Chemotherapy-related adverse events: GI complication

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Contents

1 Introduction

CTx-related GI Adverse Event

Mucositis; Stomatitis

Nausea & vomiting

Decreased appetite

Diarrhea

Constipation

Pathophysiology of CTx-related GI Adverse Event

Direct damage to GI mucosal cells

rapidly dividing GI mucosal cells (from the mouth to the anus)

2-5 days post treatment

➔ vomiting, diarrhea, constipation, and mouth sores.

Stimulation of CRTZ

➔ acute nausea

GI adverse event Grading

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Gastrointestinal Toxicity

ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with activities of daily living; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per 24 hours over baseline; IV fluids indicated < 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of 7 stools per 24 hours over baseline; incontinence; IV fluids 24 hours; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluids indicated < 24 hours	6 episodes in 24 hours; IV fluids or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death

Risk factors of GI toxicities

VARIABLE	CONSTIPATION	DIARRHEA	NAUSEA	VOMITING
Patient characteristics	Adults older than 65 years Sedentary or bedridden	Adults older than 65 years Recent stay in a hospital or nursing home.	Age younger than 50 Female Nausea and vomiting during previous anticancer treatments Sweating, dizziness, or warmth after last anticancer treatment	More likely in children than in adults Female History of motion sickness and anxiety History of emesis and dehydration caused by cancer therapy
Diet	Low-fiber diet Poor fluid intake	Herbal supplements, including milk thistle, aloe, cayenne, saw palmetto, and ginseng	Current or prior heavy alcohol use	Current or prior heavy alcohol use
Medications	Particularly opioids and dexamethasone; also antacids, antiemetics, antiseizure medications, and iron supplements	Laxatives, antibiotics, antacids containing magnesium, colchicine, propanolol, diuretics, angiotensin-converting enzyme inhibitors, and antidepressants	Chemotherapy, opioids, levodopa, digitalis, pilocarpine, nicotine, nonsteroidal anti-inflammatory agents, antibiotics, and iron supplements	Chemotherapy, opioids, levodopa, digitalis, pilocarpine, nicotine, and nonsteroidal anti-inflammatory agents
Comorbidities	Diabetes, hypertension, hypothyroidism, tumor pressing on spinal cord, bowel obstruction, and peripheral neuropathy	History of irritable bowel syndrome, colitis, or diverticulitis; and graft-versus-host disease following bone marrow transplantation	Older patients with declining organ function and multiple illnesses and conditions, bowel obstruction, brain metastases, or gastrointestinal infections or bleeding	Bowel obstruction; brain metastases; gastrointestinal infections or bleeding; electrolyte imbalance
Medical procedures	Surgery involving the intestinal tract	Surgery involving the intestinal tract or bone marrow transplantation	Radiation therapy	Radiation therapy

2 구강 및 목의 통증, 식도염

Mouth sores

- **Chemotherapy can damage the cells lining the mouth, throat, and gastrointestinal tract. This damage is called mucositis.**
- **Mucositis affects the mouth as painful mouth sores, called stomatitis.**
- **This chemo side effect is common and can be very painful.**

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change				
	Soreness/ erythema	Erythema, ulcers; can eat solid food	Ulcers; requires liquid diet only	Alimentation (nourishment) not possible

Causes of mouth sores

Up to 40% of people receiving chemotherapy.

Radiation therapy to the head and neck area

Bone marrow/stem cell transplant. Mouth sores are a possible sign of graft-versus-host disease, which is a side effect of these procedures.

Factors to increase mouth sores:

- Poor oral health prior to and during treatment
- Having other diseases in addition to cancer

Diagnosis of mouth sore

- **Symptoms start around 5-7days after the start of chemo and last about 10 days**
- **Treating mouth sores is important because pain from mouth sores may make it difficult to eat, talk, or swallow.**
- **Open sores in the lining of the mouth may allow bacterial, fungal, or viral organisms to enter the body and cause infection**

Managing mouth sores

Suck on ice chips immediately before and during each chemotherapy.

Brush teeth gently with fluoride toothpaste several times a day.

If the mouth sores are severe, use a toothette (sponge on a stick) instead of a toothbrush.

Rinse or gargle with a solution of saltwater and baking soda.

Avoid mouth rinses that have alcohol in them.

Avoid wearing dentures at night, and consider removing them between meals to help reduce mouth irritation.

Choose foods that require little or no chewing.

Avoid acidic, spicy, salty, coarse, and dry foods.

Managing mouth sores

Pain medications.

- Lidocaine solution
- Acetaminophen (Tylenol)
- Pain medicine including narcotics

Antibiotics, antiviral drugs, and/or antifungal drugs are used to treat infections.

Artifical saliva

Case

Pain 5day after CTx

7day after CTx

3day after Tx

Esophagitis

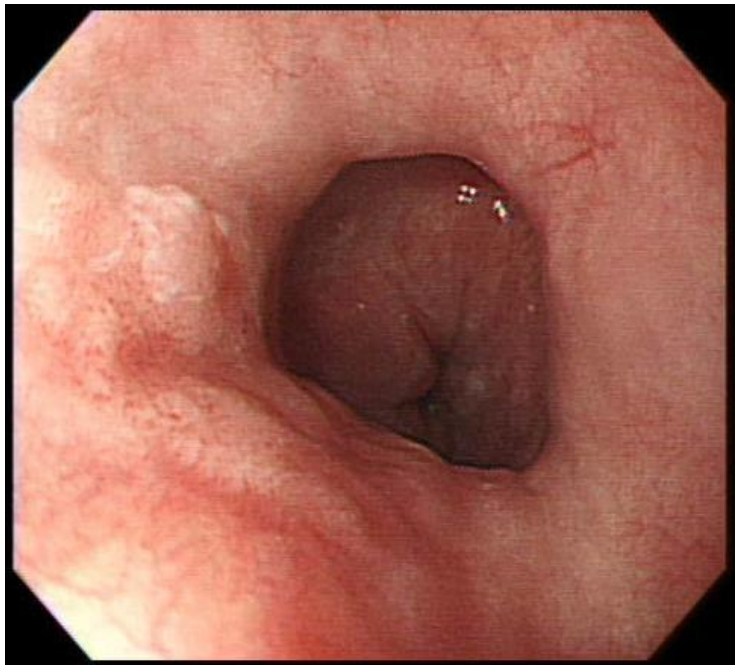
- **Chemotherapy and radiotherapy are important causes of iatrogenic esophagitis**

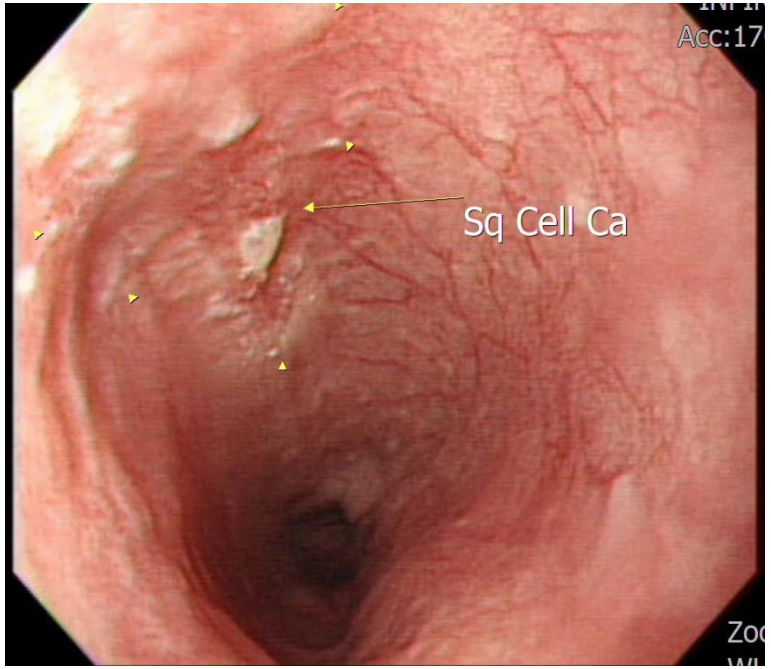
Radiation-esophagitis

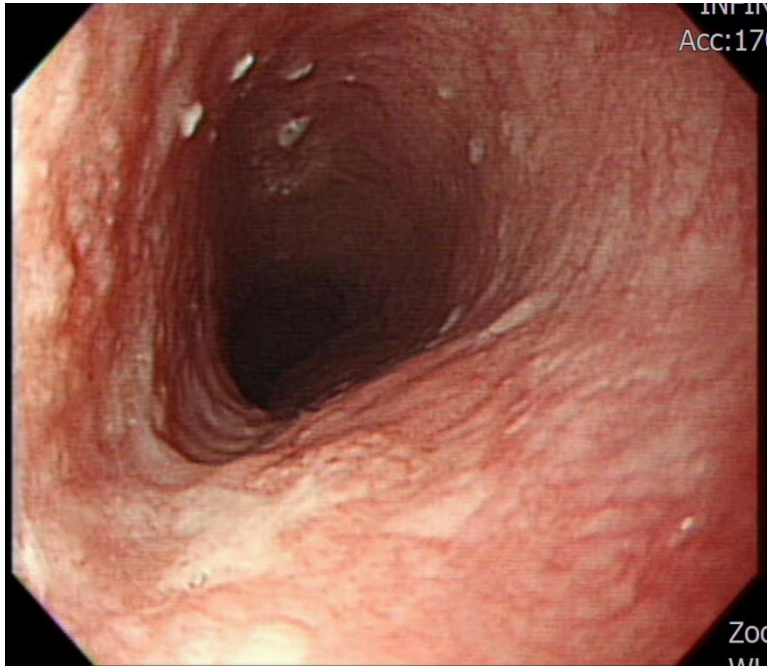
Grade	Description
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, total parenteral nutrition, or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Case. M, 74

Early esophageal cancer 로 내원: multiple superficial cancer (2017. 3.22)





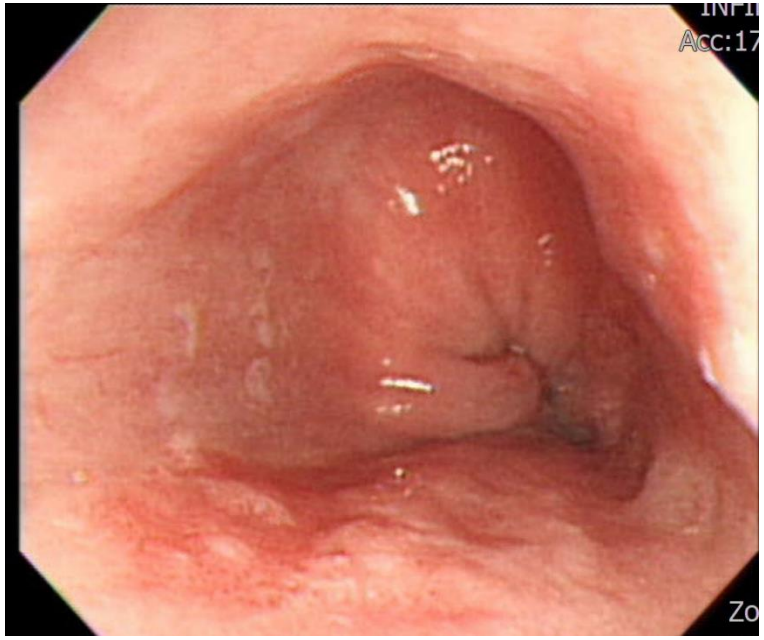


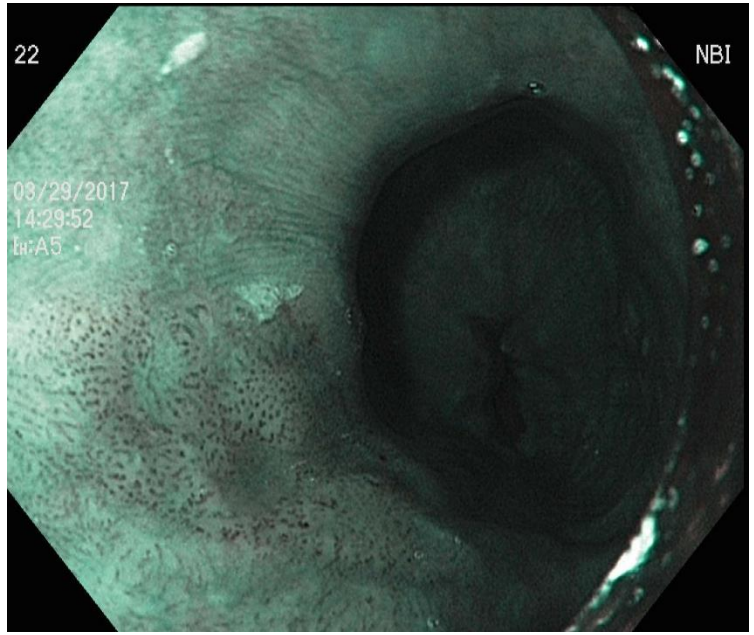
RUL: 2cm mass

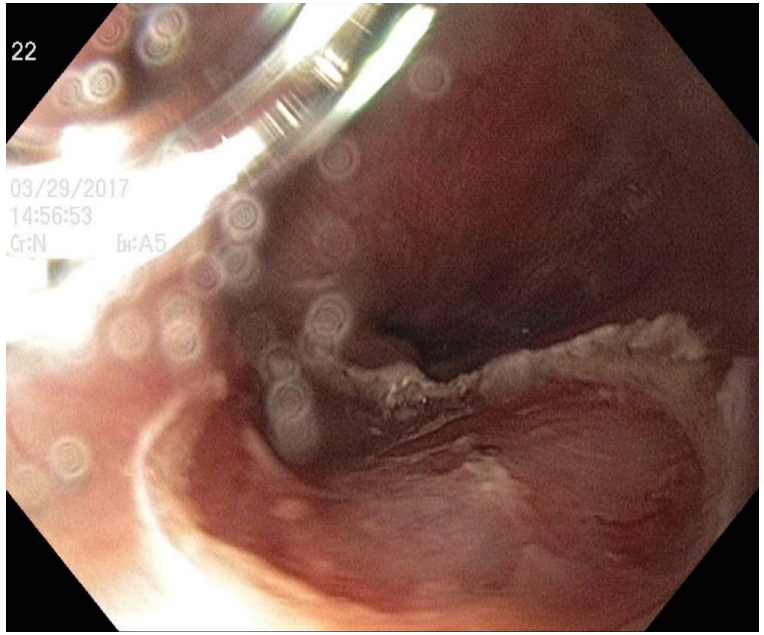
Treatment strategy

1) above GEJ : Endoscopic resection
2) Lung Ca – Lobectomy
3) midesophagus, multiple superficial cancer → CCRT

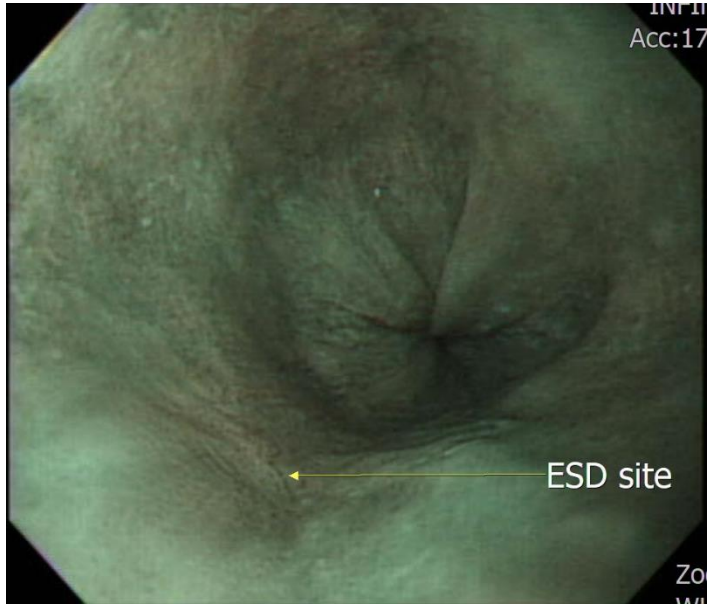
Endoscopic resection (2017.3. 29)

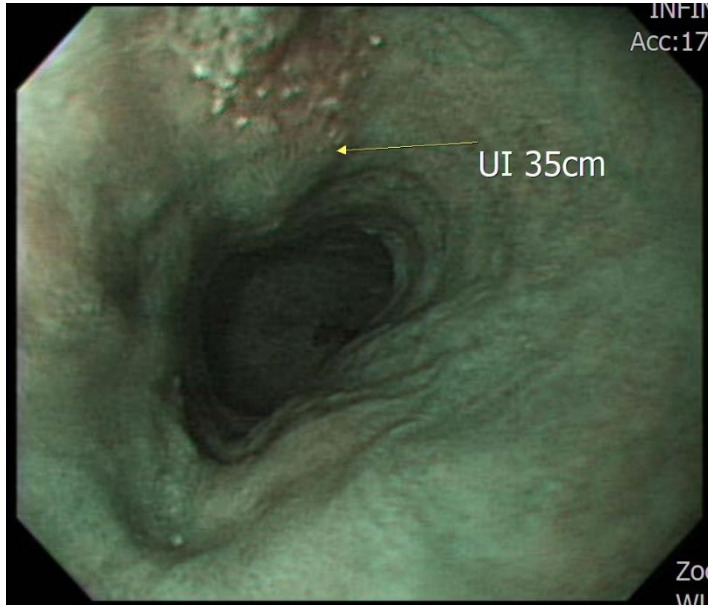


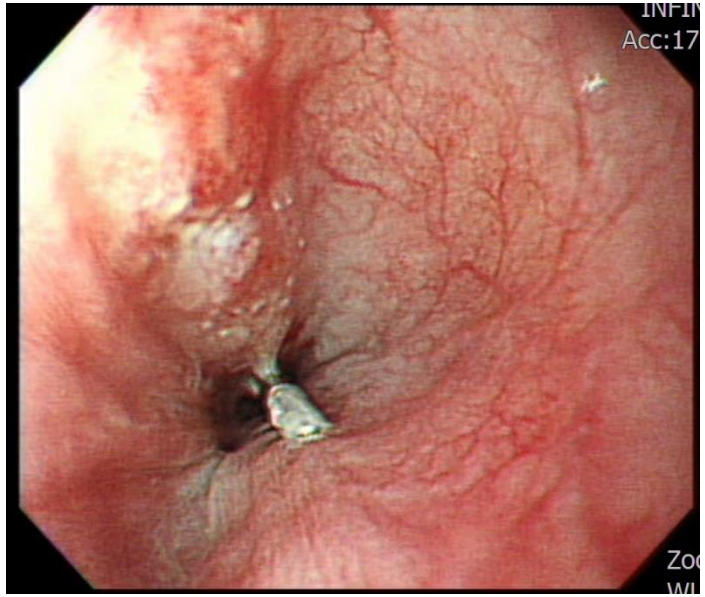


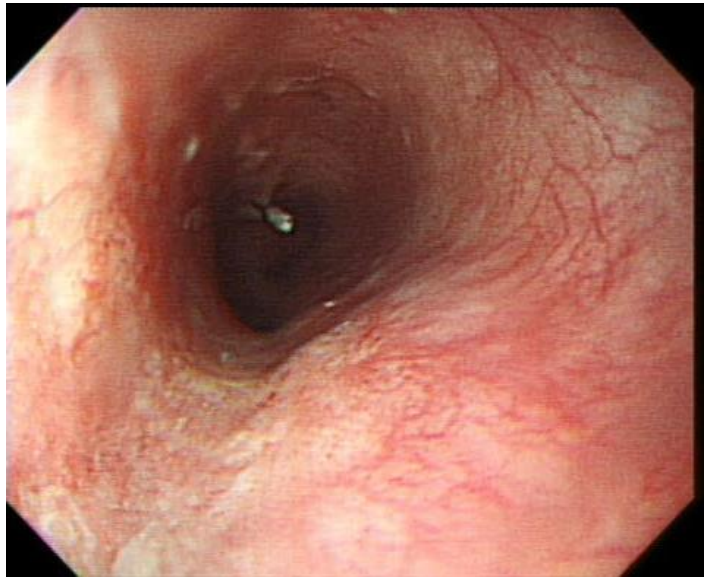


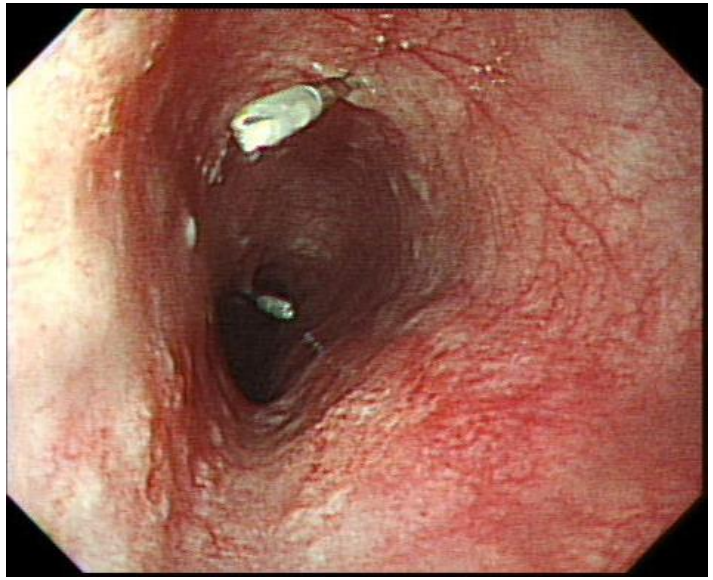
RUL lobectomy → EGD (2017.5.31)

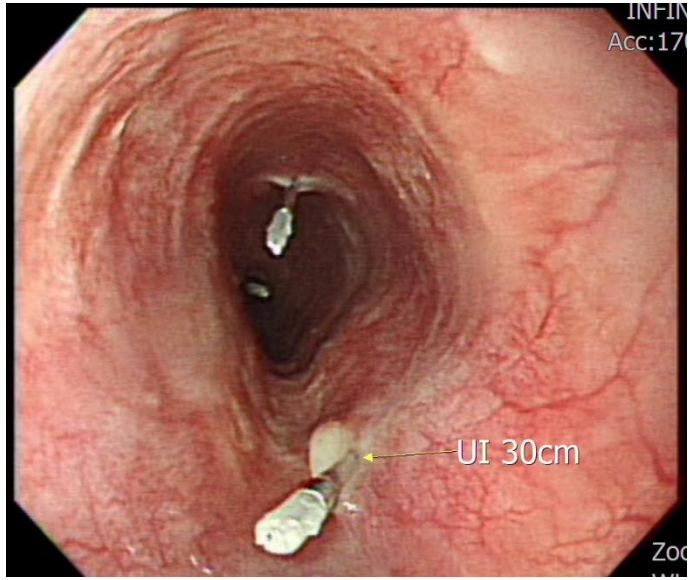












CCRT FP #1 (6/7-6/11), FP #2 (7/3-7)

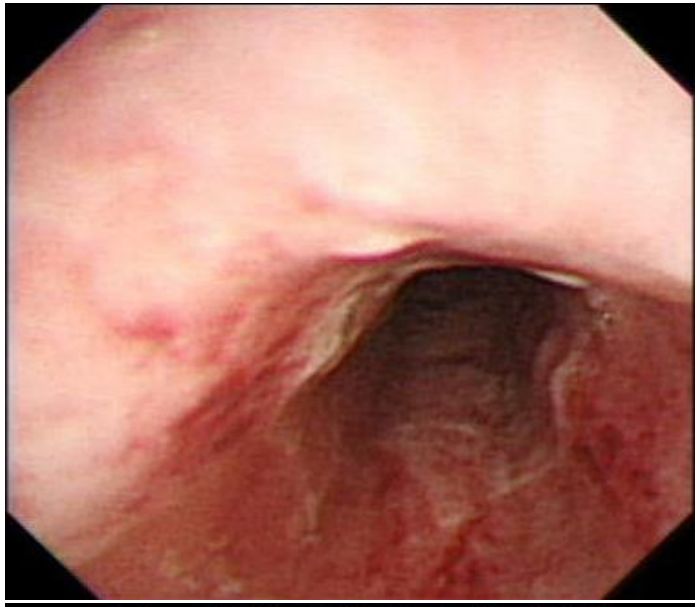
10 days after 2nd FP start: odynophagia

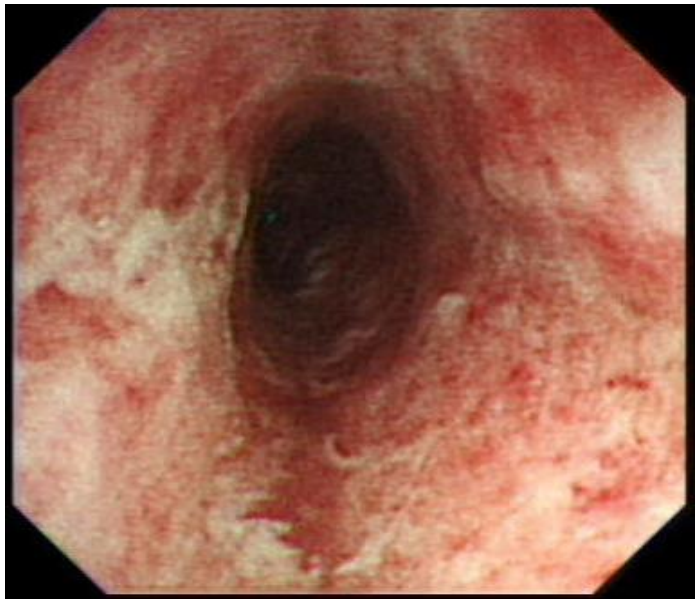
→ ER (2017.7.18): 물만 삼켜도 아픔. mild fever,

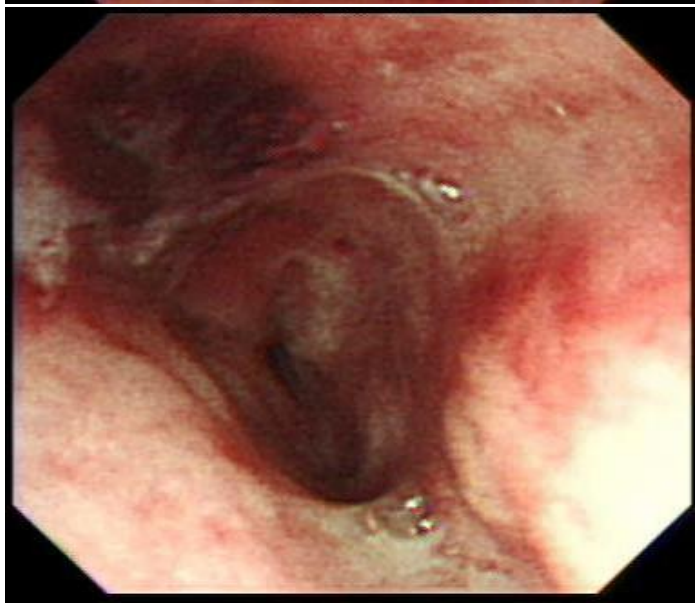
CRP 18, WBC 1.98k, ANC 1.32k

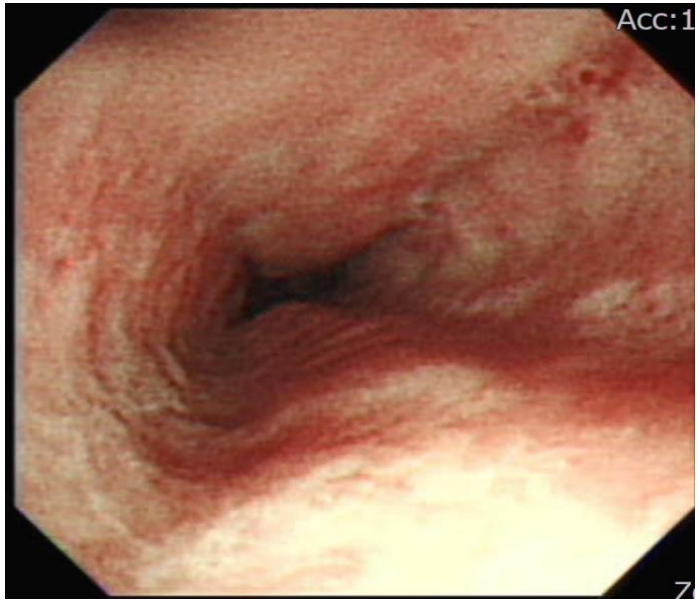
→ NPO, TPN, antibiotics

EGD (2017.7.24)









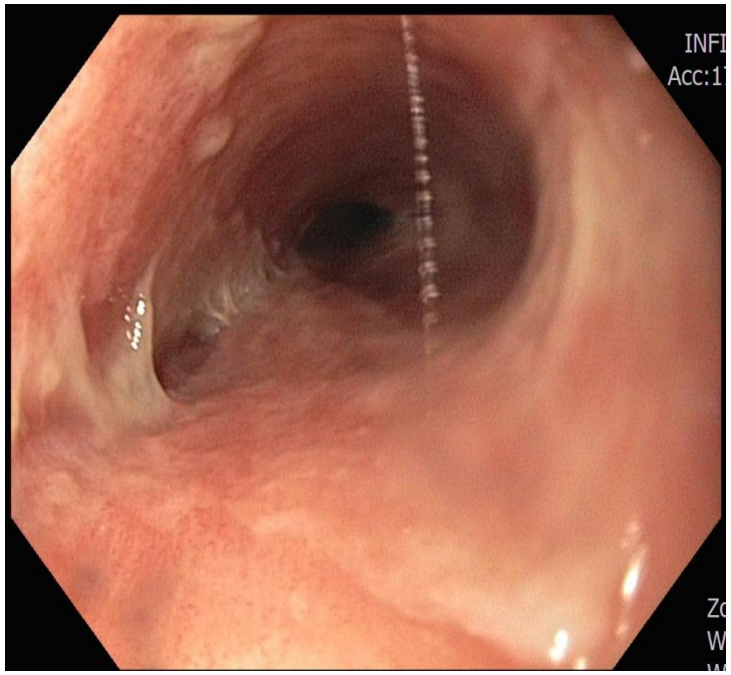
UI 25cm-above GEJ

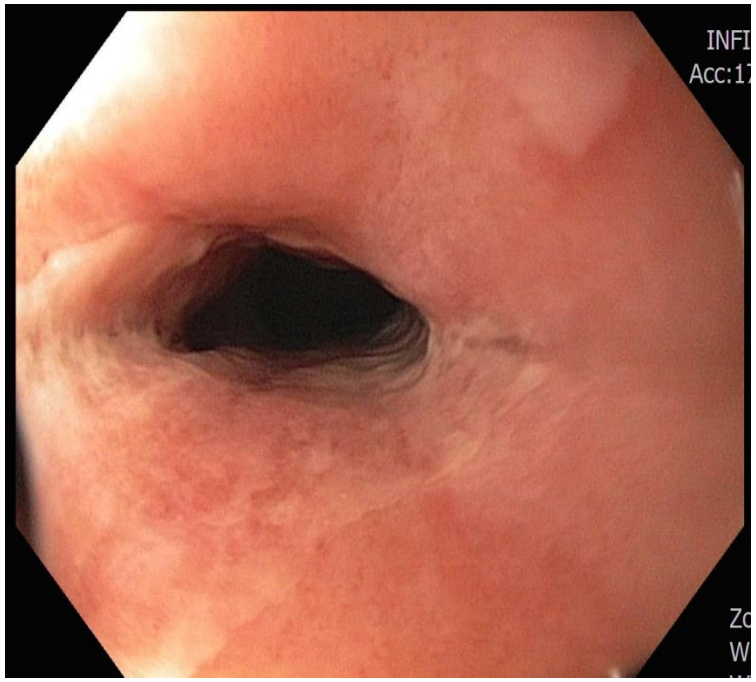
CCRT related Esophagitis, Grade III

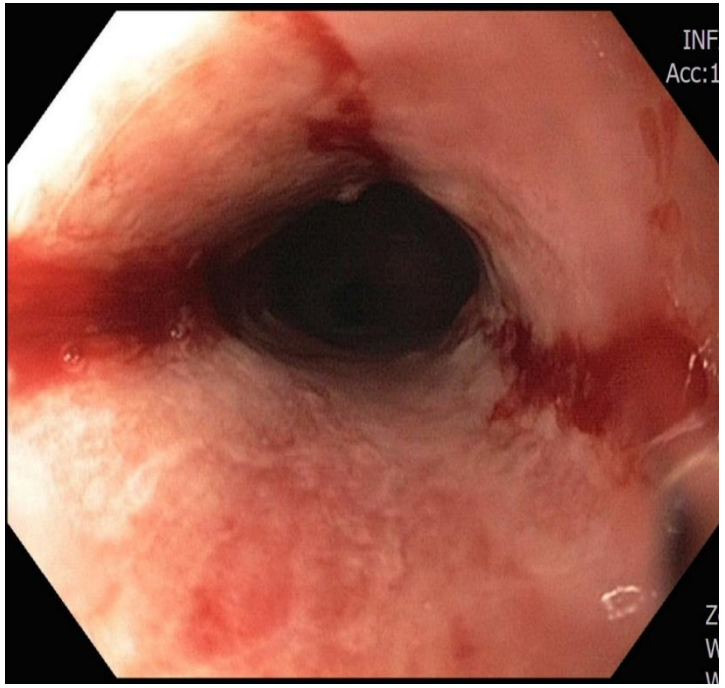
- **CT – esophageal wall diffuse mild thickening**

- **NPO, antibiotics, TPN, PPI keep**
  → Soft diet : D/C (2017.7.31)

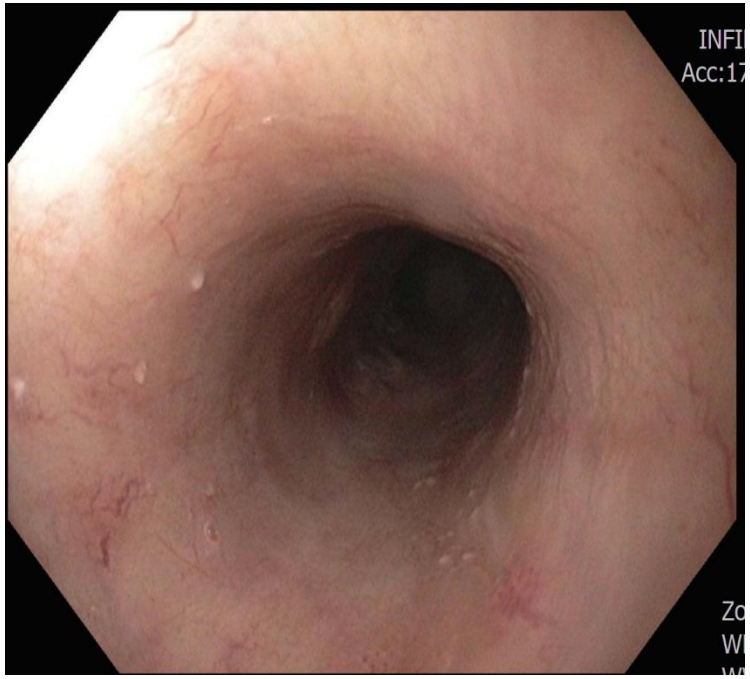
EGD (2017.8.23)

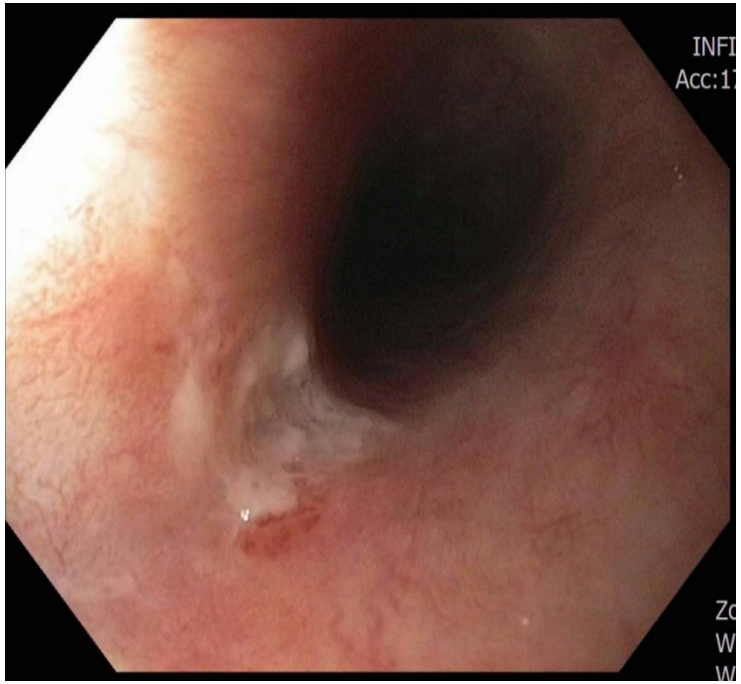


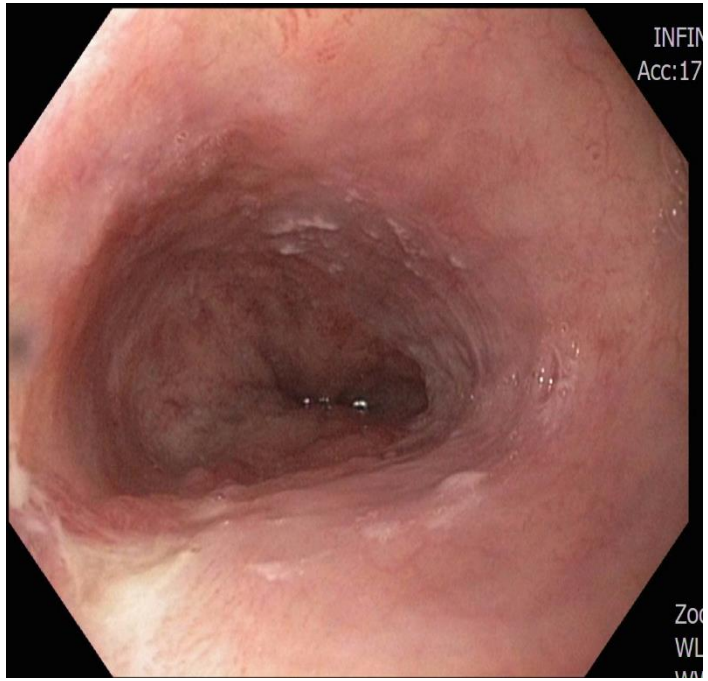




EGD (2017.11.1)







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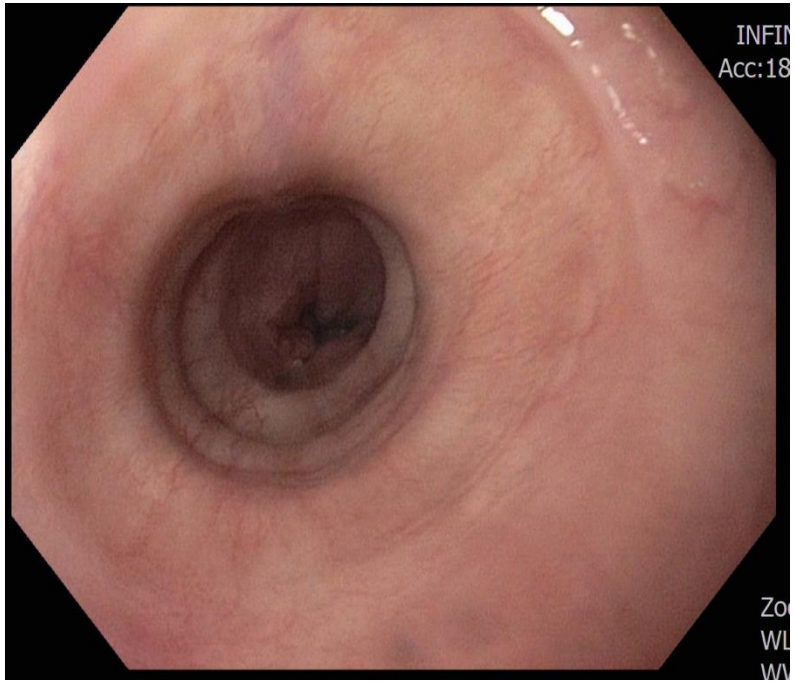
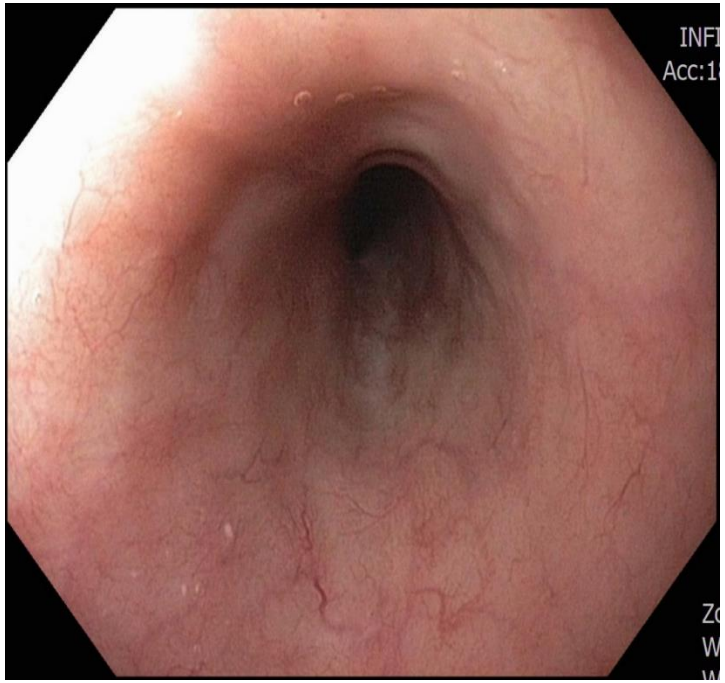
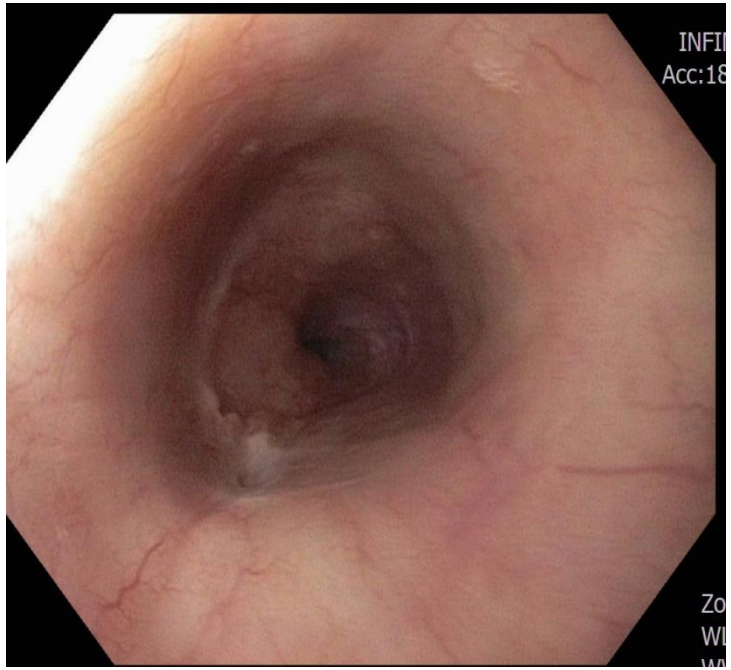






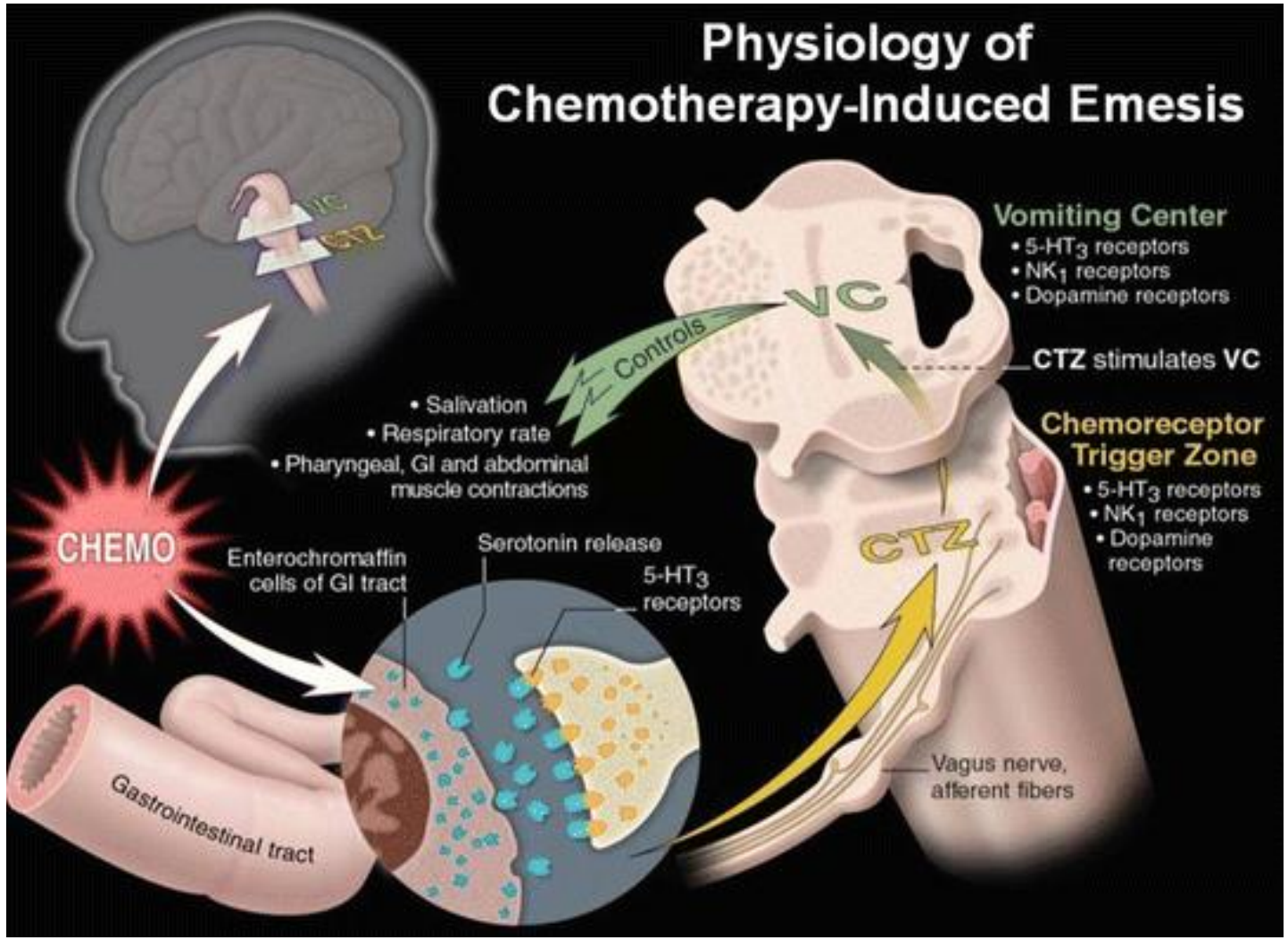
3 구역 및 구토

Physiology of Chemo-induced vomiting (CINV)

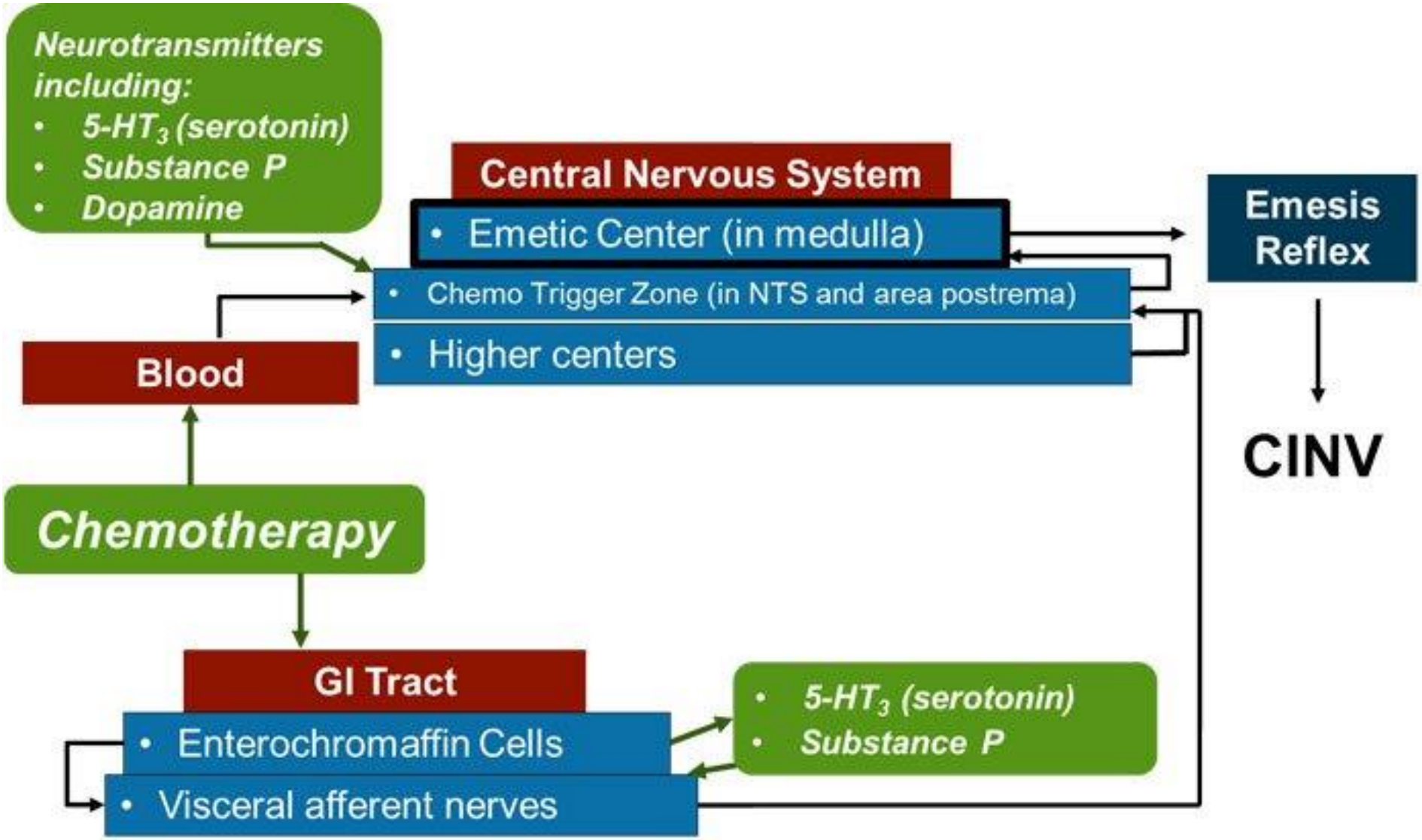
Chemotherapy

→ release of serotonin and other chemicals

➔ a signal that activates the "vomiting center".



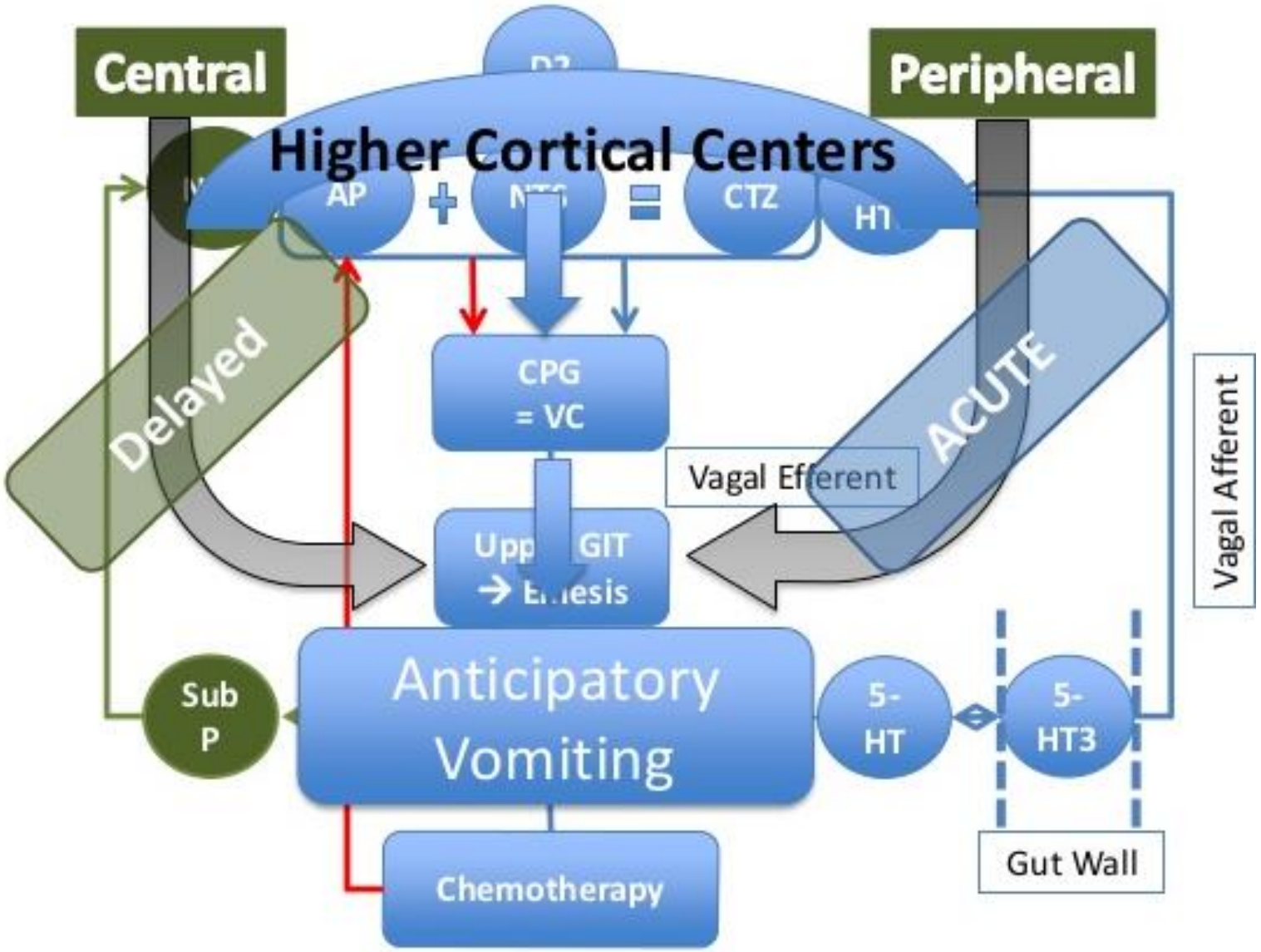
Chemo-induced vomiting (CINV)



3 types of CINV

Acute: Occurs within minutes to the first few hours after chemo administration

Anticipatory: Occurs as a conditioned response, meaning it happens in response to stimulus that has caused nausea or vomiting in the past, such as the sight or smells of the treatment room



Causes of Nausea and Vomiting

Chemotherapy and Radiation therapy (the spinal cord, abdomen, and pelvis).

Whole body radiation therapy, such as before stem cell/bone marrow transplantation.

Brain meta

Blocked intestine (gastrointestinal obstruction)

Electrolyte imbalance, which is the loss of minerals such as potassium and sodium

Infections or bleeding in the stomach and intestines

Mild nausea and vomiting does not cause serious problems.

Vomiting a lot → dehydration, electrolyte imbalance, weight loss.

Vomiting grading

- Veterinary Cooperative Oncology Group Grading Scheme for Vomiting

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<3 episodes in 24 hours, no medical intervention needed	3-10 episodes in 24 hours or <5/day for 48 hrs; medications +/- parenteral fluids indicated for < 48 hours	Multiple episodes for >48 hrs and IV fluids or PPN indicated for >48 hrs	Life-threatening (hemodynamic collapse)	Death

Management of N/V

Antiemetics

: block the signal in the brain and gut that causes nausea and vomiting.

Diet modification

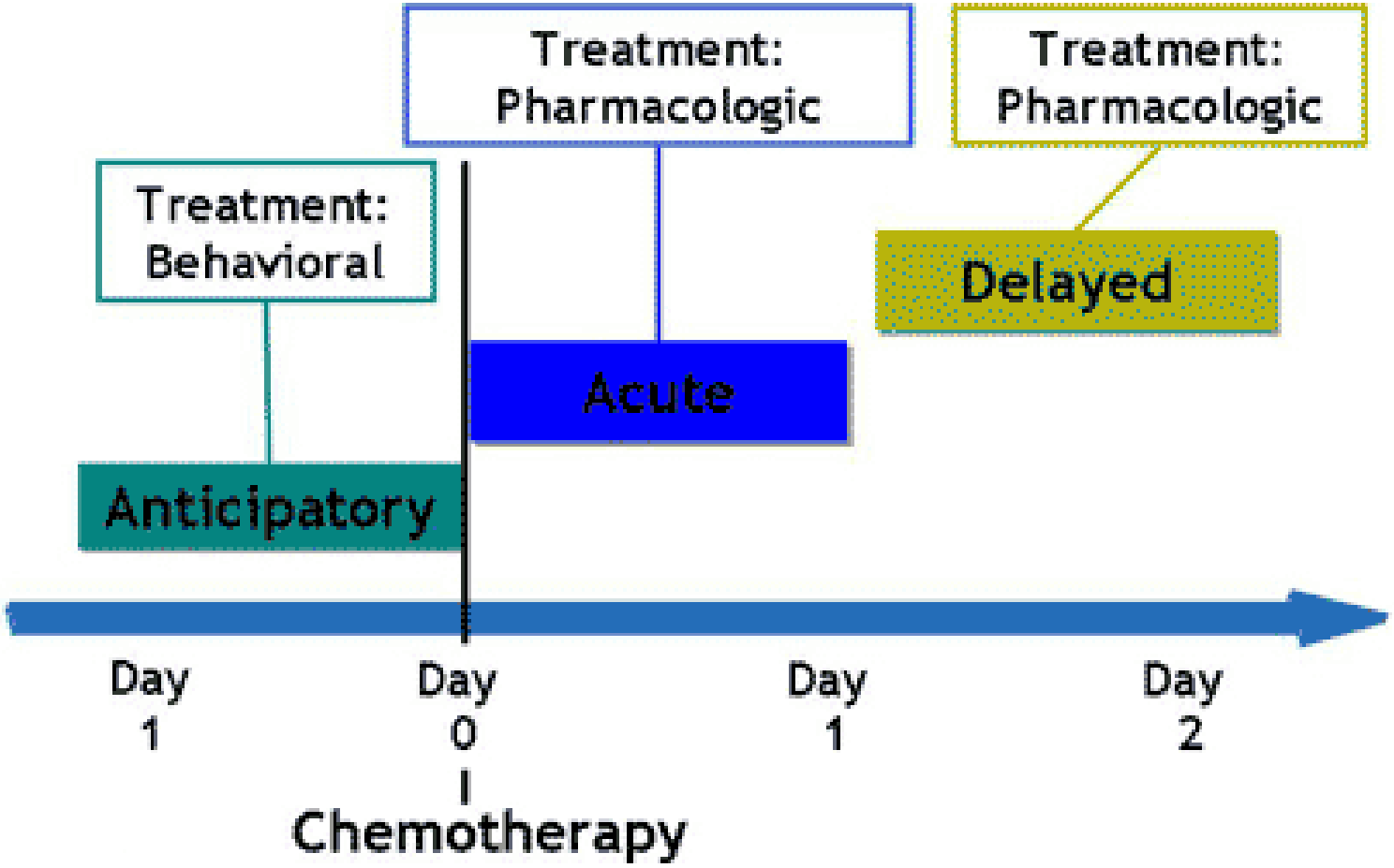
- **Eat 5 - 6 smaller meals, rather than 3 large meals.**
- **Eat foods that are easy to digest.**
- **Avoid onions, garlic, coffee, and other strong-smelling foods.**
- **Wait at least 1 hour after your chemo before eating or drinking anything.**
- **Consume foods and drinks at room temperature or cool.**

Types of medicine for nausea and vomiting

TABLE: DRUGS USED FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Drug Class	Notes
5-HT_3–receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)	• Used for acute emesis with corticosteroids and NK_1-receptor antagonists
Antihistamines (diphenhydramine)	• Useful additions to antiemetic drugs
Benzodiazepines (alprazolam, lorazepam, midazolam) and thienobenzodiazepine (olanzapine)	• Useful additions to antiemetic drugs • Drugs of choice for anticipatory emesis • Olanzapine is reserved for refractory CINV
Butyrophenones (droperidol, haloperidol)	• Usually used for breakthrough symptoms
Cannabinoids (dronabinol, nabilone)	• Second-line therapy
Corticosteroids (dexamethasone, methylprednisolone)	• Increase 5-HT_3 receptor antagonists effectiveness • Can be used alone with chemotherapy of low emetogenic risk
Dopamine-receptor antagonists (metoclopramide, prochlorperazine)	• Usually used for delayed CINV
NK_1-receptor antagonists (aprepitant, fosaprepitant)	• Used for acute emesis

3 types of CINV : management



Management of N/V

High risk of nausea and vomiting.

Adults usually receive a combination of 4 medicines to prevent vomiting:

- **NK1 receptor antagonist**
- **5-HT3 receptor antagonist**
- **Dexamethasone**
- **Olanzapine**

Children usually receive a combination of 2 or 3 medicines to prevent vomiting:

- **5-HT3 receptor antagonist**
- **Aprepitant**
- **Dexamethasone**

Moderate risk of nausea and vomiting

Adults usually receive a combination of 2 or 3 medicines to prevent vomiting:

- NK1 receptor antagonist in certain instances
- 5-HT3 receptor antagonist
- Dexamethasone

Children usually receive a combination of 2 medicines to prevent vomiting.

- 5-HT3 receptor antagonist and dexamethasone
- (or aprepitant if a child cannot receive dexamethasone)

Low risk of nausea and vomiting

Adults usually receive a 5-HT3 receptor antagonist or dexamethasone

Children usually receive ondansetron or granisetron

Minimal risk of nausea and vomiting.

Adults and children usually do not receive medicine when the risk is very low.

Management of CINV

CINV Type	Preferred Treatment
Acute emesis and highly emetogenic therapy	5-HT_3 receptor antagonists with dexamethasone and NK_1 receptor antagonists
Acute emesis and moderately emetogenic therapy	Dexamethasone and 5-HT_3 receptor antagonist
Low emetic risk	Prochlorperazine, domperidone, metoclopramide, or dexamethasone alone
Anticipatory emesis	Lorazepam for its amnestic, sedative, and anxiolytic effects
Delayed emesis	Dexamethasone alone, with or without oral metoclopramide, prochlorperazine, 5-HT_3 or NK1 receptor antagonists

4 변비

Constipation

: difficulty passing stools and experience a decrease in the frequency of stools.

Constipation can be accompanied by bloating, stomach cramps, or nausea.

Chronic constipation can lead to something called stool impaction.

Impaction can be a very serious complication of constipation.

If it occurs, need to remove the impacted stool.

Causes of Constipation

Chemo reagents
Pain killers, Fe supplements
Decreased physical activity
Not eating enough foods with fiber
Not drinking enough water or other fluids

A tumor or scar tissue partially or completely blocking the bowel (bowel obstruction)
Cancer pressing on the spinal cord
High levels of calcium / Low potassium levels
Thyroid problems
Diabetes

Symptoms

Fewer bowel movements than what is normal for you

Hard, difficult-to-pass bowel movements

Cramping or stomach-ache

Flatulence (gas)

Grade of CTx-induced constipation & diarrhea

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline.	Increase of 4–6 stools per day over baseline.	Increase of >7 stools per day over baseline. Incontinence. Hospitalization.	Life threatening consequences. Urgent intervention indicated.	Death
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema.	Persistent symptoms with regular use of laxatives or enemas indicated.	Symptoms interfering with activities of daily living; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon).	Death

Diagnosing constipation

Rectal examination or imaging scans.

: exclude tumor blocking rectum or GI tract.

Meticulous history taking

- **Bowel habits, before the cancer and now**
- **Use of medicines that may cause constipation**
- **What you've been eating and drinking recently**
- **Other diseases or illnesses**

Prevention & Treatment

Life style modification

Drink plenty of water.

Fluids keep the stool soft.

Eat foods high in fiber; these include fruit, vegetables, and nuts.

(if scar tissue or a tumor narrowing your bowel, a low-fiber diet.)

Tolerable Exercise helps stimulate digestion and prevent constipation.

Laxatives

5 설사

Diarrhea

Bowel mucosal damage → loose, watery bowel movements.

Diarrhea is a common side effect of many types of chemo.

Persistent diarrhea can lead to:

Dehydration.

Electrolyte imbalance: hyponatremia → confusion, coma

Hypokalemia → muscle weakness, spasms, or paralysis.

Malnutrition: vitamins, minerals, and calories 흡수 장애

Causes of diarrhea

Chemotherapy

Immunotherapy

Cancer that affects the pancreas

Radiation therapy to the pelvis

The removal of a portion of the bowel

Graft-versus-host disease, a side effect of bone marrow transplantation

These conditions unrelated to cancer may cause diarrhea:

Irritable or inflammatory bowel disease

Viral infection

The inability to digest certain foods

Infection with *Clostridium difficile*, a diarrhea-causing bacteria

Antibiotics

Grades of diarrhea

Grade 1. This is an increase from a patient's own baseline of less than 4 stools a day.

Grade 2. This is an increase from patient's own baseline of 4 to 6 stools a day.

Grade 3. This may require treatment in the hospital.

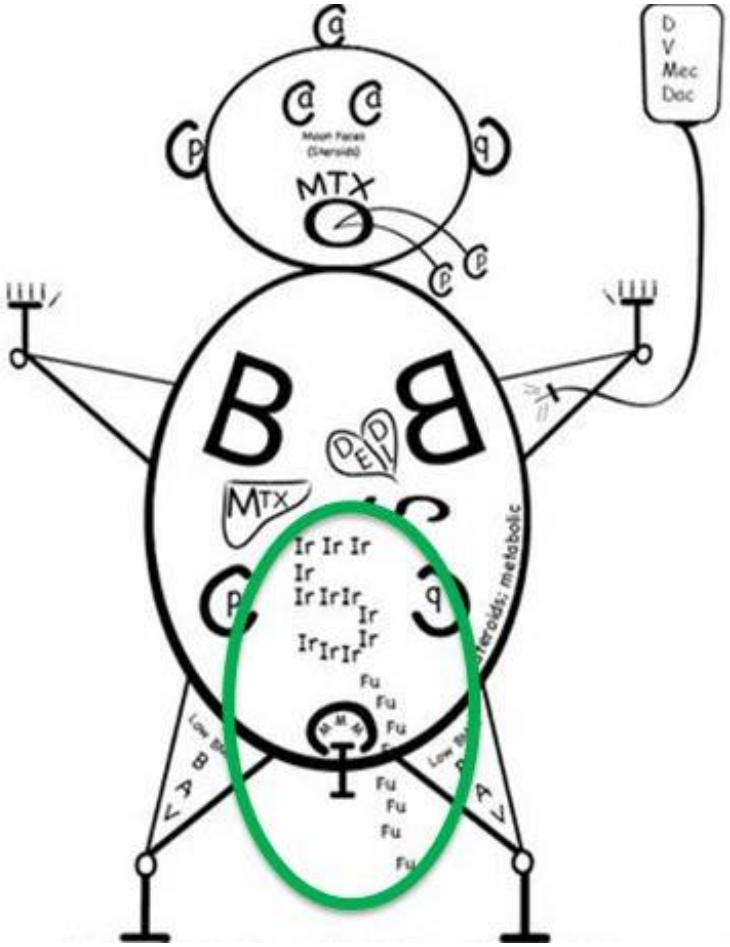
An increase of 7 or more stools a day.

An inability to control bowel movements, known as incontinence.

A reduced ability to care for your daily needs.

Grade 4. This is a life-threatening condition that requires immediate intensive care.

Physiology of CTx-induced diarrhea



- Fluorouracil, Capecitabine
  - Mitotic arrest of intestinal cells
  - Mild colitis to severe necrotizing enterocolitis
- Irinotecan
  - Acute: Cholinergic reaction
    - Atropine 0.25 mg IV or SQ
  - Delayed: MOA unknown, suspected to induce apoptosis of intestinal epithelia

Prevention & managements

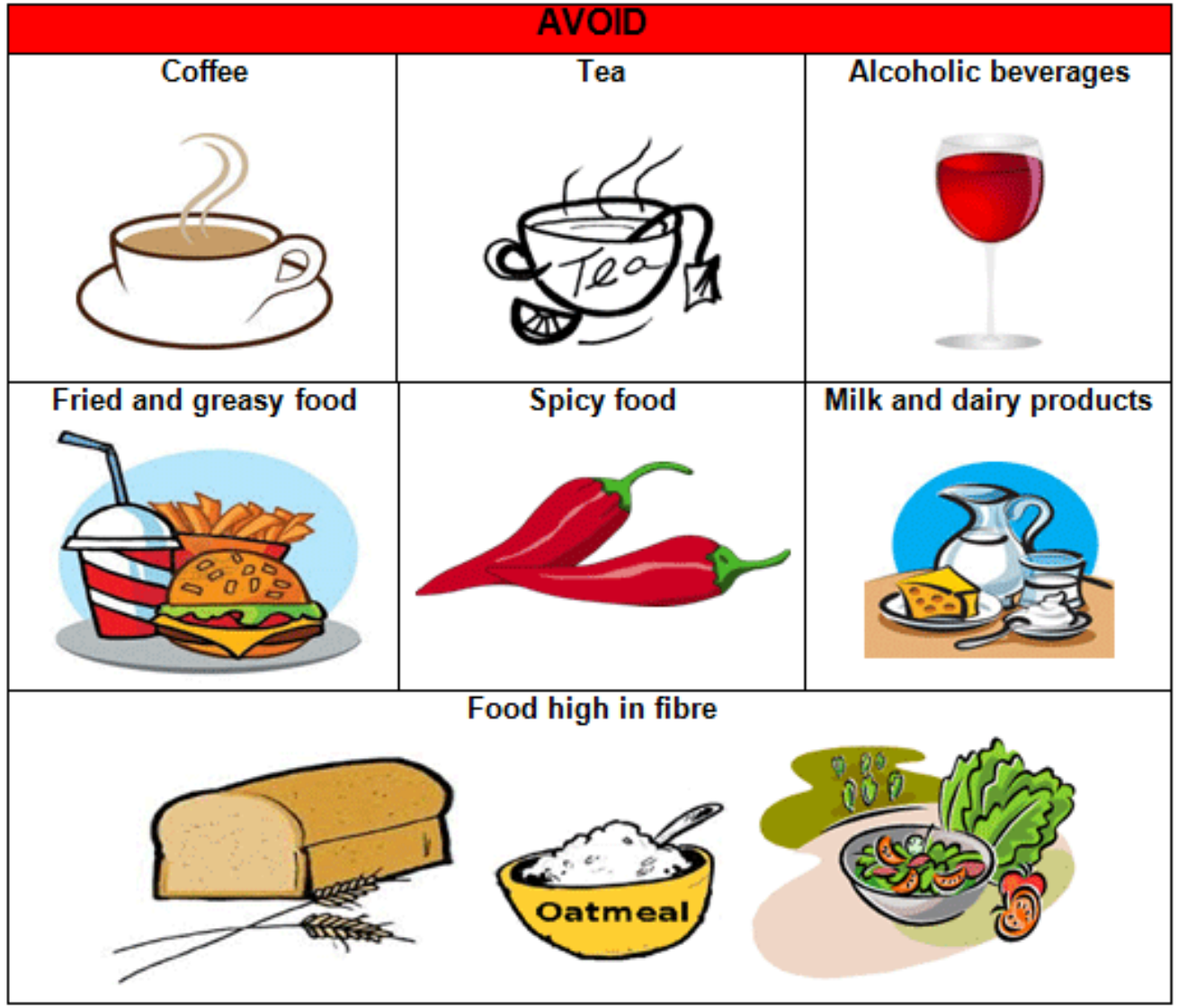
Diet modification

Avoid caffeine, alcohol, fat, orange juice, prune juice, and spicy foods.

Avoid milk and dairy products

Avoid high-fiber foods that may be difficult to digest

Easy-to-digest foods: bananas, rice, applesauce, toast (called the BRAT diet)



Prevention & managements

Avoid medicines such as laxatives, stool softeners, and metoclopramide.

Stay hydrated

Clear liquids may help if diarrhea is not severe.

Severe dehydration: intravenous (IV) fluids.

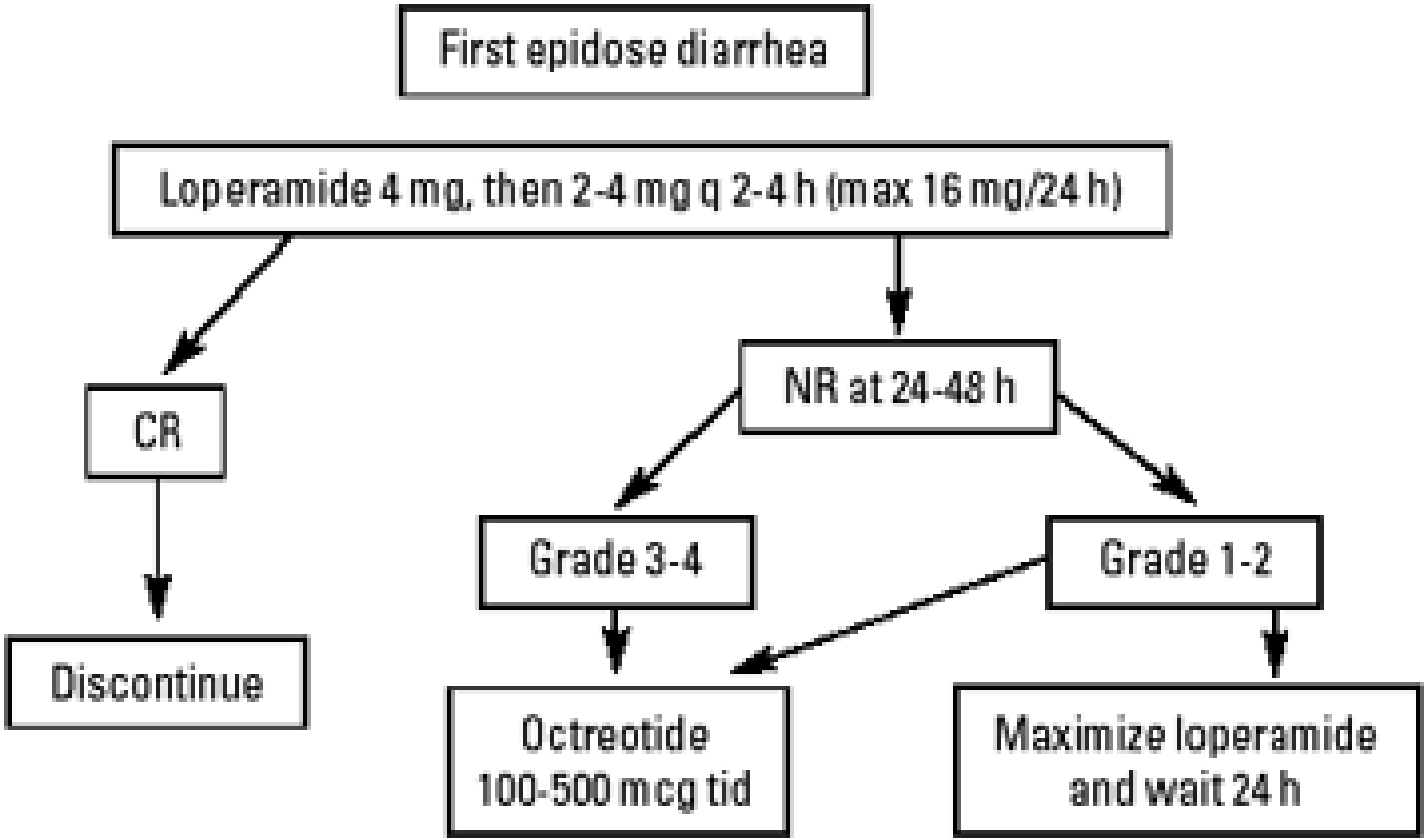
If diarrhea is from the pancreas not working well, replacing pancreatic enzymes may help.

For severe diarrhea from chemotherapy: consider changing the schedule or dose of chemotherapy.

Medication

Anti-motility drug (loperamide, octreotide)

Pharmacologic Tx of CTx-induced diarrhea



Summary

1. Physiology of CTx induced GI adverse event

Direct damage to GI mucosal cells

➔ vomiting, diarrhea, constipation, mouth sores.

Stimulation of CRTZ

➔ acute nausea

2. Management by Grade of GI adverse event

Dietary & Life style modification

Pharmacologic Tx

IV fluid, TPN

Thank you for your attention