PALLIATIVE PEARLS
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Managing Hiccups at End of Life
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Introduction[1,2]

Hiccups are involuntary, intermittent contractions of the diaphragm and intercostal muscles. The medical term for hiccups is singultus, which derives from the Latin "*singult*" meaning 'to catch one's breath while sobbing'. These contractions are often caused by irritation of the phrenic or vagus nerves, disturbances to the central nervous system (e.g., encephalitis, Parkinson's disease, stroke), toxic or metabolic changes, medications, or psychological factors. While typically benign and self-limiting, hiccups can become a significant source of distress in hospice settings, impacting the quality of life of patients and their caregivers.

Case: BT is 75 year old male patient with advanced metastatic pancreatic cancer who was admitted to hospice three weeks prior. He is noted to have persistent hiccups for the past 72 hours, which is causing pain and fatigue. Upon assessment by the hospice care team, the patient reported that the hiccups significantly disrupted his sleep and ability to communicate with family members.

Understanding Hiccups[1,2]

Hiccups occur due to a disruption in the reflex arc between the phrenic and vagus nerves and the brainstem, which serves as the central reflex center. They are more prevalent in males, particularly tall men, and can be categorized based on duration:

- **Hiccup bout**: Lasts from a few seconds to 48 hours
- **Persistent hiccups**: Last more than 48 hours but less than a month
- **Intractable hiccups**: Last more than one to two months

In the context of hospice and palliative care, hiccups can arise from various conditions, including gastrointestinal, intrathoracic, or central nervous system disorders; infections; metabolic changes; and psychogenic causes (Table 1). Certain medications, notably chemotherapy, sulfonamides, barbiturates, benzodiazepines, and corticosteroids, can also induce hiccups (Table 2). Interestingly, benzodiazepines such as lorazepam have a dose-dependent, inverse relationship with hiccups: They can cause hiccups at lower doses, but can also be useful for treating hiccups at higher doses.

Table 1: Selected Etiologies of Hiccups

Gastrointestinal disorders	GERD, bowel obstruction, gastric distention, esophageal cancer, gallbladder disease, hepatitis, GI cancers, peptic ulcer disease
Central nervous system disorders	Encephalitis, meningitis, multiple sclerosis, neoplasms, Parkinson's disease, stroke
Infections	*H. pylori*, herpes simplex, herpes zoster, influenza
Intrathoracic disorders	Asthma, bronchitis, diaphragmatic tumor, hernia, neoplasms, pulmonary embolus
Metabolic changes	Hypocapnia, hypocalcemia, hypokalemia, hyponatremia
Psychogenic disorders	Excitation, hyperventilation, somatization, stress

Source: Reference 2

Table 2: Selected Medication Causes of Hiccups

Aripiprazole (Abilify®)
Azithromycin (Z-pak®)
Benzodiazepines (at low doses) (e.g., lorazepam (Ativan®))
Dexamethasone (Decadron®)
Donepezil (Aricept®)
Levodopa (Sinemet®)
Morphine
Tramadol (Ultram®)

Source: Reference 2

Clinical Implications in Hospice

Untreated hiccups can interfere with critical aspects of daily life, such as eating, sleeping, and breathing, potentially leading to exhaustion. This is particularly concerning for terminally ill patients, for whom the focus is on comfort and quality of life.

Effective management of hiccups begins with a thorough assessment of modifiable causes:

1. Review the patient's existing medical diagnoses and habits to identify potential causes. Distention of the stomach by large meals or carbonated beverages, and irritation from spicy foods or alcohol can contribute to hiccups, especially during periods of excitement or emotional stress.

2. Evaluate prescribed medications that could contribute to hiccups (Table 2). Of note, patients receiving dexamethasone for chemotherapy-induced nausea who developed intractable hiccups were shown to benefit from switching to methylprednisolone.[3]

3. Assess for new or untreated gastrointestinal diseases like GERD or dyspepsia or local irritation caused by gastric distension or disease progression. Research suggests GERD may be responsible for as many as 80% of persistent hiccup cases, so a trial of famotidine or a proton pump inhibitor (e.g. omeprazole) may be successful.[2]

Case: A review of BT's medications reveals a regimen of the following:

- **Dexamethasone:** 4 mg tablet, 1 tablet twice daily, prescribed to reduce inflammation and manage cancer-related symptoms such as pain and nausea.
- **Morphine:** Morphine ER 30 mg, 1 tablet twice daily (scheduled) and morphine immediate release 15 mg tablet, ½-1 tab every 4 hours as needed for pain management.
- **Omeprazole:** 20 mg, 1 capsule daily to manage gastric acid and prevent reflux.
- **Lorazepam:** 0.5 mg, 1 tablet every 6 hours as needed for anxiety and to assist with sleep.

Of note, the patient and caregiver report the patient has not been taking the lorazepam.

Non-Pharmacologic Management Strategies[2]

Symptom relief should be the focus of hiccup management in hospice and palliative care, since the exact cause of hiccups in these patients can be elusive. Both non-pharmacologic and pharmacologic strategies can be used. Physical maneuvers, which affect a portion of the hiccup reflux arc, can be effective in treating a hiccup bout that has persisted for less than 48 hours:

- Since the frequency of hiccups decreases as carbon dioxide (pCO_2) rises, maneuvers such as breath holding and/or breathing into a paper bag may be beneficial.
- Pulling on the tongue, pressing on eyeballs, drinking cold drinks, or taking a teaspoon of sugar may affect the reflux arc by interrupting respiratory function, stimulating the nasopharynx or uvula, increasing vagal stimulation, or relieving diaphragm irritation.

Pharmacologic Treatments[2,4,5]

Pharmacologic treatment should be considered when hiccups are persistent or intractable, especially if non-pharmacologic interventions have failed to provide relief. Several medications have been found effective in managing hiccups (Table 3):

- **Chlorpromazine**: Chlorpromazine is the only FDA-approved medication for hiccups. It is an antipsychotic that acts on dopamine, serotonin, histamine, alpha-adrenergic, and muscarinic receptors. Its efficacy in treating hiccups is well-documented. However, its action on multiple receptor types contributes to its significant adverse effect profile. Chlorpromazine can be administered orally or via intramuscular injection, with the latter being useful in cases where rapid relief is needed.

- **Baclofen**: This muscle relaxant is particularly effective for hiccups associated with neurological conditions such as stroke. Baclofen acts as a GABA receptor agonist, reducing neuronal excitability that may contribute to hiccup generation.

- **Metoclopramide**: Metoclopramide is known to act centrally by blocking dopamine and peripherally by increasing gastric motility. It has shown benefit for relieving hiccups from cancer, stroke and brain tumors, as well as from gastric sources such as gastric distension or reflux.
- **Gabapentin:** Gabapentin modulates neuronal activity, which can help interrupt the reflex arc responsible for hiccups. Gabapentin can be considered when hiccups are resistant to other treatments or when a neuropathic component is suspected.
- **Haloperidol**: Acting on dopamine receptors, haloperidol can be used as an alternative to chlorpromazine if chlorpromazine adverse effects are a concern.
- **Midazolam**: A short-acting benzodiazepine, midazolam can be effective for hiccups for patients in the last few days of life. It can be given by subcutaneous infusion to relieve intractable hiccups. Doses of 10-60 mg per day, given subcutaneously, can be used.

Combinations of two or more of the above therapies have also been used for management of intractable hiccups.

Table 3: Selected Oral Medications for Treatment of Hiccups

Medication	**Usual Dosing**
Chlorpromazine	10-50 mg PO three times daily
Baclofen	5-15 mg PO three times daily
Metoclopramide	10 mg PO three times daily
Gabapentin	100-400 mg PO three times daily
Haloperidol	1-4 mg PO daily (can also be SC or IM)

Case: Treatment Plan

The interdisciplinary hospice team, including physicians, nurses, and a pharmacist, developed a treatment plan focusing on symptomatic relief of hiccups. The plan included educating BT on breathing techniques (to encourage slow, controlled breathing) and dietary interventions (to encourage small meals, avoiding spicy foods, alcohol, and carbonated beverages). BT's caregiver was also advised to adjust the patient's position in the bed to semi-upright to reduce diaphragmatic irritation.

BT's dexamethasone was decreased to 4 mg daily, which he tolerated well.

Baclofen 5 mg twice daily was initiated. BT was noted to tolerate baclofen well, with an initial decrease in hiccup frequency after 48 hours, at which time baclofen dosing was titrated up to 10 mg twice daily.

After four days of baclofen therapy, hiccup frequency was significantly decreased, although hiccups persisted and continued to be a cause of discomfort. The hospice team added gabapentin 100 mg at bedtime.

Within a week of initiating treatment, the patient's hiccups resolved significantly, allowing for improved sleep and interaction with family.

Conclusion

The successful management of intractable hiccups in hospice care can significantly enhance the quality of life for patients facing terminal illnesses. Interdisciplinary collaboration and individualized care plans are critical in addressing challenging symptoms such as persistent hiccups in this vulnerable population.

References

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