

# Hyperhidrosis

Hyperhidrosis is a condition characterised by abnormally increased sweating, in excess of that required for regulation of body temperature. Hyperhidrosis can either be generalised or localised to specific parts of the body, such as hands, feet and axillae. Hyperhidrosis can be divided into primary or idiopathic, and a secondary type. The primary type usually starts during adolescence or even earlier, while secondary hyperhidrosis can start at any point in life. The latter form may be due to a disorder of the thyroid or pituitary gland, diabetes mellitus, tumours, gout, menopause, or certain medications. This article highlights the clinical features and the treatment options for this condition.

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Hyperhidrosis is sweating in excess of that required for normal thermoregulation. It is a condition that usually begins in either childhood or adolescence and can affect any site on the body. However, the sites most commonly affected are the palms, soles, and axillae. Excessive sweating may be primary (idiopathic) or secondary to medication use, certain diseases, metabolic disorders, or febrile illnesses. Hyperhidrosis often causes great emotional distress and occupational disability for the patient, regardless of the form and the extent of the problem. Hyperhidrosis is difficult to treat effectively. With the newer treatment modalities now available, the patient has numerous options and is offered a better prognosis.

## Types

Hyperhidrosis exists in three forms: emotionally induced hyperhidrosis, which affects palms, soles, and

axillae; localised hyperhidrosis, and generalised hyperhidrosis.<sup>1,2</sup> Localised hyperhidrosis, unlike generalised hyperhidrosis, usually begins in childhood or adolescence. Localised unilateral or segmental hyperhidrosis is rare and of unknown origin. The condition usually presents on the forearm or forehead in otherwise healthy individuals, without evidence of the typical triggering factors found in essential hyperhidrosis. Unilateral hyperhidrosis with accompanying contra-lateral anhidrosis is also rare.<sup>3</sup> Palmar hyperhidrosis is a benign functional disorder that is a psychological and social handicap. Harlequin syndrome is characterised by unilateral hyperhidrosis and flushing, predominantly induced by heat or exercise.<sup>4</sup> The sympathetic deficits are usually limited to the face.<sup>4</sup> Night sweats among older people could be related to certain systemic conditions and clinical assessment is always required to rule out the presence of these causes (Box 1).

## Epidemiology

People of all ages can be affected by hyperhidrosis. Primary hyperhidrosis affects men and women equally, and most commonly occurs among people aged 25–64 years. Some may have been affected since early childhood, and about 30–50% have another family member afflicted, implying a genetic predisposition.<sup>5</sup> Localised hyperhidrosis, unlike generalised hyperhidrosis, usually begins in childhood or adolescence. In a study of 850 patients with palmar, axillary, or facial hyperhidrosis, 62% of patients reported that sweating began since before they could remember; 33% since puberty; and 5% during adulthood.<sup>6</sup> In a cross-sectional primary care study among 795 older patients (older than 64 years), 10% reported being bothered by night sweats, 9% by day sweats, and 8% by hot flushes.<sup>7</sup> All three symptoms were associated with reduced quality of life.<sup>7</sup>

**Box 1:** Common causes of night sweats among older patients

The condition	Clinical features
Menopause	Women would also experience hot flushes
Pulmonary tuberculosis (TB)	Usually associated with fatigue and anorexia However, atypical presentation is not uncommon
Diabetes mellitus	This type of hyperhidrosis could be a manifestation of autonomic dysfunction
Medications*	Several medications may induce excessive sweating at night In general, the drugs listed below can be associated with hyperhidrosis
Lymphoma	Nights sweats are a symptom of certain types of Hodgkin's disease found in older patients
Parkinson's disease	The condition can be associated with localised or generalised hyperhidrosis
Mental disorder/stress	Anxiety and depression may cause night sweats

\* These include: Calcitonin, fentanyl, acyclovir, ceftriaxone, levothyroxine, levodopa and carbidopa, quetiapine, amlodipine, omeprazole, insulin, medroxyprogesterone, testosterone, prednisolone and tamoxifen.

## Pathophysiology

The pathophysiology underlying hyperhidrosis is complex and not well understood. There are two distinct types of sweating: thermal sweating, which tends to occur on the trunk and is controlled by the hypothalamus via the thermo-sensitive preoptic sweat centre, and emotional sweating, which is predominately on the palms and soles and is regulated by the cerebral cortex. Thermoregulation and

sweat production are mainly controlled by the cerebral cortex, anterior hypothalamus and the sympathetic nervous system. In addition, there are three types of sweat glands: eccrine, apocrine and apoeccrine. The eccrine type is the most numerous type, predominantly occurring on the soles of the feet, palms, axilla and face, and this type is innervated by the sympathetic nervous system, with acetylcholine as the principle neurotransmitter.<sup>8</sup> Apocrine glands are androgen-dependent,

less numerous and are found in the axilla and genital regions. The apoeccrine glands are found only in the adult axilla. The eccrine type is the one mainly involved in hyperhidrosis. Hyperhidrosis is usually stimulated by emotion and stress, so it does not occur during sleep or sedation. While normal sweating is controlled primarily by thermoregulation and, thus, occurs independently of level of consciousness. The primary defect in patients with hyperhidrosis may be hypothalamic hypersensitivity to emotional stimuli from the cerebral cortex.<sup>8</sup> Generalised hyperhidrosis may be the consequence of autonomic dysregulation, or it may develop secondary to a metabolic disorder, febrile illness, or malignancy. In its localised form, hyperhidrosis may result from a disruption followed by abnormal regeneration of sympathetic nerves or a localised abnormality in the number or distribution of the eccrine glands, or it may be associated with other (usually vascular) abnormalities. When caused by stress, hyperhidrosis may be generalised or limited to the palms, soles, and forehead.<sup>8</sup>

## Aetiology

Hyperhidrosis can be idiopathic or sometimes secondary to other diseases, metabolic disorders, febrile illnesses, or medication use. Use of medications may affect one or more components of human thermoregulation and induce hyperhidrosis. Hyperhidrosis beginning later in life should prompt a search for secondary causes such

**Box 2:** Secondary causes of hyperhidrosis**Generalised hyperhidrosis**

(an area &gt;100 square cm)

- Affecting almost any skin area
- Starts at older age
- Symmetry is not very distinctive
- Could be related to secondary causes, including medications and systemic disorders

**Localised hyperhidrosis**

(an area &lt;100 square cm)

- Affects axillae more than hands
- Starts at early age (<25) and improve later (>50)
- Usually bilaterally symmetrical
- Tends to cease during sleep
- Mainly related to autonomic dysfunction.
  1. Neurologic or neoplastic diseases
  2. Spontaneous periodic hypothermia and hyperhidrosis
  3. Metabolic disorders or processes: thyrotoxicosis, diabetes mellitus, hypoglycemia, gout, pheochromocytoma, menopause
  4. Febrile illnesses
  5. Medications: propranolol, physostigmine, pilocarpine, tricyclic antidepressants, and serotonin reuptake inhibitors.
  6. Chronic alcoholism
  7. Hodgkin disease or tuberculosis (causing nocturnal hyperhidrosis)
    - 1) Gustatory stimuli:
- Seen in Frey syndrome, encephalitis, syringomyelia, diabetic neuropathies, herpes zoster parotitis, and parotid abscess
  - 2) Eccrine nevus & Blue rubber-bleb nevus
  - 3) Eccrine angiomatous hamartoma\*
  - 4) Glomus tumor
  - 5) POEMS syndrome: Peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder, and skin changes.
  - 6) Burning feet syndrome
  - 7) Pachydermoperiostosis
  - 8) Pre-tibial myxoedema

\* A rare benign malformation characterised by both eccrine and vascular components, usually first evident at birth or during early infancy as a nodule/plaque, usually solitary, involving acral skin and although it is often asymptomatic, it may be associated with focal hyperhidrosis, hypertrichosis, and pain.

as systemic diseases, adverse effects of medication use, or metabolic disorders. Secondary causes may include endocrine diseases such as diabetes mellitus, hyperthyroidism, and hyperpituitarism.<sup>8</sup> In one series, one third of cases were neurologic in origin, including peripheral nerve injury, Parkinson disease, reflex sympathetic dystrophy, spinal injury, and Arnold-Chiari malformation.<sup>9</sup> Other secondary causes to be considered may include pheochromocytoma, respiratory disease, and psychiatric disease (Box 2). Asymmetric hyperhidrosis may suggest neurologic disease.<sup>9</sup> Primary hyperhidrosis usually starts during adolescence or even before and seems to be inherited as an autosomal dominant genetic trait. Primary hyperhidrosis must be distinguished from secondary hyperhidrosis, which can start at any point in life. Primary hyperhidrosis can be differentiated from secondary type by certain clinical criteria (Box 3). These criteria discriminate well between the two types (sensitivity: 0.99; specificity: 0.82; positive predictive value: 0.99; negative predictive value: 0.852) and may facilitate optimal clinical management.<sup>10</sup> Essential hyperhidrosis is a dermatologic and neurologic disorder characterised by excessive sweating of the eccrine sweat glands.<sup>11</sup> It is a disorder of the eccrine sweat glands and is associated with sympathetic overactivity.<sup>12</sup> Essential hyperhidrosis does not appear to be a generalised disorder involving vascular endothelium. Patients note excessive sweating in affected areas, which ultimately prompts

**Box 3:** Criteria for the clinical diagnosis of primary (idiopathic) hyperhidrosis

**Diagnostic criteria favouring primary hyperhidrosis:**

- Excessive sweating of six months or more in duration, with four or more of the following:
  1. Primarily involving eccrine-dense (axillae/palms/soles/craniofacial) sites
  2. Bilateral and relatively symmetric sweating
  3. Cessation of sweating during sleep (absent nocturnally)
  4. At least one episode per week
  5. Onset at 25 years of age or younger
  6. Family history of idiopathic hyperhidrosis (positive family history)
  7. Impairing daily activities.

them to seek medical attention. Palmoplantar hyperhidrosis, excessive sweating of the palms and soles, is observed in persons with chronic alcoholism and it could be inherited in an autosomal dominant manner.<sup>13,14</sup>

### Clinical assessment

Diagnosis of this potentially embarrassing and socially disabling condition is based on the patient's history and visible signs of sweating. Clinical examination may be normal, but will often reveal obvious areas of focal sweating or skin maceration. The primary objective of clinical examination is to reveal any evidence of underlying chronic illness suggestive of a secondary cause, for example lymphadenopathy. The main aims of clinical assessment should be:

1. Identifying anatomical sites with excessive sweating
2. Ensure the absence of

physical findings suggestive of secondary hyperhidrosis.

### Investigation

Laboratory tests are not required to make a diagnosis of primary hyperhidrosis, but they only serve to rule out and work-up potential secondary causes of excessive sweating. A number of specialised tests have been developed that quantify both sweat production and the impact on quality of life, such as starch iodine test. However, they are not required, nor are they particularly useful in the clinical setting. The work-up for generalised sweating or secondary hyperhidrosis can be complicated, and often includes a number of investigations.

#### Laboratory studies

Important laboratory studies in the hyperhidrosis workup may include the following:

- i. Thyroid function tests

may reveal underlying hyperthyroidism or thyrotoxicosis

- ii. Blood glucose levels may reveal diabetes mellitus or hypoglycaemia
- iii. Urinary catecholamines may reveal a possible pheochromocytoma
- iv. Uric acid levels may reveal gout
- v. Screening test for tuberculosis, such as purified protein derivative (PPD) test.

#### Imaging studies

Chest radiography may be used to rule out tuberculosis or a neoplastic cause of the hyperhidrosis.

### Management

Therapy for hyperhidrosis can be challenging for both the patient and the physician. Both topical and systemic medications have been used in the treatment of hyperhidrosis. Other treatment options for hyperhidrosis include iontophoresis and botulinum toxin injections. In addition to pharmacological therapy, other treatments include surgical sympathectomy, surgical excision of the affected areas, and subcutaneous liposuction. Each modality could be used effectively. In general, management of hyperhidrosis 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

**Box 4:** Therapy options for hyperhidrosis (starting with the least invasive)

Affected area	Topical therapy	Systemic therapy	Ionto-phoresis	Treatment options		
				Focal Botulinum injections	Surgery (ETS & others)	Subcutaneous liposuction & laser therapy
Axillae	√			√	√	√
Face/head	√	√		√	√	
Palms/hands	√		√		√	
Feet/soles	√	√	√			
Groin	√					
Generalised		√				

location of focal hyperhidrosis, the severity and patient tolerance (Box 4).

## Pharmacological therapy

### Topical medications

Topical agents for hyperhidrosis therapy include topical anticholinergics, boric acid, 2-5% tannic acid solutions, resorcinol, potassium permanganate, formaldehyde, glutaraldehyde, and methenamine.<sup>15</sup> All of these agents are limited by staining, contact sensitisation, irritancy, or limited effectiveness. Because of the limitations of other agents, Drysol, a 20% aluminum chloride hexahydrate in absolute anhydrous ethyl alcohol, is more commonly used as the first-line topical agent.<sup>16</sup> Drysol should be applied nightly on dry skin until a positive result is obtained, after which the intervals between applications may be lengthened. To minimise irritation, the remainder of the medication should be washed off when the patient awakes, and the area may

be neutralised with the topical application of baking soda.<sup>16</sup> Aluminum chloride (frequently used in antiperspirants) is thought to obstruct sweat pores and induce atrophy of secretory cells within the sweat glands. The only contraindication to this treatment is documented hypersensitivity, and aluminum chloride should not be used on irritated, broken, or recently shaven skin. In addition, axillary hyperhidrosis may be treated with aluminium chloride gel, although the gel may cause mild cutaneous irritation.<sup>17</sup>

### Systemic medications

Systemic agents used to treat hyperhidrosis include anticholinergic medications, such as propantheline bromide, glycopyrrolate, oxybutynin, and benzotropine. These agents are effective because the preglandular neurotransmitter for sweat secretion is acetylcholine; although the sympathetic nervous system innervates the eccrine sweat glands.<sup>18,19</sup> However, the use of anticholinergics is limited because their adverse effect

profile may include mydriasis, blurring of vision, dry mouth and eyes, difficulty with micturition, and constipation. However, other systemic medications, such as sedatives and tranquilisers, indomethacin, and calcium channel blockers, may be beneficial in the treatment of palmo-plantar hyperhidrosis.

### Other therapies

#### Iontophoresis

Iontophoresis consists of passing a direct current across the skin.<sup>20</sup> The exact mechanism of action remains under debate.<sup>21,22</sup> In palmo-plantar hyperhidrosis, the daily treatment of each palm or sole for 30 minutes at 15-20mA with tap water iontophoresis is effective.<sup>23</sup> Intact skin can endure 0.2-mA/cm<sup>2</sup> galvanic current without negative consequences, and as much as 20–25mA per palm may be tolerated.<sup>23</sup> Numerous agents have been used in iontophoresis to induce hypohidrosis, including tap water and anticholinergics; however, treatment with anticholinergic iontophoresis is more effective than tap water iontophoresis.<sup>24</sup>

### Botulinum toxin

Botulinum toxin injections are effective because of their anticholinergic effects at the neuromuscular junction and in the postganglionic sympathetic cholinergic nerves in the sweat glands.<sup>25,26,27</sup> Adverse effects of intradermal injections of botulinum A toxin may result from diffusion into underlying muscles.<sup>28,29</sup> Treatment of axillary hyperhidrosis with botulinum toxin type A reconstituted in lidocaine was associated with less pain (from the injection) when compared with the one reconstituted in normal saline.<sup>30</sup> The results were the same in the two groups, thus, lidocaine-reconstituted botulinum toxin A may be preferable for treating axillary hyperhidrosis. In cases with palmar hyperhidrosis, multiple (50) subepidermal injections result in anhidrosis lasting 4–12 months, and each injection produces an area of anhidrosis approximately 1.2cm in diameter.<sup>31</sup> The only adverse effect is mild transient thumb weakness that resolves within three weeks.

## Surgical treatment

### Sympathectomy

Sympathectomy has been used as a permanent effective treatment for almost 90 years. It is usually reserved for the final treatment option.<sup>32</sup> Sympathectomy involves the surgical destruction of the ganglia responsible for hyperhidrosis, T2 and T3 thoracic ganglia in palmar hyperhidrosis, T4 thoracic ganglia in axillary hyperhidrosis, and T1 thoracic ganglia in facial

hyperhidrosis.<sup>33,34,35</sup> Two surgical approaches are available: an open approach and a newer endoscopic approach, such as endoscopic thoracic sympathectomy (ETS). The endoscopic approach has become favored because of its improvements in terms of complications, surgical scars, and surgical times. In palmar hyperhidrosis, a survey showed thoracoscopic sympathectomy to be minimally invasive and to improve the patient's quality of life, even if compensatory hyperhidrosis occurs.<sup>36</sup> Numerous complications are associated with the endoscopic treatment option; including compensatory sweating (induction of sweating in previously unaffected areas of the body), gustatory sweating, pneumothorax, intercostal neuralgia, Horner syndrome, recurrence of hyperhidrosis, and the sequelae of using general anesthetic. Topical glycopyrrolate application may be effective and safe for the treatment of excessive facial sweating in primary craniofacial and secondary gustatory hyperhidrosis following sympathectomy.<sup>37</sup> Lumbar sympathectomy is a relatively new procedure aimed at those patients for whom ETS has not relieved excessive plantar sweating. The success rate is about 90% and the operation should be carried out only if patients first have tried other conservative measures.<sup>38</sup>

### Other surgical techniques

Surgical excision of the affected area identified using iodine starch testing, removes the appropriate sweat glands, thereby eliminating sweating. This technique is particularly useful in axillary hyperhidrosis.

Subcutaneous liposuction is another means of removing the eccrine sweat glands responsible for axillary hyperhidrosis. Compared with classic surgical excision, this modality results in less disruption to the overlying skin, resulting in smaller surgical scars and a diminished area of hair loss.<sup>39</sup>

Laser treatment of axillary hyperhidrosis using the 1064-nm Nd-YAG laser was found to be effective and safe as well.<sup>40</sup>

## Conclusion

Hyperhidrosis is a condition in which excess sweating affects various parts or the whole body. The condition usually is idiopathic and can be secondary to various disorders or medications use. Hyperhidrosis beginning later in life should prompt a search for secondary causes, including systemic diseases and adverse effects of certain medications. Treatment options for hyperhidrosis include topical agents, iontophoresis and botulinum toxin injections. In addition to pharmacologic therapy, endoscopic sympathectomy and surgical excision of the affected areas have been used. However, the condition is difficult to treat effectively and a logical approach must be taken to individualise therapy based on the degree of functional impairment.

**Conflict of interest: none declared**

**References available on online version at [www.gmjournals.co.uk](http://www.gmjournals.co.uk)**