Hyperhidrosis

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Doris Hexsel and Fernanda Oliveira Camozzato

Key Points

- Sweating is a normal and important mechanism of thermoregulation which is essential for survival. When excessive, it is called hyperhidrosis.
- It is necessary to understand the biology of eccrine, apocrine, and apoeccrine sweat glands to understand hyperhidrosis.
- Hyperhidrosis can be primary (idiopathic/essential) or secondary to another condition. Hyperhidrosis can be further classified as focal or generalized.
- Primary hyperhidrosis is most often focal, affecting the palms, soles, and axillae. Thighs and gluteal and inguinal regions may also be involved. One or more regions can be affected in the same patient.
- Secondary hyperhidrosis must be ruled out before a diagnosis of primary hyperhidrosis is made. A variety of conditions can induce hyperhidrosis.
- There are many treatments for hyperhidrosis, including aluminum compounds, iontophoresis, botulinum toxin, drugs, microfocused ultrasound, and endoscopic thoracic sympathectomy.

Introduction

Hyperhidrosis is a chronic autonomic disorder whereby the production of sweat exceeds the amount required for thermoregulation. This condition is not merely characterized by excessive sweating but also by any amount of sweating that causes physical, emotional, and social discomfort for the patient [1]. Hyperhidrosis may impair the ability to perform daily functions and, in some cases, may increase the risk of cutaneous infections because of the continuous dampness of the skin [2]. Patients with hyperhidrosis have a decreased quality of life, which is comparable with that observed in patients with acne vulgaris or psoriasis [3, 4].

Hyperhidrosis can be classified as a primary or secondary disorder, and may have focal or generalized manifestations [5]. Primary hyperhidrosis

D. Hexsel (✉)
Brazilian Center for Studies in Dermatology,
Porto Alegre, Brazil

Hexsel Dermatology Clinic,
Porto Alegre, Rio de Janeiro, Brazil
e-mail: doris@hexsel.com.br

F.O. Camozzato
Brazilian Center for Studies in Dermatology,
Porto Alegre, Brazil

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is most often focal and usually causes idiopathic, symmetrically bilateral excessive sweating [6]. Secondary hyperhidrosis manifests most often as generalized excessive sweating related to an underlying medical condition or to the use of a medication [5]. The cause of hyperhidrosis should always be investigated and treated whenever possible.

Epidemiology

Currently hyperhidrosis affects about 1–3% of the population [7, 8]. One epidemiologic survey estimated that 0.5% of the US population may be suffering from the effects of hyperhidrosis, with major interference in daily activities [6]. However, this number may be underestimated, because hyperhidrosis is underreported by patients and underdiagnosed by healthcare professionals [6]. A study conducted in the United States to determine the prevalence of hyperhidrosis sent a survey inquiring about excessive sweating to 150,000 US households and concluded that 2.8% of the US population is affected by hyperhidrosis [6].

Data suggest no difference in the incidence between men and women [6]. However, studies in Japan [7] and Germany [8] found that the incidence of hyperhidrosis is higher in men than in women: 16.66% versus 10.66% and 18.1% versus 13.3%, respectively. Men reported higher intensity of hyperhidrosis symptoms than women in a study of Polish students [9], but in a study of Canadian patients, women reported being more severely affected than men [10]. Another study found that the most patients with hyperhidrosis (93%) had primary hyperhidrosis [5].

The onset of primary hyperhidrosis usually takes place between the ages of 14 and 25 years. When the onset happens at a prepubertal age, normally the palmar or plantar areas are affected, with presentations in the axillary, facial, or abdominal and dorsal regions less likely. A postpubertal onset is more often associated with an axillary distribution [10].

A positive family history is present in 35–56% of patients with hyperhidrosis. The inheritance pattern has a variable penetrance and is most likely autosomal dominant [2, 6, 10]. However, one study found a higher association with a positive family history in patients with primary palmar hyperhidrosis, with 65% of patients having a positive family history [11]. Earlier age at onset (<20 years of age) also correlated with a positive family history [10].

Hyperhidrosis is potentially underdiagnosed and undertreated. To properly diagnose this condition the physician should question the patients, during a routine review of systems, about sweating and how it affects the patient's quality of life.

Etiopathogenesis

The skin appendages are composed of the eccrine and apocrine sweat glands, the hair follicles, the sebaceous glands, and the nails. All of these are embryonically derived from buds of epidermis that grow down into the dermis to form these specialized structures.

Eccrine sweat glands are distributed all over the body surface, except in the external auditory conduit, vermilion border, nail bed, clitoris, and labia minora [12]. These glands are most numerous on the palms, soles, face, axilla, and, to a lesser extent, the back and chest [13]. The number varies greatly with site, occurring more densely on the soles compared with the thighs, and also vary in size from person to person [12]. Histologically, the eccrine gland is divided into three subunits with a snarled secretory portion located at the dermal–hypodermal junction or lower dermis; in an intradermal sweat conduit, which also constitutes half of the basal layer; and in an intraepidermal sweat conduit [14]. The secretory portion consists of an external layer of contractile myoepithelial cells that mobilize sweating secretion. These cells secrete a hypotonic saline solution and are innervated by cholinergic postganglionic sympathetic nerve fibers [15, 16] responding to the cholinergic stimuli. There is no relationship between the density of eccrine glands in normal individuals and the density of eccrine glands in those who suffer from focal hyperhidrosis [17].

Apocrine sweat glands (ASG) are part of the pilosebaceous unit [15] that is composed of hair follicles and sebaceous glands. Apocrine glands are specialized sweat glands that secrete a solution with high oil content and are under adrenergic control [18]. Apocrine glands are usually restricted to a few regions such as axillae, anogenital region, periumbilical region, perimammary area, prepuce, scrotum, in a modified form of glands in the external auditory conduit (ceruminous glands), eyelids (Moll glands), and mamma (mammary glands) [18, 19]. In the normal axillary region, apocrine glands outnumber eccrine glands by approximately 10 to 1 [13]. Histologically, ASG may be divided in three segments: a secretory portion, an intradermal channel, and an intraepidermal channel [17]. The secretory portion is composed of a single layer of columnar cells whose size reflects their secreting activity [18]. These glands release a portion of their cytoplasm into the glandular lumen, which is called decapitation secretion [18]. Proteins, ammonia, sugars, fatty acids, and sometimes chromogens constitute the apocrine secretion. The secretion is odorous, and it is assumed that the odor is due to products excreted by local bacterial skin flora [19]. The function of apocrine glands in humans is not fully elucidated, although it is thought that they may be important for body odor and pheromones [17]. They are activated after reaching sexual maturity.

A third type of gland, described by Sato et al., was termed "*apoeccrine*" because they contain morphologic features common to the other two types [20]. Histologically this gland is subdivided into three portions, with a secretory portion, which features an irregular dilated segment and another nondilated segment; an intradermal channel; and an intraepidermal channel. Secreting cells resemble the eccrine gland light cells in the nondilated segment; however, they resemble apocrine glands in the dilated region [20]. Ductal opening occurs at the epidermal level, as is the case for eccrine glands [21]. Apoeccrine glands receive sympathetic innervation and respond to cholinergic stimuli and epinephrine. They apparently develop after adolescence in both sexes [20]. These glands produce copious, watery fluid and can represent 10–45% of all axillary glands [19].

The degree to which each gland type is involved in hyperhidrosis is unknown, but is believed to be of eccrine origin because of its profuse nature and watery consistency [17, 21]. This fact, however, does not exclude the possibility that other glands may be involved [17, 21].

The cause of hyperhidrosis is unknown, but it has been postulated that this condition occurs as a primary process of autonomic neuronal dysfunction, as the sweat glands and their innervation do not show any histologic abnormalities. This dysfunction tends to occur in areas where there is a higher concentration of eccrine glands such as the palms, soles, and axillae, which are sweat-producing glands. Less common sites are the scalp or face [15].

A central sudomotor efferent pathway is suggested for hyperhidrosis with the following connections: (1) cerebral cortex to hypothalamus; (2) hypothalamus to medulla; (3) fibers crossing in the medulla oblongata and travelling to the lateral horn of the spinal cord; (4) the lateral horn to sympathetic ganglia; and (5) sympathetic ganglia to sweat glands as postganglionic C fibers [15]. Sweat gland innervation is sympathetic and postganglionic, with acetylcholine as primary neurotransmitter [18]. These fibers consist of unmyelinated class C fibers [15]. Norepinephrine and vasoactive intestinal peptide (VIP) may play a role, but neither of these amplifies cholinergic sweat secretion [22].

Emotional stimuli alone can activate sweat glands. Frontal and premotor projections to the hypothalamus probably promote sweating during enhanced emotions [18]. The hypothalamic sweat center, which is in charge of the palms, soles, and in some individuals the axilla, seems to be distinct from the other hypothalamic sweat centers and is actually under exclusive control of the cortex, with no input from the thermosensitive elements. Because emotional sweating does not occur during sleep or sedation, one of the criteria for primary hyperhidrosis is that the individual does not experience sweating during sleep. Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating and are controlled by different central nervous system neurons. It is possible that primary hyperhidrosis is due to abnormal

central control of emotional sweating, given that it affects the same body areas as those affected in emotional sweating (hands, feet, and axillae) [23].

Classification

Primary Hyperhidrosis

Primary hyperhidrosis is excessive sweating in specific regions of the body, the sweating itself being the medical problem [5]. *Primary hyperhidrosis* is usually symmetric, starts in childhood or in the second decade of life, and is often hereditary. This form of hyperhidrosis is not secondary to medical conditions or medications, and the diagnostic criteria are shown in Table 67.1.

Table 67.1 Criteria for diagnosis of Hyperhidrosis [5, 54, 67]

Primary hyperhidrosis	Excessive sweating focal and visible of at least 6 months' duration without any apparent cause and at least two of the following:
	Bilateral and relatively symmetric
	Impairs daily activities
	At least one episode per week
	Age of onset <25 years
	Family history of hyperhidrosis
	Cessation of focal sweating during sleep
	Exclusion of secondary causes of excessive sweating
Secondary generalized hyperhidrosis	Generalized excessive sweating attributable to a definitive underlying medical cause: most commonly drugs, cardiovascular disorders, respiratory failure, infections, malignancies, endocrine disease, metabolic disorders, neurologic disease, among others
Secondary focal hyperhidrosis	Excessive sweating in typical anatomic sites as palms, soles, axillae, craniofacial, or in a well-defined anatomic distribution such as trunk, inguinal folds, buttocks, legs, submammary folds, neck, or wrist *and* identification of a definitive underlying cause; most commonly Frey syndrome, eccrine nevus, social anxiety disorder, neurologic disorder, or tumor

Adapted from Walling [5]

When excessive sweating affects only a specific part of the body it is called localized hyperhidrosis [1]. Common focal sites for primary hyperhidrosis include palms, soles, axillae, craniofacial area, inguinal area, and gluteal region. Palmar, plantar, and axillary hyperhidrosis are the most common [5, 6]. Patients with primary hyperhidrosis may have one or multiple sites of involvement, as palmar hyperhidrosis alone, palmar and axillary hyperhidrosis, or various other combinations of focal involvement [6, 24].

Axillary Hyperhidrosis

Axillary hyperhidrosis (AH) is excessive sweating specifically in the area of the axillae and usually presents with a bilateral pattern. While it can be continuous, it is more commonly phasic. It may be precipitated by heat, mental stress, or exercises [25] and is associated with dermatologic complications including pompholyx, contact dermatitis, bromhidrosis, chromhidrosis, and intertrigo [26]. Its onset is usually after puberty.

Plantar and Palmar Hyperhidrosis

In palmoplantar hyperhidrosis the feet and hands are often cold because of perspiration evaporation, which also stimulates the sympathetic nervous system and contributes to aggravating hyperhidrosis [27]. This form of hyperhidrosis constitutes a substrate for the establishment of fungal infection and contact dermatitis. It fosters the appearance of bacterial infections and keratolysis plantare sulcatum, whereas palmar hyperhidrosis may be associated with dyshidrosis.

Inguinal Hyperhidrosis or Hexsel's Hyperhidrosis

Hexsel's hyperhidrosis is often associated with other forms of hyperhidrosis [28]. It symmetrically affects the groin region, including the suprapubic area, the shallow depression that lies immediately below the fold of the groin, the medial surfaces of the upper inner thighs, and the genital area. It may also include the lower part of the gluteus maximus, gluteal fold, and natal cleft [29]. Patients with this condition have difficulty in concealing the often-embarrassing sweat-drenched clothing in this area that typically results from having the disorder.

Prevalence is largely unknown because of underreporting, but the condition appears less frequently than other forms of focal hyperhidrosis. Fifty percent of patients with Hexsel's hyperhidrosis have a positive family history of some form of hyperhidrosis, suggesting an inherited mechanism [29].

Localized Unilateral Hyperhidrosis

Localized unilateral hyperhidrosis is usually seen as a sharply demarcated region of sweating on the forearm or forehead restricted to less than 10 × 10 cm. Most cases are idiopathic with no triggering factors. The pathogenesis is unclear [30], and one case report suggests that there is a hypohidrotic element to the disorder [31]. Fewer than 40 cases have been reported in the literature [31].

Secondary Hyperhidrosis

Secondary hyperhidrosis is usually generalized and is due to an underlying cause. This condition can be further classified as focal or generalized.

Secondary Generalized Hyperhidrosis

Secondary generalized hyperhidrosis is caused by a medication or a medical condition. Conditions that may cause secondary hyperhidrosis can be physiologic, such as pregnancy, menopause, fever, excessive heat; or pathologic, including malignancy, lymphoma, carcinoid syndrome, diabetes mellitus, thyrotoxicosis, diabetes insipidus, hyperthyroidism, pheochromocytoma, tuberculosis, HIV (human immunodeficiency virus), endocarditis, and autonomic dysreflexia, among others [5, 32, 33]. There are many drugs that are known to cause secondary hyperhidrosis, including antidepressants, hypoglycemic agents, tryptans, antipyretics, cholinergics, sympathomimetic agents, and many others. Psychiatric disorders can also present with hyperhidrosis. Secondary hyperhidrosis is a clinical feature in 32% of persons with social anxiety disorder [34, 35]. Some debate exists, however, over whether the relationship between these two entities is causal [36].

Secondary causes of hyperhidrosis must be ruled out before diagnosing primary hyperhidrosis [5, 32]. This is best accomplished by a complete review of systems and additional follow-up as appropriate based on the patient response. Some clinical features help distinguish between primary and secondary types of hyperhidrosis and include onset of the disease, characteristics of the sweating, and associated symptoms [5]. The onset of symptoms in patients with secondary hyperhidrosis is more likely later than in patients with primary hyperhidrosis. Patients with secondary hyperhidrosis are more likely to exhibit unilateral or asymmetric sweating, or be generalized, and to have symptoms during sleep ("night sweats"). Secondary hyperhidrosis is less often associated with positive family history [5].

Secondary Focal Hyperhidrosis

Although rare, multiple types of focal secondary hyperhidrosis exist.

Gustatory Sweating

Gustatory sweating is characterized by profuse sweating of the face, scalp, and neck [37]. A physiologic type of gustatory sweating occurs as bilateral facial sweating secondary to heat or to the ingestion of hot or spicy foods. Nonphysiologic types of gustatory sweating are caused by sympathetic nerve damage from neoplasm or sympathectomy, auriculotemporal nerve syndrome, diabetic neuropathy, or infection [37–39].

Gustatory sweating is a common postsurgical complaint occurring in patients after parotidectomy, usually for adenoma. It can be a component of Frey's syndrome, which also includes parotid flushing. Frey's syndrome may occur in up to 60% of patients after parotidectomy with facial nerve dissection [39]. Auriculotemporal nerve syndrome can occur sporadically as a familial trait or be due to a preceding trauma to the nerve. Diabetic gustatory sweating may occur as a by-product of sympathetic denervation, which is compensated by innervation of aberrant parasympathetic fibers [38]. These fibers stem from the minor petrous nerve and innervate the

parotid gland, causing sweating when salivation is induced. This finding is seen in 69% of patients with diabetic nephropathy and 36% of patients with diabetic neuropathy [37]. Gustatory sweating may also occur after infection, most commonly secondary to herpes zoster infection [33].

Cutaneous Disorders

Secondary focal hyperhidrosis may be seen in conjunction with a variety of cutaneous disorders, although a causal relationship has not been established. Disorders include eccrine nevus, pachyonychia congenita, palmoplantar keratodermas, glomus tumor, blue rubber bleb nevus syndrome, nevus sudoriferous, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome, speckled lentiginous nevus syndrome, Riley–Day syndrome, pachydermoperiostosis, Gopalan syndrome, pretibial myxedema, Buerger disease, eccrine pilar angiomatous hamartoma, local injury, and increased size of eccrine glands [40, 41].

Eccrine nevus or nevus sudoriferous can cause localized hyperhidrosis in an area of skin with increased numbers of eccrine glands [42]. Associated hypertrichosis and comedones can be seen in the area. A similar lesion, eccrine angiomatous hamartoma [43], shows an abundance of eccrine glands and a proliferation of vascular channels. Because of clinical and histologic similarities, these lesions may share a similar genetic pathway.

Pachyonychia congenita is a rare autosomal dominant genodermatosis that is often associated with focal palmar and plantar hyperhidrosis. One study found hyperhidrosis in 51.5% of all patients with pachyonychia congenita and in 22.7% of children with the disorder [44].

Other Forms of Secondary Hyperhidrosis

Some types of secondary hyperhidrosis are characterized by anhidrosis in one area with compensatory hyperhidrosis in another area. Most commonly the condition is iatrogenic, in the form of compensatory sweating following surgical treatment of primary focal hyperhidrosis. It may also manifest as part of Ross syndrome or in one of several neurologic conditions [45, 46].

Compensatory hyperhidrosis is a known potential complication of endoscopic thoracic sympathectomy (ETS), which occurs in areas that do not present abnormal preoperative sweating. Its intensity varies [47] and can worsen with climate changes and heat, as well as with psychological and emotional alterations. It can affect the inferior portion of the chest (generally below the nipple), dorsal and lumbar region, abdomen, pelvic waist, popliteal fossa, and lower limbs. An expert consensus of the Society of Thoracic Surgeons reported that 3–98% of patients having had ETS develop iatrogenic compensatory hyperhidrosis [48]. One large-scale study found that only 55% of patients developed compensatory sweating [49].

Ross syndrome is a rare nervous system disorder, with about 50 case reports in the literature [50] characterized by a tonic pupil (“Adie pupil”), deep tendon hyporeflexia, and unilateral or bilateral anhidrosis [46]. It can present with associated segmental hyperhidrosis. Recent studies suggest that Ross syndrome may have autoimmune etiology [45].

Secondary regional hyperhidrosis may be related to stroke, spinal cord lesion, neoplasm, or peripheral neuropathies [51, 52]. One pathophysiologic explanation for this phenomenon is that the primary lesion causes impairment of preganglionic neurons and subsequent anhidrosis, but bladder distension and other visceral stimuli enter the spinal cord distal to the lesion, causing a spinal dysreflexia that manifests as abnormal sweating. The phenomenon has also been called “perilesionary hyperhidrosis” or “border-zone sweating” [51]. Hyperhidrosis can also be associated with syringomyelia and other central nervous system diseases [53].

Associated Factors and Conditions

Heat, stress levels, and physical activities can aggravate hyperhidrosis. Other possible aggravating factors are sexual activity, excessive intake of liquids, weight increase, premenstrual tension, prolonged sitting, and wearing synthetic clothing. Cold acts as an attenuating factor. Some patients also refer to the absence of stress as an attenuating factor.

Hyperhidrosis can also be a triggering and a sustaining factor of other diseases in the affected

sites. Besides the excessive sweating, these associated diseases can be aggravated by contact with clothing or products used in the area to decrease perspiration [11], or by the increase in local moisture, with consequent skin maceration and proliferation of microorganisms. The most frequent associated diseases are bacterial and fungal infections, but pompholyx, contact dermatitis [26], folliculitis, erythrasma, and dermatitis can occur. Patients suffering from hyperhidrosis frequently mention bromhidrosis, chromhidrosis, and skin color changes in the inguinal region.

Diagnosis

The criteria for diagnosis of hyperhidrosis are summarized in Table 67.1 [5, 54]. Patient history usually provides all the information required to differentiate common primary hyperhidrosis from potentially worrisome causes (Fig. 67.1) [55]. Asymmetric hyperhidrosis should prompt an investigation for a neurologic lesion. Generalized primary hyperhidrosis is rare, and the diagnosis is made after causes of secondary sweating are excluded.

Some tools are useful for the diagnosis and assessment of hyperhidrosis severity. The Minor test is an important instrument to localize the hyperactive sweat glands in different forms of hyperhidrosis and to assess the response to treatment. This test does not quantify the severity of hyperhidrosis [56], but identifies different sweating intensities. Hexsel and coworkers proposed the Sweating Intensity Visual Scale to classify the sweating intensity. This is a visual 6-grade scale based on the final color resulting from the Minor test: Grade 0 = minimal or no sweating; Grade I = initial, discrete sweating; Grade II = mild sweating; Grade III = moderate sweating; Grade IV = intense sweating; and Grade V= excess sweating [57]. There are also other tools for the assessment of

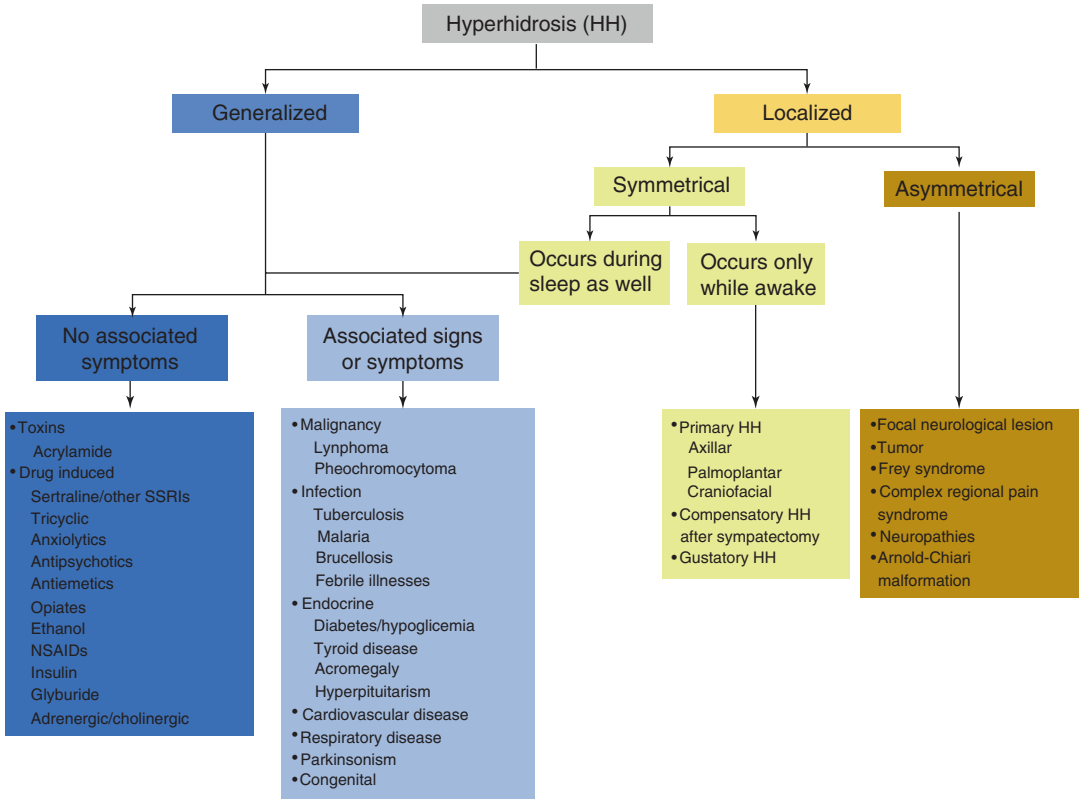

Fig. 67.1 Diagnostic algorithm for evaluation of the patient with pruritus (Adapted from Vary [55])

hyperhidrosis severity, such as the 4-point single-question Hyperhidrosis Disease Severity Scale [56], gravimetry, [58] and the Hyperhidrosis Area and Severity Index [59].

Therapeutic Approach

Depending on the type, location, and severity of the hyperhidrosis, different treatments can be used, including topical, oral, and iontophoretic treatments, botulinum neurotoxin (BoNT) injections, and surgery. To date, an established level of evidence (level A, two or more class I papers) [60] exists only for BoNT-A treatment of axillary hyperhidrosis. Some nonpharmacologic treatments can control the disease.

The Canadian Hyperhidrosis Advisory Committee designed an algorithm to guide the treatment of hyperhidrosis [56]. Mild axillary, palmar, and plantar hyperhidrosis should firstly be treated with topical aluminum chloride. In case of failure, BoNT-A or iontophoresis should be considered. In severe cases, BoNT-A and topical aluminum chloride are first-line therapy. For palmar and plantar hyperhidrosis, iontophoresis is also first-line therapy. First-line therapies for craniofacial hyperhidrosis, regardless of disease severity, include oral medications, BoNT-A, or topical aluminum chloride. Local surgery and endoscopic thoracic sympathectomy should be considered in severe cases of hyperhidrosis, mainly when the patient fails to respond to all other treatment options [56].

Nonpharmacologic Treatment

Weight control In general, an increase in body mass index is associated with an increased need to sweat. Therefore, keeping body mass index within the normal range helps patients with hyperhidrosis [47].

Nonthermogenic diet Some foods activate the sympathetic nervous system, leading to metabolic and endocrine responses after their intake. Such foods include certain legumes, pepper, garlic, coriander, cinnamon, ketchup, salt, ginger, chocolate, coffee, pork, viscera, red meat, milk, milk derivatives, strawberries, cola-based soft drinks, and mate (*Ilex paraguariensis*) infusion, as well as black, green, and chamomile tea [47]. Regarding the diet composition, proteins are the highest contributors to activating the sympathetic nervous system (i.e., they activate thermogenesis), followed by carbohydrates. The intake of food supplements with high quantities of proteins and carbohydrates can also trigger increased sweating.

Physical exercise A daily 30-min walk can help avoid weight increase in sedentary individuals, and additional exertion is sufficient to lose weight and reduce the body mass index.

Clothing Clothes, either social or professional, have to be tolerable to the patient. A thin dry-fit T-shirt or cotton shirt can help distribute the sweat more evenly when used under the clothes [47]. Changing clothes one or more times a day is often necessary, especially on hot, humid days.

Weather conditions Ambient temperature plays an important role in cooling the human body. The thermal sensation of heat increases when the environment is hotter, more humid, and less ventilated, with a consequent increase in sweating intensity. The patients present improvement of the symptoms in cold environments with low humidity and good ventilation [47].

Topical Treatments

Aluminum salts are the main topical agents for hyperhidrosis. Their mechanism of action is attributed either to an interaction between aluminum chloride and keratin in the sweat ducts or to a direct action on the excretory eccrine gland epithelium [61]. Solutions of aluminum chloride concentrations vary between 12% and 20% formulations. Higher concentrations of aluminum chloride and higher salt content in preparations commonly cause irritation or burning, which can limit use. The sweat glands of primary hyperhidrosis are less active during sleep, allowing the metal salts to remain in place when applied at night [62]. Topical agents can be used

in all forms of hyperhidrosis (axillary, palmoplantar, and gustatory), although these are more commonly used for axillary and palmar hyperhidrosis. These solutions are effective in milder [62] and severe cases [56] of hyperhidrosis as the duration of effect is often limited to 48 h.

Newer topical preparations have shown an improvement in tolerability, such as a combination of 15% aluminum chloride with 2% salicylic acid gel [63]. The addition of salicylic acid may improve tolerability by hydrating and mitigating the drying effect of alcohol, and may also act synergistically with aluminum chloride given its astringent and antiperspirant properties. Tolerability may also be improved with use of a 20% aluminum chloride spray in a silicone base [63].

Topical anticholinergic preparations such as topical glycopyrrolate improved sweating in certain patients, but efficacy is not consistent [64, 65]. Furthermore, some evidence suggest that the effect may involve systemic absorption of the anticholinergic medication [66–68].

Oral Treatments

Oral treatments can offer significant benefit, but the doses required for clinically meaningful effect cause significant and undesired side effects. Anticholinergic agents (glycopyrrolate, methantheline bromide, oxybutynin, atropine, and scopolamine) and α-adrenergic agonists (clonidine) are the most used in clinical practice. Anticholinergic agents work by inhibiting the production of acetylcholine at muscarinic receptors [69].

Oxybutynin chloride is a promising medication. This drug can be of great help in the control of primary hyperhidrosis or in compensatory hyperhidrosis when patients tolerate its side effects. The use of oxybutynin has been reported as a therapeutic option in children with hyperhidrosis [70, 71]. It is effective for 6–10 h, or even up to 24 h if continuous-use formulations are taken. The lowest dose of oxybutynin is 5 mg at bedtime, at which dosage patients are not likely to present side effects. Generally the effective dosage requires the intake of 15 mg a day: three intakes of 5 mg fractionated over the course of the day.

A retrospective study [72] included 110 patients with hyperhidrosis treated with oxybutynin. After 3 months of treatment, 79% responded. After 12 months, 62% continued to respond, and the response was considered excellent in 50%. Most of the patients who responded at 3 and 12 months reported mild adverse events. No serious adverse events were observed. Uptitrating the dosing regimen resulted in higher treatment adherence rates than a fixed-dose regimen.

In some cases, the side effects of anticholinergic drugs result in noncompliance with treatment, leading many patients to use these drugs only on social occasions and at the lowest necessary dose. Side effects can be very disabling and include dry mouth, blurring of vision, urinary hesitancy, dizziness, tachycardia, and confusion [69]. Contraindications include myasthenia gravis, pyloric stenosis, narrow-angle glaucoma, and paralytic ileus. Gastroesophageal reflux disease, glaucoma, bladder outflow obstruction, and cardiac insufficiency are relative contraindications.

Oral agents can be used in all subtypes of hyperhidrosis such as axillary, palmoplantar, craniofacial/gustatory, and generalized. However, double-blind studies are available only for axillary and palmoplantar hyperhidrosis. Current evidence indicates that both oxybutinin (one class I study and one class II study) and menthatheline bromide (two class II studies) are probably effective, with level B evidence. Retrospective studies suggested oral glycopyrrolate and clonidine are also effective. Collectively, oral agents have level B evidence (probably effective) with one class I study and three class II studies present in the literature [73].

Iontophoresis

Iontophoresis is the introduction of an ionized substance through application of a direct current on intact skin [74]. Although the exact mechanism of action is unknown, this technique facilitates transdermal movement of solute ions by generation of an electrical potential gradient. This process decreases the perspiration production in the treated areas, partially improving the symptoms [75, 76]. Repeated treatments are

required [76]. Although there are devices with special configurations to treat the axilla, palm, and sole regions, there is no special configuration for the inguinal region. Devices for home use are very cost-effective after the initial investment. Tap water over the metal plates improves contact with the skin and provides a source of ions. Iontophoresis is performed initially every 2–7 days, until a therapeutic effect is achieved, after which the treatment can be performed once every 2–3 weeks [74]. Implantable electronic devices such as pacemakers or defibrillators, artificial joints, and application in pregnant women are contraindications.

Botulinum Neurotoxin Type A (BoNT-A) Treatment

BoNT-A is one of the most effective therapies for localized hyperhidrosis. BoNT-A is an inhibitor of acetylcholine release from the presynaptic membranes of neuromuscular junctions, thus preventing cholinergic transmission to postganglionic neuroreceptors. The treatment is applied in focal sites of localized hyperhidrosis such as axilla, palms, soles, face, and scalp. Compensatory hyperhidrosis can be also treated with BoNT-A [47]. Side effects include pain and possible transitory muscle weakness.

As a painful procedure, anesthetic creams and local or truncal anesthesia are useful to increase patient comfort. Trichotomy of the region may be necessary. Minor's test performed in the hyperhidrosis zone delimits the area. Bearing in mind that the sweat glands are located about 2.5 mm below the skin [77], the application should be intradermic, preferably using fine-gauge needles, such as 30-gauge. A simple technique to avoid overly deep injections is to use a cut needle lid over the needle as a shield [78]. Minor's test can be repeated about 1 month after the procedure to identify any residual perspiring areas.

The field of anhidrotic effects of BoNT-A does not vary significantly when the same doses in different dilutions and depths are injected on the back of patients suffering from compensatory hyperhidrosis [79]. However, areas of more intense sweating such as midline demand higher doses to achieve a similar field of anhidrotic effects [79]. These results support that dose is more important than brand, usual dilutions, and depths in determining the size or area of the field of anhidrotic effects [79]. Ideal doses have been the focus of discussion, aiming to obtain more efficacious and lasting results Table 67.2 lists some articles and the proposed doses for the treatment of axillary, inguinal, and palmar hyperhidrosis and the average duration of effects.

Lasers and Microwave-Based Treatment

The efficacy of laser treatments for hyperhidrosis remains unclear. A pilot study evaluated a long-pulsed neodynium yttrium aluminum garnet (1,064 nm Nd:YAG) laser and showed improvement of sweating in patients with axillary hyperhidrosis for up to 9 months compared with the control group [89]. However, another study of Nd-YAG laser hair removal therapy showed a side effect of hyperhidrosis in the treated areas [90].

Microwave energy is a new technology and a nonsurgical option for hyperhidrosis treatment [91–93]. It targets the skin and subcutaneous tissue interface, which causes irreversible thermolysis of eccrine glands. Nestor and Park [94] reported the results of two randomized double-blind, sham-controlled pilot studies with the Ulthera® system (Ulthera, Mesa, AZ, USA) to treat patients with axillary hyperhidrosis. The results showed significant and long-lasting reductions in baseline sweat production, high levels of patient satisfaction, and only minor transient discomfort during treatment [94].

Surgical Therapy

Surgical approaches for focal hyperhidrosis include excision of sweating areas, curettage, liposuction, and thoracic sympathectomy [48]. These procedures are typically reserved for patients who have failed conservative therapy or are not candidates for previously described therapies [56].

Table 67.2 Proposed dose regimens for the treatment of axillary, inguinal, and palmar hyperhidrosis

Authors	HH area	Study design	Patients	Treatment	Results	Duration
Heckmann [80]	Axillary	R, DB, PC, multicenter	158	200 U (ABO) unilaterally vs placebo. Placebo-treated side received 100 U (ABO) after 2 weeks	Equal reductions in sweating with the two doses	26 weeks for both groups
Naumann and Lowe [81]	Axillary	R, DB, PC, parallel group	320	50 U (ONA) vs placebo	Response at week 4: 94% (active group) vs 36% (placebo). At week 16: 82% (active) vs 21% (placebo),	16 weeks
Saadia et al. [23]	Palmar	R, SB comparison of 2 doses, intraindividual	24	50 U (ONA) vs 100 U (ONA) in each palm	At 1 month: significant decrease in sweating. At 6 months: anhidrotic effect evident in both dose groups	6 months
Odderson [82]	Axillary	R, DB, PC	18	100 U (ONA) vs placebo	At 2 weeks: sweat production decreased 91.6% in BoNT ($p < 0.05$). At 5 months: 88.2% reduction in BoNT	5 months
Simonetta Moreau et al. [83]	Palmar	R, DB, active comparator, intra-individual comparison	8	69 U (ONA) or 284 U (ABO) (mean dose)	At 1 month: decrease in mean palmar sweating area: 76.8%, ABO vs 56.6% ONA At 3 months: decrease in sweating area was 69.4%, ABO and 48.8%, ONA	17 weeks ABO 18 weeks ONA
Hexsel [29]	Inguinal	Case series	26	100 U (ONA) 60 and 80 U (ONA) can be used to treat less severe cases	Improvement showed for inguinal HH for first time	6–8 months
Lowe [84]	Axillary	R, DB, PC, multicenter, parallel-group	322	50 or 75 U (ONA) or placebo	At 4 weeks: 75% of subjects in active groups vs 25% from placebo	197 days in the 75-U group and 205 days in 50-U group
Vadoud-Seyedi and Simonart [85]	Axillary	R, DB, side by side	29	100 U (ONA) total dose in both axillae, reconstituted in saline or lidocaine	Similar time of onset and duration of effect, and decrease in sweating. Significantly lower pain in axillae treated with lidocaine-BoNT (29.3 vs 47.5)	8 months

(continued)

Table 67.2 (continued)

Authors	HH area	Study design	Patients	Treatment	Results	Duration
Talarico [86]	Axillary	DB, R, prospective	10	50 U (ONA) in one axilla and 150 U (ABO) in the other	Sweat rate decreased 97.7% in ONA axilla and 99.4% in ABO axilla	260 days for ONA and 290 days for ABO
Gregoriou [87]	Palmar and plantar	Open label	36	100 U (ONA) per palm	Significant improvement in palmar HH	6.2 months
Dressler and Adib Saberi [88]	Axillary	DB, intra-individual comparison	51	First: 100 U (ONA) bilaterally; then: direct comparison 100 U (ONA) unilaterally vs 50 U (ONA) contralaterally	Both doses had similar effects	3–4 months

ABO abotulinumtoxin A, *BoNT* botulinum neurotoxin, *DB* double-blind, *HH* hyperhidrosis, *ONA* onabotulinumtoxin A, *PC* placebo-controlled, *R* retrospective, *SB* single-blind

Curettage or liposuction cannula and surgical excision of glands are mainly indicated for axillary hyperhidrosis. Insertion of a liposuction cannula or curette via a small incision allows near-complete removal of the glands. Local hematoma, seroma, or necrosis can occur, as well as recurrence [95]. In other focal forms, these procedures may result in unacceptable scars.

ETS is mostly indicated for palmar, craniofacial, or axillary hyperhidrosis. This technique interrupts signaling to the sweat glands by disrupting or destroying a portion of the sympathetic trunk at the thoracic level [96, 97]. The main complications are compensatory hyperhidrosis, Horner's syndrome, hemothorax, neuralgia, pneumothorax, and lesion in the phrenic nerve [47].

Glossary

Apocrine sweat glands Larger sweat glands that occur in hair follicles. They appear after puberty.

Apoeccrine sweat glands Contain morphological features common to the eccrine and apocrine sweat glands.

Eccrine sweat glands Small sweat glands that produce a fluid secretion without removing cytoplasm from the secreting cells and that are restricted to the human skin.

Hyperhidrosis Sweating greater than necessary for the maintenance of normal body thermoregulation.

Primary hyperhidrosis Excessive sweating in specific regions of the body and not caused by other medical conditions or by medications.

Secondary hyperhidrosis Excessive sweating caused by medications or medical conditions.

Sympathectomy Procedures that break the sympathetic innervation, thereby blocking stimulation of eccrine glands.

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