administration Committee, August 2004
Available for comment August 11-September 24, 2004
Medical Policy Group, January 2006 (1)
Medical Policy Administration Committee, January 2006
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Medical Policy Group, April 2012 (3): 2012 Updates-Added Microwave to Policy Section, Updated Description, Key Points, Key Words & References
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Medical Policy Panel, May 2013
Medical Policy Group, May 2013 (3): 2013 Updates – Added Radiofrequency Ablation as investigational to Policy Section for palmar surfaces; updated Key points, Approved by Governing Bodies & References
Available for comment May 22 through July 5, 2013
Medical Policy Group, October 2013 (3): Removed ICD-9 Diagnosis codes; no change to policy statement.
Medical Policy Panel, May 2014

Medical Policy Group, June 2014 (3): 2014 Updates to Description, Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case by case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.