The etiology, diagnosis, and management of hyperhidrosis: A comprehensive review

Therapeutic options

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Learning objectives
After completing this learning activity, participants should be able to identify and contrast the treatment options available for hyperhidrosis; recognize side effects and limitations of each treatment modality; determine the best treatment option based on severity and location of symptoms; and assess the validity and reliability of existing studies related to hyperhidrosis.

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Hyperhidrosis (HH) is a chronic disorder of excess sweat production that may have a significant adverse effect on quality of life. A variety of treatment modalities currently exist to manage HH. Initial treatment includes lifestyle and behavioral recommendations. Antiperspirants are regarded as the first-line therapy for primary focal HH and can provide significant benefit. Iontophoresis is the primary remedy for palmar and plantar HH. Botulinum toxin injections are administered at the dermal-subcutaneous junction and serve as a safe and effective treatment option for focal HH. Oral systemic agents are reserved for treatment-resistant cases or for generalized HH. Energy-delivering devices such as lasers, ultrasound technology, microwave thermolysis, and fractional microneedle radiofrequency may also be utilized to reduce focal sweating. Surgery may be considered when more conservative treatments have failed. Local surgical techniques, particularly for axillary HH, include excision, curettage, liposuction, or a combination of these techniques. Sympathectomy is the treatment of last resort when conservative treatments are unsuccessful or intolerable, and after accepting secondary compensatory HH as a potential complication. A review of treatment modalities for HH and a sequenced approach are presented. (J Am Acad Dermatol 2019;81:669-80.)

Key words: aluminum chloride hexahydrate; BTX; botulinum neurotoxin; botulinum toxin; compensatory sweating; endoscopic sympathectomy; fractional microneedle radiofrequency; hyperhidrosis; injectable therapy; iontophoresis; laser therapy; microwave thermolysis; oral anticholinergics; topical antiperspirants; ultrasound technology.

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TRIGGER AVOIDANCE AND CLOTHING

Patients should avoid hyperhidrosis (HH) triggers, including crowded areas, emotional provocations, spicy foods, and alcohol.[1] The avoidance of tight clothing, man-made synthetic fabrics, and occlusive footwear may also help. Other strategies include masking sweat using underarm liners or dress shields,[2-4] frequent sock and shoe changes, leather shoes, absorbent shoe insoles, foot powder, and cotton or wool socks.[5]

TOPICAL ANTIPERSPIRANTS

Key points

- **Aluminum chloride hexahydrate is the most commonly used topical medication for mild to moderate hyperhidrosis**
- **Antiperspirants should be applied to dry skin before bedtime**
- **Antiperspirants need to stay on the skin for 6 to 8 hours before being washed off**
- **Aluminum chloride hexahydrate blocks the lumen of the distal eccrine sweat gland ducts**
- **No evidence exists that links the use of aluminum-containing antiperspirants to Alzheimer disease**
- **No clear link exists between the use of aluminum-containing antiperspirants and breast cancer**

Aluminum chloride hexahydrate (ACH) is the most frequent and effective topical medication that is used to relieve mild to moderate symptoms.[6] Its wide availability, cost effectiveness, and ease of use render it a first-line treatment.[7] ACH concentrations range from 6.25% to 40% in water, alcohol, ether, or glycerol.[8] Over-the-counter (OTC) antiperspirants contain a maximum concentration of 12.5% ACH. Frequently used prescription formulations include 20% aluminum chloride in ethyl alcohol, 6.25% aluminum tetrachloride, and 12% aluminum chloride in sodium carbonate—water.[6]

Metal salts of aluminum interact with sweat mucopolysaccharides to form precipitates that block the eccrine sweat gland duct lumen.[9,10] Sweat is still produced, as shown by the appearance of miliaria during heat stress behind the obstruction.[10] The effect is transient and the mechanical plug is shed with normal skin renewal.[11] Histologic analysis reveals atrophy of eccrine sweat glands and cells lining the secretory ducts.[10] Other less commonly used metallic salts, including zirconium, vanadium, and indium, are thought to work through the same mechanism.[9] Patients reported excellent to good satisfaction rates in 94% of axillary, 84% of plantar, and 60% of palmar cases.[11]

Prescription strength and OTC antiperspirant formulations should be applied to dry skin at bedtime when sweat rates are low and should stay on the skin for 6 to 8 hours before being washed off.[6,7,12-14] Lotion formulations may help achieve an even application compared with stick or roll-on applicators.[13] ACH applications should be repeated every 24 to 48 hours until anhidrosis is attained.[15] Clinical efficacy in many cases is noted in 1 to 2 weeks.[11] After symptom relief, maintenance therapy can be tailored individually depending upon the resultant effect, side effects, and events anticipated by the patient to entail excessive perspiration. Maintenance therapy usually consists of ACH application 1 to 2 times a week.[15] Skin irritation occurs in 21% of patients,[15] correlating with higher aluminum chloride concentrations.[16] Irritation can be ameliorated by increasing the interval between applications, using the lowest concentration of ACH possible, using aluminum chloride formulations in a salicylic acid gel base rather than aqueous alcohol,[17,18] applying triethanolamine,[19] moisturizers,[20] or topical hydrocortisone[18] after antiperspirant application, or using prescription-strength antiperspirant sparingly with OTC antiperspirant on other days.[13]

Early research suggested a possible link between aluminum exposure and Alzheimer disease through neurofibrillary tangles induced by aluminum in rabbit brains.[21] In addition, aluminum levels in the brains of patients with Alzheimer disease were determined to be 1.4 times higher than those in control subjects.[22] Later studies showed only a negligible association, with no evidence linking the use of aluminum-containing antiperspirants to Alzheimer disease.[23] The Alzheimer's Association and experts no longer believe that exposure to everyday sources of aluminum (including antiperspirants) causes Alzheimer disease.[24-26]

It has also been theorized that aluminum antiperspirants increase the risk of breast cancer because most breast cancers develop in the upper outer part of the breast near the axilla.[27] It was speculated that chemicals in antiperspirants, including aluminum, that are absorbed into the skin, especially through nicked skin during shaving, may lead to cancerous cellular DNA or interfere with the action of estrogen, thus promoting the growth of both cancer and noncancer breast cells.[28] It was hypothesized that aluminum ions can penetrate the cells' nuclei and cause instability of the genome that can potentially be expressed by defective DNA repair systems (eg, interfering with cross-linking of DNA strands), creating DNA replication errors and decreasing the rate of DNA synthesis.[29] Despite these assumptions, no substantial evidence supports that any underarm

Abbreviations used:

ACH: aluminum chloride hexahydrate
BTX: botulinum toxin
HH: hyperhidrosis
MU: mouse unit

cosmetic chemical (including aluminum) increases the risk of breast cancer.[30] According to the American Cancer Society, because of the low absorption of aluminum, there is no clear link between antiperspirants containing aluminum and breast cancer.[31]

Several other topical formulations have been developed, including aluminum zirconium trichlorohydrex, anticholinergics, BTX, and multiple astringent agents. Clinical strength OTC antiperspirants use aluminum zirconium trichlorohydrex as the active ingredient. They create superficial duct blockages that last several days without significant skin irritation.[13] Topical anticholinergic medications, including propantheline, scopolamine, diphemanil methylsulfate, atropine sulfate, and glycopyrrolate, have been used to treat HH[6,32-35] with inconsistent efficacy. Topical glycopyrrolate (0.5% to 4% solution, gel, cream, or pads) and 3% topical oxybutynin are the most commonly used topical anticholinergic agents.[36,37] Adverse effects include skin irritation, pruritus, headache, dizziness, sore throat, mydriasis, dry mouth, constipation, and nasopharyngitis.[34,36,38-41]

BTX is a common effective injectable medication for HH, but its large molecular size prevents it from crossing intact skin.[42] New topical BTX preparations are being explored, including transdermal drug delivery by jet nebulization and the noncovalent binding of the toxin to a proprietary peptide to transport it across intact skin.[41,43,44]

In the 1960s and 1970s, astringent medications, including 10% glutaraldehyde, 5% to 20% formalin solution, or 2% to 5% tannic acid, were topically used to manage HH. These preparations temporarily clog the eccrine sweat gland duct by altering keratin in the stratum corneum.[6] Disadvantages of their use include skin staining,[45] frequent contact dermatitis, inadequate long-term efficacy,[46,47] and central nervous system toxicity.[16,48]

ORAL AGENTS

Key points

- **Oral systemic medications are reserved for treatment-resistant cases or generalized hyperhidrosis**
- **Anticholinergics are the most commonly used oral medications for hyperhidrosis treatment**
- **Adverse effects of anticholinergic agents force one-third of patients to discontinue treatment**

Although not approved by the US Food and Drug Administration (FDA), oral anticholinergics are commonly used for generalized or multifocal primary HH.[49,50] Anticholinergics operate by competitively inhibiting the effect of acetylcholine, which stimulates postsynaptic muscarinic receptors to induce eccrine sweat gland secretion.[51] Forms of anticholinergic medications include topical gel, tablet, slow-release tablet, and transdermal patch.[52-54] Adverse effects of anticholinergic agents force up to one-third of patients to discontinue treatment[55] and include dry mouth, blurred vision, dry eyes, hyperthermia, orthostatic hypotension, gastrointestinal complaints, urinary retention, tachycardia, drowsiness, dizziness, and confusion.[6,49,52,55-57] Simultaneous use of other medications with anticholinergic activity, including anti-Parkinson drugs, phenothiazines, and tricyclic antidepressants, add to the antimuscarinic effects of the anticholinergic agents.[52]

Oral anticholinergics are contraindicated for use in patients with pyloric stenosis, paralytic ileus, and myasthenia gravis.[6,55] They are relatively contraindicated in individuals with gastroesophageal reflux disease, cardiac insufficiency, closed-angle glaucoma, and bladder outlet obstruction.[6,55]

Glycopyrrolate, the most commonly used anticholinergic for HH,[52] is a quaternary amine. It has limited ability to cross lipid membranes, including the blood–brain barrier, and therefore it has fewer side effects.[55] The initial glycopyrrolate dose is 1 to 2 mg twice daily.[52] Oxybutynin, another common anticholinergic drug used in HH, is a tertiary amine that crosses lipid membranes. Oxybutynin dosage starts at 2.5 mg once daily but can gradually be increased up to 10 to 15 mg daily.[50,58-62] Gradually increasing doses of anticholinergic medications may reduce side effects and increase tolerability.[58,63] Maximum efficacy is typically achieved in 1 week, followed by continued maintenance treatment.[64]

Other potential oral medications with limited available data include beta-blockers and benzodiazepines, which can be successful in anxiety-triggered HH.[52] Oral clonidine reduces sweating in generalized HH and paroxysmal localized HH.[52,65,66] Indomethacin is reportedly efficient in the treatment of generalized HH, presumably by inhibiting prostaglandin E2 formation, which stimulates sweat secretion in vitro.[6,67,68] Calcium channel blockers also reduce sweating, likely by inhibiting calcium-dependent acetylcholine release.[69]

IONTOPHORESIS

Key points

- **Iontophoresis is effective and is considered the primary treatment for palmar and plantar hyperhidrosis**
- **At-home iontophoresis treatment devices may yield improved compliance**
- **Alterations to the liquid medium used in iontophoresis devices may amplify the anhidrotic effect**

Iontophoresis is a cost-effective, safe therapy approved by the US FDA that is most appropriate for palmar and plantar HH.[15,70] Three devices are registered by the FDA: RA Fischer (RA Fischer Co, Northridge, CA), Hidrex USA (Hidrex USA, LLC, Austin, TX), both of which require a prescription, and Drionic (General Medical Co, Los Angeles, CA), which is available without a prescription. Iontophoresis treatment uses galvanic current transfer through undamaged skin immersed in liquid.[6,70-74] The anode (positively charged) electrode, when submerged in simple tap water iontophoresis, repels hydrogen ions (H+) into the eccrine ducts. Theories concerning the underlying mechanism of action include blockage of sweat secretion and flow by a hyperkeratotic plug,[75] interference with the sweat secretion electrochemical gradient,[76] blockage of sympathetic nerve transmission,[77] and a reduction in pH due to hydrogen ion accumulation.[70,74,75,77-79] Iontophoresis is principally restricted to the palmoplantar locations,[78,80] even though special axillary electrodes (foam pads soaked in water) have been developed.[81]

Iontophoresis is performed 3 to 4 times per week for 20 to 30 minutes at a current of 15 to 20 mA.[15,82-84] Approximately 6 to 15 treatments are commonly required to attain anhidrosis,[6,15,85] and the effects usually last for 2 to 14 weeks.[86] Maintenance treatments are performed every 1 to 4 weeks.[15,46,82] Available at-home treatment devices yield better compliance.[87] Iontophoresis is effective in 80% of cases,[88] but symptoms can initially worsen before improving. Therapeutic success and side effect incidence depend on current intensity.[6,89]

Modifications to simple tap water iontophoresis with aluminum chloride, anticholinergic agents, or BTX added to the medium can amplify the anhidrotic effect.[55,56,90-97] Potential contraindications to iontophoresis include pregnancy, substantial metal implants, cardiac conditions, epilepsy, and implantable electronic devices, including pacemakers.[46,91,98-100] Of concern are the possible hazardous effects that can derive from the electric current involved in the procedure. Parts of the body that the current must go through should not contain metal. Adverse effects include discomfort,[101] dryness,[101] paresthesias,[74,88] erythema,[101] and transient vesiculation of the affected area.[74,88,101] Side effects can be ameliorated with moisturizers, topical corticosteroid cream,[12] or a decrease in treatment frequency or intensity.[6,45,89]

INJECTABLE THERAPIES: BTX

Key points

- **Botulinum toxin is a common, safe, and effective injectable medication for focal hyperhidrosis**
- **Botulinum toxin injections are administered at the dermal–subcutaneous junction**
- **The most common complaint related to botulinum toxin treatment is pain**
- **Most patients with axillary hyperhidrosis experience excellent results from botulinum toxin treatment**
- **Most patients with hyperhidrosis require 1 to 2 botulinum toxin treatments annually**

BTX-A and, to a lesser degree, BTX-B are the serotypes frequently used for HH.[6] The FDA approved onabotulinum toxin-A for severe primary axillary HH treatment.[102] BTX-B (Myobloc; Solstice Neurosciences, Inc, San Francisco, CA) is approved only for cervical dystonia.[6] Four commercial types are clinically available for use in the USA: 3 BTX-A formulations, including onabotulinum (Botox; Allergan, Irvine, CA), incobotulinum (Xeomin; Merz Pharmaceuticals, Greensboro, NC), and abobotulinum (Dysport; Galderama Laboratories, Fort Worth, TX), and 1 BTX-B formulation, namely rimabotulinum (Myobloc).[103]

BTX is a natural protein produced by the Gram-positive anaerobe *Clostridium botulinum*.[6] BTX cleaves the soluble NSF attachment protein receptor that facilitates fusion of the synaptic vesicles with the presynaptic membrane, inhibiting presynaptic exocytosis and cholinergic transmission to postganglionic receptors that innervate eccrine sweat glands.[104-111] BTX-A breaks the 25-kD synaptosomal-associated protein, and BTX-B splits the vesicle-associated membrane protein (synaptobrevin).[6,104,112-114]

Contraindications to BTX include peripheral motor neuropathy or neuromuscular junction diseases (myasthenia gravis or Lambert–Eaton syndrome), pregnancy, lactation, allergy to any of the injectable components, and medications, such as aminoglycosides, penicillamines, cholinesterase inhibitors, quinine, and calcium channel antagonists.[6,106,107,109,115-118] Regarding dosing, 1 mouse unit (MU) of onabotulinum is equivalent to 3 MUs of

abobotulinum[112] and 40 MUs of rimabotulinum.[119-122] For each administration, the highest onabotulinum dose should not exceed 300 to 400 units. The onabotulinum dose should not surpass >400 units over a 4-month period.[6,104] Onabotulinum and abobotulinum are diluted with 0.9% saline for clinical use.[113,123] Rimabotulinum does not require reconstitution.[112] BTX is placed at the dermal–subcutaneous junction, approximately 2.5 mm below the skin.[124] Typically, 10 to 20 injections are administered, spaced 1 to 2 cm apart. For onabotulinum toxin A, the average dose is 1 unit/cm^2 (3-4 U every 1.5-2 cm) and up to 50 to 100 units per axilla.[15,125] Abobotulinum toxin A treatment usually requires 100 to 300 units per axilla. The palms and soles usually require higher total doses.[126]

The most common complaint is pain caused by injections, particularly in the palmar and plantar regions. On average, discomfort lasts for 2.4 days, although it may extend up to 10 days.[6,127] Techniques to reduce pain include needle-free anesthesia,[128] cryoanalgesia,[129] vibration analgesia,[130] pocketed microneedles,[131] topical anesthetics,[132,133] dilution with lidocaine,[134,135] sedation, intravenous regional anesthesia,[136] and nerve blocks.[137] For the palms, ulnar, median, and radial nerve blocks or a modified Bier block can be effective.[138-141] For plantar applications, posterior tibial nerve and sural nerve blocks may be used.[6,118] A common side effect associated with palmar BTX injections is temporary weakness of the thenar eminence muscles,[64] demonstrated by grip weakness.[142] A potential side effect of craniofacial BTX injections is functional or cosmetic defects caused by inadvertent muscle weakness.[143-146] Most patients experience excellent axillary BTX treatment results[126] with 82% to 87% efficacy.[7,8,106] Plantar BTX treatment is less effective, with approximately 50% of patients dissatisfied.[102] Sweat reduction is observed within 2 to 4 days and becomes significant after approximately 2 weeks.[125] The typical therapeutic result is similar regardless of the location treated and persists for 6 to 8 months,[105-107,110,147-149] requiring 1 to 2 BTX therapy sessions annually.[6,111,123,125,127,150] Concerns regarding seroconversion and treatment resistance to BTX-A formulations have led to the interest in the use of BTX-B. Compared with BTX-A, BTX-B exhibits a quicker response (5-7 days) but with a reduced period of action (2-3 months),[112,119,151] a broader side effect range,[6,151] and more painful administration.[112]

Many insurance companies consider BTX treatment for HH necessary only after other topical treatments have failed; otherwise, BTX therapy can become costly to the patient.

Sweat reduction devices

Microwave thermolysis. A microwave thermolysis device, MiraDry (Miramar Labs, Sunnyvale, CA), has been approved by the FDA for the treatment of primary axillary HH.[152,153] It creates irreversible thermolysis and destruction of eccrine sweat glands by rotation of water molecules.[76,152-157] Overall efficacy of 90%, persisting for >12 months, has been reported.[155] Histologically, a substantial decrease in the amount of eccrine and apocrine sweat glands, as well as deep dermal fibrosis, has been shown.[155,158,159] Side effects include discomfort, edema, erythema, ecchymosis, axillary tenderness or pain, numbness, temporary altered sensation, subcutaneous nodules, permanent patchy alopecia, compensatory HH and, rarely, brachial plexus injury with transient median and ulnar neuropathy.[76,152,153,155,160-162]

Ultrasound therapy. Ultrasound therapy provides low levels of focused thermal injury to the eccrine units, leading to wound healing and collagen remodeling. An intense focused ultrasound device (Ulthera Inc, Mesa, AZ) was approved by the US FDA for skin tightening and lifting procedures.[163] Side effects include temporary tenderness, redness, numbness, and bruising.[164] An 80% reduction in sweating and a 90% satisfaction rate have been reported.[165] Another ultrasound system, VASER (SoltaMedical, Inc, Hayward, CA), has been approved by the US FDA for soft tissue emulsification and body contouring. It concentrates ultrasonic power that is introduced inside the soft tissue via the machine's probe.[41]

Fractional microneedle radiofrequency. Fractional microneedle radiofrequency involves the insertion of microneedles into the skin and emission of bipolar thermal energy directly to the eccrine sweat glands with minimal epidermal trauma.[166,167] Adverse effects include mild pain, swelling, and redness.[167] Histologic analysis shows reduction in the size and number of eccrine and apocrine sweat glands.[167-170]

Noninvasive laser treatments. Noninvasive laser treatments using 1064-nm neodymium-doped yttrium aluminum garnet laser,[171] pulsed-diode laser,[172] and long-pulsed 800-nm diode laser[173] have shown mixed results, with some resulting in reduced sweating and others exacerbating HH.

Subdermal laser procedures. Subdermal laser procedures using 1064- and 1320-nm neodymium-doped yttrium aluminum garnet lasers and 924- and 975-nm diode-powdered lasers[170,174,175] cause damage to eccrine sweat glands through microvesiculation, desquamation, cell rupture, decapitation, or vaporization.[176,177] Side effects include transient

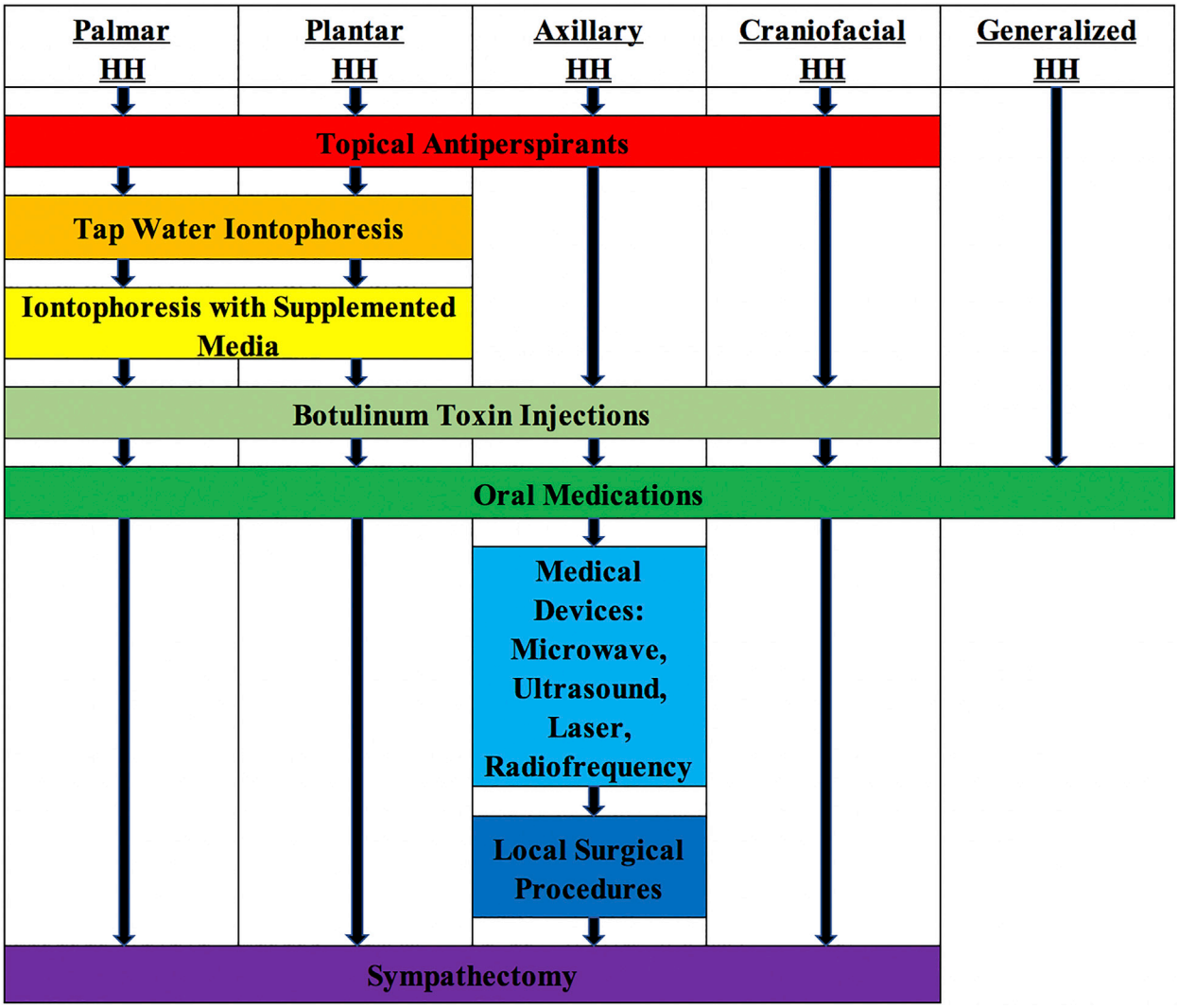

Fig 1. The treatment approach for a patient presenting with hyperhidrosis. *HH*, Hyperhidrosis.

local pain, reduced sensation lasting up to 3 to 5 weeks, hair reduction, hematoma, edema, burns, skin erosion, and compensatory HH.[175-178]

SURGICAL TREATMENT OF HYPERHIDROSIS

Key points

- **Surgery is considered when conservative treatments have failed**
- **Local surgical techniques include excision, curettage, liposuction, or a combination of these techniques**
- **Sympathectomy is the treatment of last resort in the management of hyperhidrosis**
- **The most common long-term complication after sympathectomy is compensatory sweating**

Surgery is used when conservative treatments have failed.[179] Local surgical techniques for axillary HH include excision, curettage, liposuction, and a combination of these techniques.[7] The excision of subcutaneous tissue removes the base of the sweat glands and thus eliminates sweat production. Radical skin excision possesses undesirable side effects including scarring and restricted arm movement,[108,180-183] whereas a skin-sparing procedure, known as the Shelley procedure, involves only nominal skin excision and therefore minimal scarring.[183,184] Subcutaneous liposuction curettage is a newer technique using a small incision through which a curette or liposuction cannula is inserted for almost complete elimination of the axillary eccrine and apocrine sweat glands.[156,176] This procedure reduces the risk of scarring but carries a risk of complications, including bleeding, pain, bruising, skin erosion, infection, ecchymosis, hyperpigmentation, seroma, damage to the brachial plexus, dysesthesia, hair loss, recurrence of HH, and compensatory sweating.[181,185-191]

Sympathectomy is the treatment of last resort in HH.[192] The procedure aims to cut off the sympathetic signals from reaching the eccrine sweat glands through bilateral sympathectomy or ganglionectomy by transecting, resecting, cutting, ablating, or clipping the involved sympathetic nerves.[192] The preferred patients for endoscopic thoracic sympathectomy include those whose HH began at an early age, are <25 years of age, have a body mass index <28 kg/m^2, do not exhibit nocturnal sweating, are relatively healthy, and do not have bradycardia.[193] Endoscopic thoracic sympathectomy is indicated for palmar (T2 and T3 ganglia), craniofacial (above the third rib), and axillary (T3 and T4 ganglia) HH.[156,193] Endoscopic lumbar sympathectomy (at the L3/L4 level) is used for plantar HH.[194] Endoscopic sympathectomy is effective in 68% to 100% of cases.[195,196] The rate of patient satisfaction is 66.7% to 93% but decreases with time.[197] Patients who are surgically treated for palmar HH are the most satisfied.[198] Postoperative complications include pneumothorax, hemothorax, subcutaneous emphysema, intrathoracic bleeding, paresthesia, upper limb neurologic impairment, stellate ganglion injury leading to Horner syndrome (ptosis, miosis, and anhidrosis), hyperthermia, phrenic nerve lesion, and bradycardia.[108,198-204] Long-term complications include recurrent primary focal HH (0-65% of patients) and compensatory sweating (98% of patients). Common sites of compensatory sweating include the abdomen, back, legs, and gluteal region.[193,205,206] Local BTX injections, oral anticholinergic agents, reversal unclipping, and nerve grafting may help improve compensatory sweating.[192,207]

Treatment approach

Treatment of HH depends on the etiology (primary or secondary), localization, severity, safety, side effects, extent of irreversibility, cost, treatment availability, and the provider's expertise and experience. Conservative measures should be attempted before the use of more aggressive and invasive treatments (Fig 1).

Treatment with topical antiperspirants should be attempted first for focal or multifocal HH, increasing ACH concentrations to a level that achieves both efficacy and tolerability.

For palmar and plantar HH, if antiperspirants are not sufficient, tap water iontophoresis should be used. Antiperspirant agents, anticholinergic agents, and BTX can be added to the iontophoresis medium if tap water iontophoresis is unsatisfactory.

For axillary HH, if topical antiperspirants are insufficient, BTX injections are the next treatment option, taking into consideration pain, cost, and insurance coverage.

Systemic oral therapy is considered after other nonsurgical treatments have failed; it can be especially useful in multifocal or generalized HH when localized therapy can be challenging.

Next, medical devices such as microwave, ultrasound, laser, and radiofrequency can be considered for axillary HH, with particular consideration of their high cost, potentially permanent and irreversible tissue destruction, limited clinical data, and the provider's level of expertise.

Finally, local surgical measures can be considered for axillary HH. Endoscopic sympathectomy is the treatment of last resort for all HH sites because of the high incidence of compensatory HH.

Treatment of secondary HH should focus on the underlying cause of HH. Antihyperhidrotic oral medications can be given as an additional measure to reduce excessive sweating in patients with secondary HH.

REFERENCES

1. Watkins J. Understanding and treating hyperhidrosis. *Pract Nurs*. 2015;26:295-297.
2. Amini M, Harmsze AM, Tupker RA. Patient's estimation of efficacy of various hyperhidrosis treatments in a dermatological clinic. *Acta Derm Venereol*. 2008;88:356-362.
3. Excessive sweating (hyperhidrosis). NHS Choices. Available at: www.nhs.uk/Conditions/Hyperhidrosis/Pages/Treatment.aspx. Accessed May 30, 2018.
4. Tidy C. Excessive sweating. Patient.info. Available at: https://patient.info/health/excessive-sweating-hyperhidrosis. Accessed April 30, 2019.
5. Vlahovic TC. Plantar hyperhidrosis: an overview. *Clin Podiatr Med Surg*. 2016;33:441-451.
6. Gee S, Yamauchi PS. Nonsurgical management of hyperhidrosis. *Thorac Surg Clin*. 2008;18:141-155.
7. Walling HW, Swick BL. Treatment options for hyperhidrosis. *Am J Clin Dermatol*. 2011;12:285-295.
8. Sammons JE, Khachemoune A. Axillary hyperhidrosis: a focused review. *J Dermatolog Treat*. 2017;28:582-590.
9. Holzle E. Topical pharmacological treatment. *Curr Probl Dermatol*. 2002;30:30-43.
10. Holzle E, Braun-Falco O. Structural changes in axillary eccrine glands following long-term treatment with aluminium chloride hexahydrate solution. *Br J Dermatol*. 1984;110:399-403.
11. Pariser DM, Ballard A. Topical therapies in hyperhidrosis care. *Dermatol Clin*. 2014;32:485-490.
12. Grabell DA, Hebert AA. Current and emerging medical therapies for primary hyperhidrosis. *Dermatol Ther*. 2017;7:25-36.
13. Swaile DF, Elstun LT, Benzing KW. Clinical studies of sweat rate reduction by an over-the-counter soft-solid antiperspirant and comparison with a prescription antiperspirant product in male panelists. *Br J Dermatol*. 2012;166(suppl 1):22-26.
14. Draelos ZD. Antiperspirants and the hyperhidrosis patient. *Dermatol Ther*. 2002;14:220-224.

15. Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg*. 2007;33:908-923.
16. White JW Jr. Treatment of primary hyperhidrosis. *Mayo Clin Proc*. 1986;61:951-956.
17. Flanagan KH, Glaser DA. An open-label trial of the efficacy of 15% aluminum chloride in 2% salicylic acid gel base in the treatment of moderate-to-severe primary axillary hyperhidrosis. *J Drugs Dermatol*. 2009;8:477-480.
18. Benohanian A, Dansereau A, Bolduc C, Bloom E. Localized hyperhidrosis treated with aluminum chloride in a salicylic acid gel base. *Int J Dermatol*. 1998;37:701-703.
19. Glent-Madsen L, Dahl JC. Axillary hyperhidrosis. Local treatment with aluminium-chloride hexahydrate 25% in absolute ethanol with and without supplementary treatment with triethanolamine. *Acta Derm Venereol*. 1988;68:87-89.
20. Dagash H, McCaffrey S, Mellor K, Roycroft A, Helbling I. Tap water iontophoresis in the treatment of pediatric hyperhidrosis. *J Pediatr Surg*. 2017;52:309-312.
21. Klatzo I, Wisniewski H, Streicher E. Experimental production of neurofibrillary degeneration. I. Light microscopic observations. *J Neuropathol Exp Neurol*. 1965;24:187-199.
22. Trapp GA, Miner GD, Zimmerman RL, Mastri AR, Heston LL. Aluminum levels in brain in Alzheimer's disease. *Biol Psychiatry*. 1978;13:709-718.
23. Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB. The association between aluminum-containing products and Alzheimer's disease. *J Clin Epidemiol*. 1990;43:35-44.
24. Exley C. Does antiperspirant use increase the risk of aluminium-related disease, including Alzheimer's disease? *Mol Med Today*. 1998;4:107-109.
25. Lidsky TI. Is the aluminum hypothesis dead? *J Occup Environ Med*. 2014;56(5 suppl):S73-S79.
26. Krishnan SS, McLachlan DR, Krishnan B, Fenton SS, Harrison JE. Aluminum toxicity to the brain. *Sci Total Environ*. 1988;71:59-64.
27. Darbre PD. Aluminium, antiperspirants and breast cancer. *J Inorg Biochem*. 2005;99:1912-1919.
28. Darbre PD, Mannello F, Exley C. Aluminium and breast cancer: sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology. *J Inorg Biochem*. 2013;128:257-261.
29. McGrath KG. An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. *Eur J Cancer Prev*. 2003;12:479-485.
30. Gikas PD, Mansfield L, Mokbel K. Do underarm cosmetics cause breast cancer? *Int J Fertil Womens Med*. 2004;49:212-214.
31. Darbre PD. Aluminium and the human breast. *Morphologie*. 2016;100:65-74.
32. Frankland JC, Seville RH. The treatment of hyperhidrosis with topical propantheline—a new technique. *Br J Dermatol*. 1971;85:577-581.
33. Grimalt R, Dominguez Tordera P, Callejas MA. Topical atropine sulfate for the treatment of axillary hyperhidrosis. *J Cosmet Dermatol*. 2006;5:294-296.
34. Shaw JE, Abbott CA, Tindle K, Hollis S, Boulton AJ. A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia*. 1997;40:299-301.
35. Laccourreye O, Bonan B, Brasnu D, Laccourreye H. Treatment of Frey's syndrome with topical 2% diphemanil methylsulfate (Prantal): a double-blind evaluation of 15 patients. *Laryngoscope*. 1990;100:651-653.
36. Mackenzie A, Burns C, Kavanagh G. Topical glycopyrrolate for axillary hyperhidrosis. *Br J Dermatol*. 2013;169:483-484.
37. Baker D. Topical glycopyrrolate spray 2% reduces axillary hyperhidrosis to a similar extent as Botox injections. *Br J Dermatol*. 2013;169(suppl 1):4.
38. Kim WO, Kil HK, Yoon DM, Cho MJ. Treatment of compensatory gustatory hyperhidrosis with topical glycopyrrolate. *Yonsei Med J*. 2003;44:579-582.
39. Kim WO, Kil HK, Yoon KB, Yoon DM. Topical glycopyrrolate for patients with facial hyperhidrosis. *Br J Dermatol*. 2008;158:1094-1097.
40. Cladellas E, Callejas MA, Grimalt R. A medical alternative to the treatment of compensatory sweating. *Dermatol Ther*. 2008;21:406-408.
41. Glaser DA, Galperin TA. Managing hyperhidrosis. Emerging therapies. *Dermatol Clin*. 2014;32:549-553.
42. Chow A, Wilder-Smith EP. Effect of transdermal botulinum toxin on sweat secretion in subjects with idiopathic palmar hyperhidrosis. *Br J Dermatol*. 2009;160:721-722.
43. Iannitti T, Palmieri B, Aspiro A, Di Cerbo A. A preliminary study of painless and effective transdermal botulinum toxin A delivery by jet nebulization for treatment of primary hyperhidrosis. *Drug Des Devel Ther*. 2014;8:931-935.
44. Glogau RG. Topically applied botulinum toxin type A for the treatment of primary axillary hyperhidrosis: results of a randomized, blinded, vehicle-controlled study. *Dermatol Surg*. 2007;33(1 spec no):S76-S80.
45. Stolman LP. Treatment of hyperhidrosis. *Dermatol Clin*. 1998;16:863-869.
46. Atkins JL, Butler PE. Hyperhidrosis: a review of current management. *Plast Reconstr Surg*. 2002;110:222-228.
47. Bergstresser PR, Quero R. Treatment of hyperhidrosis with topical methenamine. *Int J Dermatol*. 1976;15:452-455.
48. Songur A, Ozen OA, Sarsilmaz M. The toxic effects of formaldehyde on the nervous system. *Rev Environ Contam Toxicol*. 2010;203:105-118.
49. Cruddas L, Baker DM. Treatment of primary hyperhidrosis with oral anticholinergic medications: a systematic review. *J Eur Acad Dermatol Venereol*. 2017;31:952-963.
50. Toledo-Pastrana T, Marquez-Enriquez J, Millan-Cayetano JF. Oral oxybutynin for local and multifocal hyperhidrosis: a multicenter study. *Actas Dermosifiliogr*. 2017;108:597-599.
51. Lakraj AAD, Moghimi N, Jabbari B. Hyperhidrosis: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. *Toxins*. 2013;5:821-840.
52. Glaser DA. Oral medications. *Dermatol Clin*. 2014;32:527-532.
53. Nguyen NV, Gralla J, Abbott J, Bruckner AL. Oxybutynin 3% gel for the treatment of primary focal hyperhidrosis in adolescents and young adults. *Pediatr Dermatol*. 2018;35:208-212.
54. Millan-Cayetano JF, Del Boz J, Toledo-Pastrana T, Nieto-Guindo M, Garcia-Montero P, de Troya-Martin M. Initial study of transdermal oxybutynin for treating hyperhidrosis. *J Dermatol*. 2017;44:717-720.
55. Bajaj V, Langtry JA. Use of oral glycopyrronium bromide in hyperhidrosis. *Br J Dermatol*. 2007;157:118-121.
56. Leung AKC, Chan PYH, Choi MCK. Hyperhidrosis. *Int J Dermatol*. 1999;38:561-567.
57. Paller AS, Shah PR, Silverio AM, Wagner A, Chamlin SL, Mancini AJ. Oral glycopyrrolate as second-line treatment for primary pediatric hyperhidrosis. *J Am Acad Dermatol*. 2012;67:918-923.

58. Del Boz J, Millan-Cayetano JF, Blazquez-Sanchez N, de Troya M. Individualized dosing of oral oxybutynin for the treatment of primary focal hyperhidrosis in children and teenagers. *Pediatr Dermatol*. 2016;33:327-331.
59. Wolosker N, Teivelis MP, Krutman M, et al. Long-term results of the use of oxybutynin for the treatment of plantar hyperhidrosis. *Int J Dermatol*. 2015;54:605-611.
60. Tupker RA, Harmsze AM, Deneer VH. Oxybutynin therapy for generalized hyperhidrosis. *Arch Dermatol*. 2006;142:1065-1066.
61. Wolosker N, de Campos JR, Kauffman P, Puech-Leao P. A randomized placebo-controlled trial of oxybutynin for the initial treatment of palmar and axillary hyperhidrosis. *J Vasc Surg*. 2012;55:1696-1700.
62. Wolosker N, de Campos JR, Kauffman P, et al. The use of oxybutynin for treating axillary hyperhidrosis. *Ann Vasc Surg*. 2011;25:1057-1062.
63. Wolosker N, de Campos JR, Kauffman P, et al. An alternative to treat palmar hyperhidrosis: use of oxybutynin. *Clin Auton Res*. 2011;21:389-393.
64. Smith CC, Pariser DM. Primary focal hyperhidrosis. Available at: https://www.uptodate.com/contents/primary-focal-hyperhidrosis. Accessed May 16, 2018.
65. Kuritzky A, Hering R, Goldhammer G, Bechar M. Clonidine treatment in paroxysmal localized hyperhidrosis. *Arch Neurol*. 1984;41:1210-1211.
66. Feder R. Clonidine treatment of excessive sweating. *J Clin Psychiatry*. 1995;56:35.
67. Tkach JR. Indomethacin treatment of generalized hyperhidrosis. *J Am Acad Dermatol*. 1982;6(4 pt 1):545.
68. Soter NA, Baden H. Normal and abnormal eccrine sweat gland function. In: Soter N, Baden H, eds. *Pathophysiology of dermatologic disease*. 2nd ed. New York: McGraw Hill; 1991:211-234.
69. James WD, Schoomaker EB, Rodman OG. Emotional eccrine sweating. A heritable disorder. *Arch Dermatol*. 1987;123:925-929.
70. Sato K, Timm DE, Sato F, et al. Generation and transit pathway of H+ is critical for inhibition of palmar sweating by iontophoresis in water. *J Appl Physiol (1985)*. 1993;75:2258-2264.
71. Levit F. Simple device for treatment of hyperhidrosis by iontophoresis. *Arch Dermatol*. 1968;98:505-507.
72. Nagar R, Sengar SS. A simple user-made iontophoresis device for palmoplantar hyperhidrosis. *J Cutan Aesthet Surg*. 2016;9:32-33.
73. Rajagopal R, Mallya NB. Comparative evaluation of botulinum toxin versus iontophoresis with topical aluminium chloride hexahydrate in treatment of palmar hyperhidrosis. *Med J Armed Forces India*. 2014;70:247-252.
74. Stolman LP. Treatment of excess sweating of the palms by iontophoresis. *Arch Dermatol*. 1987;123:893-896.
75. Hill AC, Baker GF, Jansen GT. Mechanism of action of iontophoresis in the treatment of palmar hyperhidrosis. *Cutis*. 1981;28:69-70, 72.
76. Kurta AO, Glaser DA. Emerging nonsurgical treatments for hyperhidrosis. *Thorac Surg Clin*. 2016;26:395-402.
77. Anliker MD, Kreyden OP. Tap water iontophoresis. *Curr Probl Dermatol*. 2002;30:48-56.
78. Thomas L, Fatah S, Carmichael AJ. Tap water iontophoresis may be ineffective for axillary hyperhidrosis. *Clin Exp Dermatol*. 2015;40:337-338.
79. Wang L, Hilliges M, Gajecki M, Marcusson JA, Johansson O. No change in skin innervation in patients with palmar hyperhidrosis treated with tap-water iontophoresis. *Br J Dermatol*. 1994;131:742-743.
80. Kreyden OP. Iontophoresis for palmoplantar hyperhidrosis. *J Cosmet Dermatol*. 2004;3:211-214.
81. Worle B, Rapprich S, Heckmann M. Definition and treatment of primary hyperhidrosis. *J Dtsch Dermatol Ges*. 2007;5:625-628.
82. Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. *J Am Acad Dermatol*. 2004;51:274-286.
83. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. *J Am Acad Dermatol*. 1989;20:537-563.
84. Hoorens I, Ongenae K. Primary focal hyperhidrosis: current treatment options and a step-by-step approach. *J Eur Acad Dermatol Venereol*. 2012;26:1-8.
85. Shrivastava SN, Singh G. Tap water iontophoresis in palmoplantar hyperhidrosis. *Br J Dermatol*. 1977;96:189-195.
86. Callejas MA, Grimalt R, Cladellas E. Hyperhydrosis update [in Spanish]. *Actas Dermosifiliogr*. 2010;101:110-118.
87. Ozcan D, Gulec AT. Compliance with tap water iontophoresis in patients with palmoplantar hyperhidrosis. *J Cutan Med Surg*. 2014;18:109-113.
88. Karakoc Y, Aydemir EH, Kalkan MT, Unal G. Safe control of palmoplantar hyperhidrosis with direct electrical current. *Int J Dermatol*. 2002;41:602-605.
89. Leow MQH, Tey HL. Treatment of primary palmar hyperhidrosis using glycopyrrolate iontophoresis: intensity of electrical current used, efficacy and side effects. *Indian J Dermatol Venereol Leprol*. 2017;83:387-388.
90. Dolianitis C, Scarff CE, Kelly J, Sinclair R. Iontophoresis with glycopyrrolate for the treatment of palmoplantar hyperhidrosis. *Australas J Dermatol*. 2004;45:208-212.
91. Shen JL, Lin GS, Li WM. A new strategy of iontophoresis for hyperhidrosis. *J Am Acad Dermatol*. 1990;22(2 pt 1):239-241.
92. Chia HY, Tan AS, Chong WS, Tey HL. Efficacy of iontophoresis with glycopyrronium bromide for treatment of primary palmar hyperhidrosis. *J Eur Acad Dermatol Venereol*. 2012;26:1167-1170.
93. Gujjar M, Banga AK. Iontophoretic and microneedle mediated transdermal delivery of glycopyrrolate. *Pharmaceutics*. 2014;6:663-671.
94. Abell E, Morgan K. The treatment of idiopathic hyperhidrosis by glycopyrronium bromide and tap water iontophoresis. *Br J Dermatol*. 1974;91:87-91.
95. Askari S, Glaser DA, King RM, Oliver D. Comparison of tap water iontophoresis to iontophoresis with glycopyrrolate. *J Am Acad Dermatol*. 2008;58(2 suppl 2):AB32.
96. Davarian S, Kalantari KK, Rezasoltani A, Rahimi A. Effect and persistency of botulinum toxin iontophoresis in the treatment of palmar hyperhidrosis. *Australas J Dermatol*. 2008;49:75-79.
97. Khademi Kalantari K, Zeinalzade A, Kobarfard F, Nazary Moghadam S. The effect and persistency of 1% aluminum chloride hexahydrate iontophoresis in the treatment of primary palmar hyperhidrosis. *Iran J Pharm Res*. 2011;10:641-645.
98. Ram R, Lowe NJ, Yamauchi PS. Current and emerging therapeutic modalities for hyperhidrosis, part 1: conservative and noninvasive treatments. *Cutis*. 2007;79:211-217.
99. Choi YH, Lee SJ, Kim DW, Lee WJ, Na GY. Open clinical trial for evaluation of efficacy and safety of a portable "dry-type" iontophoretic device in treatment of palmar hyperhidrosis. *Dermatol Surg*. 2013;39:578-583.
100. Pariser DM, Ballard A. Iontophoresis for palmar and plantar hyperhidrosis. *Dermatol Clin*. 2014;32:491-494.

101. Kim DH, Kim TH, Lee SH, Lee AY. Treatment of palmar hyperhidrosis with tap water iontophoresis: a randomized, sham-controlled, single-blind, and parallel-designed clinical trial. *Ann Dermatol*. 2017;29:728-734.
102. OnabotulinumtoxinA injections (Botox). International Hyperhidrosis Society. Available at: https://www.sweathelp.org/hyperhidrosis-treatments/botox.html. Accessed May 30, 2018.
103. Weinberg T, Solish N, Murray C. Botulinum neurotoxin treatment of palmar and plantar hyperhidrosis. *Dermatol Clin*. 2014;32:505-515.
104. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl*. 1997;6:S146-S168.
105. Swartling C, Naver H, Pihl-Lundin I, Hagforsen E, Vahlquist A. Sweat gland morphology and periglandular innervation in essential palmar hyperhidrosis before and after treatment with intradermal botulinum toxin. *J Am Acad Dermatol*. 2004;51:739-745.
106. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med*. 2001;344:488-493.
107. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *BMJ*. 2001;323:596-599.
108. Connolly M, de Berker D. Management of primary hyperhidrosis: a summary of the different treatment modalities. *Am J Clin Dermatol*. 2003;4:681-697.
109. Lonsdale-Eccles A, Leonard N, Lawrence C. Axillary hyperhidrosis: eccrine or apocrine? *Clin Exp Dermatol*. 2003;28:2-7.
110. Haider A, Solish N. Hyperhidrosis: an approach to diagnosis and management. *Dermatol Nurs*. 2004;16:515-517.
111. Thorne CH, Beasley RW, Aston SJ. *Grabb and Smith's plastic surgery*. 6th ed. Philadelphia: Wolters Kluwer; 2007.
112. Yamauchi PS, Lowe NJ. Botulinum toxin types A and B: comparison of efficacy, duration, and dose-ranging studies for the treatment of facial rhytides and hyperhidrosis. *Clin Dermatol*. 2004;22:34-39.
113. Trindade De Almeida AR, Secco LC, Carruthers A. Handling botulinum toxins: an updated literature review. *Dermatol Surg*. 2011;37:1553-1565.
114. Rosell K, Hymnelius K, Swartling C. Botulinum toxin type A and B improve quality of life in patients with axillary and palmar hyperhidrosis. *Acta Derm Venereol*. 2013;93:335-339.
115. Glaser DA, Hebert AA, Pariser DM, Solish N. Primary focal hyperhidrosis: scope of the problem. *Cutis*. 2007;79(5 suppl):5-17.
116. Lowe NJ, Yamauchi PS, Lask GP, Patnaik R, Iyer S. Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. *Dermatol Surg*. 2002;28:822-827.
117. Klein AW. Contraindications and complications with the use of botulinum toxin. *Clin Dermatol*. 2004;22:66-75.
118. Grunfeld A, Murray CA, Solish N. Botulinum toxin for hyperhidrosis: a review. *Am J Clin Dermatol*. 2009;10:87-102.
119. Baumann L, Slezinger A, Halem M, et al. Pilot study of the safety and efficacy of Myobloc (botulinum toxin type B) for treatment of axillary hyperhidrosis. *Int J Dermatol*. 2005;44:418-424.
120. Nelson L, Bachoo P, Holmes J. Botulinum toxin type B: a new therapy for axillary hyperhidrosis. *Br J Plast Surg*. 2005;58:228-232.
121. Dressler D, Adib Saberi F, Benecke R. Botulinum toxin type B for treatment of axillar hyperhidrosis. *J Neurol*. 2002;249:1729-1732.
122. Frasson E, Brigo F, Acler M, Didone G, Vicentini S, Bertolasi L. Botulinum toxin type A vs type B for axillary hyperhidrosis in a case series of patients observed for 6 months. *Arch Dermatol*. 2011;147:122-123.
123. Lowe PL, Cerdan-Sanz S, Lowe NJ. Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: efficacy and duration with repeated treatments. *Dermatol Surg*. 2003;29:545-548.
124. Almeida AT, Cernea SS. Tratamento da hiperidrose. In: Hexsel D, Almeida AT, eds. *Uso cosmético da toxina botulínica*. Porto Alegre: AGE; 2002:226-227.
125. Eisenach JH, Atkinson JLD, Fealey RD. Hyperhidrosis: evolving therapies for a well-established phenomenon. *Mayo Clin Proc*. 2005;80:657-666.
126. de Almeida AR, Montagner S. Botulinum toxin for axillary hyperhidrosis. *Dermatol Clin*. 2014;32:495-504.
127. Lowe NJ, Glaser DA, Eadie N, Daggett S, Kowalski JW, Lai PY. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *J Am Acad Dermatol*. 2007;56:604-611.
128. Benohanian A. Needle-free anaesthesia prior to botulinum toxin type A injection treatment of palmar and plantar hyperhidrosis. *Br J Dermatol*. 2007;156:593-596.
129. Smith KC, Comite SL, Storwick GS. Ice minimizes discomfort associated with injection of botulinum toxin type A for the treatment of palmar and plantar hyperhidrosis. *Dermatol Surg*. 2007;33(1 spec no):S88-S91.
130. Moraru E, Auff E, Schnider P. Hyperhidrosis of the palms and soles. *Curr Probl Dermatol*. 2002;30:156-169.
131. Torrisi BM, Zarnitsyn V, Prausnitz MR, et al. Pocketed microneedles for rapid delivery of a liquid-state botulinum toxin A formulation into human skin. *J Control Release*. 2013;165:146-152.
132. O'Riordan JM, Fitzgerald E, Gowing C, O'Grady H, Feeley TM, Tierney S. Topical local anaesthetic (tetracaine) reduces pain from botulinum toxin injections for axillary hyperhidrosis. *Br J Surg*. 2006;93:713-714.
133. Elibol O, Ozkan B, Hekimhan PK, Caglar Y. Efficacy of skin cooling and EMLA cream application for pain relief of periocular botulinum toxin injection. *Ophthalmic Plast Reconstr Surg*. 2007;23:130-133.
134. Gulec AT. Dilution of botulinum toxin A in lidocaine vs. in normal saline for the treatment of primary axillary hyperhidrosis: a double-blind, randomized, comparative preliminary study. *J Eur Acad Dermatol Venereol*. 2012;26:314-318.
135. Vadoud-Seyedi J, Simonart T. Treatment of axillary hyperhidrosis with botulinum toxin type A reconstituted in lidocaine or in normal saline: a randomized, side-by-side, double-blind study. *Br J Dermatol*. 2007;156:986-989.
136. Wang R, Solish N, Murray CA. Primary focal hyperhidrosis: diagnosis and management. *Dermatol Nurs*. 2008;20:467-470.
137. Hayton MJ, Stanley JK, Lowe NJ. A review of peripheral nerve blockade as local anaesthesia in the treatment of palmar hyperhidrosis. *Br J Dermatol*. 2003;149:447-451.
138. Solomon P. Modified Bier block anesthetic technique is safe for office use for botulinum a toxin treatment of palmar and plantar hyperhidrosis. *Dermatol Online J*. 2007;13:6.
139. Ponce-Olivera RM, Tirado-Sanchez A, Arellano-Mendoza MI, Leon-Dorantes G, Kassian-Rank S. Palmar hyperhidrosis. Safety efficacy of two anaesthetic techniques for botulinum toxin therapy. *Dermatol Online J*. 2006;12:9.
140. de Almeida AR, Kadunc BV, de Oliveira EM. Improving botulinum toxin therapy for palmar hyperhidrosis: wrist block and technical considerations. *Dermatol Surg*. 2001;27:34-36.

141. Fujita M, Mann T, Mann O, Berg D. Pearls: surgical pearl: use of nerve blocks for botulinum toxin treatment of palmar-plantar hyperhidrosis. *J Am Acad Dermatol*. 2001;45:587-589.
142. Campanati A, Penna L, Guzzo T, et al. A quality-of-life assessment in patients with hyperhidrosis before and after treatment with botulinum toxin: results of an open-label study. *Clin Ther*. 2003;25:298-308.
143. George SM, Atkinson LR, Farrant PB, Shergill BS. Botulinum toxin for focal hyperhidrosis of the face. *Br J Dermatol*. 2014;170:211-213.
144. Bjerkhoel A, Trobbe O. Frey's syndrome: treatment with botulinum toxin. *J Laryngol Otol*. 1997;111:839-844.
145. Boger A, Herath H, Rompel R, Ferbert A. Botulinum toxin for treatment of craniofacial hyperhidrosis. *J Neurol*. 2000;247:857-861.
146. Glaser DA, Hebert AA, Pariser DM, Solish N. Facial hyperhidrosis: best practice recommendations and special considerations. *Cutis*. 2007;79(5 suppl):29-32.
147. Lowe N, Campanati A, Bodokh I, et al. The place of botulinum toxin type A in the treatment of focal hyperhidrosis. *Br J Dermatol*. 2004;151:1115-1122.
148. Naumann M, Hamm H. Treatment of axillary hyperhidrosis. *Br J Surg*. 2002;89:259-261.
149. Nasr MW, Jabbour SF, Haber RN, Kechichian EG, El Hachem L. Comparison of microwave ablation, botulinum toxin injection, and liposuction-curettage in the treatment of axillary hyperhidrosis: a systematic review. *J Cosmet Laser Ther*. 2017;19:36-42.
150. Naumann M, Lowe NJ, Kumar CR, Hamm H. Botulinum toxin type a is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. *Arch Dermatol*. 2003;139:731-736.
151. Baumann LS, Halem ML. Botulinum toxin-B and the management of hyperhidrosis. *Clin Dermatol*. 2004;22:60-65.
152. Jacob C. Treatment of hyperhidrosis with microwave technology. *Semin Cutan Med Surg*. 2013;32:2-8.
153. Glaser DA, Coleman WP, Fan LK, et al. A randomized, blinded clinical evaluation of a novel microwave device for treating axillary hyperhidrosis: the dermatologic reduction in underarm perspiration study. *Dermatol Surg*. 2012;38:185-191.
154. Johnson JE, O'Shaughnessy KF, Kim S. Microwave thermolysis of sweat glands. *Lasers Surg Med*. 2012;44:20-25.
155. Hong HC, Lupin M, O'Shaughnessy KF. Clinical evaluation of a microwave device for treating axillary hyperhidrosis. *Dermatol Surg*. 2012;38:728-735.
156. Hexsel D, Camozzato FO. Hyperhidrosis. In: Bonamigo RR, Dornelles SIT, eds. *Dermatology in public health environments: a comprehensive textbook*. Cham: Springer International Publishing; 2018:1379-1393.
157. Glaser DA, Galperin TA. Local procedural approaches for axillary hyperhidrosis. *Dermatol Clin*. 2014;32:533-540.
158. Lee SJ, Chang KY, Suh DH, Song KY, Ryu HJ. The efficacy of a microwave device for treating axillary hyperhidrosis and osmidrosis in Asians: a preliminary study. *J Cosmet Laser Ther*. 2013;15:255-259.
159. Chang Y-Y, Chen C-H, Hui RC-Y, Jung S-M, Yang C-H. A prospective clinical and histologic study of axillary osmidrosis treated with the microwave-based device. *Dermatologica Sinica*. 2015;33:134-141.
160. Suh DH, Lee SJ, Kim K, Ryu HJ. Transient median and ulnar neuropathy associated with a microwave device for treating axillary hyperhidrosis. *Dermatol Surg*. 2014;40:482-485.
161. Chang CK, Chen CY, Hsu KF, et al. Brachial plexus injury after microwave-based treatment for axillary hyperhidrosis and osmidrosis. *J Cosmet Laser Ther*. 2017;19:439-441.
162. Sanchez-Carpintero I, Martin-Gorgojo A, Ruiz-Rodriguez R. Microwave treatment for axillary hyperhidrosis and bromhidrosis. *Actas Dermosifiliogr*. 2017;108:418-422.
163. Brobst RW, Ferguson M, Perkins SW. Ulthera: initial and six month results. *Facial Plast Surg Clin North Am*. 2012;20:163-176.
164. Macedo O, Matayoshi L, Matsumoto L. The new ultrasound technology for hyperhidrosis treatment: two case reports. *J Am Acad Dermatol*. 2013;4:AB66.
165. Nestor MS, Park H. Safety and efficacy of micro-focused ultrasound plus visualization for the treatment of axillary hyperhidrosis. *J Clin Aesthet Dermatol*. 2014;7:14-21.
166. Schick CH, Grallath T, Schick KS, Hashmonai M. Radiofrequency thermotherapy for treating axillary hyperhidrosis. *Dermatol Surg*. 2016;42:624-630.
167. Kim M, Shin JY, Lee J, Kim JY, Oh SH. Efficacy of fractional microneedle radiofrequency device in the treatment of primary axillary hyperhidrosis: a pilot study. *Dermatology*. 2013;227:243-249.
168. Fatemi Naeini F, Abtahi-Naeini B, Pourazizi M, Nilforoushzadeh MA, Mirmohammadkhani M. Fractionated microneedle radiofrequency for treatment of primary axillary hyperhidrosis: a sham control study. *Australas J Dermatol*. 2015;56:279-284.
169. Naeini FF, Saffaei A, Pourazizi M, Abtahi-Naeini B. Histopathological evidence of efficacy of microneedle radiofrequency for treatment of axillary hyperhidrosis. *Indian J Dermatol Venereol Leprol*. 2015;81:288-290.
170. Kotlus BS. Treatment of refractory axillary hyperhidrosis with a 1320-nm Nd:YAG laser. *J Cosmet Laser Ther*. 2011;13:193-195.
171. Aydin F, Pancar GS, Senturk N, et al. Axillary hair removal with 1064-nm Nd:YAG laser increases sweat production. *Clin Exp Dermatol*. 2010;35:588-592.
172. Obeid G, Helou J, Maatouk I, Moutran R, Tomb R. Depilatory laser: a potential causative factor for inguinal hyperhidrosis: report of three cases. *J Cosmet Laser Ther*. 2013;15:286-289.
173. Bechara FG, Georgas D, Sand M, et al. Effects of a long-pulsed 800-nm diode laser on axillary hyperhidrosis: a randomized controlled half-side comparison study. *Dermatol Surg*. 2012;38:736-740.
174. Maletic D, Maletic A, Vizintin Z. Laser assisted reduction of axillary hyperhidrosis (LARAH) — evaluation of success up to 24 months after the treatment. *J Laser Health Acad*. 2011;2011:37-42.
175. Leclere FM, Moreno-Moraga J, Alcolea JM, et al. Efficacy and safety of laser therapy on axillary hyperhidrosis after one year follow-up: a randomized blinded controlled trial. *Lasers Surg Med*. 2015;47:173-179.
176. Goldman A, Wollina U. Subdermal Nd-YAG laser for axillary hyperhidrosis. *Dermatol Surg*. 2008;34:756-762.
177. Klöpper M, Fischer G, Blugerman G. Laser-assisted suction of axillary sweat glands and axillary epilation. In: Schiffman MA, Di Giuseppe A, eds. *Liposuction: Principles and Practice*. Berlin, Heidelberg: Springer; 2016:505-515.
178. Schavelzon D, Blugerman G, Chomyszyn A, Ponton J, Lanfranchi L, Martinez L. Noninvasive treatment of axillary hyperhidrosis with Nd:Yag laser. *Upd Plast Surg*. 2010;3:1-4.
179. Cameron AE. Selecting the right patient for surgical treatment of hyperhidrosis. *Thorac Surg Clin*. 2016;26:403-406.
180. Breach NM. Axillary hyperhidrosis: surgical cure with aesthetic scars. *Ann R Coll Surg Engl*. 1979;61:295-297.
181. Wollina U, Kostler E, Schonlebe J, Haroske G. Tumescent suction curettage versus minimal skin resection with subcutaneous curettage of sweat glands in axillary hyperhidrosis. *Dermatol Surg*. 2008;34:709-716.

182. Payne CM, Doe PT. Liposuction for axillary hyperhidrosis. *Clin Exp Dermatol*. 1998;23:9-10.
183. Bechara FG, Sand M, Hoffmann K, Boorboor P, Altmeyer P, Stuecker M. Histological and clinical findings in different surgical strategies for focal axillary hyperhidrosis. *Dermatol Surg*. 2008;34:1001-1009.
184. Lawrence CM, Lonsdale Eccles AA. Selective sweat gland removal with minimal skin excision in the treatment of axillary hyperhidrosis: a retrospective clinical and histological review of 15 patients. *Br J Dermatol*. 2006;155:115-118.
185. Bechara FG, Gambichler T, Bader A, Sand M, Altmeyer P, Hoffmann K. Assessment of quality of life in patients with primary axillary hyperhidrosis before and after suction-curettage. *J Am Acad Dermatol*. 2007;57:207-212.
186. Darabaneanu S, Darabaneanu HA, Niederberger U, Russo PA, Lischner S, Hauschild A. Long-term efficacy of subcutaneous sweat gland suction curettage for axillary hyperhidrosis: a prospective gravimetrically controlled study. *Dermatol Surg*. 2008;34:1170-1177.
187. Ibrahim O, Kakar R, Bolotin D, et al. The comparative effectiveness of suction-curettage and onabotulinumtoxin-A injections for the treatment of primary focal axillary hyperhidrosis: a randomized control trial. *J Am Acad Dermatol*. 2013;69:88-95.
188. Coleman WP 3rd. Liposuction for axillary hyperhidrosis. *J Am Acad Dermatol*. 2013;69:1062.
189. Lee MR, Ryman WJ. Liposuction for axillary hyperhidrosis. *Australas J Dermatol*. 2005;46:76-79.
190. Feldmeyer L, Bogdan I, Moser A, et al. Short- and long-term efficacy and mechanism of action of tumescent suction curettage for axillary hyperhidrosis. *J Eur Acad Dermatol Venereol*. 2015;29:1933-1937.
191. Field LM. Re: Insufficient aggressiveness with tumescent suction curettage. *Dermatol Surg*. 2009;35:555-556.
192. Moraites E, Vaughn OA, Hill S. Endoscopic thoracic sympathectomy. *Dermatol Clin*. 2014;32:541-548.
193. Cerfolio RJ, De Campos JR, Bryant AS, et al. The Society of Thoracic Surgeons expert consensus for the surgical treatment of hyperhidrosis. *Ann Thorac Surg*. 2011;91:1642-1648.
194. Singh S, Kaur S, Wilson P. Plantar hyperhidrosis: a review of current management. *J Dermatolog Treat*. 2016;27:556-561.
195. Lin TS, Fang HY. Transthoracic endoscopic sympathectomy in the treatment of palmar hyperhidrosis—with emphasis on perioperative management (1,360 case analyses). *Surg Neurol*. 1999;52:453-457.
196. Doolabh N, Horswell S, Williams M, et al. Thoracoscopic sympathectomy for hyperhidrosis: indications and results. *Ann Thorac Surg*. 2004;77:410-414.
197. Dumont P, Denoyer A, Robin P. Long-term results of thoracoscopic sympathectomy for hyperhidrosis. *Ann Thorac Surg*. 2004;78:1801-1807.
198. Herbst F, Plas EG, Fugger R, Fritsch A. Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limbs. A critical analysis and long-term results of 480 operations. *Ann Surg*. 1994;220:86-90.
199. de Andrade Filho LO, Kuzniec S, Wolosker N, Yazbek G, Kauffman P, Milanez de Campos JR. Technical difficulties and complications of sympathectomy in the treatment of hyperhidrosis: an analysis of 1731 cases. *Ann Vasc Surg*. 2013;27:447-453.
200. Lin TS, Kuo SJ, Chou MC. Uniportal endoscopic thoracic sympathectomy for treatment of palmar and axillary hyperhidrosis: analysis of 2000 cases. *Neurosurgery*. 2002;51(5 suppl):S84-S87.
201. Shih C-J, Wu J-J, Lin M-T. Autonomic dysfunction in palmar hyperhidrosis. *J Auton Nerv Syst*. 1983;8:33-43.
202. Gorenstein LA, Krasna MJ. Less common side effects of sympathetic surgery. *Thorac Surg Clin*. 2016;26:453-458.
203. Hashmonai M. The history of sympathetic surgery. *Thorac Surg Clin*. 2016;26:383-388.
204. Lyra Rde M, Campos JR, Kang DW, et al. Guidelines for the prevention, diagnosis and treatment of compensatory hyperhidrosis. *J Bras Pneumol*. 2008;34:967-977.
205. de Campos JR, Kauffman P, Werebe Ede C, et al. Quality of life, before and after thoracic sympathectomy: report on 378 operated patients. *Ann Thorac Surg*. 2003;76:886-891.
206. Atkinson JL, Fealey RD. Sympathotomy instead of sympathectomy for palmar hyperhidrosis: minimizing postoperative compensatory hyperhidrosis. *Mayo Clin Proc*. 2003;78:167-172.
207. Thomas I, Brown J, Vafaie J, Schwartz RA. Palmoplantar hyperhidrosis: a therapeutic challenge. *Am Fam Physician*. 2004;69:1117-1120.