PALLIATIVE PEARLS
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Palliative Management of Sweating at End-of-Life
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PATIENT CASE

SL is a 66 y/o male admitted to hospice today with a primary diagnosis of Non-Hodgkin Lymphoma. Comorbid conditions include celiac disease and depression. He has no drug allergies and lives at home with his wife, daughter and two teenage grandsons.

Current medications:

- Methadone 10mg; 1 tablet PO every 8 hours for pain
- Dexamethasone 4mg; 1 tablet PO daily for pain, inflammation and appetite
- Morphine 20mg/mL; 0.75mL (15mg) PO/SL every 3 hours as needed for pain/shortness of breath
- Promethazine (Phenergan®) 25mg; 1 tablet PO every 6 hours as needed for nausea/vomiting
- Duloxetine (Cymbalta®) 30mg; 1 capsule PO BID for mood and nerve pain

In the 6 months prior to hospice admission, SL has lost 25 lbs (baseline 210 lbs.) and has experienced drenching night sweats as well as excessive sweating in the daytime. The excessive sweating is distressful for SL who is exhausted and frustrated with the multiple changes of clothes daily and the additional laundry it is producing and is embarrassed engaging with others at his grandsons' sporting events when he is well enough to attend.

HYPERHIDROSIS AT END-OF-LIFE

Sweating, also known as diaphoresis, is a key part of the human thermoregulatory system. Specific thermoreceptors are located in the skin, spinal cord and brainstem. Sweating allows the body to maintain normal physiologic temperature (around 37˚C). When the body's internal temperature goes above the acceptable range, sweating will occur, allowing the body to cool and return to normal temperature.

In the palliative care setting, most patients with abnormal sweating report hyperhidrosis (excessive sweating) or nocturnal diaphoresis (night sweats). Hyperhidrosis can be confined to the forehead, feet, palms, or armpits, or it can be all over the body. Sweating problems may occur throughout the day, but usually worsen at night.

Hyperhidrosis is difficult to treat effectively. It is not associated with mortality however may adversely affect the patient's quality of life by causing great emotional distress, social embarrassment, and work-related disability (due to palmoplantar hyperhidrosis) and may be linked with depressive symptoms.[1]

ETIOLOGY OF GENERALIZED, SECONDARY HYPERHIDROSIS

Hyperhidrosis may be idiopathic or secondary to other diseases, metabolic disorders, febrile illnesses, or medication use. It exists in 3 forms: emotionally-induced (in which it affects the palms, soles, and axillae), localized and generalized.[1] For the sake of applicability to the larger palliative care population, we will focus on the etiology of generalized, secondary hyperhidrosis.

Endocrine disturbances: Estrogen deficiency, androgen deficiency, hyperthyroidism, induced by cancer-related treatments, diabetes insipidus (rare), diabetes mellitus, gout[1,2]

Neurological disorders: Autonomic neuropathy, cerebral and brainstem lesions (tumors, infarctions, or hemorrhages), spinal injuries or lesions, parkinsonism[1,2]

Malignancies (typically advanced disease): Hodgkin lymphoma, non-Hodgkin lymphoma, solid tumors, liver metastasis, carcinoid syndrome[1,2]

Tuberculosis and febrile illnesses[1,2]

Intoxication/withdrawal from alcohol or other substances, including opioids[1,2]

Medications: [1,2,3,4]

Antidepressants

- Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine (Prozac®))
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine (Cymbalta®))
- Bupropion (Wellbutrin®)
- Tricyclics (e.g., nortriptyline (Pamelor®), amitriptyline (Elavil®))

Hormone therapies such as selective estrogen receptor modulators

- e.g., tamoxifen (Nolvadex®), raloxifene (Evista®)

Aromatase inhibitors

- e.g., exemestane (Aromasin®), anastrozole (Arimidex®), letrozole (Femara®)

Others

- Flutamide (Eulexin®)
- Opioids (e.g., morphine, hydromorphone, fentanyl)
- Hypoglycemics (e.g., insulin, glyburide, rosiglitazone (Avandia®))
- Propranolol (Inderal®)
- Cholinergic agonists (e.g., physostigmine, pilocarpine, bethanechol)

ASSESSMENT OF GENERALIZED, SECONDARY HYPERHIDROSIS

Initial assessment should include a history, medication review, symptom assessment and physical examination. Identify possible etiologies, any aggravating factors that may increase sweating, and the severity.[2]

Questions to aid in the assessment include:

- How significant is the sweating problem? (frequent toweling, change of clothing, changing pillow case)
- Is the sweating generalized or localized?
- Is the sweating associated with a fever?
- How long has the sweating been a problem?
- Is the sweating the same during the day and night?
- Any new medications or changes to existing medications?

The Hyperhidrosis Disease Severity Scale (HDSS)[5] is a validated single-question survey with four grades of tolerability of sweating and impact on quality of life. A score of 2 is considered mild, whereas a score of 3 or 4 is considered severe.[4]

- Score 1: My (underarm) sweating is never noticeable and never interferes with my daily activities
- Score 2: My (underarm) sweating is tolerable but sometimes interferes with my daily activities
- Score 3: My (underarm) sweating is barely tolerable and frequently interferes with my daily activities
- Score 4: My (underarm) sweating is intolerable and always interferes with my daily activities

MANAGEMENT OF GENERALIZED, SECONDARY HYPERHIDROSIS

NON-PHARMACOLOGICAL

- Manage underlying cause(s), if possible
- Removal of offending medications(s), if possible
- Minimize clothing or wear light-weight, loose clothing made of cotton
- Utilize cotton linens/bedsheets
- Frequent showering or wiping patient down with a cool cloth
- Keep windows open and/or use a fan or air conditioner
- Increase fluid intake when appropriate
- Avoid alcohol and hot and/or spicy food

PHARMACOLOGICAL

Infection-induced:
Based on goals of care, consider a formal infectious disease workup and/or an empiric course of antibiotics[2]

Tumor-related fever:
Consider empiric treatment with acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID), followed by a glucocorticoid for refractory symptoms[2]

Related to vasomotor symptoms (e.g., hot flashes):
Consider treatment approaches including megestrol (Megace®), gabapentin (Neurontin®), or antidepressants[2,6]

General Topical Agents:
Most agents occlude the pores of the sweat glands to reduce perspiration. Anticholinergic topical agents may additionally inhibit acetylcholine production in the sweat glands to some extent, but lesser than systemic agents. Side effects include staining, contact sensitization, application site irritation and limited effectiveness.[1]

- Aluminum chloride hexahydrate (Xerac AC®, Drysol®) for affected areas **(first line agent)**
- Aluminum zirconium trichlorohydrate (over-the-counter "clinical strength" antiperspirants) for axillae
- Glycopyrronium tosylate (Qbrexza®) topical cloth for axillae
- Various other active ingredients have been utilized historically in compounded formulations including glycopyrrolate, glutaraldehyde, formaldehyde, boric acid, tannic acid solutions, resorcinol, and potassium permanganate[1]

General Systemic (Oral) Anticholinergic Agents (second line to topical):

Anticholinergics inhibit acetylcholine in sweat glands. Their use for this indication is based on expert consensus and off-label due to scarcity of clinical trial data.[4,5] Side effects include mydriasis, blurry vision, dry mouth and eyes, difficulty urinating, and constipation.

- Glycopyrrolate (Robinul®)
- Oxybutynin (Ditropan®)
- Benztropine (Cogentin®)
- Propantheline bromide (Pro-Banthine®)

Other Agents (Consider as adjuncts or for refractory cases):

- Gabapentin (Neurontin®)[7]
- Thalidomide[8,9]
- Olanzapine (Zyprexa®)[10]

Other Measures:

- Botulinum toxin injections (OnabotulinumtoxinA (Botox®)) for axillae, palms, soles or face – Produces anticholinergic effects in the sweat glands. This therapy is the most studied hyperhidrosis treatment however may not be feasible to provide in the hospice population.[1,3,4]

- Iontophoresis for palmar and plantar hyperhidrosis - the passing of an ionized substance, usually water, through the skin by the application of a direct electrical current. Its mechanism of action is unknown and remains under debate.[1,4]

- Microwave technology for axillary hyperhidrosis - the application of microwave energy destroys eccrine sweat glands by creating local heat, resulting in cellular thermolysis[1,4]

- Fractionated microneedle radiofrequency – microneedles are placed 2 to 3 mm under the skin and radiofrequency energy is applied[1,4]

- Local surgery for axillary hyperhidrosis – radical surgical, limited skin excision, liposuction, curettage and liposuctioncurettage[1,4]

ASSESSMENT

SL has lost 12% of his body weight over the past 6 months and has experienced daily and nightly generalized hyperhidrosis symptoms for the past 3 months with a score of 4 on the HDSS scale. The sweating is associated with temperatures ranging from 99-99.8°F although he is currently afebrile. SL notes that his bed linens need to be changed daily and he goes through 3-4 changes of clothes each day.

Malignancy is a common etiology of secondary hyperhidrosis. Up to 40% of patients with non-Hodgkin lymphoma have systemic complaints termed “B symptoms”. Symptoms include fever (temperature > 38°C (>100.4°F), unexplained loss of >10% of body weight over the past 6 months and the presence of drenching night sweats.[11] SL is prescribed opioids (methadone, morphine) and duloxetine that additionally contribute to the occurrence of hyperhidrosis. It is noted that pain is controlled, and mood is managed on current therapies. He’s had no recent changes of medications and denies alcohol use or eating spicy food.

RECOMMENDATIONS

1. Continue methadone and morphine despite potential contribution to hyperhidrosis. Pain is effectively managed, and all opioids are culprits, so opioid rotation would be ineffective at managing this symptom.

2. Continue duloxetine despite potential contribution to hyperhidrosis. Depression is effectively managed, and all antidepressants possess the same potential. A trial of dose reduction to 30mg/day may be considered and assessed for lessening of hyperhidrosis symptoms while maintaining antidepressant and nerve pain effects.

3. Initiate the following non-pharmacological measures, if not already: Minimize clothing or wear light-weight, loose clothing made of cotton, utilize cotton linens/bedsheets, frequent showering or wiping patient down with a cool cloth, keep windows open and/or use a fan or air conditioner, increase fluid intake when appropriate and continue to avoid alcohol and hot and/or spicy food

4. Initiate Aluminum chloride hexahydrate (ACH) (Xerac AC®, Drysol®)[1,3,4,5]
    - Apply solution sparingly to affected area daily at bedtime for up to 1 week. Then decrease application frequency as necessary. With repeated application, the dosing interval can be reduced to 1-2 times a week.
    - ACH is most useful when rapid control of focal sweating is desired, but effects disappear within 48 hours of stopping treatment. Though patients stop sweating in the area where ACH is applied, sweating may begin in other areas as the body compensates.
    - ACH therapy may cause skin irritation in the axillary region. To minimize irritation, wash off any remaining medication in the morning and apply baking soda to neutralize the area.

FOR ADDITIONAL INFORMATION ON THIS TOPIC, PLEASE REVIEW THESE REFERENCES:

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