Somatostatin analogues

- Octreotide
  - Lack the adverse effects of antimuscarinic agents
  - Somatostatin decreases the release of gastrin, insulin, glucagon, gastric acid and pancreatic enzymes
  - Also inhibits neurotransmission in peripheral nerves of the gastrointestinal tract leading to decreased peristalsis and a decrease in splanchnic blood flow
  - Octreotide is administered as a SQ injection or as continuous IV or SQ infusion, beginning at 10-20 mcg/hr

Other drugs

- Prokinetic drugs (e.g. metoclopramide) may be beneficial if there is a partial obstruction
  - If total obstruction some advocate the discontinuation of prokinetic agents as they may exacerbate crampy pain
  - Metoclopramide may inhibit the reverse peristalsis from obstruction and decrease nausea

- Corticosteroids to decrease the inflammatory response and resultant edema, as well as relieve nausea, through both central and peripheral antiemetic effects
Invasive management

- The optimal procedure is that which offers the quickest, safest, and most efficacious ability to alleviate the obstruction and improve symptoms
  - Bowel resection, Bypass, Gastrostomy...

- Surgical risks must be carefully considered prior to an operation, as morbidity (42%) and mortality (5-32%) are common, and the re-obstruction rate is high (10-50%)
  - Poor prognostic indicators for surgical intervention include ascites, carcinomatosis, palpable intra-abdominal masses, multiple bowel obstructions, prior obstructions and very advanced disease with poor performance status.

- Cytoreductive procedures (resection of intraperitoneal tumor) frequently carry a high morbidity and usually are only considered with very low grade tumors

ENDOSCOPIC STENTING

- Stenting may include procedures to initially canalize the lumen (e.g. laser or balloon dilatation).
- Endoluminal wall stents have a high success rate for relief of symptoms (64-100%) in complete and incomplete colorectal obstructions, and in over 70% of upper intestinal malignant obstructions including gastric outlet, duodenal and jejunal obstructions.

- PEG tubes are generally well tolerated “venting” procedures that can alleviate symptoms of intractable vomiting and nausea for upper GI obstructions.
Our patient - JD

- Scopolamine patch
- Ondansetron
- Octreotide SQ gtt
- Lorazepam
- Promethazine
- Morphine PCA
- Steroid wean
- Stool softener

Symptoms to discuss

- Bone pain
- Bowel obstruction
- Nausea and vomiting
- Delirium
- Anorexia-Cachexia
- Death
Pathophysiology of Nausea

CTZ
• All transmitters

Other CNS
• Vestibular
  • ACH
  • Histamine
• ICP

Cortical Anticipation

Vagal
• Acetylcholine

GI Tract
• Serotonin - vagal
• ACH - peristalsis
• ? Dopamine

Neurotransmitters
• Serotonin
• Dopamine
• Acetylcholine
• Histamine

Vomiting Center (Brainstem)

Nausea & Vomiting

- Ondansetron/granisetron
  - Serotonin antagonist
  - Mostly for chemotherapy induced N/V @ CTZ

- Metoclopramide
  - Prokinetic (cholinergic) promotes gastric and small bowel activity
  - CTZ

- Dexamethasone
  - Other CNS i.e., ICP

- Benzodiazepines
  - Cortical

- Diphenhydramine
  - Promethazine
  - Antihistamines
  - Vomiting center

- Haloperidol
  - Antidopaminergic
  - Neuroleptic
  - CTZ

- Aprepitant – Emend
  - NK-1 @ CTZ

Treatment Algorithms

<table>
<thead>
<tr>
<th>Cortical</th>
<th>Focal neurologic signs or mental status changes</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS tumor/meningeal irritation</td>
<td>Consider palliative radiation</td>
<td></td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td>Projectile vomiting and headache</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Anxiety or psychogenic</td>
<td>Anticipatory nausea, conditioned responses</td>
<td>Counseling</td>
</tr>
<tr>
<td>Uncontrolled pain</td>
<td>Pain and nausea</td>
<td>Relaxation techniques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase pain medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use adjuvants</td>
</tr>
</tbody>
</table>
### Vestibular

<table>
<thead>
<tr>
<th>Vestibular disease</th>
<th>Antihistamines (meclizine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo or vomiting after</td>
<td></td>
</tr>
<tr>
<td>head motion</td>
<td></td>
</tr>
</tbody>
</table>

| Middle-ear infections      | Antibiotic therapy and    |
|                            | other supportive care     |
| Ear pain or bulging        |                           |
| tympanic membrane          |                           |

<table>
<thead>
<tr>
<th>Motion sickness</th>
<th>Anticholinergics (scopolamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel-related nausea</td>
<td></td>
</tr>
</tbody>
</table>

### Chemoreceptor trigger zone

<table>
<thead>
<tr>
<th>Medications</th>
<th>Nausea worse after medication dosage or exacerbated after increasing dose</th>
<th>Decrease dose or discontinue medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic (renal or liver failure)</td>
<td>Increased blood urea nitrogen (BUN), creatinine, bilirubin, etc.</td>
<td>Dopamine antagonist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypercalcemia</th>
<th>Hydration Corticosteroid Bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence, delirium, high calcium</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Algorithms

<table>
<thead>
<tr>
<th>Gastrointestinal tract</th>
<th>Irritation from medications</th>
<th>Use of NSAIDs, iron, alcohol, antibiotics</th>
<th>Add histamine (H2) blocker, proton pump inhibitor, or misoprostol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor infiltration or infection</td>
<td>Evidence of abdominal tumor, candida esophagitis, colitis</td>
<td>Antihistamines, Treat infection, Anticholinergics</td>
<td></td>
</tr>
<tr>
<td>Constipation or impaction</td>
<td>Abdominal distension, no bowel movement for many days</td>
<td>Laxatives, Manual disimpaction, Enema</td>
<td></td>
</tr>
<tr>
<td>Obstruction by tumor or poor motility</td>
<td>Constipation unrelieved by treatment</td>
<td>Prokinetic agents</td>
<td></td>
</tr>
<tr>
<td>Malignant bowel obstruction</td>
<td>Severe pain, abdominal distension, visible peristalsis</td>
<td>Analgesics (opioids), Anticholinergics, Dopamine antagonists, Corticosteroids, Consider octreotide</td>
<td></td>
</tr>
</tbody>
</table>

Our patient JW

- Antiemetic regimen included:
  - Lorazepam 1 mg IV q 6 hrs
  - Granisetron 1 mg IV q 12 hrs
  - Scopolamine 1.5 mg/72 hrs
  - Diphendramine 50 mg IV q 6 hrs
  - Promethazine 12.5 mg IV q 6 hrs
  - Haloperidol 1 mg IV q 8 hrs
  - Dexamethasone burst
  - Change pain medication to hydromorphone PCA with 1 mg/hr and 0.5 mg q 15 minutes and 0.5 mg q 30 minute nurse
  - Chemotherpy was the only thing that seemed to work predictably and well
Symptoms to discuss

- Bone pain
- Bowel obstruction
- Nausea and vomiting
- Delirium
- Anorexia-Cachexia
- Death

What is delirium?

• DSM IV Criteria:
  – Disturbance of consciousness with reduced ability to focus, sustain or shift attention.
  – Change in cognition or development of a perceptual disturbance.
  – Development of this disturbance over a short time period and a tendency to wax and wane.
  – Evidence that the change is directly related to general medical condition (history, labs, physical exam).

Prospective evaluation at EoL

• High occurrence rates of delirium
  – 42% in patients during admission
  – 45% first onset after admission
  – 88% of patients who ultimately died during admission.

• Reversibility rate of 49%
  – Opioids
  – Nonopioid psychoactive medications
  – ? Hydration status
Treatments

- Management includes treatment of underlying causes if possible.
  - Hydration
  - Opioids
  - Removal of causative medications

- Management of symptoms
  - Pharmacologic (neuroleptics, benzo, and other sedatives)
  - Nonpharmacologic

- Neuroleptics are the first-line pharmacological agents for symptomatic management

- Haloperidol is the best studied neuroleptic, and the agent of choice for most patients.
  - Favorable side effect profile
  - Administered safely through oral and parenteral routes.
  - Starting doses are 0.5 – 1 mg PO or IV (IM route is also available)
  - Titration can occur every 1 hour until a total daily requirement is established → administer in 2-3 divided doses per day
  - Intravenous haloperidol may cause less extrapyramidal symptoms than oral haloperidol
Treatments

• Benzodiazepines should be avoided
  – Can cause “paradoxical” worsening of confusional states
  – Unless the source of delirium is drug withdrawal or when severe agitation is not controlled by the neuroleptic

• Non-pharmacological treatments should always be used in delirium management: reduce or increase the sensory stimulation in the environment as needed

Treatments

• Other neuroleptics
  – Other ‘older’ neuroleptics are probably comparable to haloperidol in controlling delirium but may have a higher incidence of side effects
  – Chlorpromazine (Thorazine) has been advocated for dying patients in whom sedation is desired, especially for terminal delirium

• Newer atypical neuroleptics
  – Olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal) may be helpful in the management of confusional states.
  – Little evidence supporting usage of atypical neuroleptics
  – Associated with fewer drug-induced movement disorders than haloperidol
  – These agents are not available in either IM or IV
    • Olanzapine is available as an orally disintegrating tablet.
  – Quetiapine is the most sedating of the newer agents and has potential applicability in treating agitated delirium, especially at the end of life
Symptoms to discuss

- Bone pain
- Bowel obstruction
- Nausea and vomiting
- Delirium
- Anorexia-Cachexia
- Death

Anorexia-Cachexia

- 4th most common symptom of most concern – not eating
- “She stopped wanting to eat or drink; it was hard to feed her.”
- “My baby lost, within those 15 days, he just lost a lot of weight.”

Case example

- At the time of his death
  - Height: 198.6 cm – 6 feet 6 inches
  - Weight: 43.8 kg – 96 pounds
  - > 20 kg weight loss from peak weight
Symptom bundle

- Anorexia
- Nausea – improves with optimal management
- Asthenia (no energy) - improves with rehabilitation
- Oral complications – additional treatment
- Psychosocial issues
- Pain - immobility, stiffness, decubitus ulcers, edema, ascites
- Dyspnea – respiratory muscle weakness

Treatment goals

- Effective cancer-directed therapy
- Inhibit fat and muscle wasting
- Improve quality of life
  - Increase appetite
  - Increase nutritional intake
  - Increase functional status
Hypercaloric feeding

• Does not increase lean body mass
• No survival benefit
• No decrease in chemotherapy induced toxicity
• Useful in patients with tumor affecting GI tract

Glucocorticoids

• Improves nausea, asthenia, pain
• Appetite stimulant; best in advanced disease
• Inhibition of cytokine production/release
• Best if given once daily in AM
  — Less HPA suppression, insomnia
• Prolonged treatment – weakness, delirium, osteoporosis, sleep abnormalities, immunosuppression
Megestrol acetate

- Progestational drug
- Improves appetite, caloric intake, nutritional status; impact on QoL not yet demonstrated.
- Best for longer term use
- Stimulation of NPY in hypothalamus, inhibition of cytokine production
- Side effects = Thromboembolism, uterine bleeding, edema, hyperglycemia, hypertension, adrenal suppression and insufficiency

Cyproheptadine

- Antiserotonergic
  - Serotonin (5HT) is satiating factor; role in anorexia
- Appetite stimulant. (Coulouris, 2008)
  - Response rate 76% (Mean gain 2.6 kg)
  - Leukemia pts 91%, others 67%.
Summary

- Debilitating and life-threatening
- Anorexia, fat and muscle tissue wasting, and psychological distress
- Poor outcomes and poor quality of life
- Complex cancer-host interaction
  - Cytokine production
  - Lipid-mobilizing factor
  - Proteolysis-inducing factor
  - Abnormal metabolism

Step-wise process

- Step 1 – Reversible causes
  - Treat potentially reversible causes – anorexia, anxiety, constipation, depression, dysphagia, nausea, vomiting, oral complications, pain.

- Step 2 – Early satiety or poor appetite
  - Metoclopramide
  - Ciproheptadine
  - Cannabinoids
Step-wise process

- **Step 3**
  - Trial of megestrol acetate or dexamethasone

- **Step 4**
  - Trial of other promising agents
    - Melatonin, thalidomide, EPA

Assure interdisciplinary care

- **Nutrition Consult**
  - Optimize nutritional support

- **Rehabilitation Consult**
  - Minimize muscle wasting through reconditioning.

- **Psychology Consult**
  - Optimize coping skills, parenting skills, minimize distress
Death

• Your experiences...

Normal End of Life Issues

• Breathing pattern changes
  – Apnea, agonal, rattle
• Sleeping more
• Appetite less
• Urination less
• Pain may lessen with loss of consciousness
Model of care delivery

Aggressive multimodal cancer-directed treatment

“Palliative” cancer-directed treatment

No cancer-directed treatment

THE USUAL ROAD

THE DIFFICULT ROAD

2 Roads to Death

Normal

Confused  Tremulous
Restless

Hallucinations
Mumbling Delirium
Myoclonic Jerks
Seizures

Lethargic

Obtunded

Semicomatose

Comatose

Dead
“I had been through all that and it was hard. And it wouldn’t guarantee that I would live…. days don’t count unless they’re good days…. You just have as much fun as you can, and make use of it, it’s like each day is a gift.”  Shawn – 8 yo

“When Liam got sick, we were so helpless, and when he relapsed for the second time in December, we were helpless all over again. It was you, and people like you, who patiently helped us understand what it was that we needed to do… Your work is hard work, but it is good work, and we are so grateful that you do it.” Matt – Bereaved father of Liam