Current and Emerging Therapeutic Modalities for Hyperhidrosis, Part 1: Conservative and Noninvasive Treatments

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Approximately 1% to 3% of the US population has hyperhidrosis (HH). HH can be an incapacitating medical condition because it not only hinders patient quality of life but also causes the secondary effect of excess cutaneous sweat. There is a broad spectrum of treatment modalities including topical and systemic therapies, iontophoresis, localized neuroinhibitory injections, and surgical interventions. This article reviews HH and the conservative treatments for the condition.

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Hyperhidrosis (HH) is a pathologic condition in which diaphoresis persists beyond the levels necessary for maintenance of thermoregulatory equilibrium.[1] This dysregulation of sweat may present in many patterns. HH may occur locally in a typical bilateral and symmetric distribution, termed *focal HH*, but also may present unilaterally.[2] When HH affects multiple areas of the body, the term *generalized HH* is applied.

Perhaps the most overlooked and underestimated aspects of HH are its prevalence (1%–3% of the US population) and secondary consequences.[3] Although HH can result from other underlying medical conditions, it may lead to a wide spectrum of secondary conditions ranging from electrochemically induced muscle spasms; palmoplantar eczematous dermatitis; and/or severe occupational, psychologic, and social impairment.[1] Table 1 outlines the complications that may result from HH. Most important to patients is the impact HH has on the quality of life as well as social habits. A survey conducted by Naumann et al[1] provided a tangible perspective on the effect HH has on daily life. The survey of 320 patients with HH revealed that nearly 75% of patients experienced less confidence overall and 50% actually changed their leisure activities or were unhappy or depressed because of their condition.[1] Furthermore, in a study that measured the severity of HH using the Illness Intrusiveness Rating Scale—a comprehensive questionnaire measuring the basic functions of life (eg, work, social activities, relationships) as well as physical symptoms—patients ranked HH as comparable with disabling conditions such as multiple sclerosis and rheumatoid arthritis.[15] Thus, the gravity of HH and the severity of its consequences can be appreciated.

PREVALENCE

An estimated 7.8 million individuals in the United States experience HH; in most cases, the axillae are the most common foci of the disease and the palms are the second most common sites.[3] There is evidence of genetic and familial elements to HH.[16]

SWEAT GLANDS

Sweat glands generally are divided into apocrine or eccrine; however, some sweat glands fall into a hybrid category termed *apoeccrine glands*.[17] Apocrine glands secrete a more viscous, opaque, lipid-based fluid than eccrine glands, and characteristically are found in the

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Table 1.

Complications That May Result From Hyperhidrosis

Complication	Source
Bacterial/Fungal overgrowth	Atkins and Butler[4]; Holzle[5]
Muscle spasms (electrochemically induced)	Filosto et al[6]
Aggravated eczematous dermatitis	Swartling et al[7]
Occupational hazard	Atkins and Butler[4]; Adar et al[8]
Anxiety, psychologic disturbance	Atkins and Butler[4]; Holzle[5]; Adar et al[8]; Klein and Glogau[9]; Glogau[10,11]
Changing social habits	Naumann et al[1]; Glogau[10,11]; Strutton et al[12,13]; Swinehart[14]
Changing clothing twice daily	Naumann et al[1]; Glogau[10,11]; Strutton et al[12,13]; Swinehart[14]

axillae, external ear, areolae of breasts, and anogenital regions. Apocrine glands are thought to be activated by adrenergic stimulation rather than cholinergic stimulation, which activates eccrine glands.[17]

Eccrine glands, which are the end targets of cholinergic sympathetic nerve stimulation or hyperstimulation, as seen in HH, have a different nature than apocrine glands. Eccrine glands emit a hypotonic secretion composed of low levels of sodium chloride, urea, lactate, and potassium, and are in close association with myoepithelial cells, whose contractile function facilitates discharge of fluid. Although eccrine glands are distributed universally in the body, they are more heavily concentrated ventrally and distally in the extremities such as the palms and soles, as well as the axillae and face,[17,18] which helps explain why these regions are most commonly affected in patients with HH.

Apoeccrine glands display overlapping features of apocrine and eccrine glands and reside in the axillae, maturing in function during puberty.[17,18] Not surprisingly, these glands commonly are seen in patients with axillary HH.

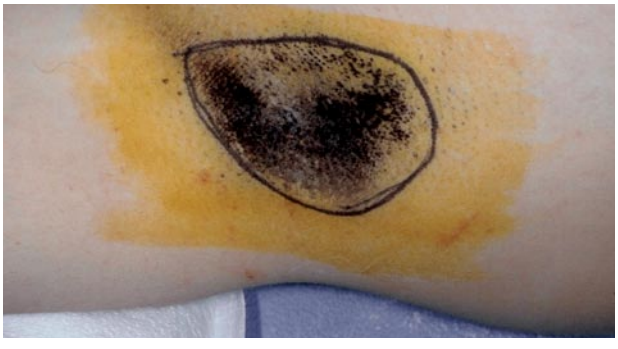
PHYSIOLOGY OF SWEATING

Sweating is the body's normal response to an elevated temperature as sensed by the thermoregulatory center, the preoptic area of the anterior hypothalamus.[17] Several motor responses are triggered to reduce body temperature, including cutaneous vasodilation and cholinergic sympathetic stimulation of the eccrine glands, thereby expelling sweat through the pores across the epidermis. The neurotransmitter acetylcholine is the terminal agent of action in the eccrine glands and has been of increasing interest as a target of therapy for HH.[17]

DIAGNOSTIC MEASURES OF HH

A thorough clinical history and physical examination are essential to diagnose HH and determine the specific classification of HH.[19] The Minor starch-iodine test often is used to elucidate areas affected by HH. The test is performed by completely drying the skin and then applying a 2% iodine solution. After the solution dries, starch powder is applied. The areas that turn purple indicate the locations and borders of hyperactive sweat glands on the skin.[19] The Figure shows an HH region of the axilla as demonstrated by a starch-iodine test.

Although the starch-iodine test indicates the local distribution of HH, it lacks quantification



Hyperhidrotic region of the axilla demonstrated by a Minor starch-iodine test.

Table 2.

Disorders and Other Factors That May Lead to Secondary Hyperhidrosis

Disorders and Other Factors	Source
Emotional state	Naumann et al[1]; Allen[22]
Exercise	Allen[22]; Stolman[23]
Fever	Stolman[23]
Thyroid dysfunction	Allen[22]; Stolman[23]
Nerve injury	Kreyden et al[2]; Lowe et al[3]; Anliker and Kreyden[24]; Kreyden[25]; Schaffner and Kreyden[26]
Diabetes mellitus	Stolman[23]
Malignant cancers	Stolman[23]
Neurologic disorders	Sato et al[27,28]
Hypoglycemia	Boni[29]; Boni et al[30]
Gout	Boni[29]; Boni et al[30]; Stolman[23]
Pheochromocytoma	Sato et al[27,28]
Pulmonary embolism	Boni[29]; Boni et al[30]; Sato et al[27,28]
Menopause	Holzle and Braun-Falco[31]
Heat	Sato et al[27,28]
Lymphoma (night sweating)	Stolman[23]
Infections (eg, malaria, mononucleosis)	Stolman[23]
Drugs	Boni[29]; Boni et al[30]; Sato et al[27,28]; Stolman[23]
Drug withdrawal	Boni[29]; Boni et al[30]

parameters. Dermatologists use a gravimetric measurement to obtain numeric values for sweat rates, which correlate with the severity of HH. The rate of sweat is calculated in milligrams per minute and cross compared with values obtained from healthy controls that do not have HH, thereby contextualizing and normalizing the results, as provided by the International Hyperhidrosis Society.[20]

Both the starch-iodine test and gravimetric analysis are helpful in diagnosing HH. Additionally, repeating these tests over time enables physicians to chart the effectiveness of therapy in terms of disease location and severity.

PRIMARY VERSUS SECONDARY HH

The hypersecretion of sweat from eccrine and/or apoeccrine glands (apocrine glands do not contribute to the clinical manifestations of HH) generally is divided into primary or secondary HH. Primary HH, also referred to as essential or idiopathic HH, by definition is not associated with an underlying medical condition; thus, it is imperative that physicians rule out any disease process that may lead to HH as a secondary effect.[21] Table 2 lists many of the disorders and other factors that may lead to secondary HH. Although emotional factors may exacerbate primary HH, emotional state alone cannot be the source of HH for a primary HH diagnosis. Rather, emotional factors may qualify the condition as secondary HH.

Primary HH typically occurs in patients younger than 25 years and in patients with a family history of primary HH. The location of primary HH tends to occur bilaterally and symmetrically rather than in a generalized fashion.[32] Furthermore, histologic evaluations of eccrine glands in HH have not revealed pathology or reactive hypertrophy compared with healthy controls.[33]

Secondary HH arises from a gamut of medical disorders and factors, including endocrine abnormalities, drugs, febrile illnesses, cardiopulmonary conditions and/or events, a variety of cancers, and central nervous system pathology.[3,29] Although most underlying diseases cause generalized secondary HH, focal and unilateral HH may be seen in association with many neurologic conditions. For instance, a spinal cord trauma may result in the emergence of HH in the form of localized unilateral HH.[2]

Primary Focal HH

The Multi-Specialty Working Group on Recognition, Diagnosis, and Treatment of Primary Focal Hyperhidrosis characterizes primary focal HH as focal, visible, excessive sweating of at least 6 months' duration without apparent cause and with at least 2 of the following characteristics[29]: bilateral relatively symmetric distribution; impairment of daily activities; at least one HH episode per week; age of onset less than 25 years; positive family history of HH; and cessation of focal sweating during sleep. Primary focal HH classically may be found on the palms, soles, axillae, or forehead.[19]

TREATMENT OPTIONS

When evaluating a patient showing evidence of HH, the physician first should make the distinction between primary and secondary HH. A checklist that includes metabolic, endocrine, neoplastic, infectious, and other groups of diseases that are associated with HH should be considered when making this distinction. Nevertheless, if no relevant pathology is observed elsewhere in the body, focus can be placed on treating the HH as an isolated primary occurrence.

The therapeutic options for HH range from conservative/noninvasive procedures to moderately invasive and invasive procedures. Conservative therapeutic measures include topical antiperspirant agents and iontophoresis. Anticholinergic or antidepressant medications are classified as noninvasive therapies. Moderately invasive procedures include botulinum toxin therapy, which has been increasingly used in Europe, Asia, Canada, and South America and recently was approved by the US Food and Drug Administration for HH.[15] Invasive procedures include surgical interventions such as local tissue resection, curettage of adipose tissue in the axillae, endoscopic thoracic sympathectomy, and percutaneous thoracic phenol sympathicolysis.[19,34]

Conservative and Noninvasive Treatments

Topical Agents—Aluminum salts, including aluminum chloride ($AlCl_3$) or aluminum chlorhydrate, are the most commonly applied and among the most effective prescriptive and nonprescriptive topical therapeutic agents available today.[5] Although these agents are more successful in treating axillary HH versus palmar HH, comparable responses may be obtained in treating palmar HH with higher concentrations.[35] As the active ingredient in most antiperspirant preparations, $AlCl_3$ is an attractive first-line treatment option for many patients because of its safety, convenience, and affordability. In fact, most individuals use over-the-counter antiperspirants, which are sold in varying formulations. The maximum concentration of $AlCl_3$ in an over-the-counter product is 12.6%. Prescription $AlCl_3$ products have concentrations as high as 25% ($AlCl_3$ hexahydrate 25%).

The risk of aluminum toxicity should be discussed with patients, and they should be reassured that topical aluminum products are safe and effective when used properly. A 2004 case report describes one reversible episode of bone pain in a woman with long-term use of high-dose topical $AlCl_3$ (1 g daily for 4 years).[36] Nevertheless, transcutaneous absorption of topical $AlCl_3$ has been shown to have negligible absorption when the product was used in milligram quantities as opposed to gram quantities[37]; therefore, when used as directed in moderate amounts for HH, the risk of toxicity from the transcutaneous absorption of aluminum is not substantial. Exceptions to this low risk include patients with renal dysfunction or those who also use products with additional sources of aluminum such as medications, aluminum hydroxide, aluminum carbonate, aluminum acetate, alumina, and almond oil.[36] Nevertheless, physicians should address the risks and benefits of both prescriptive and nonprescriptive aluminum-based medications for dermatologic purposes in HH just as internists routinely do when prescribing aluminum-containing antacids.

A review of the mechanism of action of aluminum agents demonstrates that when aluminum salts complex with mucopolysaccharides, a precipitation occurs distally in the sweat gland ducts and causes a clog that precludes the expulsion of sweat. The usefulness of aluminum products can be seen in several prospective studies.[5,31,35] Of note, $AlCl_3$ concentrations as high as 30% were used in some subjects, and the side effects (ie, local irritation, itching) were well-tolerated. Application of $AlCl_3$ should follow a prescribed treatment schedule to optimally reduce HH. It is suggested that the product be applied at night before sleep to minimize moisture and should be washed off upon awakening, before any daily perspiration begins.[5,19,31,35]

Other topical products include anticholinergic and anesthetic agents and astringent agents such as formaldehyde and glutaraldehyde.[5] These products should not be considered as first-line therapies;

rather, they should be used as conservative alternatives to more invasive therapeutic options if the $AlCl_3$ therapy is insufficient. Moreover, one important problem with local anticholinergic agents (eg, scopolamine, propantheline) is the risk of penetration and absorption of these drugs into systemic circulation. Because a large concentration of these agents is needed to have an effect on local nerves that innervate the eccrine glands, the concern of systemic infiltration and spread of these medications limits their widespread application. Although there is a decrease of HH in patients who use these agents, the adverse effects profile is dissatisfying.[9,32,38,39]

Oral Agents—A variety of oral agents have been used to manage HH. Although some medications show long-term patient satisfaction, several side effects—some of which are sometimes tolerable—invariably are reported. Among the most commonly used oral agents are anticholinergic drugs such as glycopyrronium bromide. Long-term treatment with these agents often is necessary, and patients commonly experience systemic anticholinergic effects including dysfunctional micturition, dry mouth, blurred vision, and constipation.[9,32,38,39] Propantheline bromide is another anticholinergic agent used for refractory cases of secondary HH. Canaday and Stanford[40] reported 2 cases in which oral propantheline reduced discomfort in patient status post–spinal cord injury. The classic anticholinergic agent side effects associated with this medication led the authors to not consider propantheline as a first-line agent in HH but rather to offer the drug to specific patients for relief from diaphoresis.[40]

Antianxiety agents, nonsteroidal anti-inflammatory drugs, calcium channel blockers, and clonidine are additional medications that have been used to treat underlying psychobiologic causes of HH.[41-44]

Iontophoresis—Used as therapy for conditions such as arthritis from as early as 1740, iontophoresis has been shown to be effective as a mechanism of drug transfer into tissue.[45] Iontophoresis therapy includes the use of electric current to deliver ionized matter through the skin. The HH site is submerged in an iontophoresis bin containing an aqueous solution; this therapy often is coupled with oral pharmacologic agents. Although anticholinergic agents have been delivered transcutaneously using the method of iontophoresis, tap water alone has been shown to be an effective medium for HH treatment.[5,45]

Although the exact mechanism of action is still debated, it is speculated that an interplay between the electric current, pH, and ionic environment found in tap water (vs saline, for example) possibly creates a prolonged interruption in sweat gland function and conduction (despite unchanged acetylcholine levels posttherapy). An interesting and reproduced fact that lends credence to this hypothesis is that anodal current is more effective than cathodal current when treating patients using iontophoresis, suggesting that ions found in tap water yield optimal results when they interact with a specific direction of electric current.[46]

Iontophoresis conventionally is used for palmoplantar HH; however, axillary HH also can be successfully treated using this modality. However, when compared with the ease of submerging the palms or soles in the trays used for iontophoresis, axillary treatment using these trays may be a cumbersome and poorly controlled effort. The regimen and detailed procedure of iontophoresis have been well-developed and have contributed to the resolution of symptoms for some patients.[19,23,45-47] Contraindications to iontophoresis include pregnancy, arrhythmia, and artificial pacemakers, as well as other devices that may cause even a temporary electric disturbance (eg, orthopedic implants).[48] Age generally is not considered a contraindication; however, for children, it is recommended that the iontophoresis current flow amperage be adjusted to more tolerable levels.[49]

The efficacy of iontophoresis in HH has been tested. In a study conducted by Dahl and Glent-Madsen,[50] 11 subjects were treated with iontophoresis as tolerated versus placebo for a median of 10 treatments over 2 to 4 weeks. After completion of the maintenance therapies, which were conducted every second week for 3 months, subjects demonstrated an 81% decrease in HH compared with baseline levels.[50]

Another option in iontophoresis therapy is the Drionic® unit, which is a portable system that patients can use at home.[51,52] A prospective study of the Drionic unit was conducted in 22 subjects diagnosed with axillary, palmar, and/or plantar HH.[51] Subjects used the device on one side of the body, leaving the contralateral side for control purposes. The therapeutic regimen included two 30-minute treatment sessions spaced 30 minutes apart for 5 days a week. Sweating was measured by a pretreated paper that subsequently was analyzed for sweat content using computerized techniques. Results of the study showed that within 2 weeks, 80% of palms responded to treatment; by 20 days, 100% of palms, 78% of soles, and 75% of axillae had responded. The subjects reported at least a 50% improvement in subjective symptoms, and after one month of treatment, the authors concluded that a statistically significant decrease in mean sweat production had been achieved compared with controls (palms and soles, $P<.001$; axillae, $P<.01$). However,

one month after therapy was terminated, the difference in sweat production remained only for the palms. The authors concluded that the Drionic device has a role in treating HH but may require multiple daily treatments for more than 2 weeks and re-treatment.[51]

Iontophoresis used as a mechanism of drug delivery along with $AlCl_3$ and anticholinergic agents has had promising results, including a 5-month relief of HH and a relatively safer therapeutic index than alternative systemic or topical anticholinergic agents.[53]

Adverse side effects of iontophoresis have been reported as generally tolerable and included irritation, vesiculation, erythema, or a burning or stinging sensation that immediately resolved on cessation of therapy or shortly thereafter.[54,55] However, these adverse effects were not severe enough to warrant the discontinuation of treatment. Some patients reported that posttreatment application of hydrocortisone sometimes reduced some of the adverse effects.[23]

COMMENT

HH may present in several forms and distributions throughout the body; additionally, it may be idiopathic or secondary to systemic disease. The multiple therapeutic modalities that have been developed and established for this disease adequately reflect the range and severity of the disease. While some patients find topical $AlCl_3$ and/or antiperspirant application to be helpful, others must undergo highly invasive procedures such as curettage or endoscopic thoracic sympathectomy to mitigate or rectify their disease.

As with most diseases, the first line of therapy for HH is conservative in nature. The physician must discuss with the patient if the side effects of therapy are worthwhile to relieve the excessive sweat. Some patients may refrain from a therapeutic option because of potential or actual intolerable complications.

Alternatively, some patients are satisfied knowing that their disease is manageable in the event that they seek further treatment; topical medications, antiperspirants containing $AlCl_3$, and iontophoresis all fall into this category and continue to play a role in the therapy for HH. Systemic medications such as anticholinergic agents also may be helpful in combating HH; however, they are considered a late option because of their systemic side effect profile.

This article is the first of a 2-part series. The second part on moderately invasive and invasive treatment options for hyperhidrosis will appear in a future issue of Cutis®.

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