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EXPERT REVIEWS

Hyperhidrosis: clinical presentation, evaluation and management

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Hyperhidrosis (HH) is defined as excessive sweating, which can affect any part of the body. Current data suggests that it affects 2–3% of the population. For many patients it is debilitating and impairs social interactions. Current management of patients diagnosed with focal HH depends on the etiology and location of the excessive sweating. For primary focal HH, nonsurgical approaches include topical agents such as aluminum chloride hexahydrate, oral agents such as anticholinergics, iontophoresis, botulinum toxin injections and psychotherapy. With careful patient selection, surgery has been shown to be extremely effective for the management of patients diagnosed with palmar and axillary HH. Surgery has evolved to be performed using videoscopic techniques either by clipping or cutting the sympathetic chain with or without resection of the ganglia. Preliminary studies suggest that surgery may also play an effective role in the management of craniofacial and plantar HH.

Keywords: botulinum toxin • compensatory sweating • hyperhidrosis • surgery • sympathectomy

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the diagnosis of hyperhidrosis
- Identify first-line treatment for mild-to-moderate hyperhidrosis
- Distinguish elements of botulinum toxin treatment for hyperhidrosis
- Characterize surgical interventions for hyperhidrosis

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Hyperhidrosis (HH) is a disorder of excessive sweating. More formally, it is the secretion of sweat by the eccrine glands in amounts greater than physiologically required for thermoregulation. HH is broadly categorized as either primary (idiopathic) or secondary, and is further classified anatomically as focal or generalized. Primary HH tends to be focal and usually affects the palms, soles, axilla or face.

Clinical presentation

Patients with idiopathic HH describe excessive sweating of their palms, soles, axilla or face. Although emotional stress or elevated environmental temperatures will worsen the perspiration, the excess sweating is present without any clear triggers. Sweating is rarely present at night. These symptoms typically develop in childhood, become worse following puberty and decrease with older age [1]. Patients will also describe significant psychosocial implications of their disease. They may describe discomfort related to damp footwear or difficulty in handling paper, tools, musical instruments or sporting equipment. More importantly, patients describe significant embarrassment related to shaking or holding hands, meeting new people, intimacy and, as a result, social withdrawal [2].

Hyperhidrosis is extremely debilitating and significantly impacts patient's recreational, occupational and social activities [3]. A national survey in the USA revealed that almost 75% of affected individuals were emotionally affected by their HH [4]. Respondents with focal HH reported decreased participation in leisure activities and less time at work as a result of their perspiration. Amir and colleagues found that patients with HH suffered increased emotional problems and poorer coping abilities when compared with normal controls [3]. To put this into perspective, studies have demonstrated that HH patients have a quality of life comparable to patients with multiple sclerosis, rheumatoid arthritis or end-stage renal failure [5,6].

Definition

A standard definition of excess sweating has not yet been established. It is difficult to quantify both normal human sweat production and a given individual's sweat production. For practical reasons clinicians measure HH qualitatively based on the patient's description of symptoms. Any sweating that significantly interferes with daily life is regarded as abnormal [2].

Epidemiology

It is difficult to estimate the incidence of HH because of the imprecise definition of the condition, but is likely to be under reported. Affected individuals often do not seek medical attention either due to embarrassment, or lack of awareness of the condition and therapeutic options. The best estimate, derived from a recent large industry-sponsored survey in the USA, places the prevalence of HH at 2.8% [4]. It affects both sexes and appears to occur in all races. There is most likely a genetic contribution to the condition, as there is a positive family history in over 25% of cases [1]. Other studies have reported a positive family history in as high as 65% of cases [7]. A genetic study in a cohort of Japanese patients identified chromosome 14 as a possible location of genes related to palmar HH [8].

Pathophysiology

The pathophysiology underlying HH is complex and poorly understood; however, it is generally believed to result from an exaggerated central response to normal emotional stress or environmental stimuli. It is not considered a psychiatric condition.

Under normal conditions, sweating cools the body through evaporative heat loss. Although there is some overlap, two types of sweating are recognized: thermal sweating and emotional sweating. Thermoregulation and sweat production are controlled by three organ systems: the cerebral cortex, the anterior hypothalamus and the sympathetic nervous system [9], and each type of sweating is controlled by a different region of the brain [10]. Thermal sweating is controlled by the hypothalamus via the thermosensitive preoptic sweat center, while emotional sweating is regulated by the cerebral cortex [10]. Thermal sweating can occur at any time and tends to occur on the trunk, while emotional sweating does not occur while sleeping and is predominately on the palms and soles.

There are more than 2 million sweat glands distributed unevenly over the body surface. Three types of sweat glands have been identified: eccrine, apocrine and apoeccrine [11]. The eccrine gland is the most numerous type, with the greatest densities occurring on the soles of the feet, palms, axilla and face. They are innervated by the sympathetic nervous system, with acetylcholine as the principle neurotransmitter. This is the only component of the predominately 'adrenergic' sympathetic nervous system that does not use norepinephrine as the neurotransmitter [1]. Sweat produced by eccrine glands is thin, clear and hypotonic to plasma. The normal sweat production by eccrine glands is estimated to be 0.5–1 ml/min; however, under thermal or emotional stress they are capable of producing 10 l of sweat per day [12].

Eccrine sweat glands are felt to be responsible for HH [12]. However, eccrine glands of patients with HH do not have any abnormalities in terms of number, size, structure or histology [13]. Therefore, HH is probably not caused by a primary abnormality of eccrine sweat glands, but by a central cortical cause.

Apocrine glands are less numerous and are distributed in the axilla and genital regions. Their development is androgen dependent and they do not become stimulated until puberty. Unlike eccrine sweat, apocrine sweat is viscous, and may become foul smelling when metabolized by bacteria on the skin [2]. The third type of sweat gland, apoeccrine glands, are found only in the adult axilla. It is thought that apocrine and apoeccrine glands do not contribute substantially to focal HH, other than possibly focal axillary HH [14].

Sympathetic innervation & the sympathetic chain

The neuroanatomy of the sweating mechanism is complicated and beyond the scope of this paper; however, there are important anatomic points that need to be understood as they relate to treatment. The sympathetic nervous system is one component of the autonomic nervous system, which innervates all the major organs of the body, including the skin and the sweat glands. The sympathetic nervous system is partly responsible for the so-called 'fight or flight' response.

The anatomy, as it relates to HH, involves nerve fibers traveling from the hypothalamic preoptic sweat center to the spinal cord where they synapse with 'preganglionic' fibers. These preganglionic fibers then exit the spinal cord along the ventral nerve roots and end in the sympathetic ganglia (Figure 1) [1,15]. Within the sympathetic ganglia, preganglionic fibers synapse with 'post-ganglionic' fibers, which then travel peripherally and terminate in their target organs or glands [1].

Evaluation

Establishing the diagnosis of hyperhidrosis

Evaluating patients with HH relies almost entirely on a complete patient history and supporting physical examination. Additional testing in the form of lab work or specialized sweating tests is rarely required. Perhaps the most important and often overlooked component of the evaluation is the prerequisite recognition that HH is a common, debilitating and potentially treatable condition. The evaluation and management of a patient with excessive sweating has the following goals:

- To establish a diagnosis, and rule out secondary causes
- To determine the severity of the HH
- To develop an appropriate treatment plan

History

The history aims to fully characterize the patient's sweating with respect to onset, location, duration, frequency, triggers, nocturnal symptoms, quality of life and emotional coping. As mentioned previously, patients with idiopathic primary HH typically experience excessive focal, bilateral sweating of the face, palms, soles or axilla, with onset beginning in late childhood and a lack of sweating during sleep. Constitutional symptoms of generalized sweating, fever, night sweats, weight loss and fatigue are not consistent with primary HH and raise the likelihood of secondary HH.

The following specific diagnostic criteria for primary HH have been suggested by a consensus panel of the Multi-specialty Working Group on Hyperhidrosis [9]: Focal, visible, excessive sweating of at least 6 months duration without apparent secondary cause, plus at least two of the following:

- At least one episode per week
- Bilateral and relatively symmetric sweating
- Impairs daily activities
- Onset before age 25 years
- Family history of idiopathic HH
- Cessation of sweating during sleep

Utilization of these diagnostic criteria helps establish a diagnosis and rule out secondary causes, listed in Box 1.

Physical examination

Physical examination may be normal, but will often reveal obvious areas of focal sweating or skin maceration. The primary objective of physical examination is to reveal any evidence of underlying chronic illness suggestive of a secondary cause, for example lymphadenopathy.

Laboratory tests

Laboratory tests are not required to make a diagnosis of primary HH. They only serve to rule out and work-up potential secondary causes of sweating. Work-up for generalized sweating or secondary HH can be complicated, and often includes a number of investigations, the details of which are beyond the scope of this chapter.

Specialized tests

Once a diagnosis of primary HH has been made, the next step in the evaluation is determining the severity of the problem, as this will guide management. Although a number of specialized tests have been developed that quantify both sweat production and the impact on quality of life, they are not required, nor are they particularly useful in the clinical setting. The best gauge of disease severity is the individual patient's experience. Nonetheless, the rate and volume of sweat production can be confirmed quantitatively or qualitatively with gravimetric testing, evaporimetry, the Minor starch-iodine test and the ninhydrin test. Similarly, various quality of life tests related to HH have been developed and validated including the Hyperhidrosis Disease Severity Scale (HDSS), the Hyperhidrosis Impact Questionnaire (HHIQ), the Dermatology Life Quality Index (DLQI) and the Illness Intrusive Rating Scale (IIRS). The HDSS is the simplest and easiest of these to administer, and consists of four questions, which individually contribute a point to a total score of 4 (Box 2). The HDSS score is easily reproduced and helps directly guide management decisions. An informative and current review of these specialized tests has been published by Solish and colleagues [2].

Management

Management of HH is typically divided into nonsurgical and surgical approaches. For this article, we will focus primarily on the management of palmar HH, but we will also briefly discuss the management of axillary, plantar and craniofacial HH. Figure 2 outlines our proposed management algorithm for palmar hyperhidrosis.

Nonsurgical management

Management of HH should follow a gradational step-wise approach, beginning first with the least invasive therapies and transitioning to progressively more invasive treatments for those patients who fail. The appropriate treatment will differ for each patient, and will depend on the location of focal HH, the severity and patient tolerance. As such, a predefined algorithm cannot be applied to all subsets of focal HH. Nonetheless, most patients should begin with nonsurgical treatments. The nonsurgical or conservative treatments can be broadly categorized into: topical antiperspirants, iontophoresis, systemic medications, botulinum toxin (BTX) injections or a combination of these. The mechanism of action of these nonsurgical treatments is summarized in Figure 3.

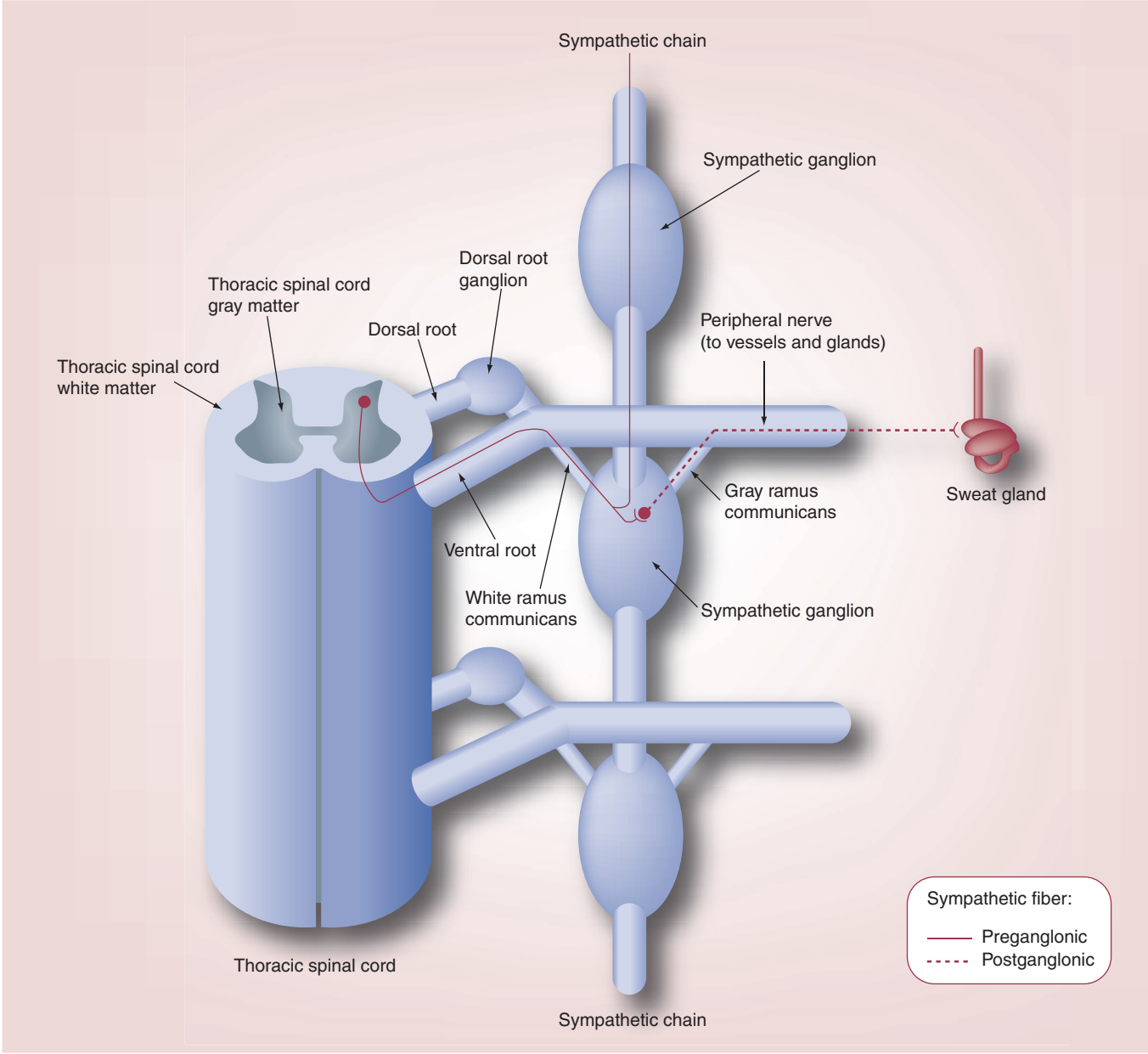

Figure 1. Anatomy of the sympathetic chain as it leaves the spinal cord.
Reproduced with permission from [1].

Antiperspirants

Topical antiperspirants are generally considered as first-line treatment for palmar, plantar and axillary HH because of their ease of application, high efficacy and safety and low cost [16,17]. As a first-line treatment, if properly planned, topical therapy can obviate the need for time-consuming or expensive therapies such as iontophoresis and BTX injections. Unfortunately, for some patients, topical antiperspirants only provide temporary, short-acting relief of sweating, and tend to be most effective for mild or moderate cases of HH (HDSS score 1 or 2) [17].

There are many varieties of topical antiperspirants. The most commonly used and most effective over-the-counter and prescription antiperspirants contain aluminum salts, most commonly aluminum chloride. Other topical treatments containing anticholinergic agents, aldehydes and anesthetic agents exist, but are generally less effective and their use is limited by significant skin irritation at required doses [18]. Evidence in favor of topical anticholinergics for focal HH is lacking overall; however, glycopyrolate 0.5% cream may be of benefit for diabetic patients with craniofacial HH [19].

Aluminum chloride is thought to work by physically obstructing the pore of the sweat gland and/or by causing atrophy of the secretory cells [20]. Most over-the-counter antiperspirant preparations contain a maximum concentration of aluminum chloride of 12.5%, while prescription concentrations most commonly contain 20–25% [18], but may be as high as 35% [16]. An effective

Box 1. Differential diagnosis of generalized sweating/secondary hyperhidrosis.

Excessive ambient heat/temperature
Systemic illness
Malignancy
- Hematologic
  - Lymphoma
  - Myeloproliferative disorders
- Solid tumors
  - Germ cell tumors
  - Medullary thyroid cancer
  - Renal cell cancer

Infectious
- Endocarditis
- Osteomyelitis
- Abscess
- Tuberculosis
- HIV

Endocrinopathy
- Hyperthyroidism
- Carcinoid syndrome
- Pheochromocytoma
- Menopause

Neurologic
- Prior spinal cord injury/autonomic dysreflexia
- Stroke
- Post-traumatic syringomyelia
- Panic disorder

Cardiovascular
- Heart failure

Alcohol/drug abuse or withdrawal
Medications
- Antiemetics
- Antidepressants

Data taken from [2,10].

regimen to achieve euhydrosis with minimal skin irritation is to begin with application of 10–12% aluminum chloride, and slowly increase the concentration to 25%, and occasionally 35% in resistant cases [16,17]. In order to achieve the higher prescription concentrations, an aqueous solvent, such as methylcellulose gel, is required, and is well-tolerated long-term [21]. Application should be on dried skin, at bedtime, washed off in 6–8 h, and repeated every 24–48 h as required.

The most limiting side effect of aluminum chloride is skin irritation, which leads to discontinuation in up to 21% of patients [17]. This irritation is thought to arise from the creation of hydrochloric acid upon mixing of sweat with the aluminum chloride, and may be limited by application of neutralizing baking soda, or hydrocortisone cream [22,23].

Iontophoresis

Iontophoresis is the introduction of ions through the skin by application of an electrical current. The mechanism of action is unknown, but it is believed that the electrical charge disrupts normal eccrine sweat secretion [24]. Iontophoresis is considered second-line therapy in mild palmar and plantar HH (HDSS score 2), and first-line treatment in severe (HDSS score 3 or 4) palmar or plantar HH when combined with aluminum chloride [17]. Treatment involves placing the hands or feet in water, through which an electrical current of 15–20 mA is passed for 20–30 min, three- to four-times per week [9,17]. Long-term maintenance therapy is required. Its use has not been studied in large randomized trials, but in smaller series iontophoresis has been effective in more than 80% of patients with palmar or plantar HH [25–27]. Side effects are uncommon and are limited to skin irritation. Its use is contraindicated in patients who are pregnant, who have a pacemaker, defibrillator or metal surgical implants. The addition of anticholinergic agents to the iontophoresis solution causes few systemic side effects and appears to enhance the anhidrotic effect of iontophoresis [28].

Systemic medications

A wide variety of oral medications have been described for the management of HH, with the most commonly used agents being anticholinergic medications such as glycopyrrolate or oxybutynin. Anticholinergics work by competitively blocking the muscarinic receptor, thus interfering with synaptic acetylcholine signaling. Although the majority of patients will typically respond to anticholinergics, their utility is limited by the intolerable side effects that tend to develop at the doses required to reduce sweating [18,29,30]. The anticholinergic side effects specifically include dry mouth, blurred vision, urinary retention, constipation, sedation, orthostatic hypotension and tachycardia.

Although systemic medications have the advantage of reducing generalized sweating, they have very limited utility for focal HH aside from craniofacial HH. The Canadian Hyperhidrosis Advisory Committee does not recommend anticholinergic medications for mild axillary, palmar or plantar HH, and only recommends the use of glycopyrrolate as second-line treatment of severe palmar and plantar HH, and third-line treatment for severe axillary HH [16]. Craniofacial HH is the one scenario where anticholinergics become one of the first-line treatment options for both mild and severe forms [16]. In general the systemic medication of choice is glycopyrrolate, taken as 1–2 mg, up to three-times per day. There are also anecdotal reports of successful HH treatment

Box 2. Hyperhidrosis Disease Severity Scale.

'How would you rate the severity of your hyperhidrosis?'
- My sweating is never noticeable and never interferes with my daily activities: 1
- My sweating is tolerable but sometimes interferes with my daily activities: 2
- My sweating is barely tolerable and frequently interferes with my daily activities: 3
- My sweating is intolerable and always interferes with my daily activities: 4

Hyperhidrosis Disease Severity Scale (HDSS) Score of 1: mild; HDSS Score of 2: moderate; HDSS Score of 3–4: severe.
Data taken from [2,4].

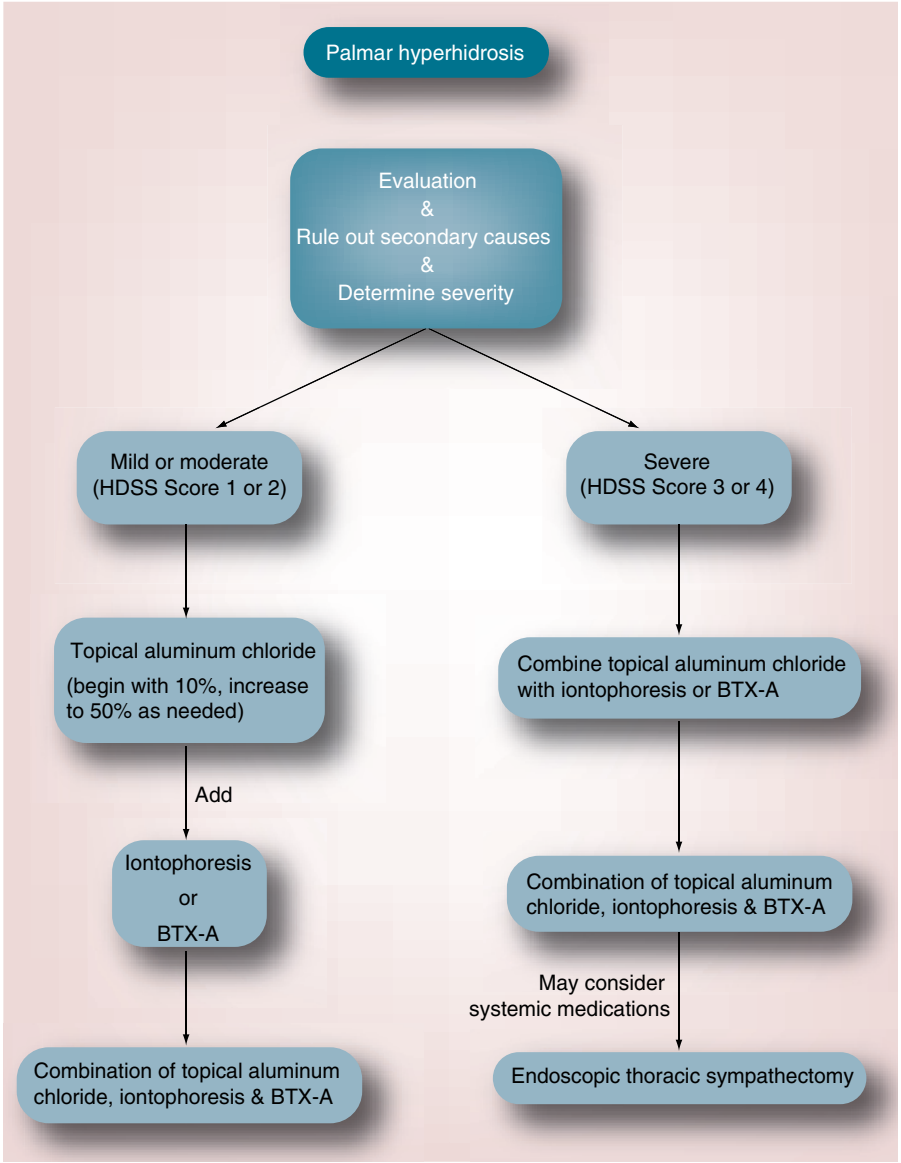

Figure 2. Proposed management algorithm for palmar hyperhidrosis.
BTX-A: Botulinum toxin A; HDSS: Hyperhidrosis Disease Severity Scale.

with α-2-adrenergic agonists [31], nonsteroidal anti-inflammatories [32], calcium channel blockers [33], benzodiazepines, β blockers [34], spasmolytics and anticonvulsants [35]; however, their use cannot be widely recommended.

Botulinum toxin

Although quite new, BTX is the best-studied treatment for focal HH. BTX was approved by the US FDA for the treatment of axillary HH in 2004, but it was used much earlier off-label for various forms of HH. Although only in use for a few years due to its efficacy and safety profile, BTX has impacted the management of all forms of HH.

Botulinum toxin is produced from the spore-forming *Bacillus Clostridium botulinum*, and acts as an irreversible inhibitor to the presynaptic release of acetylcholine. BTX effectively inhibits eccrine glands because they are innervated by cholinergic sympathetic fibers. There are seven forms of BTX (A to G); however, almost all studies have investigated BTX-A, and to a lesser extent BTX-B. Dozens of prospective, observational or placebo-controlled studies have demonstrated the safety and efficacy of BTX-A, used in doses of 50–250 U, for treatment of the axilla, palms, soles and forehead. Interestingly, the effects of BTX for HH are much longer lasting (8 months to beyond a year) when compared with the usual 3–4 months of benefit for neuromuscular disorders. The potency of BTX is expressed in mouse units. One mouse unit is the median lethal dose in mice (LD50), while the LD50 for BTX in humans is estimated at 3000 units. As a result, the maximum recommended dose of BTX is 300–400 U at any one time [16,36]. To prepare BTX for injection, each 100 unit vial should be diluted with 1–4 ml of 0.9% saline to create a final concentration of 2.5–10 U/0.1 ml [37]. Most patients notice a reduction in sweating as early as 2–4 days after injection.

The use of BTX has been best studied for the axillary subtype of focal HH. Multiple randomized, double-blind, placebo-controlled trials have demonstrated significant objective and subjective decreases in axillary sweating following intradermal injections of BTX-A in greater than 90% of patients [6,38,39]. A number of small trials have demonstrated the efficacy of BTX for palmar HH. In a small randomized trial [37], and in a nonrandomized series [40], 100% of patients described a reduction in sweating in the BTX-treated hand(s).

Although BTX is safe, as many as 25% of patients will experience some adverse event related to injection. Pain upon injection is by far the most frequently reported event, being most common in palmar and plantar injection sites. Described options to help reduce this pain are to reconstitute the BTX with lidocaine [41], needle-free pressurized tissue injection [42] or use of regional nerve blocks. It is notable that in addition to pain, there is a clear risk of palmar BTX injection causing weakness of the intrinsic muscles of the hand, which can be eliminated with a meticulously placed injection high into the dermis [37]. Contraindications for BTX are uncommon, but include hypersensitivity to albumin, peripheral motor neuropathies and neuromuscular junction disorders. Aminoglycosides, penicillamines, quinine and calcium channel blockers may potentiate the effects of BTX and concomitant use should be avoided [16,43].

The Canadian Hyperhidrosis Advisory Committee recommends BTX as second-line therapy for mild (HDSS score 2) axillary, palmar, plantar and craniofacial HH, and as one of the options for first-line therapy for severe (HDSS score 3 or 4) axillary, palmar, plantar or craniofacial HH [17]. Table 1 summarizes the non-surgical treatment modalities for focal primary hyperhidrosis.

Surgical management

To properly manage patients with palmar HH, an understanding of the anatomy of the upper limb sympathetic nervous system is necessary.

As described earlier, the sympathetic supply to the upper limb comes from the thoracic or dorsal sympathetic chain. Preganglionic fibers arise in the spinal cord and brain stem and exit the spinal canal with the anterior spinal roots. They synapse with postganglionic fibers in the thoracic ganglia entering through the white rami. Postganglionic fibers pass to the corresponding spinal nerve via gray rami. The twelve sympathetic ganglia are joined by longitudinal fibers that together constitute the sympathetic chain [1].

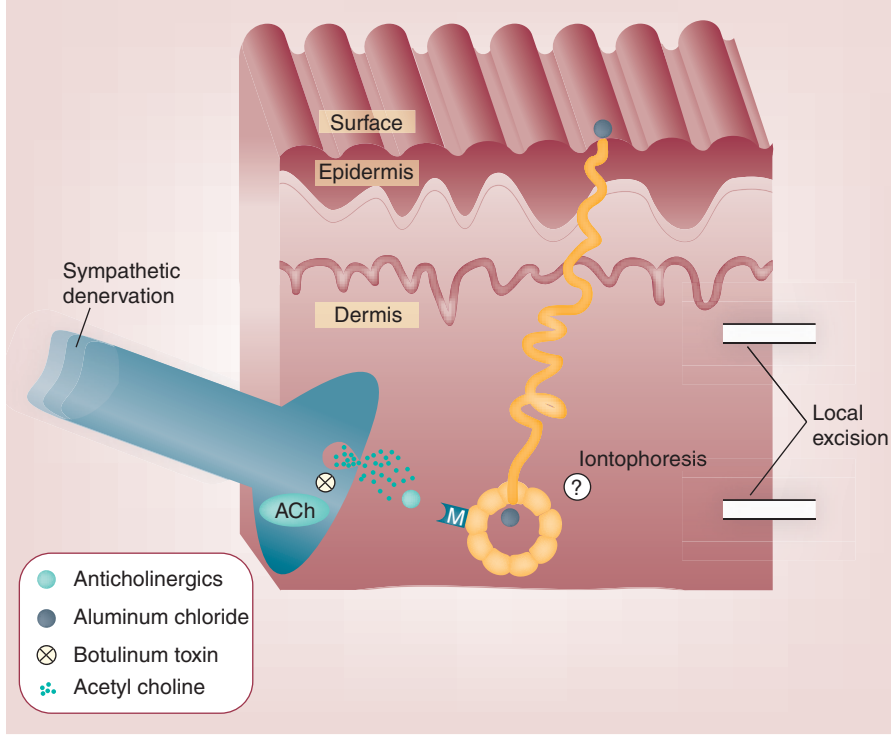

Figure 3. Hyperhidrosis therapies and their respective targets. A sympathetic nerve and an eccrine sweat gland in skin. Surgical sympathetic denervation is performed more proximally, with video-assisted thoracoscopy, interrupting the corresponding extremity innervation along the thoracic sympathetic chain. The mechanism of action for iontophoresis is unknown.
Ach: Acetylcholine; M: Muscarinic cholinergic receptor.
Reproduced with permission from [70].

Surgical management of HH involves either interruption of the sympathetic supply to the upper limb (sympathectomy), or local excision of skin and sweat glands in the axilla. Complications resulting from axillary gland excisions or liposuction curettage, including hematoma formation, skin necrosis, scarring and reductions in arm movement, as well as a lower overall success rate, have limited its role in more recent years. Nonetheless, there are small nonrandomized series demonstrating success rates of approximately 65% following local excisional procedures [44,45]. For this paper, we focus on endoscopic thoracoscopic sympathectomy (ETS) as the primary surgical option for HH.

Two anatomic points are worth careful consideration in the surgical management of HH. The first is the relation of the oculopapillary pathway to the upper extremity sympathetic supply. The inferior cervical ganglion is responsible for sympathetic supply to the head and fuses with the first thoracic ganglion to form the stellate ganglion. Because of this, any attempt to affect the T1 nerve roots poses a risk of injury to the inferior cervical ganglion, resulting in Horner's syndrome to the affected side. Until the early 1990s, the commonly held belief was that complete denervation of the upper extremity required interruption of the T1 to T4 ganglia. While anatomically correct, from a practical viewpoint this extensive denervation is unnecessary. With this realization and the avoidance of the T1 nerve roots, the risk of developing Horner's syndrome after sympathectomy today has become extremely small. The second issue is that of the nerve of Kuntz. This is an intrathoracic ramus between the first and second thoracic ganglia, whose presence is quite variable, and consists of fibers that reach the upper limb without passing through the sympathetic trunk [46]. Thus, this portion of the upper limb sympathetic supply may be missed during sympathectomy, resulting in a poor postoperative result. Similarly, the very existence and surgical management of the nerve of Kuntz is controversial and variable amongst surgeons.

Indications for sympathectomy & patient selection

Indications for surgical procedures are generally classified as absolute or relative. There are no absolute indications for sympathectomy for HH. Relative indications include those discussed in the following sections.

Severe palmar & axillary HH

Sympathectomy is generally reserved for patients with severe palmar and axillary HH. Patients with plantar or craniofacial sweating respond much less favorably and the role of surgery in these conditions is controversial.

As mentioned earlier, assessing the severity of HH is largely based on the patient's history; however, several other techniques are available. Measurement of the rate and volume of sweat

production is possible by several techniques, including gravimetric testing, the Minor starch-iodine test and the ninhydrin test [2]. These are frequently impractical in clinical practice. Clinical assessment is possible using instruments such as the HDSS that assesses the impact of the problem on activities of daily living [4]. Surprisingly, patients may show minimal signs when seen in the office. On other occasions, patients may show profound HH, and adequate severity to warrant surgery may be readily demonstrable (i.e., the 'drip' test).

Failure of medical management

Surgery for HH is an attractive treatment. It is very safe, extremely effective, has minimal complications and does not require recurrent and potentially costly treatment, in contrast to other therapies such as BTX injections. However, it is a surgical procedure, with all the inherent risks. It is essential that patients have explored alternative nonsurgical therapies prior to surgery. Many patient's HH can be adequately controlled with medical therapy, but this is not to say that surgery is the therapy of last resort. Patients may be ill served by undergoing years of costly medical therapy with modest efficacy when a well-performed sympathectomy can alleviate a disabling condition.

Prior to any surgical therapy, careful discussion of all the risks and benefits must be undertaken in order to obtain informed consent. Patients are often young, and ensuring an appropriate understanding of the surgical risks may be challenging. It is incumbent upon the surgeon to ensure patients adequately understand the procedure and the possibility of adverse outcomes.

Contraindications to sympathectomy

Contraindications to sympathectomy are also essential to establish the conditions that are explained in the following sections.

Secondary HH

Hyperhidrosis can occur secondary to underlying causes that include malignancy, endocrine, infectious and neurological conditions (**Box 1**) [47]. Treatment of the underlying cause is appropriate, surgery is not. Extreme care should be undertaken to rule out such disorders.

Co-morbid conditions

Sympathectomies are most commonly performed in young healthy patients with few medical conditions. However, severe medical comorbidities may argue against surgical intervention. In particular, a history of arrhythmias may be of concern if considering bilateral sympathectomies at a single sitting due to potential cardiac issues.

Previous thoracotomy

Previous thoracotomy is a relative contraindication to sympathectomy. Reoperative surgery can be substantially more difficult and patients should be carefully apprised of the increased risks. Thoracoscopy can be considered, but conversion to an open transaxillary thoracotomy may be necessary.

Previous lumbar sympathectomy

Concern has been raised about performing lumbar and thoracic sympathectomies due to increased complications such as compensatory HH or hypotension.

Surgical technique: clipping versus cutting

A detailed discussion of the surgical technique is beyond the scope of this paper; however, it is important to understand the basic technique for interruption of the sympathetic chain. Clipping of the sympathetic chain can be done on the main trunk or above and below the ganglion at the level of interest. Alternatively, electrocautery has

Table 1. List of nonsurgical treatment modalities for focal primary hyperhidrosis.

Treatment modality	Indications	Advantages	Disadvantages	Initial dose	Ref.
Topical antiperspirants (aluminum chloride salts)	First-line treatment for axillary, palmar and plantar HH	Effective for mild HH; inexpensive; easy to apply; painless	Ineffective for moderate/severe HH; temporary and short acting; irritation to skin at higher doses	Start with 10–12% mixtures, slowly increase to 25% as required	[17,18]
Iontophoresis	First-line treatment for severe palmar and plantar HH when combined with topical aluminum chloride; second-line for mild palmar and plantar HH	Effective for mild HH; limited side effects	Cumbersome; time consuming; temporary; short acting; requires long-term therapy	15–20 mA of current, 3–4 times per week, for 20–30 min per time	[9,18]
Oral medications	First-line treatment for mild and severe craniofacial HH; option for second line treatment of severe palmar and plantar HH	Ease of administration	Intolerable side effects at doses required for most forms of focal hyperhidrosis	Glycopyrrolate 1–2 mg, up to 3 times per day	[17]
Botulinum toxin	Option for first-line treatment of severe axillary, palmar, plantar, craniofacial HH; second line for mild axillary, palmar, plantar, craniofacial HH	Effective for many forms of HH; long duration of effect (8–12 months)	Pain on injection; risk of muscular weakness; very high cost; temporary	Site dependent Total doses per treatment range from 50–250 mouse units	[17]

HH: Hyperhidrosis; mA: Milliamps.

been used by many authors to divide the sympathetic chain at the appropriate level [48,49]. Advocates recommend electrocautery over clipping because of its simplicity, the minimal dissection required and the potential failure in placing clips due to dislodgement.

A small percentage of patients undergoing sympathectomy will develop profound compensatory HH. With electrocautery, reversal of the procedure is not possible, except with elaborate nerve grafting, the efficacy of which is unclear [50]. Clip removal is thought to offer the potential for reversal of the procedure. Unfortunately the efficacy of clip removal is far from clear [51].

Complications & side effects of endoscopic thoracic sympathectomy

Complications and side effects that occur in patients undergoing surgery for HH can be a source of anxiety and frustration for surgeons (Table 2). Complications are rare, and in many cases avoidable; however, they do occur, and result in poor outcomes despite a surgeon's experience or careful technique. Side effects are usually unavoidable and occur in many patients despite good surgical technique and technical success [52].

Compensatory sweating (CS) is one of the most common side effects encountered by surgeons and is the leading cause of patient dissatisfaction. When CS occurs, it usually manifests itself as an increase of sweating to the torso, groin and lower extremities. The mechanism whereby CS occurs is unclear, but it is thought to occur due to an abnormal thermoregulatory response after sympathectomy, whereby residual sweat glands increase their activity in an attempt to compensate for the loss of neural regulated sweat glands. It is also possible that CS occurs due to an altered feedback mechanism in the hypothalamus [53]. The intensity of CS is subjective and can vary among patients from mild to disabling. Recent studies suggest that the rates of mild CS vary from 14–90%, whereas the rates of severe CS range from 1 to 30% [52].

Controversy exists over the best surgical techniques to minimize the risk of CS. Some surgeons believe that the rate of CS depends on the level and extent of sympathectomy, with a larger and higher resection of sympathetic chain resulting in a higher incidence of CS [54,55]. Conversely, some believe that CS occurs independent of the extent of sympathectomy [56,57]. Regardless of the mechanism, many surgeons have altered their surgical technique from resecting the sympathetic chain to clipping in the hopes that the procedure could be reversed if a patient develops severe CS. Unfortunately, removal of clips in patients with CS has only been partially successfully in reversing severe CS [58,59]. Similarly, reconstruction with a nerve graft has enjoyed limited success [50]. Some research is underway to assess the use of topical glycopyrrolates for the management of CS after sympathectomy, with one author reporting an improvement in the majority of treated patients [60].

Table 2. Complications and side effects associated with endoscopic thoracic sympathectomy.

Complication	Occurrence
Intraoperative complications	
Failure to adequately locate sympathetic chain	Uncommon
Pleural adhesions/lung injury	Uncommon
Arterial vascular injury	Very rare
Venous vascular injury	Rare
Cardiac dysrhythmia	Rare
Pulmonary embolism/re-expansion pulmonary edema	Very rare
Cerebral injury	Very rare
Postoperative complications	
Pneumothorax/subcutaneous emphysema	Occasional
Pleural effusion/hemothorax/chylothorax	Rare
Chest wall pain and dysesthesia	Uncommon
Brachial plexus injury	Very rare
Infection	Rare
Atelectasis	Rare
Horner's syndrome	Rare
Bradycardia	Uncommon
Recurrence vs transient rebound sweating	Uncommon
Side effects	
Mild compensatory sweating	Common
Severe compensatory sweating	Uncommon
Gustatory sweating	Uncommon
Phantom sweating	Uncommon
Cardiac effects	Uncommon
Respiratory effects	Uncommon
Excessive dry hands	Uncommon

Data taken from [52].

New International Society of Sympathetic Surgeons classification for ETS

Approaches to sympathetic surgery vary amongst surgeons. The lack of concise terminology and a unified and reproducible classification system to describe the operations has led to difficulties in interpreting clinical results and comparing study data. In order to minimize these problems and to improve communication between colleagues, the International Society of Sympathetic Surgeons (ISSS) has recently proposed a descriptive classification for sympathetic surgery. The proposed classification is as follows:

- The method used to interrupt the sympathetic fibers, including the surgical technique and instruments used (scissors cut [sc], electro cut [ec], coagulation [cg], resection [rs] and clipping [cp])
- The level operated on with anatomical orientation towards the ribs (R): followed by its anatomic number and a closer specification of the level (above [a], middle [m], below [b] the rib)
- Optional other anatomical structures used for orientation: ganglia (G), interganglionic segment of the trunk (IG) with adjacent ganglia, or rami communicantes (RC)

- The body half for asymmetrical approaches

Therefore, in a patient who undergoes a right sympathectomy with clipping below the second rib and resection of the second ganglia, the classification would be a right cpR2b + rsG2 [61].

Axillary hyperhidrosis

In the USA, it is estimated that over 1 million people are affected by axillary HH [4]. As with palmar HH, nonsurgical management is often successful, with topical agents and BTX injections being the most common therapies. Major drawbacks to these approaches include costs, difficulty of use, irritation, pain and the need for frequent and long-term treatment.

Surgical intervention for the treatment of axillary HH includes axillary gland excision and ETS [62,63]. Although frequently successful, en bloc axillary gland excision is not commonly performed due to the possibility of developing disfiguring scarring and limited arm movement. Newer techniques such as suction curettage are being evaluated and may provide a simplified method of axillary gland excision with higher success and lower complication rates [64]. ETS is successful for the management of axillary HH, with most authors reporting success rates ranging from 60 to 100% [65]. In most cases, surgeons perform a lower division or clipping of the sympathetic chain (T3 or T4) for axillary HH [66].

Craniofacial & plantar hyperhidrosis

First-line therapy for craniofacial HH includes topical aluminum chloride, oral medications and BTX injections [17]. Alternatively, ETS has been used successfully in carefully selected patients, but is more commonly associated with side effects such as compensatory sweating than nonsurgical treatments [65].

Plantar HH is a distressing problem that may be associated with palmar HH. Various conservative modalities are used for the treatment of plantar HH, such as topical or oral agents, BTX injections and iontophoresis. Combinations of treatments for plantar HH produce better results and should be encouraged before resorting to higher doses of BTX or surgery [67]. Unfortunately, these approaches often provide unsatisfactory long-term results [68]. Recently, lumbar sympathectomy using percutaneous techniques has been advocated as an alternative approach to treat severe plantar HH. In this method, the sympathetic ganglion or chain is resected using neurolytic agents (alcohol or phenol) or radiofrequency [69]. Further evaluation of these surgical techniques is currently underway.

When plantar HH is associated with palmar HH, it is termed palmoplantar HH. This disease appears to be an autosomal dominant disorder transmitted genetically, with a familial pattern observed in 50% of patients [7]. This pattern of sweating is most amenable to cure by surgical sympathectomy when the following four characteristics are reported:

- Profound level of palmar sweating, resulting in dripping or near dripping
- Quantitatively similar level of plantar HH, bimodal onset, either in infancy or puberty, frequently exacerbated by puberty
- Provocation of the sweating with ordinary hand lotion

Although debatable, some authors believe that thoracic sympathectomy should be first-line treatment in patients with classic severe palmoplantar HH based on the high failure rate of nonoperative treatment modalities [68].

Expert commentary

Patients with HH are now able to access a great deal of information on this common condition through the internet. In addition to learning that they are not alone with their problem, patients are often directed to care givers, many of whom offer a variety of treatment options. As HH is a 'quality of life' disorder, ensuring that patients receive accurate information on the pros and cons of these various management options is critical for ensuring patient satisfaction.

When assessing a patient with focal HH, it is critical to determine the location and severity of the sweating. For patients with mild sweating, reassurance or topical therapy may be all that is required. For more severe cases, a multidisciplinary approach to management involving primary care givers, dermatologists and surgeons may be required for optimal results. In cases of focal palmar and axillary HH, topical agents such aluminum chloride are the first-line therapy. These agents are often helpful but are limited by the untidy application and skin irritation. If additional care is required, BTX injections have been shown to be very effective for axillary HH; however, its use may be limited by the cost and frequency of application. Although not FDA approved for the treatment of palmar HH, BTX is being used with some success. Unfortunately, due to the cost and frequency of therapy, as well as adverse effects such as pain, numbness and weakness, many patients seek out alternative therapies. Oral agents such as anticholinergics are rarely used due to their side effects and the lack of scientific evidence to support their use in the management of HH. Iontophoresis is generally safe and helpful for the treatment of palmar and plantar HH. Unfortunately this modality is limited because it is labor intensive, time consuming and has adverse effects including skin dryness and irritation.

For patients with severe focal palmar and axillary HH, ETS has been shown to be a safe and effective therapy. Data supporting its effectiveness is largely observational, however, and confounded by variations in surgical technique and inconsistent terminology used to describe the operations that have been performed. Side effects such as compensatory sweating also continue to be the Achilles heel of ETS surgery, with studies reporting wide ranges of complications and side effects for what appears to be similar operative approaches performed by experienced surgeons. In an attempt to address some of these issues, the ISSS has proposed a new classification system. For craniofacial and plantar HH, surgery may play a role in carefully selected patients, but does not enjoy the same success as palmar or axillary disease.

In summary, given the myriad of disease subtypes and management options, the successful management of patients with focal HH involves a multidisciplinary team that includes

primary care givers, dermatologists and surgeons. With this approach, patients can be properly evaluated, educated, referred and managed, with the best chance at a successful outcome.

Five-year view

Over the next 5 years, the following advancements will likely assist healthcare providers with our understanding and management of HH. Firstly, the development of new methods to better quantify sweating, such as the ventilated capsule, will be important as we search for improved objective methods to evaluate patients with HH or CS. Secondly, our understanding of the anatomy of the sympathetic chain is evolving, along with our knowledge of mediators such as nitrous oxide as it relates to the pathophysiology of HH. Thirdly, the evaluation of brain pathology associated with HH will improve with the assistance of functional magnetic resonance imaging. This new imaging modality uses diffusion tensor imaging to detect nerve fibers and analyze the pattern of anatomic connectivity in the brain. With this technique, the neural pathways associated with HH may be elucidated, which may allow healthcare providers to stratify patients into optimal treatment groups. Finally, the standardization of surgical nomenclature using classification such as that proposed by the ISSS for ETS will be critical in allowing the comparison of scientific data from different countries around the world. Further dissemination, research and improvements in minimally invasive surgical techniques will continue to better define the growing role of surgery in the management of primary focal HH.

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Key issues

- Hyperhidrosis (HH) is a debilitating disorder that affects 2–3% of the population.
- Careful evaluation of patients with HH is critical to rule out secondary causes of sweating.
- The suggested treatment of a patient with HH varies based on the disease severity and distribution of sweating.
- Nonsurgical modalities of treatment, such as topical agents, iontophoresis, oral agents and botulinum toxin injections, are generally used as first-line therapies.
- Several observational studies suggest that endoscopic thoracic sympathectomy (ETS) is a safe and effective therapeutic strategy in patients with palmar and axillary HH.
- To ensure appropriate expectations, patients should be fully informed about the potential complications and side effects of ETS.
- With careful patient selection, excellent long-term results and a high rate of patient satisfaction have been reported when ETS is used to treat palmar and axillary HH.
- Recent work suggests that ETS may be an effective approach for the treatment of patients with severe craniofacial or plantar HH.
- A multidisciplinary approach with input from primary care givers, dermatologists and surgeons is often helpful in determining the best management strategy.

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CME Hyperhidrosis: clinical presentation, evaluation and management

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Which of the following statements about the diagnosis of hyperhidrosis is most accurate?
   - ☐ **A** Sweating is most profound at night
   - ☐ **B** Symptoms usually begin during early adulthood
   - ☐ **C** There is no standard definition of hyperhidrosis
   - ☐ **D** Patients with suspected hyperhidrosis should undergo gravimetric testing

2. Which of the following treatments is considered first-line therapy for mild-to-moderate palmar, plantar or axillary hyperhidrosis?
   - ☐ **A** Iontophoresis
   - ☐ **B** Botulinum toxin (BTX) injections
   - ☐ **C** Topical anticholinergic agents
   - ☐ **D** Antiperspirants that contain aluminum salts

3. Which of the following statements about the use of BTX injections for hyperhidrosis is most accurate?
   - ☐ **A** The maximum recommended dose of BTX is 300–400 U at any one time
   - ☐ **B** The duration of efficacy of BTX for hyperhidrosis is less than that of BTX for neuromuscular disorders
   - ☐ **C** Symptoms of hyperhidrosis improve only 3–4 weeks after the injection
   - ☐ **D** Muscle weakness is the most common side effect of BTX injections for hyperhidrosis

4. Which of the following statements about surgical treatment for hyperhidrosis is most accurate?
   - ☐ **A** Sympathectomy is most effective for plantar hyperhidrosis
   - ☐ **B** Surgery is always the last option after the failure of multiple medical treatments
   - ☐ **C** Compensatory sweating after sympathectomy is most profound in the craniofacial area
   - ☐ **D** Removal of surgical clips has been only partially successful in reversing severe compensatory sweating