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Treatment Options for Hyperhidrosis

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Contents

Abstract

Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Primary hyperhidrosis has an estimated prevalence of nearly 3% and is associated with significant medical and psychosocial consequences. Most cases of hyperhidrosis involve areas of high eccrine density, particularly the axillae, palms, and soles, and less often the craniofacial area. Multiple therapies are available for the treatment of hyperhidrosis. Options include topical medications (most commonly aluminum chloride), iontophoresis, botulinum toxin injections, systemic medications (including glycopyrrolate and clonidine), and surgery (most commonly endoscopic thoracic sympathectomy [ETS]). The purpose of this article is to comprehensively review the literature on the subject, with a focus on new and emerging treatment options. Updated therapeutic algorithms are proposed for each commonly affected anatomic site, with practical procedural guidelines.

For axillary and palmoplantar hyperhidrosis, topical treatment is recommended as first-line treatment. For axillary hyperhidrosis, botulinum toxin injections are recommended as second-line treatment, oral medications as third-line treatment, local surgery as fourth-line treatment, and ETS as fifth-line treatment. For palmar and plantar hyperhidrosis, we consider a trial of oral medications (glycopyrrolate 1–2 mg once or twice daily preferred to clonidine 0.1 mg twice daily) as second-line therapy due to the low cost, convenience, and emerging literature supporting their excellent safety and reasonable efficacy. Iontophoresis is considered third-line therapy for palmoplantar hyperhidrosis; efficacy is high although so are the initial levels of cost and inconvenience. Botulinum toxin injections are considered fourth-line treatment for palmoplantar hyperhidrosis; efficacy is high though the treatment remains expensive, must be repeated every 3–6 months, and is associated with pain and/or anesthesia-related complications. ETS is a fifth-line option

for palmar hyperhidrosis but is not recommended for plantar hyperhidrosis due to anatomic risks. For craniofacial hyperhidrosis, oral medications (either glycopyrrolate or clonidine) are considered first-line therapy. Topical medications or botulinum toxin injections may be useful in some cases and ETS is an option for severe craniofacial hyperhidrosis.

Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions.[1,2] Hyperhidrosis may be primary or secondary to medications or general medical conditions. Primary hyperhidrosis has an estimated prevalence of nearly 3% of the population.[3] The pathophysiology of hyperhidrosis is not well understood. Eccrine glands, found in high concentration in the palms, soles, forehead, and axillae, are innervated by cholinergic fibers of the sympathetic nervous system. A complex dysfunction of this system is likely to be contributory to the disorder.[2] Primary hyperhidrosis increases the risk of cutaneous infection[4] and has a significant psychosocial burden and a negative impact on quality of life.[3]

Multiple therapies are available for the management of hyperhidrosis. The purpose of this article is to comprehensively review the literature on the subject, with a focus on new and emerging treatment options. Updated therapeutic algorithms are proposed for each commonly affected anatomic site. The PubMed database was reviewed using the keywords 'hyperhidrosis' and 'treatment' or 'therapy,' to search the world literature from January 1966 to 2 June 2011, with the limits 'English language' and 'human.' This strategy yielded 1836 publications. Abstracts of titles of interest were reviewed, and full-text articles of interest were accessed.

1. Assessment

For the patient presenting with excessive sweating, the first step in evaluation is a careful clinical history, focusing particularly on those features that will support a diagnosis of primary focal hyperhidrosis (table I).[1] Knowledge of the patient's medical and surgical history, as well as medications taken daily, is essential. A targeted systems review is necessary, with particular attention to general constitution and the endocrine and neurologic systems. Physical examination will often confirm the presence of excess sweating, although the symptoms may be intermittent. Palpation of the neck (for lymphadenopathy and thyroid enlargement) may be useful.

If the presentation is characteristic of primary hyperhidrosis, additional laboratory testing is not required.[4] If secondary hyperhidrosis is suspected, a directed evaluation including neurologic examination, blood pressure measurement, complete blood count, fasting serum glucose, and thyroid function may be appropriate. Objective tests such as gravimetry and evaporimetry are of interest in the setting of research or clinical trials, but are rarely used in a clinical setting.[2] Starch iodine testing is straightforward and may be used to qualitatively assess the distribution and magnitude of hyperhidrosis. This is often useful to delineate the affected areas prior to procedural treatment, though is generally not necessary for diagnosis.

The Hyperhidrosis Disease Severity Scale (HDSS)[5] is a rapid diagnostic tool that provides a qualitative measure of the impact of hyperhidrosis on a patient's life (table II). It is easily completed by the patient during the office visit. Attention to the HDSS allows the clinician to tailor therapy to both the objective and subjective severity of the case. Documentation of the patient's responses may also be invaluable to obtaining insurance approval for the various therapy options.

2. Therapy Overview

The treatment of hyperhidrosis is clinically dynamic due to the variety of treatment options available. Therapy options may be broadly classified as nonsurgical and surgical. Nonsurgical options include medical treatments (topical and systemic medications) and procedural treatments (iontophoresis and botulinum toxin [BTX] injection). Surgical treatments include local dermatologic surgery (for axillary hyperhidrosis) and, for severe and refractory cases, cardiothoracic surgery (sympathectomy).

Table I. Diagnostic features of primary hyperhidrosis

Excessive sweating occurring in at least one of the following sites: axillae, palms, soles, or craniofacial region
At least 6 months duration
Without apparent secondary causes (e.g. medications, endocrine disease, neurologic disease)
Including two or more of the following characteristics:
bilateral and relatively symmetric
age of onset under 25 years
frequency of episodes at least once per week
positive family history
cessation of excessive sweating upon sleep
impairment of daily activities

Table II. Hyperhidrosis Disease Severity Scale (HDSS)[5]

Subjective	Score	Clinical interpretation
My sweating is never noticeable and never interferes with my daily activities	1	Mild
My sweating is tolerable but sometimes interferes with my daily activities	2	Moderate
My sweating is barely tolerable and frequently interferes with my daily activities	3	Severe
My sweating is intolerable and always interferes with my daily activities	4	Severe

3. Nonsurgical Therapy

3.1 Topical Therapy

Because of its safety and a reasonable chance of efficacy, topical therapy is generally considered first-line therapy for most cases of focal hyperhidrosis, particularly axillary and palmoplantar. Aluminum chloride is the most commonly used topical agent. Though its exact mechanism of action remains debated, the aluminum salt is thought to block the distal acrosyringium, leading to functional and structural degeneration of the eccrine acini.[6,7] Mild cases will respond to over-the-counter-strength antiperspirant products. If this is ineffective, prescription-strength aluminum chloride (generally as a 20% solution) is often effective. It is usually applied nightly at bedtime; when clinical efficacy is noted (in 1–2 weeks for most patients), the frequency can be reduced.

In a 1978 study, 64 of 65 patients attained excellent control of axillary hyperhidrosis with the application of 20% aluminum chloride in ethanol.[8] A study of 30 patients with axillary hyperhidrosis found 25% aluminum chloride in ethanol to be highly effective; post-treatment with 50% triethanolamine to one axilla reduced the irritancy but also reduced the efficacy.[9] Twenty-five percent aluminum chloride in ethanol was also effective in treating 16 patients with palmar and/or plantar hyperhidrosis.[10] In a 1979 study of patients awaiting surgical intervention for severe axillary hyperhidrosis, 35 of 42 patients experienced a satisfactory response to a saturated solution of aluminum chloride in ethanol; three found the treatment too cumbersome and four experienced treatment-limiting irritation.[11]

In a half-side controlled, single-blind (assessor-blind) study, all 12 patients with severe palmar hyperhidrosis experienced significant improvement with 20% aluminum chloride in ethanol, with the results measured quantitatively with an evaporimeter. One of the 12 patients experienced treatment-limiting irritation.[12]

Irritancy is a common limitation of topical aluminum chloride. A study of 38 patients with axillary hyperhidrosis reported treatment-limiting irritation in ten (26%) patients.[13] In many cases, irritancy will be mild and can be controlled with occasional application of 1% hydrocortisone cream the morning after treatment.[8]

A newer formulation of 15% aluminum chloride in salicylic acid gel may provide similar efficacy with decreased irritancy. In a study of 238 patients with hyperhidrosis at various anatomic sites, treatment with aluminum chloride (compounded at 10–40% based on treatment site) in 4% salicylic acid gel was well tolerated and associated with good to excellent results in 93% of subjects on the axillae (n = 139), 84% of subjects on the soles (n = 139), 60% of subjects on the palms (n = 46), and 100% of subjects on the groin (n = 6).[14]

In a series of seven patients with hyperhidrosis (sites included axillae in six and palms in two) who previously did not tolerate 20% aluminum chloride solution, all achieved control of hyperhidrosis without irritation using 15% aluminum chloride in 2% salicylic acid gel.[7] In an open-label trial, 30 patients with axillary hyperhidrosis were treated with 15% aluminum chloride in 2% salicylic acid gel; 18 patients (60%) completing the 12-week study responded to treatment, and 2 (6.7%) withdrew due to irritancy.[15]

Topical glycopyrrolate may also be effective for focal hyperhidrosis. A topical application of 0.5% or 1% glycopyrrolate was initially studied in 16 patients with Frey syndrome (gustatory sweating following parotidectomy-induced facial nerve injury) and was found to be effective and free of adverse effects in all subjects.[16]

In a double-blind, placebo-controlled, crossover study, all 13 diabetic patients with gustatory hyperhidrosis treated with topical glycopyrrolate experienced a significant improvement in the magnitude of sweat response challenge, as well as a decrease in the frequency of episodes during the study period.[17] Eight of ten patients with compensatory hyperhidrosis post-sympathectomy responded to a daily application of 2% glycopyrrolate solution, though two discontinued due to systemic anticholinergic effects (visual changes and xerostomia).[18]

In a study of 25 patients with craniofacial hyperhidrosis, all patients had half their forehead treated with 2% glycopyrrolate and the other half treated with placebo. Ninety-six percent of patients were satisfied with the effectiveness; one did not tolerate it due to headache. Improvement lasted 1–2 days for most patients.[19]

Other topical agents such as glutaraldehyde,[20] formaldehyde, and tannic acid are seldom used today due to irritancy, skin discoloration, and the availability of better alternatives.

3.2 Iontophoresis

Iontophoresis is the introduction of an ionized substance through intact skin by the application of a direct current (DC).[21]

Iontophoresis is most practical for treating hyperhidrosis of the palms and soles.

The precise mechanism of action of iontophoresis is unknown. The technique generates an electrical potential gradient that facilitates the transdermal movement of solute ions and also promotes the penetration of neutral compounds.[22] Neither microscopic changes in the cutaneous ultrastructure nor ductal obstruction has been observed after iontophoresis.[23] The mechanism is currently believed to involve changes in the resorption of sodium ions by the sweat ducts, as both the sodium concentration and sweat volume has been shown to decrease following iontophoresis.[24]

The concept of using iontophoresis to treat hyperhidrosis was first introduced to the medical literature in 1936; a 1952 report demonstrated the efficacy of tap water iontophoresis for treating 113 patients with palmar and plantar hyperhidrosis.[21] Levit[25] reported an 85% efficacy for tap water iontophoresis using a simple galvanic device that patients could learn to use at home. Complete symptom control was reported in 71 patients with palmoplantar hyperhidrosis treated with either a conventional (DC) galvanic unit or a battery-operated home unit (alternating current with DC offset; AC/DC).[26] Similar results, with 100% efficacy, were noted in a single-blind, controlled study of 21 patients with palmoplantar hyperhidrosis treated with either DC or AC/DC iontophoresis.[27]

Home iontophoresis units have been commercially available for over 25 years and may be used by the unassisted patient. The patient places the hands or feet into electrode-containing plastic trays of tap water, with the water level just above the skin of the tops of the fingers and hands. The treatment is generally performed daily for 10 minutes, initially every 2–3 days, with the energy intensity increased over time to a therapeutic range of 10–18 mA. After a therapeutic effect is achieved with daily treatments for about 2 weeks, the treatment interval may often be reduced to once every 1–2 weeks.[21] Adverse effects include minor pain and skin irritation (including burning, tingling, and erythema), the incidence and magnitude of which is generally proportional to the amperage utilized.

While tap water iontophoresis is highly effective, several studies have reported augmented effects with the addition of BTX[28,29] or glycopyrrolate[30] to the iontophoresis solution. In one controlled left-right study, eight patients with palmar hyperhidrosis experienced a more rapid onset of sweat reduction (at week 1 vs week 3) when BTX was added to the iontophoresis solution compared with saline alone.[28] In another left-right comparison study of 20 patients with palmoplantar hyperhidrosis, bilateral glycopyrrolate iontophoresis had a significantly longer duration of effect compared with either unilateral glycopyrrolate iontophoresis or tap water in most patients.[30]

3.3 Botulinum Toxin

BTX, produced by the bacteria *Clostridium botulinum*, is a neurotoxin that irreversibly inhibits the presynaptic release of acetylcholine from postganglionic sympathetic nerve endings at the neuromuscular junction and at eccrine sweat glands.[31] Since 2004, BTX type A (BTX-A) has been approved by the US FDA for the treatment of axillary hyperhidrosis and is often used off-label for the treatment of palmar, plantar, and craniofacial hyperhidrosis. Currently, in the US, BTX-A is commercially available in the form of three products, Botox® (Allergan, Irvine, CA, USA), Dysport® (Ipsen Biopharm Ltd, Wrexham, UK), and Xeomin® (Merz Pharmaceuticals, Greenboro, NC, USA), though only the Botox® brand is currently approved by the FDA for axillary hyperhidrosis. In studies comparing Botox® with Dysport,® there was no significant difference in efficacy or duration of effect, in the treatment of hyperhidrosis, between the two different formulations.[32] However, the two formulations demonstrate different potencies, with 1 unit of Botox® equaling approximately 3–4 units of Dysport®.[33-35]

The efficacy of BTX-A in the treatment of axillary hyperhidrosis is well established, with 82–87% reduction in sweating noted post-treatment.[36-54] Before treatment, the hyperhidrotic area is best visualized using the Minor starch-iodine test as outlined by Swinehart.[55] First, a 1% povidone-iodine solution is applied to the clean, dry, shaved axillae and allowed to air dry. Next, powdered corn starch is applied with cotton wool. As the patient begins to sweat, the corn starch combined with iodine forms a blue-black precipitate in the presence of moisture, highlighting the area of sweating. The hyperhidrotic areas can then be mapped and outlined with an indelible ink marker. Patients should discontinue all anti-hyperhidrotic therapeutic agents (including antiperspirants) 5 days prior to iodine-starch testing to improve accuracy of the test.[32] Approximately 50 units of Botox® or approximately 200 units of Dysport® are needed for the treatment of one axillae.[40,42] Approximately 20 injections are distributed evenly, spaced 1–2 cm apart, in the hyperhidrotic area outlined by the starch test.[56] Pain associated with intradermal injections of BTX-A in the axillae is usually minimal, with local anesthetic techniques not routinely required for performance of the procedure. Skin and air cooling can be used to reduce the pain of intradermal injections[57] or BTX-A can be injected subcutaneously with a similar level of efficacy as intradermal administration.[58] Within 2–4 days after treatment, patients notice a reduction in sweating that is maximal within 2 weeks.[42,59] The duration of anhidrosis is usually 4–12 months with some studies showing efficacy for up to 14 months.[36-38] Adverse events associated with BTX-A treatment of axillary hyperhidrosis are uncommon. Minimal pain and mild subjective compensatory hyperhi-

drosis in non-axillary regions in 5% of patients have been described.[41]

Efficacy of 80–90%, similar to that seen in axillary hyperhidrosis, has been described with the use of BTX-A in the treatment of palmar hyperhidrosis.[38,40,45,60-65] However, response to therapy varies more than that seen in axillary hyperhidrosis.[66] In addition, the duration of anhidrosis with palmar hyperhidrosis, approximately 6 months, is shorter than that seen with axillary hyperhidrosis.[32] In comparison with the axillae, 100–240 units of Botox® are needed for the treatment of one palm.[32] Doses of approximately 2–3 units of Botox® placed every 1–2 cm are appropriate.[32] Injections should be placed in the dermis to reduce the incidence of weakness of the intrinsic muscles of the hand. However, despite meticulous injection technique, transient weakness of the intrinsic muscles of the hand is common post-treatment.[32] Handgrip strength is usually normal while finger pinch strength is often reduced.[32] In addition, treatment of palmar hyperhidrosis is associated with pain during the procedure and for up to 1–2 days post-procedure.[67] Techniques to reduce injection-associated pain include application of ice,[68] cold air,[57] dichlorotetrafluoroethane,[69] topical anesthetics,[66] regional nerve block,[70] and vibration anesthesia.[71]

Fewer studies exist regarding the use of BTX-A for the treatment of plantar hyperhidrosis. Treatment efficacy may be lower than that for the palms and axillae, with up to 50% of patients being unsatisfied with treatment.[32] BTX-A treatment of plantar hyperhidrosis is dosed similar to the treatment of palmar hyperhidrosis.[72,73] Similar to palmar hyperhidrosis, pain with injection is a limiting factor with BTX-A treatment of plantar hyperhidrosis.[32]

In the treatment of hyperhidrosis on all body sites, but especially on the palms and soles, BTX-A has a tendency to backflow from the injection tract post-injection.[2] Techniques to minimize backflow include the following: (i) needle bevel up injection technique; (ii) angling the needle parallel to the skin surface with injection; (iii) advancing the needle 2 mm into the skin prior to injection; (iv) slow insertion of the needle with no pressure on the plunger during insertion; and (v) waiting 1–2 seconds post-injection before withdrawing the needle.[66,74]

Other locations for which BTX-A has successfully been used for the treatment of idiopathic localized hyperhidrosis include the forehead,[75] anal fold,[76] and inguinal fold.[77] Contraindications include allergy to BTX-A, infection or inflammation at the injection site, pregnancy (pregnancy category C) or lactation, neuromuscular diseases such as myasthenia gravis and Lambert-Eaton syndrome, and concomitant use of medications that also affect neuromuscular transmission (i.e. aminoglycosides, macrolide antibacterials, calcium channel antagonists, cholinesterase inhibitors, curare-like depolarizing agents, magnesium sulfate, polymyxins, quinidine, and succinylcholine).[32]

3.4 Systemic Therapy

Only limited data are available regarding the use of oral medications in the management of hyperhidrosis. A 2007 practice guideline correctly states that "compelling evidence is lacking for the safety and efficacy of systemic anticholinergic agents" for the treatment of hyperhidrosis.[2] Medications reported to be useful for hyperhidrosis most commonly include anticholinergic agents, antihypertensive agents, anxiolytics, and antidepressants. Anticholinergic agents are probably the most common type of medication used in clinical practice. A prospective clinical trial of oral agents for hyperhidrosis would be of great interest.

3.4.1 Glycopyrrolate

Glycopyrrolate has been recommended as second- to third-line therapy for severe hyperhidrosis involving the palms, soles, or axillae, and as one of several first-line options for craniofacial hyperhidrosis.[2]

In the authors' experience, 45 patients with hyperhidrosis, including 39 with hyperhidrosis involving the palms, soles, or axillae, have been treated with oral glycopyrrolate, generally dosed at 1–2 mg once to twice daily; 30 patients (67%) responded to treatment; six did not respond, and nine discontinued due to self-limited adverse effects.[78]

In a retrospective study, 15 of 19 patients (79%) with hyperhidrosis affecting a variety of body sites responded to glycopyrrolate, most commonly at a dosage of 2 mg twice daily.[79] In that study, five patients stopped the medication due to adverse effects and four patients discontinued for lack of efficacy,[79] corresponding to a 53% (10/19) treatment success rate.

The mechanism of action of glycopyrrolate is competitive inhibition of acetylcholine at muscarinic receptors. At least five subtypes of muscarinic receptors have been identified.[79] The efficacy of glycopyrrolate in treating hyperhidrosis corresponds to its affinity for M_3 receptors (found in glandular tissue); the adverse effects correspond to actions on the other muscarinic receptor subtypes (found in the heart and nervous tissue).[79] Glycopyrrolate has a highly polar quaternary ammonium group that reduces its lipophilicity. This may explain the lower incidence of CNS adverse effects compared with other anticholinergic agents.[79] It is indicated for use as a perioperative antimuscarinic agent, as an adjunctive therapy for peptic ulcer disease, and to inhibit excessive salivation. Adverse effects include xerostomia, urinary hesitancy, ocular effects (mydriasis leading to blurred

vision and photophobia, cycloplegia, increased ocular pressure), tachycardia, dizziness, constipation, and rarely confusion. Glycopyrrolate is contraindicated in patients with myasthenia gravis, pyloric stenosis, and paralytic ileus, and should be used cautiously in patients with gastroesophageal reflux disease, glaucoma, bladder outflow obstruction, and cardiac insufficiency.[79]

3.4.2 Clonidine

Clonidine is an antihypertensive agent that functions as a centrally acting α-adrenergic receptor agonist that reduces sympathetic outflow. Adverse effects include dry mouth, dizziness, constipation, and sedation. Systemic clonidine has been reported as a treatment for hyperhidrosis in only a limited number of case reports[80,81] and a series of 12 patients in the French literature.[82] Clonidine administered as a transcutaneous patch (0.2 mg/day) was reported to be helpful in a single case of gustatory hyperhidrosis.[83]

In the authors' experience, 13 patients with hyperhidrosis, including six with craniofacial hyperhidrosis and five with generalized hyperhidrosis, were treated with clonidine 0.1 mg twice daily; six (46%) responded to treatment; three (23%) did not respond, and four (31%) had symptomatic decreases in blood pressure necessitating discontinuation.[78]

3.4.3 Other Agents

Two patients with palmar hyperhidrosis demonstrated objective improvement during therapy with the calcium channel-blocking medication diltiazem.[84] The anticholinergic/antimuscarinic agent propantheline bromide was reported to be effective for two patients with generalized hyperhidrosis secondary to spinal cord injury.[85] Similarly, five of seven patients with generalized hyperhidrosis secondary to spinal cord injury responded to the α-adrenergic blocking agent, phenoxybenzamine.[86]

No specific studies in the literature have supported the use of antidepressants for the treatment of hyperhidrosis. Some authors have anecdotally found that patients whose hyperhidrosis relates to specific anxiety-producing events or social anxiety disorder may respond to antidepressants and/or anxiolytic agents.[21] Disturbances of sweating (both hyper- and hypohidrosis) are listed as possible adverse effects of tricyclic antidepressants, and hyperhidrosis is listed as a possible adverse effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors.[87,88] The serotonin antagonist/antihistamine cyproheptadine was reported useful in treating SSRI-induced hyperhidrosis in a series of five patients.[89] The benzodiazepine clonazepam was useful in a single case of unilateral hyperhidrosis.[90]

4. Surgical Treatments

4.1 Sympathectomy

Sweating is controlled by the sympathetic arm of the autonomic nervous system. The preganglionic sympathetic nerves originate from the intermediolateral horn of the spinal cord from segments T-1 to L-2 and course up and down the paravertebral sympathetic chain to synapse with postganglionic neurons in the sympathetic chain or pass through the chain to exit via the gray communicating ramus to one of the spinal nerves to synapse with an outlying sympathetic ganglion.[91] Segmental sympathetic fibers from T-1 supply the head; T-2 the neck; T-3 through T-6 the thorax; T-7 through T-11 the abdomen; and T-12 through L-2 the legs.[91] Sympathetic fibers from spinal segments T-2 and T-3 innervate the hand.[91] Consequently, denervation of sympathetic tone to the arms requires surgical division of the sympathetic chain above the T-2 ganglion and below the T-3 ganglion.[91]

Kotzareff[92] was the first physician to perform surgical sympathectomy for disabling recalcitrant hyperhidrosis in the 1920s. Historic open surgical procedures included transthoracic, transaxillary, and posterior approaches that have progressed to the present day, minimally invasive, video-assisted endoscopic thoracic sympathectomy (ETS) technique.[91,93] This procedure is generally performed by a cardiothoracic surgeon.

ETS is performed under general anesthesia with one to three small intercostal incisions for thoracoscopic access. Excision, electrocautery, or clamping methods are used for sympathectomy.[56,94] More than 95% of patients will experience long-term measurable anhidrosis with ETS performed by an experienced surgeon.[56,95] For plantar hyperhidrosis, a variant procedure involving removal of the L3 ganglia can be performed, with improvement in sweating in up to 97% of patients.[96,97] However, there is a high risk of sexual dysfunction with lumbar sympathectomy for plantar hyperhidrosis.[98] Treatment of axillary hyperhidrosis by sympathectomy is difficult as the T-3 through T-6 ganglia must be destroyed to be efficacious.[96]

With ETS, perioperative complications such as life-threatening great vessel injury (0.08%) and hemo/pneumothorax requiring chest tube placement (1%) are rare.[96,99] In addition, postoperative Horner syndrome from damage to the stellate ganglion is markedly reduced with ETS compared with open surgery. The former 5% complication rate for Horner syndrome from older open surgical approaches has been lowered to 1–2% with ETS.[100] Postoperative problems, such as hematoma, swelling, and pain are common with ETS.[93]

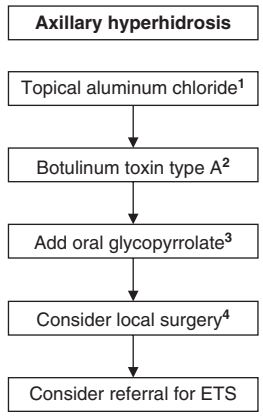

Fig. 1. Treatment algorithm for axillary hyperhidrosis. 1 Apply to dry skin at bedtime and wash off in the morning; use nightly as tolerated until euhidrotic then decrease to maintenance frequency 2–3 times per week. 2 Recommended dose is 1 U/cm^2 or 50 U per axilla for Botox®. 3 Glycopyrrolate 1–2 mg can be taken up to three times per day. 4 Local surgery options include simple excision, curettage, or liposuction. **ETS** = endoscopic thoracic sympathectomy.

Compensatory hyperhidrosis is the most common negative complication of sympathectomy, occurring in some form from 37% to as high as 100% of patients post-ETS.[96,100] In addition, gustatory sweating (in approximately one-third of patients) and subjective phantom sweating (in approximately one-quarter of patients) can occur post-ETS.[96] Compensatory hyperhidrosis usually occurs in body segments just below the areas made dry by sympathectomy including the trunk/back, buttocks, groin, and thighs.[93] However, severe compensatory hyperhidrosis is seen in only 1–2% of patients post-ETS as opposed to 10–40% of patients following traditional open surgical sympathectomy.[93,99] Despite the high incidence of postoperative compensatory hyperhidrosis, 85% of patients report "overall satisfaction" with ETS. Further reducing the incidence of postoperative compensatory hyperhidrosis is a recent surgical technique termed sympathotomy.[56] In traditional ETS, ablation of the T2 and T3 sympathetic ganglion is performed. However, in sympathotomy, the sympathetic chain is disconnected between the T2 ganglion and the stellate ganglion, producing similar results to traditional ETS with a reduced chance of severe compensatory hyperhidrosis.[56,95]

4.2 Local Surgery

Localized surgical removal of the eccrine sweat glands is an invasive treatment option for axillary hyperhidrosis only. Complete en bloc surgical excision of the axillary skin region can be performed, with relapse rates of 10–25%.[101] However, scarring with resulting displeasing cosmetic appearance and functional impairment limit the usefulness of this technique.[96]

Less invasive options include axillary curettage or liposuction to remove sweat glands at the axillary dermis-subcutaneous junction.[55,96,102,103] Both procedures can be performed under local anesthesia with small incisions. Improvements in sweating with both techniques are reported in 80–90% of patients.[55,102-105] Self-limited postoperative complications include pain, bruising, and swelling.[104] Less common complications include scarring, axillary alopecia, and paresthesia.[96,104] The largest study on axillary curettage involved 161 patients who underwent bilateral procedures. Recurrences were seen in 15% of patients, and postoperative complications occurred in 11% of patients.[102] A recent study found that an ultrasound device was useful in reducing axillary hyperhidrosis in 11 of 13 patients, with improvement still present after 6 months of follow-up.[106]

5. Treatment Algorithms

Treatment approaches by site are based upon previous literature[2] while taking into account new data and focusing in particular on the safety, efficacy, cost, patient convenience, and availability of therapies. Different modes of treatment can generally be combined when necessary. These practical algorithms are intended to be utilitarian rather than utopian. They represent the evidence- and experienced-based opinions of the authors and are meant to guide therapy decisions. Physicians who exercise their own clinical judgment in each case, taking into account both patient and physician factors (expectations, experience), will maximize the opportunity for the best outcome.

For axillary hyperhidrosis (figure 1), topical aluminum chloride is an excellent first option that may be sufficient for most

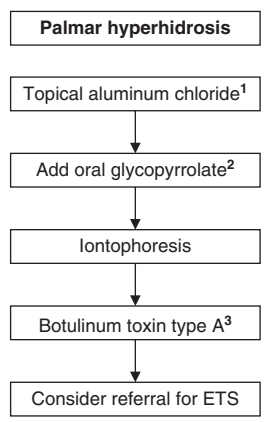

Fig. 2. Treatment algorithm for palmar hyperhidrosis. 1 Apply to dry skin at bedtime and wash off in the morning; use nightly as tolerated until euhidrotic then decrease to maintenance frequency 2–3 times per week. 2 Glycopyrrolate 1–2 mg can be taken up to three times per day. 3 Recommended dose is 1.5–2 U/cm^2 or 100–150 U per palm for Botox®. **ETS** = endoscopic thoracic sympathectomy.

cases and may be continued if other therapies are added. BTX is safe and well tolerated for the treatment of the axillae and requires no local anesthetic; cost, insurance authorization, and need for repeat treatment are limiting factors. Oral glycopyrrolate is a convenient and safe addition that may offer noticeable benefit; any adverse effects quickly remit on discontinuation. Local surgery may be helpful, though adverse effects may not be reversible and many dermatologists do not routinely perform such surgeries. ETS may be curative though is associated with higher risk and expense, and is generally available only at tertiary referral centers. Moreover, the less invasive surgical procedures discussed in section 4.2 (including axillary excision, curettage, and liposuction) are routinely performed by few dermatologists. Those with experience in these procedures may consider their place in treatment on an individual basis.

The treatment algorithms for palmar (figure 2) and plantar (figure 3) hyperhidrosis are similar. Topical aluminum chloride is the first-line treatment, which may be sufficient for most cases and may be continued if other therapies are added. Oral glycopyrrolate is recommended as the next step in therapy due to its safety, convenience, and low cost. Iontophoresis is recommended as the third step in therapy. This modality will have the highest efficacy for most patients and has the advantage of at-home, patient-controlled treatment. The primary disadvantages are the barriers to acquisition of the unit (cost, limited insurance coverage), initial patient education on operating the unit, and the time required for treatment. Consideration of BTX is recommended as the fourth-line therapy for palmar and plantar hyperhidrosis, due to the factors noted above plus the usual requirement for anesthesia, which introduces procedural complexity and increased risk. ETS is recommended only for palmar hyperhidrosis and may be curative when other options fail and when the severity is sufficient to warrant it. When palmar hyperhidrosis is severe enough to substantially interfere with daily activities, the clinical threshold for ETS referral may be lower.

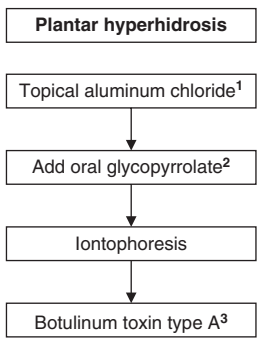

Fig. 3. Treatment algorithm for plantar hyperhidrosis. 1 Apply to dry skin at bedtime and wash off in the morning; use nightly as tolerated until euhidrotic then decrease to maintenance frequency 2–3 times per week. 2 Glycopyrrolate 1–2 mg can be taken up to three times per day. 3 Recommended dose is 1.5–2 U/cm^2 or 100–200 U per sole for Botox®.

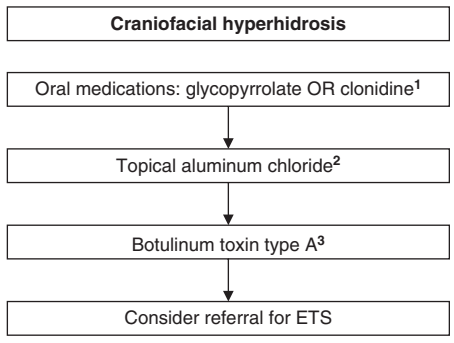

Fig. 4. Treatment algorithm for craniofacial hyperhidrosis. 1 Glycopyrrolate 1–2 mg can be taken up to three times per day; clonidine 0.1 mg can be taken twice daily. 2 Apply to dry skin at bedtime and wash off in the morning; use nightly as tolerated until euhidrotic then decrease to maintenance frequency 2–3 times per week. 3 Recommended dose is 0.5–1 U/cm^2 depending on site up to 50–100 U total for Botox®. **ETS** = endoscopic thoracic sympathectomy.

For craniofacial hyperhidrosis (figure 4), oral medications are considered first-line therapy, due primarily to a reasonable chance of efficacy and anatomic limitations to local therapies. Glycopyrrolate 1–2 mg one to three times daily may be helpful. Adequate evidence also supports a trial of oral clonidine as a viable option.[78] In a healthy patient, either may be tried initially. The presence of any co-morbid conditions may favor the use of one medication over the other. Topical aluminum chloride is second-line therapy due to practicality and irritancy, but may be a particularly helpful addition for hyperhidrosis of the forehead and/or bald scalp. BTX, though highly efficacious, is a third-line option due to the factors discussed above plus the added complexity of the facial musculature, necessitating varying dosing and injection technique and introducing increased risk of adverse effects. Treatment of the scalp and forehead is safer and more predictable than treating the lower face. The clinical overlap between hyperhidrosis control and secondary cosmetic benefit for facial treatment may also introduce additional challenges in obtaining insurance coverage. ETS may be curative if warranted by the clinical severity.

6. Conclusions

Primary hyperhidrosis is a common disorder with significant clinical consequences. The clinical presentation is variable with regard to distribution patterns, severity, and patient impact. A variety of treatment options are available. In most cases, it is possible to tailor therapy to each individual patient for a satisfactory outcome.

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