Subtle Signs and Symptoms of Illness and Injury

Developmental Disabilities Support Division

Resource Packet D

Dehydration, Malnutrition,
and
Medication: Intended and Unintended Effects

Required for:
RN, LPN, SLP, PT, OT, BSC,
and
Optional for RD/LD/LN and Other

NEW MEXICO
Department of Health
Developmental Disabilities Supports Division

2021

Consequences of Dehydration

THIRST

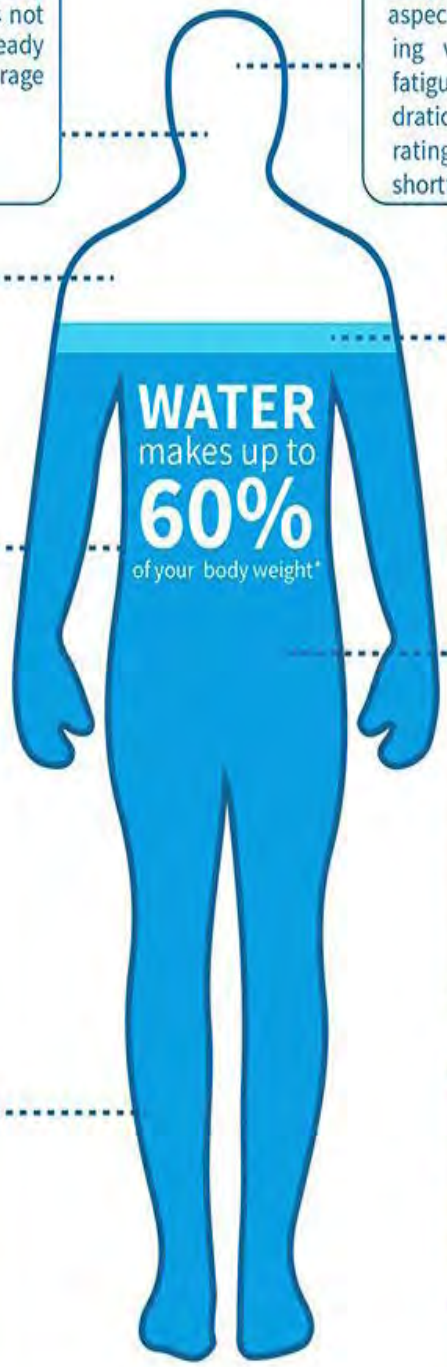
Thirst is a useful indicator of daily fluid requirements. Unfortunately, it's not fully reliable since the body is already mildly dehydrated by the time an average person starts to notice thirst.[1]

MENTAL

Dehydration can degrade specific aspects of cognitive performance including visual vigilance, tension, anxiety, fatigue and visual working memory. Dehydration was also linked to negative mood rating, impaired motor performance and shortterm memory.[6]

SKIN

Dehydration results in dry skin and wrinkles.[2]



DEHYDRATION

A 1% loss of body mass due to fluid loss is defined as dehydration.[7]

KIDNEYS

Higher water intake is shown to have a protective impact on the kidneys, and there is initial evidence that CKD (Chronic Kidney Disease) may be inversely related to higher water intake.[3]

A study by Dai et al found a strong protective effect of fluid intake in preventing kidney stone formation in men.[4]

WEIGHT LOSS

Opting for water instead of sugary drinks can help reduce body weight and fat levels. According to Stookey,[8] just drinking 500 ml (17 oz) of water increases energy expenditure by 100kJ. Findings in the same study indicate that an absolute increase in drinking water to to ≥ 1l (34 oz)/day was associated with ~2 kg or 5 lbs weight loss over 12 months.

PHYSICAL

Studies have shown that the modest level of dehydration (2% of body mass) can result in around a 20% decrease in physical performance levels in temperate climates and up to a 40% decrease in hot temperatures.[5]

*WATER

Water plays crucial roles, in transporting nutrients and waste products between our major organs and helping regulate temperature.[9]

1) Kolasa, K.M., Lackey, C.J. & Grandjean, A.C. Hydration and Health promotion. Nutrition Today. 2009; 44: 190-201
2) Atlanta dermatologist Kenneth Ellner, MD.
3) Sontorp et al. (2013) Am. J. Of Nephrology
4) Dai et al. (2013). J: of Renal Nutrion (23) 2
5) Péronnet F PhD(2010) Healthy Hydration for Physical Activity. Nutrition Today, Volume 45, No. 6S
6) Ganio et al., 2010; D'Anci et al., 2009; Smith et al., 2012
7) Kleiner SM. Water: An essential but overlooked nutrient. J Am Diet Assoc 1999;99:201-7.
8) Stookey, J. D., Constant, F., Popkin, B. M. and Gardner, C. D. (2008) Obesity, 16: 2481–2488.

http://www.steveaoki.com/site/wp-content/uploads/2015/11/dehydration-infographic.png

Cleveland Clinic

Dehydration

What is dehydration?

Warm weather brings with it thoughts of cool ocean breezes, napping in a hammock and sipping a tall glass of lemonade. Now hold on to the mental image of that lemonade because summer is also a time to be wary of dehydration: the lack of sufficient water in your body, specifically in your cells and blood vessels. Even losing a little bit, as little as 1.5% of your body's water, can cause symptoms. Those symptoms can be as simple as a slight headache, or the dehydration could contribute to a life-threatening illness like heatstroke (hyperthermia).

Your body's natural response to inadequate hydration is thirst. You should respond to thirst right away by drinking fluids – preferably water. Drink enough water to prevent yourself from feeling thirsty! Water has zero calories!

What does water do for your body?

Between about 55% to about 78% of your body is made of water. Newborn babies are about 78% water, a year-old baby is 65%, adult men are about 60% and adult women are about 55%. Your brain is made up of 73% water, and so is your heart. Your bones are 31% water, muscles and kidneys are 79% and your skin is 64%. A whopping 83% of water makes up your lungs.

Water helps:

- Aid digestion and get rid of waste.
- Work your joints. Water lubricates them.
- Make saliva (which you need to eat).
- Balance your body's chemicals. Your brain needs it to create hormones and neurotransmitters.
- Deliver oxygen all over your body.
- Cushion your bones.
- Regulate your body temperature.

Act as a shock absorber for your brain, your spinal cord and, if you're pregnant, your fetus.

Water is important to your body, especially in warm weather. It keeps your body from overheating. When you exercise, your muscles generate heat. To keep from burning up, your body needs to get rid of that heat. The main way the body discards heat in warm weather is through sweat. As sweat evaporates, it cools the tissues beneath. Lots of sweating reduces the body's water level, and this loss of fluid affects normal bodily functions. Drink water!

Are hypovolemia and dehydration the same?

No, these terms do not mean the same thing. Hypovolemia defines many conditions where extracellular fluid volume is reduced. Dehydration can be one of several causes of hypovolemia, but it is not the same thing as it.

Are dehydration and hypernatremia the same?

No. Again, dehydration can be a cause of hypernatremia, but it is not the same thing.

Possible Causes

What causes dehydration?

Dehydration happens when you don't drink enough water, or when you lose water quickly through, for example, sweating, vomiting and/or diarrhea. Certain medications such as diuretics (water pills) can result in increased urination and dehydration.

Who's at risk of becoming dehydrated?

Anyone can become dehydrated if they don't take care of themselves and drink water. However, infants and children, especially when they're sick, are at a higher risk because they may be unable to communicate that they're thirsty. Monitor the amount of fluids your kids take in.

Older adults are also at a higher risk. Their body's fluid reserves shrink and their body's ability to tell them they're thirsty doesn't work as effectively. This means they don't carry as much water in their bodies and they can't tell as easily when they're thirsty. If you're a caretaker of an elderly individual, especially one who may have memory problems, offer them drinks frequently. Even if they're enduring an uncomfortable infection like a UTI (urinary tract infection), they still need to consume liquids.

What are the signs of dehydration? What does dehydration feel like?

If you suspect that you or someone else is severely dehydrated, seek immediate medical attention.

Signs of dehydration include:

- Headache, delirium, confusion.
- Tiredness (fatigue).
- Dizziness, weakness, light-headedness.
- Dry mouth and/or a dry cough.
- High heart rate but low blood pressure.
- Loss of appetite but maybe craving sugar.
- Flushed (red) skin. Swollen feet. Muscle cramps.
- Heat intolerance, or chills.
- Constipation.
- Dark-colored pee (urine). Your pee should be a pale clear color.

The best way to beat dehydration is to drink before you get thirsty. If you wait until after you're thirsty, you're already dehydrated.

In what other ways does dehydration affect me?

Dehydration does more than you might expect. If affects you not only physically (note the signs stated above), but mentally and emotionally as well. If you're dehydrated, you may feel:

Mental affects:

- Confused.
- Like you can't remember.

Emotional affects:

- Cranky.
- Anxious.

Note that these symptoms may be worse in someone who has dementia.

How does dehydration affect the brain?

Severe hydration shrinks the blood vessels in the brain. When there aren't high enough fluid levels in your brain, that affects your memory and coordination.

How does dehydration affect the heart? Can dehydration cause high blood pressure?

Your heart has to work harder when there's less water in your blood.

How does dehydration affect the kidneys?

The average person urinates (pees) about six or seven times a day. If you're dehydrated, you may urinate less. This is because less water in your blood causes your kidneys to hold on to the urine.

Does dehydration cause cramping?

Loss of electrolytes, like sodium and potassium, can cause cramping. They're expelled through perspiration (sweating). Drink water, but also a sports drink to replenish your electrolytes if your fluid losses are extensive from sweating, vomiting or diarrhea.

Can medications cause dehydration?

Diuretic medications, which are prescribed to treat heart failure and high blood pressure, can increase your risk of dehydration.

Can dehydration cause shortness of breath?

Shortness of breath is not a symptom of dehydration. However, it may go alongside dehydration. For example, you might be playing a sport outside in the hot sun and get dehydrated from lack of water and also feel short of breath from all the activity.

Care and Treatment

How is dehydration diagnosed?

Don't forget that if you feel thirsty, you're already dehydrated. That's the easiest way to tell that you need more fluids.

Laboratory tests can also diagnose dehydration. Tests include:

- Low urine sodium concentration.
- Elevated plasma serum osmolality. This measures how concentrated some particles are in your blood plasma.
- Elevated creatinine. This tests kidney function.
- Elevated blood urea nitrogen. This also relates to kidney function.

What are the levels of dehydration?

Dehydration may be categorized as:

- **Mild.** You just have to take in more fluids orally (by mouth). Drink water, but replace fluids with a drink that contains electrolytes if you experience significant sweating or fluid losses from vomiting and diarrhea. You should feel better after five or 10 minutes.

- **Moderate.** Moderate dehydration requires an IV (intravenous hydration). You'll get this in an urgent care, emergency room, or hospital.
- **Severe**. See a healthcare provider if your symptoms of dehydration are severe. Call 911 or go to an emergency room.

If you're seeing a healthcare provider, they'll figure out what level you're at in order to assign you treatment.

How is dehydration treated?

Drink water. You could also try increasing your hydration with oral rehydration sachets – powders you mix in with your water.

How long does it take for the symptoms to stop after water is ingested?

You may see the symptoms of dehydration improve in as little as five to 10 minutes.

How do I prevent dehydration?

Exactly how much water do you need? That depends on your weight, age, level of activity, age, the climate of your environment and other factors. Those with diabetes, heart disease, cystic fibrosis and other conditions may need to be cautious. The amount of water you need can also depend on the climate and what clothes you're wearing. Although the standard advice is eight glasses of water per day (about 2.2 liters or 2.3 quarts per day for an adult female and about 3 liters or 3.2 quarts per day for an adult male), talk to your healthcare provider to confirm the right amount for you.

Keep track of how much fluid you drink. Drink water throughout the day, including at meals. Avoid soda, alcohol and caffeinated drinks. One way to make sure you are properly hydrated is to check your urine. If it's clear, pale or straw-colored, it's OK. If it's darker than that, keep drinking!

To avoid dehydration, active people – people playing a sport or exercising – should drink at least 16 to 20 ounces of fluids one to two hours before an outdoor activity. After that, you should consume six to 12 ounces of fluid every 10 to 15 minutes when you're outside. When you are finished with the activity, you should drink more. How much more? To replace what you have lost: at least another 16 to 24 ounces.

Which beverages hydrate the body, and which dehydrate?

Some beverages are better than others at preventing dehydration. Water is all you need if you're planning to be active in a low or moderate intensity activity, such as walking for only an hour or less. If you plan to exercise longer than that, or if you anticipate being out in the sun for more than a few hours, you may want to hydrate with some kind of sports drink. These replace not only fluid, but also electrolytes like sodium and potassium, which are lost through sweating. Too much or too little sodium and potassium in the body can cause trouble. Muscle cramping may be due to a deficiency of electrolytes.

Alcoholic and caffeinated beverages, such as coffee, teas and colas, are not recommended for optimal hydration. These fluids tend to pull water from the body and promote dehydration. Fruit juice and fruit drinks may have too many carbohydrates, too little sodium and they may upset your stomach.

Adequate hydration will keep your summer activities safer and much more enjoyable. Keep an extra pitcher of water in the refrigerator and add fresh lemons, limes, cucumber or mint for a dash of flavor.

How do I get myself and my loved ones to drink more water?

- Carry a water bottle with you. Keep it filled!
- Choose water instead of sugary drinks, including at meals.
- Add flavor. A wedge of lime or lemon might make it tastier, and more fun! You can also try some flavored drink mixes, but watch out for the sugar!
- Eat foods that are high in water content. Many soups, fruits and vegetables meet this description.

- If you don't like drinking a lot of water at once, try smaller doses spread out throughout the day.

When to Call the Doctor

When should I contact a healthcare provider about dehydration? At what point is dehydration dangerous?

The amount of water needed on a daily basis depends on many factors, so it's best to check in with your healthcare provider to determine exactly how much will keep you healthy.

Always drink water immediately if you feel thirsty. Remember – if you feel thirsty, you're already dehydrated. You may see the symptoms of dehydration improve in as little as five to 10 minutes.

If you think your symptoms of dehydration are severe, don't hesitate to seek help! Dehydration can contribute to kidney stones, kidney failure and heatstroke, all life-threatening illnesses. Call 911 or go to the emergency room right away if you have symptoms of severe dehydration, or (see below) heatstroke:

- A temperature of 103 degrees Fahrenheit or higher.
- Muscle twitching.
- Red, hot, dry skin.
- Nausea.
- Rapid pulse.
- Seizures.
- Lack of sweating.
- Confusion, altered mental state, slurred speech.
- Dizziness.
- Fainting, loss of consciousness.
- Hallucinations.

References:

- American Heart Association. Accessed 2/13/2021.Staying Hydrated - Staying Healthy. (https://www.heart.org/en/healthy-living/fitness/fitness-basics/staying-hydrated-staying-healthy)
- American Hiking Society. Accessed 2/13/2021.Avoiding Dehydration. (https://americanhiking.org/wp-content/uploads/2013/04/Avoiding-Dehydration-fact-sheet.pdf)
- Better Health While Aging. . Accessed 2/13/2021. How to Prevent, Detect, & Treat Dehydration in Aging Adults (https://betterhealthwhileaging.net/qa-how-to-prevent-diagnose-treat-dehydration-aging-adults/)
- Centers for Disease Control and Prevention Accessed 2/13/2021.. Drinking Water. (https://www.cdc.gov/healthywater/drinking/nutrition/index.html)
- Centers for Disease Control and Prevention. . Accessed 2/13/2021. Foods and Drinks for 6 to 24 Months Old (https://www.cdc.gov/nutrition/InfantandToddlerNutrition/foods-and-drinks/index.html)
- Centers for Disease Control and Prevention. . Accessed 2/13/2021. Water and Healthier Drinks (https://www.cdc.gov/healthyweight/healthy_eating/water-and-healthier-drinks.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhealthywater%2Fdrinking%2Fnutrition%2Findex.html)
- HealthFirst. ? Accessed 2/13/2021. What Happens to Your Body When You're Dehydrated (https://healthyliving.healthfirst.org/happens-body-youre-dehydrated/)
- MedlinePlus. . Accessed 2/13/2021.Dehydration (https://medlineplus.gov/dehydration.html)
- NHS. . Accessed 2/13/2021. Dehydration (https://www.nhs.uk/conditions/dehydration/)

- Renal Fellow Network. . Accessed 2/13/2021. Hypovolemia versus Dehydration (https://www.renalfellow.org/2009/04/23/hypovolemia-versus-dehydration/#:~:text=HYPOVOLEMIA%20refers%20to%20any%20condition,alone%2C%20which%20is%20termed%20DEHYDRATION.)
- U.S. Department of the Interior. . Accessed 2/13/2021. The Water in You: Water and the Human Body (https://www.usgs.gov/special-topic/water-science-school/science/water-you-water-and-human-body?qt-science_center_objects=0#qt-science_center_objects)

Terms Linked In This Article:

- headache *(https://my.clevelandclinic.org/health/diseases/9639-headaches)*
- heatstroke *(https://my.clevelandclinic.org/health/diseases/16425-heat-illness)*
- hypernatremia *(https://my.clevelandclinic.org/health/diseases/17762-hyponatremia)*
- infants and children *(https://my.clevelandclinic.org/health/articles/8276-dehydration-and-your-child)*
- urinary tract infection *(https://my.clevelandclinic.org/health/diseases/9135-urinary-tract-infections)*
- dementia *(https://my.clevelandclinic.org/health/diseases/9170-dementia)*
- electrolytes *(https://my.clevelandclinic.org/health/diagnostics/16954-electrolytes)*
- kidney stones *(https://my.clevelandclinic.org/health/diseases/15604-kidney-stones)*
- kidney failure *(https://my.clevelandclinic.org/health/diseases/17689-kidney-failure)*
- heatstroke *(https://my.clevelandclinic.org/health/diseases/16425-heat-illness)*

Last reviewed by a Cleveland Clinic medical professional on 02/16/2021.

ORIGINAL ARTICLE | https://my.clevelandclinic.org/health/treatments/9013-dehydration

DATE PUBLISHED | February 16, 2021

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National Institute of Diabetes and Digestive and Kidney Diseases

Gastroparesis

Return to Overview Page

Definition & Facts

In this section:

What is gastroparesis?

Gastroparesis, also called delayed gastric emptying, is a disorder that slows or stops the movement of food from your stomach to your small intestine. Normally, after you swallow food, the muscles in the wall of your stomach grind the food into smaller pieces and push them into your small intestine to continue digestion. When you have gastroparesis, your stomach muscles work poorly or not at all, and your stomach takes too long to empty its contents. Gastroparesis can delay digestion, which can lead to various symptoms and complications.

How common is gastroparesis?

Gastroparesis is not common. Out of 100,000 people, about 10 men and about 40 women have gastroparesis[1]. However, symptoms that are similar to those of gastroparesis occur in about 1 out of 4 adults in the United States[2, 3].

Who is more likely to get gastroparesis?

You are more likely to get gastroparesis if you

- have diabetes
- had surgery on your esophagus, stomach, or small intestine, which may injure the vagus nerve NIH. The vagus nerve controls the muscles of the stomach and small intestine.
- had certain cancer treatments, such as radiation therapy NIH on your chest or stomach area

What other health problems do people with gastroparesis have?

People with gastroparesis may have other health problems, such as

- diabetes
- scleroderma NIH
- hypothyroidism
- nervous system disorders NIH, such as migraine NIH, Parkinson's disease NIH, and multiple sclerosis NIH
- gastroesophageal reflux disease (GERD)
- eating disorders NIH
- amyloidosis NIH

What are the complications of gastroparesis?

Complications of gastroparesis may include

- dehydration due to repeated vomiting
- malnutrition due to poor absorption of nutrients NIH
- blood glucose, also called blood sugar, levels that are harder to control, which can worsen diabetes
- low calorie intake
- bezoars
- losing weight without trying
- lower quality of life

References

[1] Jung HK, Choung RS, Locke GR III, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*. 2009;136(4):1225–1233.

[2] Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Digestive Diseases and Sciences*. 1993;38(9):1569–1580.

[3] Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clinical Gastroenterology and Hepatology*. 2005;3(6):543–552.

Symptoms & Causes

What are the symptoms of gastroparesis?

The symptoms of gastroparesis may include

- feeling full soon after starting a meal
- feeling full long after eating a meal
- nausea
- vomiting
- too much bloating
- too much belching
- pain in your upper abdomen
- heartburn
- poor appetite

Certain medicines may delay gastric emptying or affect motility, resulting in symptoms that are similar to those of gastroparesis. If you have been diagnosed with gastroparesis, these medicines may make your symptoms worse. Medicines that may delay gastric emptying or make symptoms worse include the following:

- narcotic pain medicines, such as codeine NIH , hydrocodone NIH , morphine NIH , oxycodone NIH , and tapentadol NIH
- some antidepressants NIH , such as amitriptyline NIH , nortriptyline NIH , and venlafaxine NIH
- some anticholinergics —medicines that block certain nerve signals
- some medicines used to treat overactive bladder
- pramlintide NIH

These medicines do not cause gastroparesis.

If you have gastroparesis, you may feel full long after eating a meal.

When should I seek a doctor's help?

You should seek a doctor's help right away if you have any of the following signs or symptoms:

- severe pain or cramping in your abdomen
- blood glucose levels that are too high or too low
- red blood in your vomit, or vomit that looks like coffee grounds
- sudden, sharp stomach pain that doesn't go away
- vomiting for more than an hour
- feeling extremely weak or fainting
- difficulty breathing
- fever

You should seek a doctor's help if you have any signs or symptoms of dehydration, which may include

- extreme thirst and dry mouth
- urinating less than usual
- feeling tired
- dark-colored urine
- decreased skin turgor, meaning that when your skin is pinched and released, the skin does not flatten back to normal right away
- sunken eyes or cheeks
- light-headedness or fainting

You should seek a doctor's help if you have any signs or symptoms of malnutrition, which may include

- feeling tired or weak all the time
- losing weight without trying
- feeling dizzy
- loss of appetite
- abnormal paleness of the skin

What causes gastroparesis?

In most cases, doctors aren't able to find the underlying cause of gastroparesis, even with medical tests. Gastroparesis without a known cause is called idiopathic gastroparesis.

Diabetes is the most common known underlying cause of gastroparesis. Diabetes can damage nerves, such as the vagus nerve and nerves and special cells, called pacemaker cells, in the wall of the stomach. The vagus nerve controls the muscles of the stomach and small intestine. If the vagus nerve is damaged or stops working, the muscles of the stomach and small intestine do not work normally. The movement of food through the digestive tract is then slowed or stopped. Similarly, if nerves or pacemaker cells in the wall of the stomach are damaged or do not work normally, the stomach does not empty.

In addition to diabetes, other known causes of gastroparesis include

- injury to the vagus nerve due to surgery on your esophagus, stomach, or small intestine
- hypothyroidism
- certain autoimmune diseases, such as scleroderma NIH
- certain nervous system NIH disorders, such as Parkinson's disease NIH and multiple sclerosis NIH
- viral infections of your stomach

Diagnosis

How do doctors diagnose gastroparesis?

Doctors diagnose gastroparesis based on your medical history, a physical exam, your symptoms, and medical tests. Your doctor may also perform medical tests to look for signs of gastroparesis complications and to rule out other health problems that may be causing your symptoms.

Medical history

Your doctor will ask about your medical history. He or she will ask for details about your current symptoms and medicines, and current and past health problems such as diabetes, scleroderma NIH, nervous system NIH disorders, and hypothyroidism.

Your doctor may also ask about

- the types of medicines you are taking. Be sure to tell your doctor about **all** prescription medicines, over-the-counter medicines, and dietary supplements NIH you are taking.
- whether you've had surgery on your esophagus, stomach, or small intestine
- whether you've had radiation therapy NIH on your chest or stomach area

Physical exam

During a physical exam, your doctor will

- check your blood pressure, temperature, and heart rate
- check for signs of dehydration and malnutrition
- check your abdomen for unusual sounds, tenderness, or pain

Your doctor will check your abdomen for tenderness or pain.

What medical tests do doctors use to diagnose gastroparesis?

Doctors use lab tests, upper gastrointestinal (GI) endoscopy, imaging tests, and tests to measure how fast your stomach is emptying its contents to diagnose gastroparesis.

Lab tests

Your doctor may use the following lab tests:

- Blood tests NIH can show signs of dehydration, malnutrition, inflam[illegible], and infection. Blood tests can also show whether your blood glucose levels are too high or too low.
- Urine tests NIH can show signs of diabetes, dehydration, infection, and kidney problems.

Upper GI endoscopy

Your doctor may perform an upper GI endoscopy to look for problems in your upper digestive tract that may be causing your symptoms.

Imaging tests

Imaging tests can show problems, such as stomach blockage or intestinal obstruction, that may be causing your symptoms. Your doctor may perform the following imaging tests:

- upper GI series
- ultrasound of your abdomen

Tests to Measure Stomach Emptying

Your doctor may perform one of more of the following tests to see how fast your stomach is emptying its contents.

- **Gastric emptying scan, also called gastric emptying scintigraphy**. For this test, you eat a bland meal—such as eggs or an egg substitute—that contains a small amount of radioactive material NIH. A camera outside your body scans your abdomen to show where the radioactive material is located. By tracking the radioactive material, a health care professional can measure how fast your stomach empties after the meal. The scan usually takes about 4 hours.
- **Gastric emptying breath test**. For this test, you eat a meal that contains a substance that is absorbed in your intestines and eventually passed into your breath. After you eat the meal, a health care professional collects samples of your breath over a period of a few hours—usually about 4 hours. The test can show how fast your stomach empties after the meal by measuring the amount of the substance in your breath.
- **Wireless motility capsule, also called a SmartPill.** The SmartPill is a small electronic device that you swallow. The capsule moves through your entire digestive tract and sends information to a recorder hung around your neck or clipped to your belt. A health care professional uses the information to find out how fast or slow your stomach empties, and how fast liquid and food move through your small intestine and large intestine. The capsule will pass naturally out of your body with a bowel movement.

Treatment

How do doctors treat gastroparesis?

How doctors treat gastroparesis depends on the cause, how severe your symptoms and complications are, and how well you respond to different treatments. Sometimes, treating the cause may stop gastroparesis. If diabetes is causing your gastroparesis, your health care professional will work with you to help control your blood glucose levels. When the cause of your gastroparesis is not known, your doctor will provide treatments to help relieve your symptoms and treat complications.

Changing eating habits

Changing your eating habits can help control gastroparesis and make sure you get the right amount of nutrients NIH, calories, and liquids. Getting the right amount of nutrients, calories, and liquids can also treat the disorder's two main complications: malnutrition and dehydration.

Your doctor may recommend that you

- eat foods low in fat and fiber
- eat five or six small, nutritious meals a day instead of two or three large meals
- chew your food thoroughly
- eat soft, well-cooked foods
- avoid carbonated, or fizzy, beverages
- avoid alcohol
- drink plenty of water or liquids that contain glucose and electrolytes, such as
    - low-fat broths or clear soups
    - naturally sweetened, low-fiber fruit and vegetable juices
    - sports drinks
    - oral rehydration solutions
- do some gentle physical activity after a meal, such as taking a walk
- avoid lying down for 2 hours after a meal
- take a multivitamin each day

If your symptoms are moderate to severe, your doctor may recommend drinking only liquids or eating well-cooked solid foods that have been processed into very small pieces or paste in a blender.

Controlling blood glucose levels

If you have gastroparesis and diabetes, you will need to control your blood glucose levels, especially hyperglycemia. Hyperglycemia may further delay the emptying of food from your stomach. Your doctor will work with you to make sure your blood glucose levels are not too high or too low and don't keep going up or down. Your doctor may recommend

- taking insulin more often, or changing the type of insulin you take
- taking insulin after, instead of before, meals
- checking your blood glucose levels often after you eat, and taking insulin when you need it

Your doctor will give you specific instructions for taking insulin based on your needs and the severity of your gastroparesis.

Medicines

Your doctor may prescribe medicines that help the muscles in the wall of your stomach work better. He or she may also prescribe medicines to control nausea and vomiting and re ain.

Your doctor may prescribe one or more of the following medicines:

- **Metoclopramide** NIH. This medicine increases the tightening, or contraction, of the muscles in the wall of your stomach and may improve gastric emptying. Metoclopramide may also help relieve nausea and vomiting.
- **Domperidone**. This medicine also increases the contraction of the muscles in the wall of your stomach and may improve gastric emptying. However, this medicine is available for use only under a special program administered by the U.S. Food and Drug Administration.
- **Erythromycin** NIH. This medicine also increases stomach muscle contraction and may improve gastric emptying.
- **Antiemetics**. Antiemetics are medicines that help relieve nausea and vomiting. Prescription antiemetics include ondansetron NIH , prochlorperazine NIH , and promethazine NIH. Over-the-counter antiemetics include bismuth subsalicylate NIH and diphenhydramine NIH . Antiemetics do not improve gastric emptying.
- **Antidepressants** NIH. Certain antidepressants, such as mirtazapine NIH, may help relieve nausea and vomiting. These medicines may not improve gastric emptying.
- **Pain medicines**. Pain medicines that are not narcotic pain medicines may reduce pain in your abdomen due to gastroparesis.

Your doctor may prescribe medicines that help the muscles in the wall of your stomach work better.

Oral or nasal tube feeding

In some cases, your doctor may recommend oral or nasal tube feeding to make sure you're getting the right amount of nutrients and calories. A health care professional will put a tube either into your mouth or nose, through your esophagus and stomach, to your small intestine. [illegible]d nasal tube feeding bypass your stomach and deliver a special liquid food directly into your small in[illegible].

Jejunostomy tube feeding

If you aren't getting enough nutrients and calories from other treatments, your doctor may recommend jejunostomy tube feeding. Jejunostomy feedings are a longer term method of feeding, compared to oral or nasal tube feeding.

Jejunostomy tube feeding is a way to feed you through a tube placed into part of your small intestine called the jejunum. To place the tube into the jejunum, a doctor creates an opening, called a jejunostomy, in your abdominal wall that goes into your jejunum. The feeding tube bypasses your stomach and delivers a liquid food directly into your jejunum.

Parenteral nutrition

Your doctor may recommend parenteral, or intravenous (IV), nutrition if your gastroparesis is so severe that other treatments are not helping. Parenteral nutrition delivers liquid nutrients directly into your bloodstream. Parenteral nutrition may be short term, until you can eat again. Parenteral nutrition may also be used until a tube can be placed for oral, nasal, or jejunostomy tube feeding. In some cases, parental nutrition may be long term.

Venting gastrostomy

Your doctor may recommend a venting gastrostomy to relieve pressure inside your stomach. A doctor creates an opening, called a gastrostomy, in your abdominal wall and into your stomach. The doctor then places a tube through the gastrostomy into your stomach. Stomach contents can then flow out of the tube and relieve pressure inside your stomach.

Gastric electrical stimulation

Gastric electrical stimulation (GES) uses a small, battery-powered device to send mild electrical pulses to the nerves and muscles in the lower stomach. A surgeon puts the device under the skin in your lower abdomen and attaches wires from the device to the muscles in the wall of your stomach. GES can help decrease long-term nausea and vomiting.

GES is used to treat people with gastroparesis due to diabetes or unknown causes only, and only in people whose symptoms can't be controlled with medicines.

How can I prevent gastroparesis?

Gastroparesis without a known cause, called idiopathic gastroparesis, cannot be prevented.

If you have diabetes, you can prevent or delay nerve damage that can cause gastroparesis by keeping your blood glucose levels within the target range that your doctor thinks is best for you. Meal planning, physical activity, and medicines, if needed, can help you keep your blood glucose levels within your target range.

Eating, Diet, & Nutrition

How can my diet help prevent or relieve gastroparesis?

What you eat can help prevent or relieve your gastroparesis symptoms. If you have diabetes, following a healthy meal plan can help you manage your blood glucose levels. What you eat can also help make sure you get the right amount of nutrients NIH, calories, and liquids if you are malnourished or dehydrated from gastroparesis.

What should I eat and drink if I have gastroparesis?

If you have gastroparesis, your doctor may recommend that you eat or drink

- foods and beverages that are low in fat
- foods and beverages that are low in fiber
- five or six small, nutritious meals a day instead of two or three large meals
- soft, well-cooked foods

If you are unable to eat solid foods, your doctor may recommend that you drink

- liquid nutrition meals
- solid foods puréed in a blender

Your doctor may also recommend that you drink plenty of water or liquids that contain glucose and electrolytes, such as

- low-fat broths and clear soups
- low-fiber fruit and vegetable juices
- sports drinks
- oral rehydration solutions

If your symptoms are moderate to severe, your doctor may recommend drinking only liquids or eating well-cooked solid foods that have been processed into very small pieces or paste in a blender.

What should I avoid eating and drinking if I have gastroparesis?

If you have gastroparesis, you should avoid

- foods and beverages that are high in fat
- foods and beverages that are high in fiber
- foods that can't be chewed easily
- carbonated, or fizzy, beverages
- alcohol

Your doctor may refer you to a dietitian to help you plan healthy meals that are easy for you to digest and give you the right amount of nutrients, calories, and liquids.

Clinical Trials

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and other components of the National Institutes of Health (NIH) conduct and support research into many diseases and conditions.

What are clinical trials and are they right for you?

Clinical trials are part of clinical research and at the heart of all medical advances. Clinical trials look at new ways to prevent, detect, or treat disease. Researchers also use clinical trials to look at other aspects of care, such as improving the quality of life for people with chronic illnesses. Find out if clinical trials are right for you NIH.

Watch a video of NIDDK Director Dr. Griffin P. Rodgers explaining the importance of participating in clinical trials.

What clinical trials are open?

Clinical trials that are currently open and are recruiting can be viewed at www.ClinicalTrials.gov NIH.

Last Reviewed January 2018

This content is provided as a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health. The NIDDK translates and disseminates research findings to increase knowledge and understanding about health and disease among patients, health professionals, and the public. Content produced by the NIDDK is carefully reviewed by NIDDK scientists and other experts.

The NIDDK would like to thank:
Michael Camilleri, M.D., Mayo Clinic, Rochester

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National Institute of Diabetes and Digestive and Kidney Diseases

Dumping Syndrome

Return to Overview Page

Definition & Facts

In this section:

What is dumping syndrome?

Dumping syndrome is a group of symptoms, such as diarrhea, nausea, or feeling light-headed or tired after a meal, that are caused by rapid gastric emptying. Rapid gastric emptying is a condition in which food moves too quickly from your stomach to your duodenum.

Are there different forms of dumping syndrome?

Dumping syndrome has two forms

- early dumping syndrome, in which you have symptoms within 30 minutes after eating a meal
- late dumping syndrome, in which you have symptoms 1 to 3 hours after eating a meal

Early and late dumping syndromes have different symptoms.

Who is more likely to have dumping syndrome?

Dumping syndrome most often occurs in people who've had surgery of the stomach or esophagus.

How common is dumping syndrome?

About 1 in 10 people who have stomach surgery develop dumping syndrome.[1] Dumping syndrome is more common after some types of surgery than others.

For example, dumping syndrome is more common after gastric bypass bariatric surgery than after other types of bariatric surgery. Dumping syndrome is also more common after a gastrectomy that removes the entire stomach than after a gastrectomy that removes only part of the stomach.

Early dumping syndrome is more common than late dumping syndrome. Some people have both forms. Among people with dumping syndrome, about 1 in 4 have late dumping syndrome alone.[2]

What are the complications of dumping syndrome?

Some people with severe dumping syndrome may avoid eating to prevent symptoms. This can lead to weight loss and malnutrition.

Avoiding eating to prevent symptoms can lead to weight loss and malnutrition.

References

[1] Berg P, McCallum R. Dumping syndrome: a review of the current concepts of pathology, diagnosis, and treatment. *Digestive Diseases and Sciences*. 2016;61(1):11–18.

[2] van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. *Obesity Reviews*. 2017;18(1):68-85.

Symptoms & Causes

What are the symptoms of dumping syndrome?

The symptoms of early and late dumping syndrome are different. Symptoms may vary from person to person.

Early dumping syndrome

Symptoms of early dumping syndrome occur within 30 minutes after you eat a meal. You may have digestive symptoms, such as

- diarrhea
- feeling uncomfortably full or bloated
- nausea
- pain and cramping in your abdomen
- stomach "growling" or rumbling sounds

Other symptoms of early dumping syndrome may include

- feeling light-headed or fainting
- feeling tired or needing to lie down
- flushing, or reddening of your face, neck, or upper chest
- having a fast or irregular heartbeat
- headache
- sweating

Symptoms of early dumping syndrome may include pain in your abdomen and feeling tired or needing to lie down.

Late dumping syndrome

Symptoms of late dumping syndrome occur 1 to 3 hours after you eat a meal. The symptoms of late dumping syndrome are caused by low blood glucose, also called low blood sugar or hypoglycemia. Symptoms of late dumping syndrome may include

- feeling light-headed or fainting
- feeling shaky or jittery
- feeling tired
- having a fast or irregular heartbeat
- trouble concentrating
- sweating
- weakness

What causes dumping syndrome?

Rapid gastric emptying, a condition in which food moves too quickly from your stomach to your duodenum, causes dumping syndrome.

Your digestive tract makes and releases hormones that control how your digestive system works. When food moves too quickly from your stomach to your duodenum, your digestive tract releases more hormones than normal. Fluid also moves from your blood stream into your small intestine. Experts think that the excess hormones and movement of fluid into your small intestine cause the symptoms of early dumping syndrome.

Experts also think that these excess hormones may cause your pancreas to produce too much insulin. Too much insulin can lead to low blood glucose 1 to 3 hours after a meal, causing the symptoms of late dumping syndrome.

Causes of rapid gastric emptying

The most common cause of rapid gastric emptying and dumping syndrome is surgery of the stomach or esophagus. Types of surgery that may lead to dumping syndrome include

- bariatric surgery, such as gastric bypass surgery and gastric sleeve surgery. These operations help people lose weight.
- esophagectomy, which is surgery to remove part of the esophagus. Doctors use this surgery to treat problems of the esophagus, such as esophageal cancer NIH and Barrett's esophagus.
- fundoplication, which is surgery to sew the top of the stomach around the esophagus. Doctors use this surgery to treat gastroesophageal reflux disease and hiatal hernia.
- gastrectomy, which is surgery to remove all or part of the stomach. Doctors use this surgery to treat stomach cancer NIH and peptic ulcers.
- vagotomy, which is surgery to cut the vagus nerve in the stomach so that the stomach makes less acid. Doctors use this surgery to treat peptic ulcers.

Rapid gastric emptying sometimes occurs in people who have not had stomach surgery. For example, rapid gastric emptying may occur in people who have

- recently developed diabetes, especially type 2 diabetes
- pancreatic exocrine insufficiency, a condition in which the pancreas doesn't make enough of certain enzymes, causing problems with digestion
- duodenal ulcers
- Zollinger-Ellison syndrome

In some cases, a person has rapid gastric emptying and dumping syndrome but the cause is unknown.

Diagnosis

How do doctors diagnose dumping syndrome?

To diagnose dumping syndrome, your doctor will review your medical history and symptoms and may order tests to confirm the diagnosis.

Medical history

Your doctor will review your medical history, including any history of stomach or esophagus surgery.

Review of your symptoms

Doctors typically diagnose dumping syndrome based on symptoms. Doctors may use a scoring system that assigns point values to different symptoms or may ask you to complete a special questionnaire. Scoring systems and questionnaires can help your doctor find out if you most likely have dumping syndrome or a different health problem.

Doctors typically diagnose dumping syndrome based on symptoms.

What tests do doctors use to diagnose dumping syndrome?

Doctors may use the following tests to confirm that you have dumping syndrome and rule out other conditions with similar symptoms.

Oral glucose tolerance test

You'll be asked to fast—not eat or drink anything except water—for at least 10 hours before the test. For the test, you'll drink a solution that contains glucose, a form of sugar. A health care professional will take blood samples and check your blood pressure and heart rate before you drink the glucose solution and then every 30 minutes for up to 3 hours.

The health care professional will use blood samples to measure your blood glucose level, also called blood sugar, and your hematocrit. A hematocrit test NIH measures how much of your blood is made up of red blood cells. When you have dumping syndrome, fluid moves from your blood stream into your small intestine after a meal. With less fluid in your blood, the portion of your blood made up of red blood cells increases.

Your doctor may diagnose dumping syndrome if

- your heart rate increases by 10 beats per minute 30 minutes after you drink the glucose solution
- your blood test results show a 3 percent increase in your hematocrit 30 minutes after you drink the glucose solution
- your blood test results show low blood glucose 1 to 3 hours after you drink the glucose solution

Gastric emptying scan

A gastric emptying scan is also called gastric emptying scintigraphy. For this test, you eat a bland meal—such as eggs or an egg substitute—that contains a small amount of radioactive material NIH. A camera outside your body scans your abdomen to show where the radioactive material is located. By tracking the radioactive material, a health care professional can measure how fast your stomach empties after the meal. The health care professional will scan your abdomen several times to see how fast your stomach empties for up to 4 hours after the meal. The test can help confirm a diagnosis of dumping syndrome.

Other tests

Your doctor may order additional tests, such as upper gastrointestinal (GI) endoscopy or upper GI series, to examine the structure of your esophagus, stomach, and small intestine and to check for signs of other health problems.

Treatment

How do doctors treat dumping syndrome?

Doctors treat dumping syndrome by recommending changes to how and what you eat, medicines, and, in some cases, surgery.

Changing your eating habits

The first step in treating dumping syndrome is changing how and what you eat. Many people with dumping syndrome have mild symptoms that improve over time with simple changes in eating and diet.

Medicines

If changing your eating habits doesn't improve your symptoms, you doctor may prescribe medicines.

Octreotide (Sandostatin) NIH may help reduce the symptoms of dumping syndrome. This medicine comes in short- and long-acting forms

- The short-acting form is injected under your skin 2 to 4 times a day before meals. A health care professional may inject the medicine or may train you, a friend, or a relative to inject the medicine.
- The long-acting form is injected into your buttocks muscles once every 4 weeks. Side effects may include pain where the medicine is injected, diarrhea, weight gain, gallstones, and steatorrhea.

Doctors may prescribe acarbose (Prandase, Precose) NIH to help reduce the symptoms of late dumping syndrome. Side effects of acarbose may include bloating, diarrhea, and flatulence.

If changing your eating habits doesn't improve your symptoms, your doctor may prescribe medicines.

Surgery

If stomach or esophagus surgery caused your dumping syndrome and other treatments don't improve your symptoms enough, your doctor may recommend another surgery to try to correct dumping syndrome. The type of surgery your doctor recommends depends on the type of surgery that led to your dumping syndrome. Surgery to correct dumping syndrome doesn't always work.

Can I prevent dumping syndrome?

Experts have not found a way for people to prevent dumping syndrome. If you have dumping syndrome, you may be able to prevent future symptoms with treatments such as changing your eating habits.

How should I change my eating habits if I have dumping syndrome?

The first step in treating dumping syndrome is changing how and what you eat. Many people with dumping syndrome have mild symptoms that improve over time with simple changes in eating and diet.

Changing how you eat

Your doctor may recommend

- eating six small meals a day, instead of three larger meals
- waiting to drink liquids until at least 30 minutes after a meal
- lying down for 30 minutes after you eat a meal

Your doctor may recommend eating six small meals a day, instead of three larger meals.

Changing what you eat

Your doctor may recommend

- eating more protein, fiber, and fat
- eating less carbohydrates NIH and choosing foods that contain complex carbohydrates—such as whole grains, fruits, and vegetables—rather than foods that contain simple sugars—such as candies, cookies, sugary drinks, and other foods and drinks that have added sugar

- avoiding milk and milk products
- adding pectin or guar gum—plant extracts used as thickening agents—to your food

Clinical Trials

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and other components of the National Institutes of Health (NIH) conduct and support research into many diseases and conditions, including digestive diseases.

What are clinical trials for dumping syndrome?

Clinical trials—and other types of clinical studies NIH—are part of medical research and involve people like you. When you volunteer to take part in a clinical study, you help doctors and researchers learn more about disease and improve health care for people in the future.

Researchers are studying many aspects of dumping syndrome, such as the risk for dumping syndrome following different types of stomach or esophagus surgery.

Find out if clinical studies are right for you. NIH

Watch a video of NIDDK Director Dr. Griffin P. Rodgers explaining the importance of participating in clinical trials.

What clinical studies for dumping syndrome are looking for participants?

You can find clinical studies on dumping syndrome at www.ClinicalTrials.gov NIH. In addition to searching for federally funded studies, you can expand or narrow your search to include clinical studies from industry, universities, and individuals; however, the NIH does not review these studies and cannot ensure they are safe. Always talk with your health care provider before you participate in a clinical study.

Last Reviewed January 2019

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The NIDDK would like to thank:
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What Is an Enteral Feeding Tube?

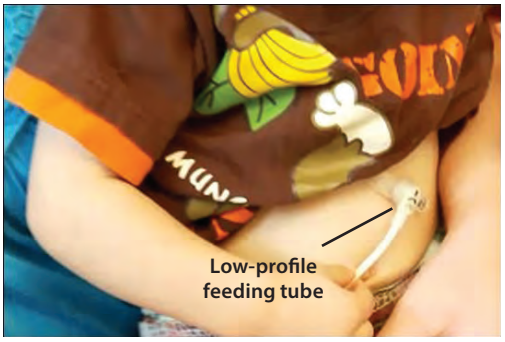
Enteral refers to within the digestive system or intestine. Enteral feeding tubes allow liquid food to enter your stomach or intestine through a tube. The soft, flexible tube enters a surgically created opening in the abdominal wall called an ostomy. An enterostomy tube in the stomach is called a gastrostomy. A tube in the small intestine is called a jejunostomy. The site on the abdomen where the tube is inserted is called a stoma. The location of the stoma depends on your specific operation and the shape of your abdomen.

Most stomas:

- Lie flat against your body
- Are round in shape
- Are red and moist (similar to the inside of your mouth)
- Have no feeling

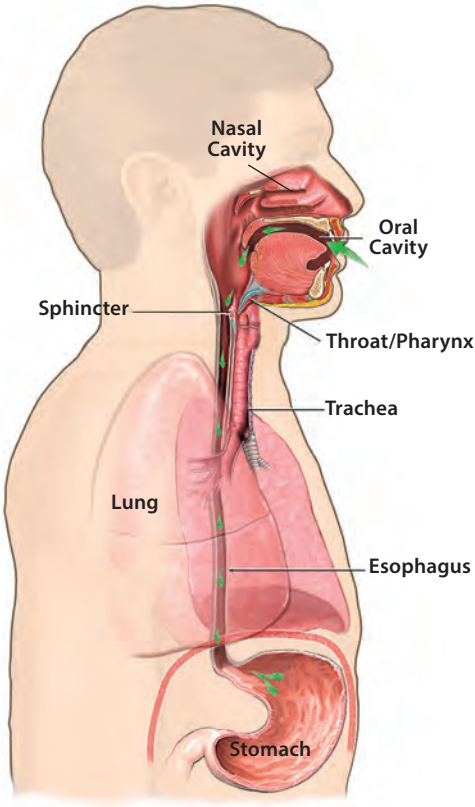
Who Needs an Enteral Feeding Tube?

Cancer, trauma, nervous system and digestive system disorders, and congenital birth defects can cause difficulty in feeding. Some people also have difficulty swallowing, which increases the chance that they will breathe in food (aspirate). People who have difficulties feeding can benefit from a feeding tube. Your doctor will explain to you the specific reasons why you or your family member need a feeding tube. For some, a feeding tube is a new way of life, but for others, the tube is temporary and used until the problem can be treated or repaired.

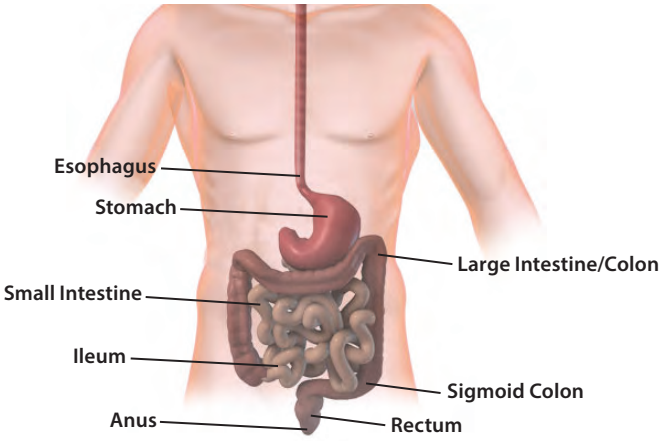


Understanding Your Digestive System

When food enters your oral cavity (mouth), the lips and tongue move it toward the back of the throat. The throat (pharynx) is the passageway leading from the mouth and nose to the esophagus and larynx (voice box). At the back of the throat, two tubes form. The trachea (airway) carries air to the lungs. The esophagus (feeding tube) moves the food down into the stomach. When food moves into the esophagus, the opening at the top of the esophagus (sphincter) tightens to stop the upward movement of the food. The pharynx acts as a doorway. When food is passing, the opening to the airway closes.

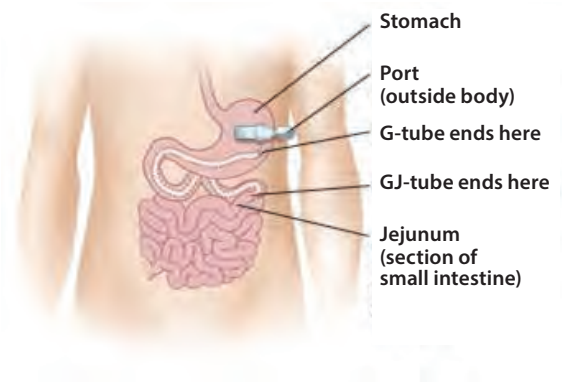


When food reaches the stomach, it is broken down into very small pieces. It then moves into the small intestine, where enzymes break down food into thick liquid. This thick liquid passes further through the small intestine, where nutrients, vitamins, and water are absorbed. The liquid then passes through the large intestine (colon). Water is absorbed from the stool in the colon. It becomes more solid and eventually moves out through the rectum.



Types of Feeding Tubes and How They Are Inserted

The type of feeding tube and the procedure to place it will depend on the patient's condition, age, and other health factors. Feeding tubes can vary in length and number of ports or openings.



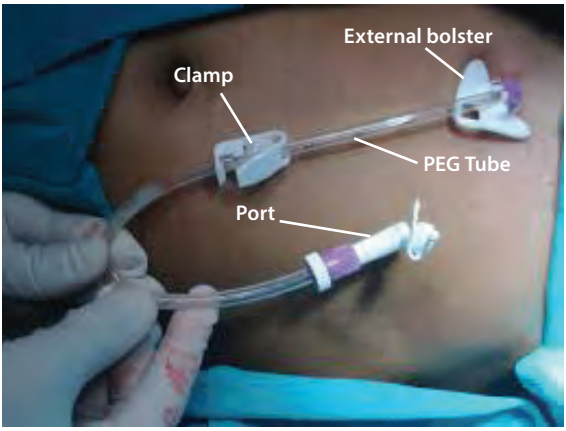
The main types of tubes include:

- **Long gastric tubes** connect directly to tubing or syringes for feedings. They may have 1 or 2 ports as well as a port for placement of water into the internal balloon.
- **Low-profile gastric tubes or gastric buttons** lay flat on the abdomen when not in use and require an extension set to be attached for feedings. They also may have a port for placement of water into the internal balloon.
- **Gastro-jejunostomy tubes (GJ-tubes or low-profile GJ-buttons)** pass through the stomach and into the small intestine (jejunum). Feedings and medication can be delivered into the stomach or small intestine depending on the patient's needs. These usually have separate ports for the stomach and the jejunum as well as a port for placement of water into the internal balloon.
- **Jejunostomy tubes (J-tubes)** enter the jejunum (small intestine) directly and allow slow feedings to the jejunum only. These look similar to long gastric tubes.

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG) TUBES

Percutaneous endoscopic gastrostomy (PEG) is the name of a procedure where a G-tube is placed by endoscopy. Placement of a PEG tube can be done under local anesthesia with sedation. A narrow tube with a light on the end (endoscope) is inserted in the mouth and moved down into the stomach. A puncture is made with large needle through the skin over the stomach, and a heavy string is pulled through it by the endoscope. The string comes out the mouth and attaches to a long tube, which is then pulled into the stomach and out of the skin incision. A bumper on the end of the tube keeps it inside the stomach, and a bolster keeps it in place from the outside. These are initially long tubes that can be changed to low-profile devices later.

The long tube may also have a Y-port that allows for one side to connect directly to the feeding and an opening for medications and water. The term "PEG" is often used to describe all G-tubes.



PERCUTANEOUS RADIOLOGIC GASTROSTOMY (PRG) TUBES

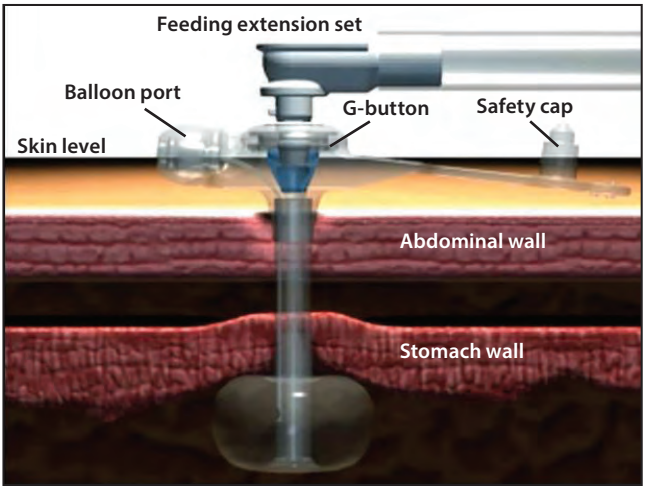
Percutaneous radiologic gastrostomy (PRG) is the name of another procedure where a G-tube is placed in the stomach. This procedure is done under local anesthesia with sedation. The abdomen is viewed by fluoroscopy, a continuous X-ray image on a monitor. A puncture is made with a large needle through the skin over the stomach. A larger opening is then created so that the gastrostomy tube can be inserted into the stomach. The tube is held in the stomach with an internal balloon and a bumper on the outside. These can be either long tubes or low-profile tubes.

SURGICAL G-TUBES AND SKIN-LEVEL DEVICES/ LOW-PROFILE BUTTONS

Surgical gastrostomy tubes are inserted in the operating room under general anesthesia. Either a minimally invasive approach (laparoscopy) or a standard open operation (surgery) is used to insert the feeding tube through the abdominal wall into the stomach. The tube has an internal balloon or bumper to hold it in place, but the stomach is also sutured (sewn) to the inside of the abdominal wall. Many pediatric patients receive a laparoscopic primary low-profile/button device. Long tubes may be changed to low-profile tubes once the tract has healed—usually 6 weeks to 3 months later, depending on the technique.

Low-profile button


Low-profile button



GASTRO-JEJUNAL (GJ) TUBES

Gastrojejunal or GJ-tubes are used when feedings need to bypass the mouth, esophagus, and stomach. These tubes or low-profile devices are usually inserted through the existing healed tract of a G-tube. The tube end is moved from the stomach into the small intestine by guide wires under X-ray imaging. They can also be positioned by endoscopy or at the time of an operation. These are occasionally placed as the first tube by any of the methods described above.

Gastrojejunal (GJ) tube

The GJ-tube has two ports: gastric and jejunal. The gastric port (marked "G") is used to access the stomach and is usually used for medication. The jejunal port (marked "J") is used for feeding.

JEJUNOSTOMY (J) TUBES

A jejunostomy (J) tube is also used when feedings need to bypass the stomach. They are usually placed at the time of a related operation but can also be placed radiologically. The J-tube is inserted through the wall of the intestine. The tube is secured on the outside of the abdomen, and a small balloon may help keep it in place inside the jejunum (small intestine).

When feedings are delivered into the small intestine by either GJ-tube or J-tube, they must be slow, continuous feedings, since the intestine cannot store food like the stomach does.

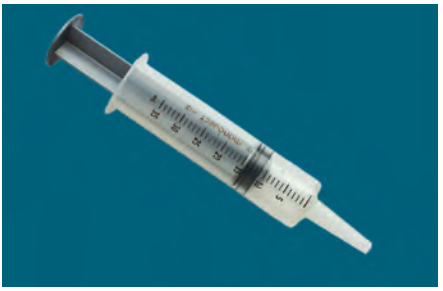
Feeding Tube Supplies

Your supplies are usually delivered to your home. Supplies may include syringes, a feeding bag, a pole, feeding solution, a pump, and a backpack for carrying the pump.

SYRINGES

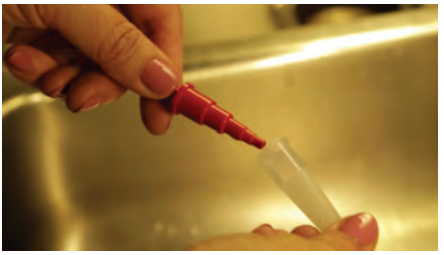
There are different types and sizes of syringes used with tube feedings. Large 60 mL syringes are used to give bolus syringe feedings, flush or check placement of a tube, or vent a tube. Smaller 10 mL syringes are generally used to flush children's tubes or give medication. Smaller 5 mL syringes are generally used to inflate the balloon that holds the tube in the stomach with water. There are markings on the outside of each syringe that you can use to measure how much formula or water to give.

Slip-tip syringe



Catheter-tip syringe

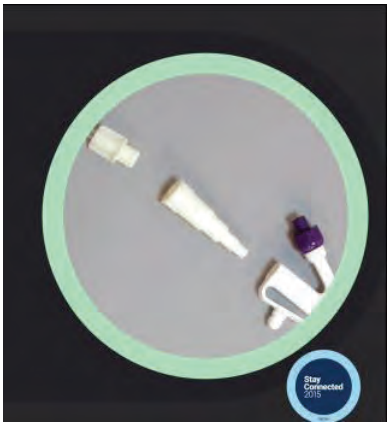
Twist-tip syringe



Transition adapter

FEEDING TUBE CONNECTORS

In 2015, a conversion took place to enable all feeding tube connectors and syringes to only fit other feeding tube supplies and not other tubes that enter the body. During this conversion, adapters will be used between syringes and tubes so older supplies may still be used with feeding tubes. You may be supplied with any of the various syringes, connectors, or adapters seen below. When the conversion is complete, all syringes and feeding tube connectors will have an ENFit™ twist tip that will secure the connection.



2015 transition connector to feeding tube

ENFit feeding set to feeding tube connector

When the connector transition is complete, all feeding tube syringes and feeding sets will have ENFit twist connector safety features

Image credit to Global Enteral Device Supplier Association (GEDSA)

For more information, go to *www.stayconnected.org*

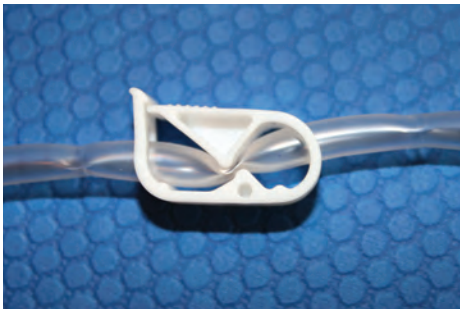
FEEDING TUBE BAGS AND EXTENSION SETS

A feeding tube bag holds the feeding solution. The bag is filled with feeding solution through the opening at the top.

Feeding tube bags can attach to a pump to deliver a consistent flow of feeding or hang for gravity flow. The bag has clamps that open and close.

One end of the extension/feed set is attached to the feeding device while the other end is connected to the food source. Between feeds, the extension/feed set can be removed after flushing the device at the end of the feeding. Extension sets are often replaced every 1 to 2 weeks.

Fill the feeding bag



Tubing clamped

Feeding extension set

PUMPS AND POLES

An enteral feeding pump can deliver feedings at a steady rate. The pump is electrical or battery operated, and it can be rented or purchased from a medical supply company. The medical supply company will help you set up the pump and give you instructions for its use.

Feeding pumps come in a variety of sizes, and some are portable for travel. The pump can be attached to a pole on wheels or placed in a backpack.

If the pump is running on battery power, it has alarms that alert you about the following problems:

- If there is a blockage in the flow of the feeding
- If there is a kink in the feeding tube
- If the feeding bag is empty

GAUZE DRESSINGS

If there is any drainage at the site, gauze dressings may be placed around the stoma site for the first few days after the tube is inserted. But they are not to be used routinely for everyday care of the feeding tube.

MEDICATIONS AND DYSPHAGIA/ SWALLOWING RISKS

[Some of the medications that can impact swallowing and why this happens]

Dysphagia as a side effect of medication

- Medications that affect the smooth and striated muscles of the esophagus that are involved in swallowing may cause dysphagia.

Medications with anticholinergic or antimuscarinic effects	
Benztropine mesylate (Cogentin)	given for movement related effects caused by some psychotropic meds
Oxybutynin (Ditropan)	improves bladder capacity
Propantheline (Pro-Banthine)	inhibits the release of stomach acid
Tolterodine (Detrol)	affects bladder capacity

- Medications that cause dry mouth (xerostomia) may interfere with swallowing by impairing the person's ability to move food

Medications that cause Dry mouth (xerostomia)	
ACE Inhibitors- used for high blood pressure	Captopril (Capoten) Lisinopril (Prinivil, Zestril)
Antiarrythmics- cardiac preparations	Disopyramide (Norpace) Mexiletine (Mexitil) Procainamide (Procan)
Antiemetics- used for nausea	Meclizine (Antivert) Metoclopramide (Reglan) Prochlorperazine (Compazine)
Antihistamines and decongestants- used for cold symptoms	Chlorpheniramine (Chlor-Trimeton) Diphenhydramine (Benadryl) Pseudoephedrine (Sudafed)
Calcium channel blockers- used for chronic chest pain due to angina	Amlodipine (Norvasc)
Diuretics- given to get rid of excess fluid in body	Ethacrynic adic (Edecrin)
SSRIs (Selective serotonin reuptake inhibitors)- antidepressant medications	Citalopram (Celexa) Fluoxetine (Prozac) Nefazodone (Serzone) Paroxetine (Paxil) Sertraline (Zoloft) Venlafaxine (Effexor)
* see also Antipsychotic/Neuroleptic medication list below	

- Local anesthetics such as Novocain which is often used for dental work may temporarily cause a loss of sensation that may affect swallowing before it wears off.

- Antipsychotic/ Neuroleptic medications given for treatment of psychiatric disorders may affect swallowing as many of them produce dry mouth and some of them can cause movement disorders that impact the muscles of the face and tongue which are involved in swallowing.

Antipsychotic/ Neuroleptic medications	
Chlorpromazine (Thorazine)	Olanzapine (Zyprexa)
Clozapine (Clozaril)	Quetiapine (Seroquel)
Fluphenazine (Prolixin)	Risperidone (Risperdal)
Haloperidol (Haldol)	Thioridazine (Mellaril)
Lithium (Eskalith, Lithobid)	Thiothizene (Navane
Loxapine (Loxitane)	Trifluoperazine (Stelazine)

Dysphagia as a complication of the therapeutic action of the medication

- Medications that depress the Central Nervous System (CNS) can decrease awareness and voluntary muscle control that may affect swallowing.

Medications that depress the CNS	
Antiepileptic drugs- for seizures	Carbamazepine (Tegretol) Gabapentin (Neurontin) Phenobarbital Phenytoin (Dilantin) Valproic acid (Depakote)
Benzodiazepines- antianxiety drugs	Alprazolam (Xanax) Clonazepam (Klonopin) Clorazepate (Tranxene) Diazepam (Valium) Lorazepam (Ativan)
Narcotics- for pain relief	Codeine (Tylenol #3) Fentanyl (Duragesic) Propozyphene (Darvon, Darvocet)
Skeletal muscle relaxants- relieves muscle spasms and relaxes muscles	Baclofen (Lioresal) Cyclobenzaprine (Flexeril) Tizanidine (Zanaflex)

Medications that can cause esophageal injury and increase risk

- Some medications can cause dysphagia because of injury to the esophagus caused by local irritation. This can happen because the person is in a reclining position shortly after taking the medication or because an inadequate amount of fluid is taken with the medication. In both instances, the medications remain in the esophagus too long, potentially causing damage and affecting swallowing.

Drugs that may cause esophageal injury	
Acid- containing products	Clindamycin (Cleocin) Doxycycline (Vibramycin) Erythromycin (Ery-tabs, E-mycin) Tetracycline (Sumycin)
Aspirin	Bayer aspirin and generic brands
Bisphosphonates- given for osteoporosis	Alendronate (Fosamax)
Iron containing products	FeoSol, Feratab, Slow-FE, Fer-Iron etc.
Methylxanthines- bronchodilators	Theophylline (Theo-Dur, Unidur, Slo-Bid)
Nonsteroidal anti-inflammatory drugs- relieves pain	Ibuprofen (Advil, Motrin) Naproxen (Aleve, Naprosyn)
Potassium chloride supplements	K-Dur, K-tabs, Klor-Con, Slow K, etc.
Vitamin C (ascorbic acid) supplements	Allbee with C Vitamin C tabs, etc.

- Other medications such as high dose steroids and chemotherapeutic (anti-cancer) preparations may cause muscle wasting or damage to the esophagus and may suppress the immune system making the person susceptible to infection.

Reference: Balzer, KM, PharmD, "Drug-Induced Dysphagia", International Journal of MS Care, page 6, Volume 2 Issue 1, March 2000. (http://www.mscare.com/a003/page_06.htm)

Invited Review

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Nutrition in Clinical Practice
Volume 36 Number 1
February 2021 111–132

DOI: 10.1002/ncp.10615
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CE Enteral Medication for the Tube-Fed Patient: Making This Route Safe and Effective

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The administration of medication through an enteral access device requires important forethought. Meeting a patient's therapeutic needs requires achieving expected drug bioavailability without increasing the risk for toxicity, therapeutic failure, or feeding tube occlusion. Superimposing gut dysfunction, critical illness, or enteral nutrition–drug interaction further increases the need for a systematic approach to prescribing, evaluating, and preparing a drug for administration through an enteral access device. This review will explain the fundamental factors involved in drug bioavailability through the gut, address the influencing considerations for the enterally fed patient, and describe best practices for enteral drug preparation and administration. (*Nutr Clin Pract.* 2021;36:111–132)

Keywords
drug availability; drug-nutrient interaction; enteral nutrition; medication administration; medication error; patient safety

Introduction

The route of administration is described for each approved drug product, with a large proportion designated as oral. Oral drug delivery is the most commonly used route of administration and preferred for its convenience and cost. The US Food and Drug Administration (FDA) drug-approval process is supported by many guidance documents for manufacturers.[1] With rare exceptions, oral drug dosage forms (ie, tablets, capsules, liquids) are designed to be taken by mouth with a cup of water. They are not designed for the operational constraints imposed by the patient requiring enteral nutrition (EN). Very few medications describe enteral administration in their approved labeling. Otherwise, a decision to administer a drug approved for oral administration by the enteral route is considered off-label use not supported by the FDA or the manufacturer. Enteral drug administration is clearly a different route than oral and requires an appreciation of how to make sure it is safe and effective.

Drug administration through an enteral access device (EAD) is not the route anticipated by the formulation scientists when designing an oral dosage form. This incongruity is a critical detail not to be overlooked. There are already numerous factors that determine a drug's absorption and bioavailability, with many additional influences in the patient being enterally fed. Before describing the best practices for ordering, preparing, and administering appropriate medication through an EAD, this article will present fundamental factors that determine drug bioavailability and address some influences of gastrointestinal (GI) tract function, critical illness, and nutrition interventions. Failing to appreciate the basic scientific foundations can lead to practices that become error-prone rote tasks and place patients at risk of therapeutic failure, drug toxicity, or tube complications.

The ultimate goal of considering the enteral route is effective drug delivery to the therapeutic target site in the patient who is unable to take medications orally without imposing additional safety risk. The improvised preparation of a drug dose from commercial drug products, containing active drug and excipients, prior to EAD administration will need to respect how this may influence GI absorption, bioavailability, clinical effect, and safety.

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Financial disclosure: None declared.

Conflicts of interest: None declared.

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Received for publication August 19, 2020; accepted for publication November 15, 2020.

This article originally appeared online on December 29, 2020.

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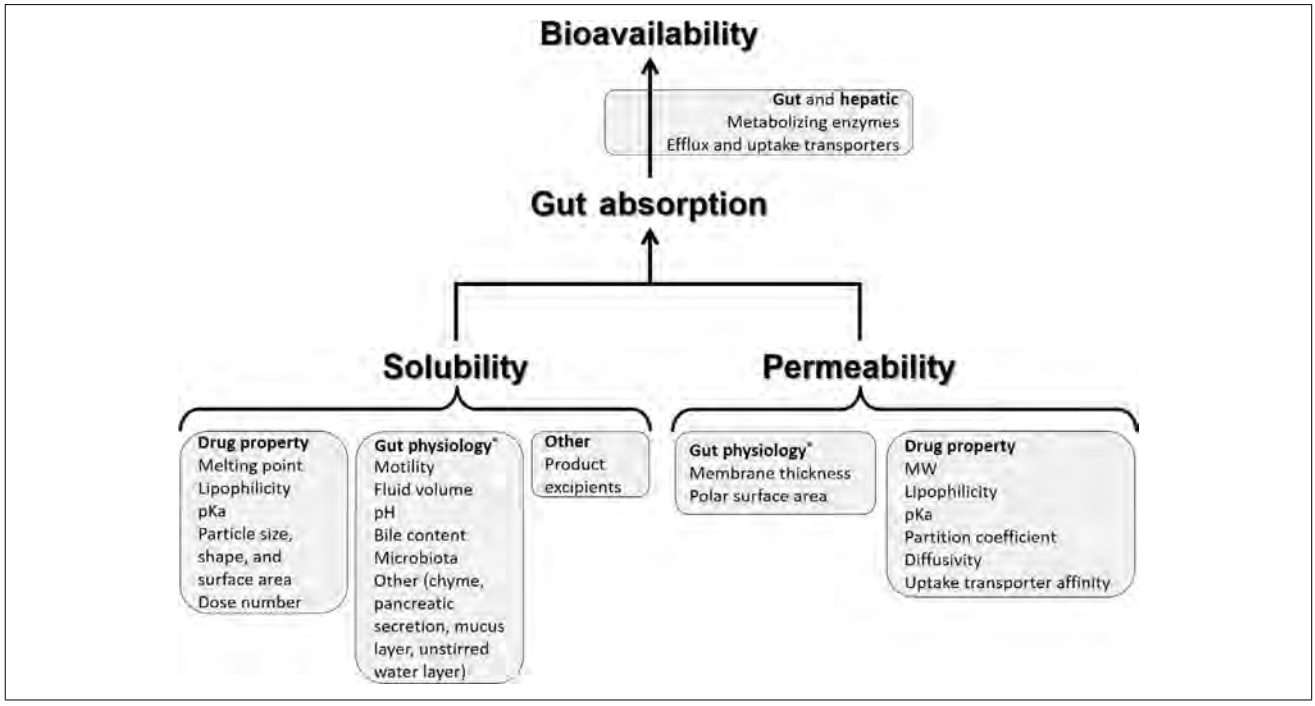

Figure 1. Determinants of drug bioavailability. *Gastric factors vary from postpyloric. MW, molecular weight.

Drug Bioavailability

Bioavailability refers to the proportion of a drug dose that reaches the systemic circulation. For the intravenous route, bioavailability is presumably 100% but is often much lower following oral administration, depending on the medication. Furthermore, the lower the oral bioavailability (especially <25%–35%), the greater the interindividual variability in systemic drug exposure.[2] Physiologic factors, especially within the GI tract, combine with drug properties to determine drug bioavailability. The ultimate systemic bioavailability of an oral drug depends on 3 physiologic steps: the fraction absorbed from the gut lumen into the enterocytes; the fraction removed by efflux transporters and/or enzymatic metabolism at the gut mucosa; and the fraction removed by transporters and enzymes at the liver.

It is important to differentiate the term *absorption* from bioavailability, as absorption refers to the drug molecule crossing the apical membrane of the enterocyte. Absorption across the gut is based on drug-specific factors (eg, particle size, solubility, lipophilicity, ionization, and dissociation constant) and gut-specific factors (eg, pH, local blood flow, bowel-wall edema, surface area, and motility).[3] The bioavailability refers to the proportion of the administered drug dose that not only is absorbed but overcomes efflux transporters and metabolic enzymes (ie, "first-pass effect") in both the gut mucosa and the liver to reach the systemic circulation.[4] A large number of factors will determine drug bioavailability through the GI tract (Figure 1). This includes preabsorptive obstacles—from acidic gastric juice and complex secretion- and enzyme-filled intestinal fluid to the microbiota and gut mucosal epithelium. Then, absorption across the gut mucosa benefits from uptake transporters and adequate permeability but suffers from the aforementioned efflux transporters and drug-metabolizing enzymes. The efflux transporters generally increase in expression down the intestinal tract, whereas the major metabolizing enzymes do the reverse.

Absorption requires the availability of the drug in solution at the absorptive site along with adequate permeability that may include uptake transporter proteins. The 2 major determinants influencing gut absorption are drug solubility (in the gut lumen) and drug permeability (across the intestinal wall membrane). After ingestion, an oral dosage form must disintegrate (if solid), dissolve, and then maintain a high enough concentration in gut fluid to diffuse toward the intestinal epithelium and set up the likelihood for absorption. The next step for the absorbed drug is to overcome barriers of membrane permeability, transport, and enzyme metabolism.

The factors that determine drug *solubility* include the physicochemical properties of the drug and the physiologic conditions within the GI tract. Dissolution refers to the process of transferring each drug molecule from its bulk form in the administered dose (containing trillions of molecules) into solution. Although simple sounding, dissolution is controlled by many factors that differ by drug, including particle shape and surface area, salt formation,

solubility, affinity for the solvent, and conditions of the local environment (eg, ionic strength, temperature). For each drug, there is a defined solubility (in water [aqueous] or other fluid) based on the energy required to remove a molecule from the other drug molecules in the dose and place it among molecules of fluid under specific conditions. So, for this reason, some drugs require more fluid than others. The thermodynamics of this process are described in detail elsewhere.[5] Any complexation or precipitation of the drug while still in the gut lumen will reduce availability for absorption.

When physicochemical properties lead to poor solubility (a large proportion of new oral drugs), a drug may instead form a dispersion. This refers to the drug particles dispersed in the fluid but not necessarily dissolved into solution. For example, many commercial liquid drug products and most EN products are best described as dispersions and not solutions, each with distinct properties. Of note, there has been increasing development of novel drug products in an attempt to get around poor solubility of active drug ingredients. This includes use of various types of nanocarriers and amorphic solid dispersions that form nanoparticles. The complex design allows nanocarriers to respond to dynamic aspects of the GI environment, but this will require more study to appreciate the general disposition of drugs in these products, let alone when administered via EAD, especially in patients receiving EN.[6]

The *permeability* of a drug may be described as the mass transport of molecules most often driven by the concentration gradient across a membrane in a given environment (eg, pH, osmolality). Permeability of an oral drug reflects the fraction of a drug absorbed (transferred) across the apical membrane of the gut epithelium. Of course, all biological membranes have selective permeability to endogenous substances, and the physicochemical properties of the lipid bilayer and structural integration of membrane proteins will influence drug permeability too. Permeability may be passive or carrier mediated but is predominantly transcellular.[2] The clinically relevant drug transporters (both the respective gene and protein expression) vary by segment along the intestines.[7] Some uptake transporters are found throughout the intestines, whereas others are region specific. So membrane transport of a specific drug can vary by intestinal region. The interindividual variability in GI function (eg, motility) and differences in intestinal permeability between gut regions can therefore influence bioavailability.[8,9] Intestinal region-specific transporter expression, protein abundance, and interindividual variability can be used in modeling drug disposition and interaction potential.[10] This can be valuable to know when placing an entire drug dose through an EAD into a specific gut site.

A drug is expected to be more permeable if lipophilic, of small molecular weight, with high diffusivity through the membrane. Any affinity for an uptake transporter is of benefit. For example, prodrugs (acted upon during absorption to liberate the active drug) often improve gut absorption of the parent drug by taking advantage of uptake transporters (and/or metabolizing enzymes). Permeability may be enhanced in the presence of reduced gut-lumen osmolality. Interestingly, oral drug products that incorporate excipients to improve solubility through its GI tract journey may impair permeability.[11] The excipients, which differ from one brand to another of the same oral drug, may also influence drug absorption by interacting with drug transporters.[12] It remains unclear what influence there may be when such a product is crushed/dispersed and administered via EAD.

Drug absorption in the stomach is limited, but the onset of intestinal drug absorption is determined by gastric emptying rate, digestive state, fluid volume, posture, and the influence of disease or concurrent drugs that may influence gastric emptying. The presence of fat or fiber generally delays gastric emptying, as does the supine position. Slower gastric emptying associated with critical illness, phase separation of EN in the stomach, and their influence on the drug is not well described. There is still considerable variability in gastric emptying even in the fasted state, depending on gastric fluid volume and phase of the interdigestive migrating myoelectric complex. The volume, as well as the composition, of fluid in the intestine varies not only between the fed and fasted states but also in the number and distribution of discontinuous fluid pockets found throughout the gut lumen.[13,14,15]

Commercial oral drug products are designed with all of the above in mind. Therefore, crushing and/or dispersing solids in minimal fluid prior to administration by EAD, especially in patients with altered physiology, can significantly change the intended therapeutic effect of the original drug design.

Influence of Critical Illness on Gut Function

The anticipated absorption behavior of oral medication is based on oral administration of the intact dosage form in healthy adults with a functional GI system. In those with gut dysfunction or systemic disease with an impact on the gut, the potential exists for significantly altered drug absorption. The knowledge about GI physiologic dysfunction and its influence on drug bioavailability remains incomplete, especially for acutely ill patients, although some data have been generated, for example, with gastric bypass.[16,17] Following bypass, the documented anatomic and physiologic alterations impact drug disposition with bioavailability increased, decreased, or unchanged, depending on the medication.[16,17] The concern in patients with altered gut function goes beyond gastric emptying to include transit time through different gut segments, pH, epithelial permeability, the microbiota, and altered gut transporter and/or metabolizing enzyme function.

The critically ill patient serves as a good example of the significant changes in physiology that impact drug pharmacokinetics and pharmacodynamics, as discussed in depth elsewhere.[3,18,19] There are more likely alterations in pharmacokinetics and pharmacodynamics in critically ill patients in general compared with other hospitalized patients.[20] The influence of critical illness, through the inflammatory response, on the activity of drug transporters and metabolizing enzymes located at the gut mucosa is well recognized.[20,21] Generally, there is a cytokine-driven decrease in transporter gene and protein expression, with some alterations in metabolizing enzymes (some increasing and others decreasing in expression).[17] So the assumption that oral drug bioavailability is unchanged in the critically ill patient compared with data derived in healthy individuals is inaccurate. Incorporating the additional layer of drug manipulation and EAD administration can further increase the variability in drug disposition and expected response. Resultant variability in systemic drug exposure using the enteral route could reduce efficacy or increase adverse effects.

GI dysmotility, including delayed gastric emptying, is commonly manifest in critically ill patients. Although dependent on the methodology used, ~50% of critically ill patients experience delayed gastric emptying.[22] Delayed gastric emptying can occur for many reasons and generally delays drug absorption. The rate of gastric emptying can determine the subsequent intestinal absorption and bioavailability of drugs administered into the stomach. For example, the longer time spent in the stomach may increase drug dissolution, which could improve absorption of some drugs. However, in the case of acetaminophen, the bioavailability is reduced.[23,24] Between gastric stasis, or dumping syndrome, and variable splanchnic blood flow, the enteral route for drug administration can be unreliable in the critically ill patient. An estimated 15% of medications are administered enterally in the intensive care unit (ICU) despite inadequate bioavailability data.[24] A less-than-ideal preparation and enteral administration technique could further detract from optimal drug effect, making close patient monitoring that much more essential.

Enteral feeding intolerance is variably defined in clinical practice, but when transient and not requiring prokinetic agents, which is often the case, intolerance is not considered an indicator of enteral drug absorption. Drug absorption testing (eg, using acetaminophen) is an indirect method of assessing gut motility, whereas gastric residual volume, although no longer considered a reliable marker, has been a surrogate for gastric emptying.[22] The variety of protocols and interpretations of the acetaminophen absorption test diminishes its ability to reflect gastric and intestinal motility, but it does shed light on variability in drug absorption in critically ill patients. A recent study of 47 stable critically ill children revealed a significant reduction in absolute enteral acetaminophen bioavailability, with less predictable drug exposure including subtherapeutic concentrations.[24] This finding occurred despite a handling technique that assured >95% drug delivery to the distal end of the EAD. The wide variability in absolute bioavailability (between 11% and 91% [mean 72%]) was unexplained by covariates that included route into the gut lumen.[24]

In the critically ill patient, the influence that altered splanchnic perfusion or use of vasopressors has on drug bioavailability remains unclear. It likely varies by the drug—with bioavailability reduced for some but not for others.[23,25] The acetaminophen absorption test (1 g followed by blood concentration at 1 hour) was used to evaluate adequate absorption (serum acetaminophen concentration $\geq$10 mg/L) in 15 critically ill patients with severe influenza (8 receiving mechanical ventilation, 7 on vasopressors, and 4 on extracorporeal membrane oxygenation).[26] These patients had therapeutic levels of oseltamivir carboxylate following oseltamivir suspension 75 mg administered twice daily by nasogastric tube for influenza treatment.[26] The acetaminophen absorption test had 100% predictive value, and of the patients with poor acetaminophen absorption (serum acetaminophen concentration $\leq$1 mg/L), half had subtherapeutic oseltamivir carboxylate.

Surgical interventions that result in open abdomen or temporary abdominal closure of wounds may influence GI drug absorption.[20] For ICU patients receiving gastric antisecretory therapy (eg, proton pump inhibitors), an unintended consequence remains the risk for reduced bioavailability of weak base drugs.

The role of the gut microbiota to impact (improve or reduce) drug bioavailability is a broad topic that has been gaining more interest.[27] This influence of the microbiota and its metabolic products interacting with drugs (ie, microbiota-drug interaction) and the subsequent influence on drug bioavailability are referred to as "pharmacomicrobiomics."[28,29] For example, among the impacts on the variable bioavailability of the immunosuppressant tacrolimus is the gut microbiota in which the many bacteria of the order Clostridiales extensively metabolize the drug.[30] Studies of bacteria-drug interactions, including those supplied in probiotic products, will continue to provide additional mechanistic data.[31] The impact of the gut microbiota is further affected by nutrition exposure.

All of this needs to be considered in the critically ill patient. And that is in addition to the considerations for drug preparation and administration by enteral access. Off-label drug use is common to managing the critically ill patient, who is already at higher risk for adverse drug events.[3] Fortunately, there is close monitoring of the critically ill patient by the pharmacist on the ICU team. The pharmacist specialist in the ICU helps decrease medication errors, other adverse drug events, and mortality.[32] A significant number of medication errors in ICU patients are related

Table 1. Examples of Drug-Nutrition Interactions.[35,36].

Precipitating factor	Object	Object
Drug	Nutrient	Carbamazepine lowers biotin absorption
Drug	Nutrition status	Quetiapine increases weight gain
Drug	Metabolic status	Olanzapine may cause hyperglycemia
Nutrition status	Drug	Obesity results in lower ertapenem levels
Nutrient or food component	Drug	Calcium reduces ciprofloxacin absorption
Food	Drug	Grapefruit juice increases simvastatin toxicity

to EAD administration.[33] A multicenter observational study reported that 46% of critically ill patients experience medication error, including drug interactions and errors in route of administration, when transitioning to the non-ICU setting.[34] Unfortunately, the authors did not specifically evaluate drug preparation and administration errors via EADs or interactions with nutrition.

Influence of Nutrition Interactions

Clinicians widely appreciate the influence of interactions on drug disposition and clinical effect. Interactions between drugs are described as pharmaceutical, pharmacokinetic, or pharmacodynamic in nature. Drug interactions with nutrition are no less important than drug-drug interactions.[35] Drug-nutrition interactions reflect a physical, chemical, physiological, or pathophysiological relationship between a medication and one (or multiple) nutrient(s), food in general, specific foods or food components, or nutrition and metabolic status.[35,36,37] As with any drug interaction, one element of the relationship is considered the "perpetrator" (precipitating factor), and the other is the "victim" (object) of the interaction. The precipitating factor may be the drug, a nutrient, food, or nutrition status, and then any other component can serve as the targeted object of the interaction. Therefore, several subtypes of drug-nutrition interaction exist, and they are individually described as "food-drug" interactions or "drug-nutrient" interactions, among others (Table 1).[35,36] The broad topic has been covered in more depth by the author elsewhere.[35,36,38,39,40] The focus here will be on drug-nutrition interactions taking place in the gut by a pharmaceutical or pharmacokinetic mechanism.

A model that links drug-nutrition interactions with their physiologic effects and clinical outcomes helps differentiate interactions by mechanism.[36] Some interactions are based on physicochemical reactions that take place in a nutrition delivery device or in the lumen of the GI tract (ie, pharmaceutical). These interactions have the distinct potential to alter the bioavailability of one or more substances. Other interactions are the result of events at cell membrane transporters or metabolizing enzymes (ie, pharmacokinetic), which can also alter bioavailability. This parallels drug-drug interactions whose mechanism involves drug transporters alone or along with metabolizing enzymes.[41] To be complete, still other interactions yield an antagonistic, additive, or synergistic effect on physiologic function (ie, pharmacodynamic). Aside from altered bioavailability, the potential consequences of these interactions include a change in clinical effect of the drug or nutrient.

In general, a drug-nutrition interaction is considered clinically significant when therapeutic drug response is altered and/or nutrition status is compromised. The time frame over which this change occurs varies with the precipitating factor and object, as does the severity of consequences, with some individuals at higher risk based on their age, genetic variants, organ function, or disease state. As a result, the clinical significance or severity of a drug-nutrition interaction may be difficult to predict. Examples of the specific and relevant topic of EN-drug interaction will be addressed later.

The influence of food (as a meal or snack) on the bioavailability of a drug (ie, food-drug interaction) is relevant at this point. Food changes the physiologic conditions of the gut into which the drug is administered. Therefore, taking a drug with a meal may significantly alter the drug's bioavailability compared with administration in the fasted state. The significance of the interaction, when present, is based on the ratio of area under the serum drug concentration-time curves (AUCs) under each condition (fed vs fasted) falling outside a defined range (eg, 80%–125%), in which food either decreases or increases bioavailability, respectively. But not all drugs exhibit a significant meal effect. Oral drugs are evaluated for the meal effect prior to FDA approval. The FDA-recommended test meal often used for food-effect bioavailability studies contains 800–1000 kcal with about 50% of energy from fat. But varying meal content may result in a different impact on the bioavailability of the same drug.[42,43] Other meal types may have different influences on gut function and therefore drug absorption.[44] Studies that examine the effects of fed vs fasted state on drug bioavailability can also expose significant interpatient variability.[45] Although gastric emptying is complete within ~45 minutes after a cup of water, it can take >6 hours after the standard FDA meal.

Let us understand why this food-drug interaction occurs. Some of what is described in this section may be applicable to EN but, more likely, has not yet been adequately studied. Following a meal, there are changes in pH, viscosity, volume, gastric emptying rates, bile flow, and pancreatic secretion that influence drug dissolution.

The influences of a meal will be different depending on individual drug properties (eg, pKa, solubility). There is additionally physiologic variability in drug dissolution and absorption based on the consistency and composition of the meal.[46] Whether the addition of a drug diluted in water to the fed stomach can evade the chyme bolus and be emptied more rapidly is of interest, as this has been noted to differ between orally administered drugs.[47] The volume and composition of the endogenous gut fluid also influences drug dissolution and absorption, with pockets of fluid noted throughout the intestines rather than in a homogeneous distribution, which will add further variability, especially for poorly soluble drugs. Lipophilic drugs are trapped in the gut's thick mucus layer but are more permeable at the epithelial membrane, which also needs to be captured by models that attempt to account for all relevant physiologic variables (eg, pH, mucus, fluid, splanchnic blood flow, transporters, metabolism, motility) in predicting bioavailability.[48] Even the presence of medium-chain triglycerides may alter the absorption of poorly permeable drugs.[49] And, finally, there is an influence of food or specific components on transporters and metabolizing enzymes.

Individual components of a food—whether individual nutrients (eg, micronutrients) or associated substances (eg, polyphenols)—including those specific ingredients that may be administered as dietary supplement products, may influence drug disposition. For example, protein and protein supplements can increase drug metabolism. The effect may be specific to a protein source (eg, soy protein vs casein) at inducing transporters and enzymes.[50] Juice components influence a number of drug-metabolizing enzymes and drug transporters to increase bioavailability of some drugs and reduce bioavailability of others.[51,52,53,54,55] Even anthocyanins and anthocyanidins, as found in common berries, can interact with enzymes and transporters.[56,57] Supplements contain higher concentrations of food components (eg, flavonoids) than what is found in the diet and are more cause for concern than food sources with regard to interactions.[58]

Aside from pharmacokinetic interactions at transporters/enzymes caused by food components, the characteristics of fluid intake may alter drug bioavailability. Solution osmolality influences gut-lumen fluid volume, which then alters drug concentration and impacts absorption by decreasing the concentration gradient, especially for low-permeability compounds.[59] For example, administering atenolol with apple juice (~750 mOsm/kg) results in a 63% decrease in bioavailability compared with administering the drug with purified water.[59] This may, in part, be a function of apple juice's ability to inhibit a specific transporter involved in atenolol absorption.[54]

In the absence of clinical data, a drug's known physicochemical properties (and susceptibility to removal) can be used to predict drug disposition with a meal. In fact, each drug's solubility and permeability characteristics in service of bioavailability has been described by several classification systems—the Biopharmaceutics Classification System (BCS), Biopharmaceutics Drug Disposition Classification System (BDDCS), and Extended Clearance Classification System (ECCS).[60,61] These have been combined and represented into 4 classes (Figure 2). Most oral drugs can be categorized into 1 of these 4 classes depending on solubility, permeability, and susceptibility to metabolism. Generally, drugs with low solubility but high permeability/metabolism (ie, Class 2 agents) can have an increased bioavailability in the presence of food, whereas a negative effect is more likely for Class 3 drugs.[60] No meal effect is expected with Class 1 drugs, and few data currently exist for Class 4 drugs. Clinical studies can then provide data on the extent to which the change in bioavailability is clinically significant (eg, AUC change of 20%–25%). The low-solubility/low-permeability medications (Class 4), especially in the uncommon case of high affinity to an enzyme (with its own interindividual/intra-individual variability), are already risk factors for high intra-individual variability in absorption.[62] The classifications may also provide a hint as to risk from preparation and administration by EAD. For example, the immediate-release form of Class 1 drugs can generally be prepared for EAD administration without concern for altered bioavailability.

It is important to appreciate that the enteral drug administration process begins with the prescriber and involves the pharmacist before the nurse or other caregiver handles the medication. Enteral medication errors can occur at each step (drug order, review, preparation, administration), keeping in mind that the vast majority of oral drugs are not approved for the enteral route.[63]

Enteral Drug-Use Process

Error Potential

Before administering medication through a patient's EAD, clinicians must consider the safety risk and error potential. Prescribers, nurses, and pharmacists recognize the challenges and limitations of using oral drug products enterally and the potential consequences to their manipulation, preparation, and administration.[64,65,66] Case reports and observational studies of enteral medication error, as well as multiple surveys, have documented inappropriate drug preparation and administration practices. Although >90% of survey respondents are confident in the appropriateness and effectiveness of their method for enteral drug preparation and administration, as many as 1–3 inappropriate techniques have been identified per respondent.[67–73]

Any necessary drug must be prepared and administered appropriately for the patient to meet therapeutic goals

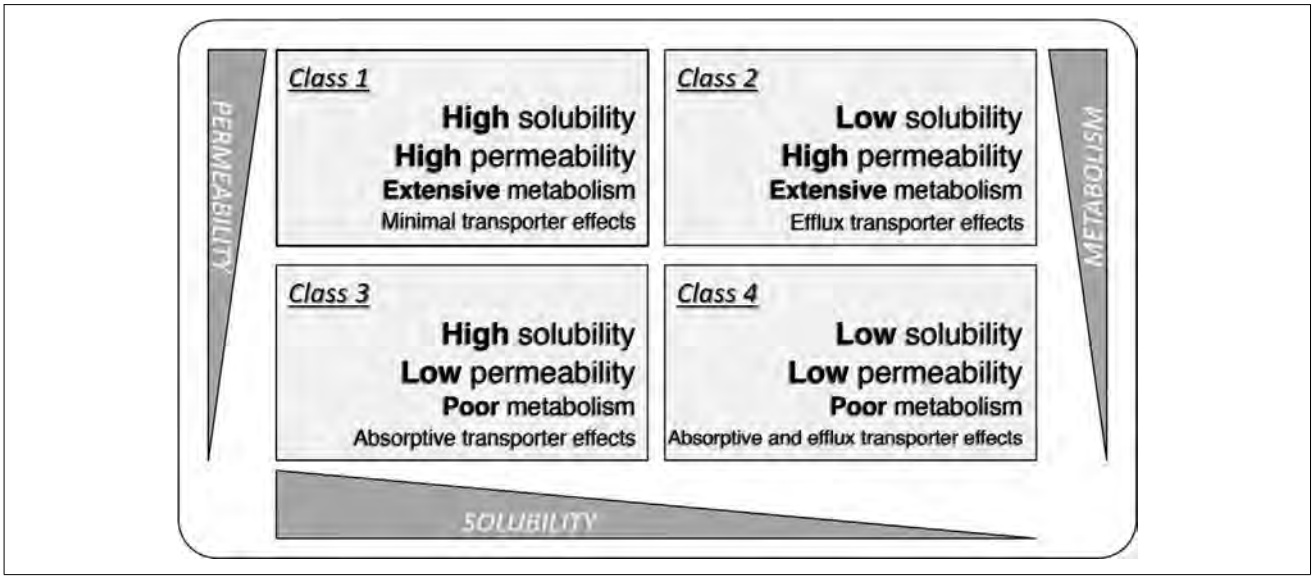

Figure 2. Classification system by drug characteristics.

without raising the risk for complications. Errors, such as using an unsuitable drug formulation, incorrect preparation technique, or inappropriate administration site, have significant consequences. Obstruction of the patient's feeding tube, therapeutic failure, and drug toxicity including fatality have all been documented.[74,75,76] Numerous errors can occur in a single patient requiring enteral medication.[77] Additionally, depending on the degree of exposure, some drugs may pose a hazard to the caregiver preparing the medication. The safety risk to the patient can also include oral medications intended for enteral administration that are inadvertently administered intravenously; 25%–40% of such errors result in sentinel events.[78–81]

Apart from the survey results and case reports that document an enteral medication–related error, prospective observational studies provide the best insight into medication handling (ie, preparation and administration) practices. In a prospective observational study, enteral medication preparation/administration errors made by nurses approached 60% of doses.[82] Enteral drug preparation and administration errors occurred in over three-quarters of ICU patients and accounted for nearly 50% of all medication errors, in an observational study of >10,000 doses.[33] Preparation errors include crushing/mixing drugs together, crushing modified-release dosage forms, not shaking suspensions, not diluting medications appropriately, and not wearing protective equipment when indicated.[33,82,83] Administration errors include not flushing the feeding tube before, between, or after drug administration.[82,83]

The focus of addressing errors has mostly been on nurses, whereas the role of the prescriber placing the order or the pharmacist involved in drug regimen review or drug preparation has not been examined as thoroughly. All steps within the process must fall within a systematic framework aimed at reducing medication errors associated with enteral medications.

Prevention of all these errors remains the key to patient safety.[84] A systems approach can help reduce the risk for medication error.[85] The approach includes working with all stakeholders involved in any of the steps for patients who may require enteral medication. This group of prescribers, nurses, dietitians, and pharmacists develops and maintains policies and procedures around enteral medication preparation and administration that are adopted by the involved departments. The documents must be clear about the responsibilities and tasks of prescribers (ordering), pharmacists (reviewing orders, preparing and dispensing medications), and nurses (preparing and administration). The dietitians often play a critical role in identifying the enterally fed patient who may have a drug ordered orally instead of by EAD. They may find that the ordered oral drug is being manipulated by the nurse for enteral administration (ie, route of administration error). Beyond federal law, state law, and *United States Pharmacopeia* (USP) mandates are the relevant clinical practice guidance documents. For example, the American Society for Parenteral and Enteral Nutrition (ASPEN) guidance document "Safe Practices for EN Therapy" includes an entire section on medication.[86] Policies and procedures should also describe how all clinicians within the organization receive education and competency assessments on enteral medication prescribing, reviewing, preparation, and administration.

Any identified enteral drug errors in an organization are best reviewed in a timely manner by an oversight

Table 2. Drug Order Review Query.[87].

Patient-related factors

- Is patient able to take medication by mouth?
- Are there any anatomical or functional abnormalities in the gastrointestinal tract that may interfere with drug absorption?
- What is the patient's enteral access device? (Assess entry point, distal site[s], and French size.)
- What is the current status of that enteral access device (position and patency)?
- What is the current enteral nutrition regimen (formulation, rate/volume, access if dual-lumen device)?

Drug-related factors

- Dosage form
  - Is it immediate release or modified release (eg, enteric-coated, sustained release, extended release)?
  - Will modification of the oral dosage form alter drug-release or solubility characteristics?
- Drug
  - What is the primary site of dissolution and absorption (if known)?
- Liquid formulation
  - Is the product or preparation designed for oral administration?
  - What is the osmolality and viscosity of the product or extemporaneously compounded preparation (if known)?

committee, which can then recommend additional systems improvements to create a safer environment. This may well include the organization's rate of feeding tube occlusion as a critical indicator. Having systems in place can help avoid the most preventable of errors.

Prescribing the Enteral Drug

For patients who require an oral medication to be administered through an enteral access, the prescriber will need to specifically order the appropriate medication, dosage form, route of administration, and correct EAD. The electronic medical record that includes an order entry system using built-in decision support or best-practice alerts can support safe enteral drug prescribing. The use of automated forcing functions may be of benefit. Oral medication that cannot be administered by EAD should be disallowed for both the gastric and postpyloric route in the electronic order. Further, in a patient with nil per os (NPO) orders or with EN orders, the order entry system should generate an alert for the prescriber and pharmacist to reconsider the route of administration for any drugs ordered for oral administration. The prescribed medication requires order elements specifying the route (ie, enteral) and site (eg, jejunostomy tube) of drug administration for the benefit of the nurse and the patient. Postpyloric administration can be a particular concern for some antimicrobials or drugs with a narrow therapeutic index if bioavailability might be significantly altered. Instructions on preparation may accompany enteral drug orders or at least be present in the medication administration record and with the dispensed drug product/preparation.[86]

Reviewing Enteral Drug Orders

Pharmacists' role in the order review process is important, as they identify each new drug order and assess it in the context of the patient's clinical status and active medication profile. This step is performed to ensure the appropriateness of each medication, communicate any potential discrepancies with the prescriber, and offer suitable alternatives. Pharmacists on the ICU team can be proactive in making appropriate patient-specific recommendations for medications, including those for enteral administration. A key consideration is whether drugs are ordered for oral or enteral administration—2 distinct routes of administration. The pharmacist should always know the patient's current oral status (ie, NPO or NPO except medication) and EAD status. The pharmacist considers and addresses both patient-related factors and drug-related factors when reviewing orders and making interventions (Table 2)[86,87]

Patient-related factors. When reviewing an order, the pharmacist identifies whether the patient can take medication by mouth or requires enteral drug administration, as well as any anatomical or functional abnormalities present in the patient's GI tract that may preclude adequate drug absorption. It is critically important that the EAD information (eg, entry point, distal site, French size) is well documented in the medical record and easily accessible in real time to all clinicians caring for the patient. The pharmacist should have full access to the health record documentation of the patient's current EAD, if that information is not already linked to the medication profile, and confirm current positioning of the distal end of the feeding tube and tube patency. To make the pharmacist review as efficient as

possible, the enteral feeding regimen, including the flushing schedule, should also be part of the medication profile.

Drug-related factors. The pharmacist identifies any enteral medication order that will require a preparation step (eg, appropriate crushing or dispersing, diluting, mixing) prior to administration. The drug *dosage form* must be appropriate for EAD administration (ie, immediate release). Any solid dosage forms must be avoided if opening it (ie, capsule) and/or crushing it (ie, tablet) would result in a significant change in the absorption profile of the active pharmaceutical ingredient or hazardous exposure to healthcare providers. Each ordered medication should be evaluated for its expected inherent solubility and release characteristics. If modifying the medication's dosage form is known or suspected to alter the release of active ingredients, an alternative dosage form, drug, or route of administration must be seriously considered.[86]

The drug and its *formulation* both need to be appropriate based on the location of the distal end of the EAD to avoid bypassing the major site of drug dissolution and absorption. This is just as important whether a commercial product or an extemporaneous preparation is ordered. Hyperosmolar liquid drug preparations need to be carefully considered in context of the distal end of the tube, especially if postpyloric. Oral liquid preparations with an osmolality that exceeds ~600 mOsm/kg contribute to adverse effects (eg, slowed gastric emptying, cramps, abdominal distension, pain, and diarrhea), especially in vulnerable patients.[88,89] This osmolality value approximates the upper end of the physiologic range found in healthy jejunum in the fed state. Many liquid medications have an osmolality that exceeds 1000 mOsm/kg because of various additives (eg, polyol sweeteners, propylene glycol).[90,91,92] Some of these liquid products are also highly viscous. Viscosity is an important consideration, especially for lengthy tubes with high surface area through which the liquid product must travel to reach the patient's gut. Besides the resistance to flow encountered when administering a dose of viscous medication, they can contribute to the cumulative risk for tube obstruction because they are more difficult to flush. Higher-viscosity products may also decrease gastric emptying, but then excessive dilution may reduce gut-lumen concentrations and reduce absorption. Therefore, preparation of an oral medication for feeding tube administration requires thoughtful consideration.

Preparing the Enteral Drug

Preparation refers to any step that will be required of the pharmacy, the nurse, or a caregiver at home to alter the drug's commercial dosage form prior to administration. This alteration could be as simple as diluting a medication in water or as complex as compounding an extemporaneous formulation. Most oral drugs are available as solid (powder, capsule, tablet) and/or liquid (solution, suspension) dosage forms.

Solids. For drugs marketed as solids, only the conventional immediate-release drug dosage forms should be considered for enteral administration. Modified release refers to a product design that delays the release of the drug dose (eg, enteric coating) or slowly releases a large drug dose over time (eg, sustained release). Modified-release dosage forms should be avoided altogether, and even some film-coated immediate-release tablets may prove difficult to crush and/or disperse sufficiently. A fine powder can be obtained from immediate-release products by emptying dry capsule contents or crushing tablets. Multiple sources can be reviewed to determine whether a solid dosage form can be reduced to powder.[93] Many drugs are listed as "Do Not Crush" because they have modified-release characteristics; others are listed because of hazards including potential allergenicity and teratogenicity. Open crushing creates significant amounts of aerosolized particulate matter ($>10^6$ particles/m^3).[94] Closed systems may be preferable for crushing tablets, especially for hazardous drugs, to avoid exposure. Unfortunately, not all available devices are effective or safe.[95] For any potentially hazardous medication, including non-neoplastic drugs, trained personnel in the pharmacy should prepare them in compliance with Occupational Safety and Health Administration, National Institute for Occupational Safety and Health, and USP chapter <800> guidance, which may require a closed system processing device (eg, containment ventilated enclosure).

For tablets that disperse easily, an alternative to crushing is to place the dose in the barrel of an enteral syringe (eg, 35 mL) and then replace the plunger, drawing up adequate purified water (eg, 10–20 mL) to allow a slurry to form in a few minutes; this method often requires some agitation. This technique avoids the risks of using a separate mixing container with loss of drug, or of exposure to hazardous particulates from crushing. Nearly half of drug products in immediate-release tablet form are considered dispersible within a 5-minute time frame.[96] Regardless of whether medications are potentially hazardous, personnel should avoid environmental cross-contamination, such as using the same mortar and pestle without cleaning between medications.

Liquids. The source of oral liquids for enteral administration may be a commercial liquid product (ie, FDA approved) or an extemporaneous formula (ie, based on an official USP method) with adequate stability and sterility data. Any preparation described in the literature that requires compounding should ensure both physical and chemical stability and, ideally, provide data on final pH, osmolality,

and viscosity. Pharmacists recognize that to compound responsibly, best practices are based on available data from the primary literature or compilations of that data.[97,98,99,100,101] The commercial or extemporaneous formulations are tailored to the properties of each drug's active ingredient and features of the product. USP chapter <795> provides enforceable guidance for compounding nonsterile drug preparations, from simple to more complex when prepared well in advance (ie, not for immediate use).[101] The practical significance of drug stability (based on a stability-indicating assay) and sterility data may be different for preparations intended for immediate use (within 30 minutes) than for those stored 24 hours or longer. If the latter is considered (eg, to make a batch for 1 or more patients), information on stability and microbial growth under specific environmental conditions (light, temperature, humidity, and packaging material) and appropriate beyond-use date (BUD) will be required. Approximately 7% of extemporaneously compounded preparations from existing dosage forms exhibited stability concerns, often related to interactions between the active ingredient and excipients in the commercial product, many of which can be managed with further manipulation.[102,103]

In the first few days of an ICU stay, a large-bore (nasogastric or orogastric) tube may be used for medication delivery. Although these may have less turbulent flow than a small-bore feeding tube, they also have larger internal lumen surface area. Therefore, nonaqueous solvents or viscous liquids have more surface on which to adhere, and so the large-bore tube may be less likely to deliver the full dose of medication to the distal end of the tube if not appropriately prepared and administered. Some liquid product formulations may enable drug adsorption to the plastic container.[102] Additionally, an ENFit multifunctional port adapter may be needed to administer medications through these larger-bore tubes using an enteral syringe.

Most of the commercially available oral liquid products and formulas for extemporaneous preparations are designed specifically for oral administration. Therefore, they usually incorporate flavoring vehicles and thickening agents, which contribute significantly to final osmolality and viscosity. Although palatability is considered more important than osmolality or viscosity for oral delivery, the opposite is true for enterally administered liquid medication. In many cases, especially for postpyloric administration, the solid dosage form as an immediate-release product is more appropriate than a liquid dosage form. For example, an acetaminophen tablet disperses in ~10–20 mL of water, whereas the liquid form delivering the same dose would require well over 100 mL to reduce the extremely high product osmolality and risk of adverse GI effects.

Dilution

For preparation of dosage forms, USP requires purified water.[101] This describes water that is free of chemical or biological contaminants following source-water selection, distillation, and filtration. Drinking water (ie, bottled, tap, or well water) may be contaminated, relative to purified water, and is not recommended for drug preparation.[86,104] The dilution of each medication with purified water (eg, sterile water for irrigation, USP) before administration improves delivery of fine powders and reduces liquid osmolality and viscosity, especially for longer EADs (see Table 3). Generally, 15–30 mL of water is adequate for a powdered drug. Dilution of the medication (dry or liquid) and irrigation (flushing) of the feeding tube with water is critical to ensure drug delivery through to the distal end of the EAD and to the patient's gut lumen for absorption, while minimizing risk for occlusion.

Most suspensions will be easier to administer once they are well diluted. For example, nearly 90% of the drug dose is not delivered to the end of a nasogastric tube if phenytoin suspension is not diluted or flushed.[105] The optimal degree of dilution likely depends on the viscosity and osmolality of the liquid medication. The viscosity of suspensions can be reduced by 1:1 (by volume) dilution followed by a flush of the same total volume. This approach allowed for the successful delivery of carbamazepine suspension through 12-French (12Fr) nasogastric tubes.[106] When undiluted, even with some post-dose flush, posaconazole suspension exhibited reduced absorption when administered via nasogastric tube.[107,108] The higher viscosity of a drug preparation typically decreases the dissolution rate of drug particles. Whereas this may be appropriate to maintain stability during transport and storage, it may be counterproductive if the preparation is introduced directly into the small-bowel lumen. Therefore, dilution serves to enhance dissolution as well as delivery of the drug to the distal end of the EAD. Although a 1:1 volume dilution is expected to be adequate to reduce viscosity of liquid drugs, a dilution volume as high as 10:1 may be necessary to reduce the final osmolality depending on the initial value of a liquid drug product. A method to estimate volume of dilution for hyperosmolar liquid medications can be found in Figure 3. Whether these drug dilutions can be prepared by the pharmacy in advance of dispensing will depend on the duration of stability. Some drugs may undergo first-order oxidation in aqueous solution and may be better prepared just before administration.[102]

Additional Considerations

Additional factors may yet influence drug bioavailability in the enterally fed patient. Many drug products contain active ingredients with poor water solubility that are expertly

Table 3. Preparing Dosage Forms for Enteral Administration[87].

Solids[a]	Liquids[a]
Capsule • Open capsule(s) and completely empty the dry powder contents constituting the prescribed dose into a container (eg, barrel of capped enteral syringe, medicine cup). • Add volume of diluent (ie, purified water) and mix well. • If prepared in an external container (eg, medicine cup), draw up the mixture into an enteral syringe, using appropriate attachments as needed; rinse additional water in container as needed to collect all visible powder particles and draw up into the enteral syringe; cap the end of the syringe. • Gently agitate to disperse the particles.	• Draw the prescribed dose up into an enteral syringe, using appropriate attachments as needed. • Draw in some air prior to drawing up volume of diluent (ie, purified water). • Cap the end of the syringe. • Gently agitate for adequate mixing.
Tablet (disperse) • Remove the enteral syringe plunger and place prescribed dose of dispersible tablet(s) into the barrel. • Replace the plunger and draw up a volume of diluent (ie, purified water). • Cap the end of the syringe. • Gently agitate to disperse the tablet.	<u>All preparations</u> • Label the enteral syringe for dispensing, unless prepared outside the pharmacy for immediate use. • Collect all prepared medications due at the time for the single patient and carry them to the bedside for administration.
Tablet (crush) • Crush tablets constituting the prescribed dose to a fine powder (preferably in a closed system). • Add volume of diluent (ie, purified water) and mix well. • Draw up the mixture into an enteral syringe, using appropriate attachments as needed. • Rinse additional water in container as needed to collect all visible tablet particles and draw up into the enteral syringe. • Cap the end of the syringe. • Gently agitate to disperse the particles.	

[a]Assumes the correct drug, dosage form, and formulation for the patient.

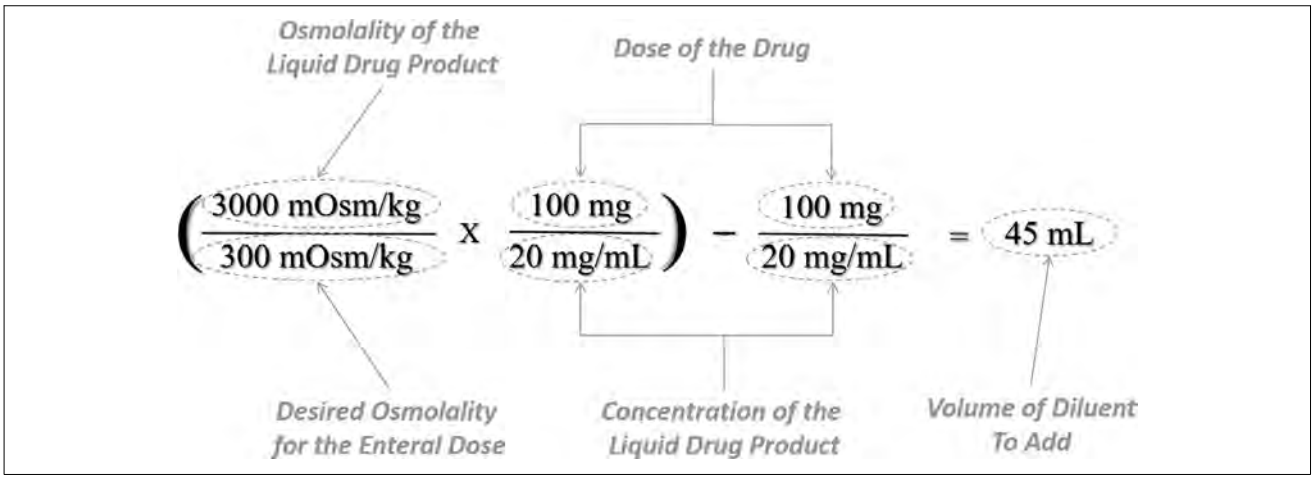

Figure 3. Equation for estimating the dilution volume for hyperosmolar liquid medications.

formulated with specific excipients (eg, solubilizers, coprecipitates, surfactants) intended for intact oral administration. Breaking down this well-designed product and diluting the ingredients prior to administration runs the risk of altering the final disposition of the drug. Complexation of an active ingredient, which then reduces its availability for absorption, can occur in the preparation of the dosage form as well as in the GI fluid. This is more likely to affect

excipient-containing liquid dosage forms. The pure powder form of the active drug might be more stable in an extemporaneous oral liquid than if the commercial tablets are used.[102]

Given the complexity of a single active drug ingredient and its excipients, the interaction potential of combining multiple medications and their respective excipients is inevitably greater. Unless data suggest otherwise, the significant physicochemical risk and complex reactions of combining 2 (or more) drug products together would lead to incompatibility and instability that impact solubility and bioavailability. Therefore, the combination or mixing together of enteral medications is best avoided altogether.[86,109]

The pharmacy's nonsterile compounding services help to support the frontline care provider from the burden of drug preparation. The exception would be those medications with such poor, or as yet undefined, stability that they need to be administered within minutes (<30) of preparation. In those cases, the nurse prepares nonhazardous medications with limited stability in a dedicated clean area of the medication room. Otherwise, drug preparation should be left to trained pharmacy personnel responsible for preparing medications that require manipulation, followed by labeling and dispensing.

Labeling and Dispensing

When the pharmacy prepares a medication in advance, the drug container is properly labeled (patient identifiers, drug name, dose, schedule, manufacturer name, lot, and BUD) before dispensing. If the dispensed preparation has been compounded from multiple ingredients, the organization's compounding record number is also included on the label.

Depending on compatibility and stability concerns, the pharmacy may dispense a drug that requires further preparation prior to administration. At minimum, appropriate directions for preparation and administration should be provided with the container being dispensed. For example, dry powder medication (pure drug or commercial product placed into a capped enteral syringe) could be labeled with directions to dilute it with water; a commercially available liquid or extemporaneously compounded liquid could be labeled with directions to administer as is or to dilute further just prior to administration. These instructions could also be listed with the drug in the medication administration record.

Administering the Enteral Drug

Administration of an enteral drug refers to using an enteral syringe to deliver the medication through an EAD into the patient's GI tract. Only an ENFit-compatible syringe can be used for the new EADs, or a multifunctional port adaptor for large-bore orogastric/nasogastric tubes. It also involves the timing of drug delivery with respect to the enteral feeding regimen, other medication, and flushing protocols.[110,111]

Enteral feeding is briefly held during drug administration times but not disconnected. The nurse (or other caregiver, in some settings) then identifies the medication administration port of the enteral access (traced from the patient). The EAD is flushed with purified water before the first medication at a scheduled administration time. The prepared medication is then administered through the EAD, using a clean enteral syringe (which may be the same enteral syringe used to prepare the dose). After administering the dose, an additional volume of water is drawn up in the enteral syringe as a rinse to be administered as a flush and to help ensure that the entire drug dose is delivered from the syringe through the EAD. After administering the last medication and flushing the EAD with water, continuous feeding is restarted in a timely manner. This process (flush-administer drug-flush) is repeated for each scheduled medication administration time throughout the day, as tolerated within the patient's volume status. The volume of the purified water flush before and after each medication will depend on the internal volume of the EAD to be sure that any residual enteral formula or medication is flushed through as completely as possible. Thorough flushing will decrease the risk for obstruction. Assuming appropriate drug preparation, a minimum flush volume of 15–30 mL is recommended but may range up to 100 mL, but requires close attention to a patient's fluid needs and any clinical restrictions.[86]

The EN formula itself is not an ideal drug solvent, and medication is therefore not added to the feeding. When evaluated, adding medication to enteral formulations has been shown to alter not only physicochemical properties but also drug bioavailability.[112,113,114]

As more data become available and support additional drug monographs, they will be incorporated into future editions of the *Guidebook on Enteral Medication Administration*.[87] But in the meantime, pharmacists can continue to be relied on to use their knowledge of a drug's physicochemical properties, a product's biopharmaceutics, and a patient's gut anatomy/physiology to come to reasonable recommendations for appropriate preparation and administration if not contraindicated. Considerations include the potential for EN-drug interaction.

EN-Drug Interactions

Each of the previously listed (Table 1) types of drug-nutrition interactions is important, and any of them may exist in patients receiving medication through an EAD. However, the potential interaction with EN (as the precipitating factor) is typically the primary concern with enteral medication (the object) administration. With the confines of the single-lumen EAD for delivering both enteral feeds and

medication, along with variability in drug preparation methods, this focus is understandable. Given the wide variability in EN formulations and delivery methods, the potential for interaction goes beyond extrapolating from food-effect data and is deserving of further study and discussion.

In recent years, several excellent publications have provided valuable information on medication administration through EADs, including the potential for interactions by EN.[86,110,111,115,116,117] These EN-drug interactions may occur in the enteral delivery device or within the GI lumen or at the gut mucosal epithelium. An appreciation of the complexity of medication administration in enterally fed patients has led to reference works with drug monographs.[87,118]

Historically, with an open enteral feeding system, there had always been an opportunity for admixing medication with the EN formula directly in the delivery container. A 2013 national survey revealed that 21% of nurse respondents still added drugs, including antimicrobials and electrolytes, directly to the EN formula.[73] Given the compatibility and stability concerns, this administration method is not recommended.[86] Adding medication directly to an EN formula requires knowledge of their compatibility together, the stability of each component, and the presumed therapeutic effectiveness of the drug when administered under conditions of typical use. The few studies that have been performed over the years have been limited by the products evaluated, the heavy reliance on visual compatibility over chemical compatibility and stability, and the relevance of the in vitro findings for subsequent bioavailability.[112,114,119,120,121,122] Important attributes such as altered pH, osmolality, or viscosity of the admixtures were also rarely described.[112,120] Although these older data with their limitations cannot be extrapolated to newer EN products or medications, the studies provided some general insight into product characteristics that may influence compatibility. These include liquid drug product pH ($\leq$4 is generally more problematic) and the presence of alcohol content, which can denature protein. Additionally problematic from the EN product is the presence of casein and fiber. Furthermore, the in vitro incompatibility between drug and EN formula predicts tube clogging that cannot be flushed clear, as well as drug concentrations that generally decline over time. The potential for EN-drug interactions to occlude EADs has been evaluated more recently.[123] Current recommendations support administration of appropriate medication through the same EAD as EN but do not support mixing together in the delivery container prior to administration.[86]

In the absence of data on EN-drug interactions in the gut lumen, it may be possible to predict the influence on the bioavailability based on physicochemical properties or food-effect data.[124] Assuming appropriate drug preparation and administration technique, a general call to treat EN as a meal and temporally dose medication accordingly may make sense for the patients being fed intermittently with meal-like volumes/rates into the stomach. However, this extrapolation is not without limitations. It turns out that liquid meals are different than solid meals. A liquid meal has a different influence on gut physiology compared with a solid meal of similar nutrient content.[46] The gut-lumen pH was similar, but drug disposition was different—ie, greater drug dissolution in the stomach with a solid meal but more drug precipitating in the intestine to reduce absorption.

Continuous feeds into the stomach or small bowel are less representative of a meal effect.[111] The influence on segmental volume in the small bowel could play a role in altering drug bioavailability. The few articles that describe the effects of administering both the drug and EN through the same EAD offer recommendations for only a handful of medications. The limitations in the literature include that most were case reports, had small sample sizes, or had unsuitable designs. The clinical decision points at the center of this discussion are (1) whether or not to hold the EN beyond the time to flush-administer drug-flush in order to avoid the interaction and (2) if EN is held, how long should it be interrupted before and after drug administration to avoid the interaction. An overriding clinical concern is that each significant interruption in feeding to accommodate drug administration, although avoiding an interaction, risks inadequate delivery of nutrition. As a result, especially in acute care settings, the option of selecting an alternative medication or route of administration needs to remain viable. As discussed earlier, the best practice is to hold EN for as long as it takes to flush the tube, administer each medication, and flush the tube. This issue of holding the feeds for any longer would only be to avoid a clinically relevant interaction as supported by data.

The remainder of the article presents a brief selection of drugs and considerations for their administration via EAD, including EN-drug interaction risk (Table 4), as an example of what may be found elsewhere[87,118]

Antiepileptic Drugs

Carbamazepine and phenytoin are classic antiepileptic agents still widely used for a number of neurologic disorders. Their solubility issues contribute to slow and variable GI absorption, but they are expected to be better absorbed in the presence of a meal, as both drugs are considered Class 2 agents. Liquid formulations (ie, suspensions) of these drugs are frequently used, especially for enterally fed patients.

In vitro studies using different solid dosage forms of carbamazepine revealed the lowest drug recovery in the presence of EN.[125] Single-dose studies with carbamazepine suspension administered by nasogastric tube revealed a 10% mean reduction in bioavailability compared with oral dosing in the fasted state, but with significant

Table 4. Selected Enteral Drugs: Preparation, Administration, and Interaction Potential.[40,87].

Drug	Comments
Antiepileptic drugs	
Carbamazepine, phenytoin	Dilute suspension (at least 1:1), and flush EAD well before/after gastric dose. No need to separate drug administration from timing of EN. Closely monitor therapeutic drug effects.
Antimicrobials[a]	
Azithromycin	
	Dilute the reconstituted suspension with water (at least 1:1) just prior to administration; film-coated tablets pose risk for tube occlusion. No need to separate drug administration from timing of EN; administration in close proximity to EN may improve GI tolerance. Potential risk for hyperkalemia and hyperphosphatemia.
Ciprofloxacin, levofloxacin	Immediate-release tablets require crushing to disperse in water (25–50 mL); levofloxacin solution may be diluted (at least 1:1) prior to administration; oral ciprofloxacin suspension is not intended for enteral administration. Avoid drug administration soon after or before EN; separate from feeding by at least 2 h. Avoid coadministration of therapeutic doses of calcium-, magnesium-, iron-, zinc-, or aluminum-containing products.
Dolutegravir	If no alternative, crush in a protective environment and disperse in water (mineral-free) just prior to administration (hazardous drug). Hold continuous EN for 2 h before/after drug administration; separate from an intermittent EN feeding. Avoid coadministration of therapeutic doses of calcium, magnesium, or iron; administer 2 h before or 6 h after any cation-containing pharmacologic agents, including calcium and iron supplements. Potential risk for hyperglycemia and hypertriglyceridemia.
Hydroxychloroquine	Disperse noncoated tablet (or crush and disperse tablet) in water (10–20 mL) prior to administration. Avoid using an extemporaneous suspension with high viscosity/osmolality. No need to separate drug administration from timing of EN; administration in close proximity to EN may improve GI tolerance. As a zinc ionophore, consider including zinc in regimen for antiviral effect. Potential risk for thiamin deficits and for hypoglycemia.
Isoniazid	Disperse tablet in water (10–20 mL) just prior to administration. Consider holding EN for at least 30 min before and 1 h after drug administration; reduced bioavailability possible when administered through an EAD. Include pyridoxine in chronic regimen to prevent deficit.
Voriconazole	Disperse a noncoated tablet (or crush in a protective environment and disperse) in water (at least 20 mL) just prior to administration (hazardous drug). Hold continuous EN for at least 1 h before/after drug administration; separate from an intermittent EN feeding. Correct hypokalemia, hypomagnesemia, or hypocalcemia prior to initiating therapy.
Others	
Levodopa	Separate drug administration from intermittent EN administration or protein administration by at least 2 h. Consider drug administration in daytime, with continuous EN at night.
Warfarin	Dilute the drug in a small volume and administer quickly. Separate drug administration from EN administration by at least 1 h.

EAD, enteral access device; EN, enteral nutrition; GI, gastrointestinal.
[a]As with all antimicrobials, consider a parenteral alternative for acutely ill patients to assure therapeutic concentrations.

interindividual variability.[126] The studies did not account for the important roles played by the 10Fr tube, administration of undiluted suspension, or enterocyte metabolism. An in vitro evaluation of multiple methods to prepare and administer carbamazepine suspension identified that the best drug recovery at the distal end of the EAD occurred when the suspension was diluted (1:1 by volume) followed by flushing.[106] Drug loss was between 2% and 24% with no EN involved. Modified-release carbamazepine granules diluted in formula resulted in 50%–100% tube occlusion

rates in patients with 14Fr–24Fr EADs.[127] When suspended in water and administered rapidly, the granules still caused tube occlusion in a proportion of these patients.[127] This reinforces the recommendations to avoid modified-release products and to dilute suspensions.

Clinical observation revealed that patients receiving phenytoin suspension via nasogastric tube along with EN had subtherapeutic drug concentrations.[128] This finding led to a prospective study to determine whether EN truly interfered with drug absorption. The conclusion that continuous EN by the nasogastric tube significantly interfered with absorption of phenytoin suspension regardless of whether the patient is stabilized on drug or EN first has been widely cited, as has the suggestion that withholding EN for 2 hours before and after drug administration will prevent the interaction.[128,129] The interaction was reported in subsequent cases.[130] A study performed in volunteers using phenytoin suspension seemed to suggest that the interaction varied with the EN formula.[131] However, neither the mechanism for the purported interaction nor best practices to prevent it have been made clear.[132] Withholding EN for 2 or more hours around the dose of phenytoin has not necessarily improved phenytoin absorption.[133] Clamping a gastrostomy tube for 1 hour after the dose of phenytoin and before restarting EN was shown to improve serum concentrations in a group of patients.[134] Of note, no description was provided of drug dilution, flushing protocol, or the EN regimen in the latter report.

Many mechanisms, none of them definitive, have been suggested for the EN-phenytoin interaction, and, because of limited data, there is no agreement on how to manage it.[135] It is possible that the interaction has nothing to do with EN and is related to the method of preparing and administering the drug through the EAD. An in vitro study of multiple methods of administration suggested not only that dilution of the suspension, with a flush before and after the dose, improves the delivery through a 16Fr nasogastric tube but also that the interaction may be with the feeding tube and not the EN.[105] This lack of an EN-phenytoin interaction was reflected in patient case reports.[136] Another in vitro study evaluated a single dose of phenytoin suspension administered through a 20Fr gastrostomy tube under various conditions.[137] Investigators described best drug recovery when the undiluted suspension was followed by a flush. The differences between the 2 in vitro studies include the type of EAD (ie, material, diameter, and surface area). Given the high pKa of phenytoin, a solubility effect of the relatively acidic EN and gastric pH has also been suggested.[138] There is additionally more binding to the tube at a lower pH. Missing from all the previous data are pharmacokinetic studies that examine bioavailability. This omission is important because of the nonlinear kinetics of phenytoin, with its erratic absorption in which a single dose may take >24 hours to be absorbed.[139] Although conducted in healthy participants, pharmacokinetic analysis available from prospective randomized controlled trials suggests no difference in phenytoin bioavailability with EN.[140,141] Another pharmacokinetic analysis more closely representing clinical use, with continuous EN administered through a nasogastric tube, used 2 different phenytoin formulations in a single-dose crossover design.[139] The drug was diluted and the feeding tube was flushed before and after drug administration. The absolute bioavailability was about 90%, with greater variability with the suspension than the sodium salt, but similar to values seen in the fasted state.

The current data do not support withholding EN for any significant time to administer carbamazepine or phenytoin, but the drug suspension should first be diluted, and the tube should be flushed prior to and following drug administration. Additionally, patients receiving these antiepileptic drugs will need to be more closely monitored when receiving EN therapy. If considering the tenuous practice of withholding EN, clinicians must be aware of the risks for the reduced delivery of nutrients or for feeding intolerance with increased EN administration rates.

Antimicrobials

Two drugs that have each been used individually for a number of unique indications for years have been used together frequently in the last year as part of the management in less severe presentations of severe acute respiratory syndrome (SARS)- coronavirus (CoV-2) infection—azithromycin and hydroxychloroquine. Although the latter possesses antiviral effects, including in vitro effects against SARS-CoV-2, clinical benefits in combination with azithromycin have been inconsistent.[142,143] Zinc's role in antiviral immunity is well recognized, which led to including this mineral in the regimen for synergistic effect, given hydroxychloroquine's action as a zinc ionophore.[144,145,146] For enteral administration, the film- coated tablets of each drug pose a risk for tube occlusion, but products with less prominent coating may crush/disperse in water. Neither drug requires separation from EN other than to flush-administer drug-flush. In fact, administration in close proximity to the feeds may improve GI tolerance with these 2 agents.

The fluoroquinolone antimicrobials are valuable for treating a variety of infections caused by susceptible microorganisms. Critical to their clinical effectiveness is achieving adequate serum concentrations that remain above a defined value relative to the minimum inhibitory concentration for the organism. Interactions that reduce bioavailability run the risk for therapeutic failure. Multivalent cations (ie, aluminum, calcium, iron, magnesium, and zinc) chelate with the fluoroquinolones and significantly reduce bioavailability.[147,148] Temporal spacing of at least 2–4 hours may be adequate to alleviate the interaction with therapeutic doses of these minerals, as found in supplements and

antacids.[147,148,149] The interaction of ciprofloxacin or levofloxacin with an EN formulation that contains multivalent cations can result in significantly reduced bioavailability of the drug, and it takes place quickly.[150,151,152] The degree of interaction will depend on cation concentrations in the EN.[150] A molar ratio of cation to fluoroquinolone of 1:1 to 3:1 and elevated pH may play a role in maximally reducing drug bioavailability. Interpatient variability is significant, thereby limiting the predictability of the interaction in an individual patient.[151,153,154] It remains prudent to avoid administration of fluoroquinolones together with EN; no single best alternative (eg, separating by at least 2–4 hours, administering higher drug doses, or using the parenteral route) is known.[155] As with all systemic infections, the parenteral route should be considered an option for the acutely ill patient to ensure therapeutic concentrations.

The antiviral drug dolutegravir is not an ideal drug for the enterally fed patient. As expected of a Class 2 agent, the drug exhibits improved bioavailability with a meal that, in this case, is directly related to fat content.[156] However, the drug is also susceptible to chelation with multivalent cations that reduce absorption. When coadministered in the fasted state with a multivitamin-mineral containing just 162 mg calcium and 100 mg magnesium, the bioavailability was reduced by 33%.[157] The drug is therefore best avoided with therapeutic doses of calcium, iron, magnesium, or zinc. Most tablet products are film-coated, creating some difficulty for crushing, which, given risk for fetotoxicity on exposure, should take place in a protected environment.

In a study in healthy participants, by using a fixed-dose triple therapy product containing dolutegravir, which was administered orally on an empty stomach after being crushed and suspended in 200 mL water, the bioavailability increased by 26% compared with taking the whole tablet with the same volume of water.[158] When the dolutegravir tablet was crushed and dispersed in 10 mL of water and administered to an HIV-positive patient via orogastric tube, separated from EN by 2 hours before and after, therapeutic effect was maintained during an ICU stay.[159] As part of a combination regimen, dolutegravir crushed and administered via nasogastric tube without an EN regimen resulted in adequate therapeutic concentrations.[160] When the drug was crushed and mixed with 3–5 mL of water for administration to an acutely ill patient with long-standing HIV via jejunostomy tube and followed by a 10-mL flush, data revealed similar bioavailability as dosing by the oral route during the same admission.[161] Of note, the bioavailability was still lower than expected.

Isoniazid is a medication that has been used for decades in the management of tuberculosis. Although products vary by manufacturer, many available uncoated tablets disperse readily in 10–20 mL of water. The drug (Class 3) is best absorbed on an empty stomach with food decreasing oral bioavailability, varying in degree with the meal content.[162] Administration through a nasogastric tube as part of a 4-drug fixed-dose combination product after crushing and dispersing in 20 mL of water resulted in subtherapeutic concentrations in 2 of 10 ICU patients.[163] Although 9 of the patients were receiving continuous EN, there was no description of holding the feeds or flushing regimen.

The antifungal agent voriconazole is available as a suspension as well as a tablet. Although some tablet products may be film-coated, they may be crushed in a closed system (reproductive risk) and dispersed in water. When administration of an intact tablet was compared with a crushed tablet across a 6-day regimen in healthy individuals, there was no difference in bioavailability when separated at least 1 hour before and after food.[164] In a cohort of critically ill patients, crushed tablet dispersed in 20 mL of water followed by a 20-mL water flush through a nasogastric tube resulted in therapeutic serum concentrations for the identified pathogen in 7 of 8 patients when EN was held long enough to administer the drug and flush.[165] Crushed tablets dispersed in 50 mL of water and administered via jejunostomy resulted in therapeutic concentrations in a patient.[166] The suspension is very viscous and cannot be diluted further, given its poor solubility and risk for precipitation if the solvent is diluted. The administration of the suspension in a patient with an EAD receiving EN resulted in undetectable serum drug concentrations compared with therapeutic levels when receiving the tablet prior to EN initiation.[167] Unfortunately, neither the tube nor the drug-preparation methods were described. Of note, a high-fat meal can significantly reduce the bioavailability of the drug.[168]

Levodopa

Levodopa is used for the management of patients with Parkinson disease. The drug competes with digested protein for intestinal absorption. This interaction can impair drug absorption, resulting in clinical exacerbations and a neuroleptic malignant-like syndrome, similar to the effect of a reduction in drug dose. This outcome has also been reported in acutely ill patients receiving EN through the gastric or postpyloric route.[169,170] Clinical exacerbations in enterally fed patients resolved with protein-dose reductions (to $\leq$1 g/kg) and/or separating drug administration from EN.[171,172] Although this interaction could be avoided by reducing protein administration, the restriction of daily protein or shifting more protein to the evening may result in nutrition deficits over time. Managing this interaction involves providing bolus feedings separated from levodopa administration by at least 2 hours, nighttime feedings with daytime medication, or an empiric increase in drug dose as needed.[170] In a pilot study of essential amino acid supplementation (16 g daily distributed apart from meals and levodopa) to address protein restriction in patients with

Parkinson disease managed with levodopa, no detrimental effects were seen after 6 months.[173]

Warfarin

Warfarin, an anticoagulant still used to manage patients with venous thromboembolism or atrial fibrillation, works by inhibiting VKORC1 activity. This interferes with vitamin K activation and its availability to carboxylate glutamate residues, which are required by several clotting factors for activation. As a result, there was a historic concern that vitamin K intake would interfere with the drug's anticoagulant effect, and the first reported treatment failures in patients receiving warfarin and EN were subsequently attributed to the vitamin K content of the formulations.[174,175] However, an interaction was still being reported after the EN manufacturers reformulated their products with much lower vitamin K content.[176,177,178] Current approaches do not support vitamin K restriction as a strategy to improve warfarin effect.[179] In fact, consistent vitamin K intake close to the recommended adequate intake value helps maintain anticoagulation.

An in vitro study revealed that a physicochemical interaction, likely due to the macromolecular fraction of EN, was the mechanism resulting in lower warfarin availability and clinical failure.[180] This finding seemed to be confirmed by patient case reports in which separating warfarin from EN administration by 1–3 hours mitigated the interaction.[181,182,183] Another in vitro study indicated that warfarin binds with the large, unfilterable component of EN, a problem that is seemingly worse in the presence of formulas with intact protein than with an amino acid–based formula.[182] A crossover case series further suggested the complexity of warfarin disposition in patients receiving EN.[184] This investigation indicated that withholding continuous EN for 1 hour before and after warfarin administration significantly improved the international normalized ratio response.[184,185] Another in vitro study identified a potential role of warfarin binding to a polyurethane feeding tube.[186] Therefore, in addition to holding the feed for an hour around the daily warfarin dose, the drug may be best delivered rapidly in a small volume of water with adequate flushing before and after.

Other Medications

Proton pump inhibitors reduce gastric acid secretion and are used in the management of patients with gastroesophageal reflux and peptic ulcer disease as well as stress-related mucosal damage. Potential tube obstruction using the enteric-coated products depends on the granule size of the product relative to the internal diameter of the EAD, which is generally problematic when the tube is smaller than 14Fr.[187] Combining these products with water tends to increase the stickiness of the enteric-coated granules toward each other, which further increases occlusion risk. The pH of water may vary considerably (4.0–9.5) depending on the source, and if the pH is >5.5, the water can damage the enteric coating within 15 minutes.[188] Fruit juices are to be avoided because they increase that stickiness even further and contribute further to occlusion when their pH is less than that of the EN. Immediate-release proton pump inhibitors (commercially available or extemporaneously prepared in sodium bicarbonate solution using the USP method) are preferred for EAD administration because their clinical effectiveness is maintained.[189] Suspensions made from lansoprazole solutabs or omeprazole immediate-release preparations are preferred when small-bore feeding tubes >6Fr are used.[187] Of course, the intravenous route remains an effective option for acutely ill patients. The FDA has noted deficiencies in the in vitro product testing of proton pump inhibitors when seeking labeling for EAD administration (especially large-bore tubes ≥14Fr).[188]

In some cases, the presumed EN-drug interaction may actually be the result of an interaction between the medication and the EAD that involves properties of the drug formulation, how it is prepared, and the physical dimensions and material of the feeding tube. For example, clonazepam and diazepam solutions may adsorb to the feeding tube.[102,111] Lanthanum, sevelamer, and sucralfate are to be avoided altogether in patients receiving EN. This is based on the drugs' limited water solubility and interaction with residual EN components and the resulting high risk for a clogged EAD.[111] Tube obstruction would pose a significant interruption and delay in the patient's EN delivery. Looking toward the future, the impact of novel nanoparticle-containing products on bioavailability when administered in patients receiving EN will need to be accounted for.[190,191]

Conclusion

Enteral medication for the tube-fed patient can be safe and effective for appropriately selected drugs using best practices for preparation and administration. Clinicians with concerns about drug handling for the tube-fed patient should consult with a pharmacist. They can help decipher the available physicochemical, pharmaceutical, and nutrition interaction data to develop the most appropriate recommendation for preparing and administering a drug through an EAD if not contraindicated. This supports achieving expected bioavailability and clinical effect while limiting risk, which is especially important for the complex acutely ill patient. More reflection will be required to further refine practices as additional data become available.

Statement of Authorship

J. Boullata conceptualized and drafted the manuscript, critically revised the manuscript, and agrees to be accountable

for ensuring the integrity and accuracy of the work and has read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. US FDA. *Guidances (drugs)*. Accessed July 2020. www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.
2. Dahlgren D, Lennernäs H. Intestinal permeability and drug absorption: predictive experimental, computational and in vivo approaches. *Pharmaceutics*. 2019;11:8, 411.
3. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill. *Chest*. 2012;141:5, 1327-1336.
4. Tian S, Li Y, Wang J, et al. ADME evaluation in drug discovery. 9: Prediction of oral bioavailability in humans based on molecular properties and structural fingerprints. *Mol Pharmaceutics*. 2011;8:3, 841–851.
5. Bergström CAS, Larsson P. Computational prediction of drug solubility in water-based systems: qualitative and quantitative approaches used in the current drug discovery and development setting. *Int J Pharm*. 2018;540:1-2, 185-193.
6. Feng YH, Zhang XP, Zhao ZQ, Guo XD. Dissipative particle dynamics aided design of drug delivery systems: a review. *Mol Pharmaceutics*. 2020;17:6, 1778-1799.
7. Drozdzik M, Groer C, Penski J, et al. Protein abundance of clinically relevant multidrug transporters along the entire length of the human intestine. *Mol Pharmaceutics*. 2014;11:10, 3547–3555.
8. Talattof A, Price JC, Amidon GL. Gastrointestinal motility variation and implications for plasma level variation: oral drug products. *Mol Pharmaceutics*. 2016;13:2, 557–567.
9. Dahlgren D, Roos C, Lundqvist A, et al. Regional intestinal permeability of three model drugs in human. *Mol Pharmaceutics*. 2016:13:9, 3013–3021.
10. Harwood MD, Zhang M, Pathak SM, Neuhoff S. The regional-specific relative and absolute expression of gut transporters in adult Caucasians: a meta-analysis. *Drug Metab Disp*. 2019;47:8, 854-864.
11. Porat D, Dahan A. Active intestinal drug absorption and the solubility-permeability interplay. *Int J Pharm*. 2018;537:1-2, 84-93.
12. Zou L, Ni Z, Tsakalozou E, Giacomini KM. Impact of pharmaceutical excipients on oral drug absorption: a focus on intestinal drug transporters. *Clin Pharmacol Ther*. 2019;105:2, 323-325.
13. Schiller C, Frohlich C-P, Giessmann T, et al. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment Pharmacol Ther*. 2005;22:10, 971-979.
14. Mudie DM, Murray K, Hoad CL, et al. Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state. *Mol Pharm*. 2014;11:9, 3039-3047.
15. Papadatou-Soulou E, Mason J, Parsons C, et al. Magnetic resonance imaging quantification of gastrointestinal liquid volumes and distribution in the gastrointestinal tract of children. *Mol Pharm*. 2019;16:9, 3896-3903.
16. Tandra S, Chalasani N, Jones DR, et al. Pharmacokinetic and pharmacodynamics alterations in the Roux-en-Y gastric bypass recipients. *Ann Surg*. 2013;258:2, 262-269.
17. Stillhart C, Vučićević K, Augustijns P, et al. Impact of gastrointestinal physiology on drug absorption in special populations – an UNGAP review. *Eur J Pharm Sci*. 2020;147:105280.
18. Farrokh S, Tahsili-Fahadan P, Ritzl EK, Lewin JJ, Mirski MA. Antiepileptic drugs in critically ill patients. *Crit Care*. 2018;22(1):153.
19. Masich AM, Heavner MS, Gonzales JP, Claeys KC. Pharmacokinetic/pharmacodynamic considerations of beta-lactam antibiotics in adult critically ill patients. *Curr Infect Dis Rep*. 2018;20(5):9.
20. Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. *Expert Opin Drug Metab Toxicol*. 2013;9:9, 1067-1084.
21. Wu K-C, Lin C-J. The regulation of drug-metabolizing enzymes and membrane transporters by inflammation. *J Food Drug Anal*. 2019;27:1, 48-59.
22. Kar P, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. *Clin Nutr*. 2015;34:4, 557-564.
23. Tarling MM, Toner CC, Withington PS, et al. A model of gastric emptying using paracetamol absorption in intensive care patients. *Intensive Care Med*. 1997;23:3, 256-260.
24. Kleiber N, Calvier E, Mooij MG, et al. Enteral acetaminophen bioavailability in pediatric intensive care patients determined with an oral microtracer and pharmacokinetic modeling to optimize dosing. *Crit Care Med*. 2019;47:12, e975-e983.
25. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *CMAJ*. 2010;182:4, 357-363.
26. May F, Peytavin G, Fourati S, et al. Paracetamol absorption test to detect poor enteric absorption of oseltamivir in intensive care unit patients with severe influenza: a pilot study. *Intensive Care Med*. 2019;45:10, 1484-1486.
27. Hitchings R, Kelly L. Predicting and understanding the human microbiome's impact on pharmacology. *Trends Pharmacol Sci*. 2019;40:7, 495-505.
28. Sharma A, Buschmann MM, Gilbert JA. Pharmacomicrobiomics: the holy grail to variability in drug response? *Clin Pharmacol Ther*. 2019;106:2, 317-328.
29. Pryor R, Martinez-Martinez D, Quintaneiro L, Cabreiro F. The role of the microbiome in drug response. *Annu Rev Pharmacol Toxicol*. 2020;60:1, 417-435.
30. Guo Y, Crnkovic CM, Won K-J, et al. Commensal gut bacteria convert the immunosuppressant tacrolimus to less potent metabolites. *Drug Metab Disp*. 2019;47:3, 194-202.
31. Selwyn FP, Cheng SL, Klaassen CD, Cui JY. Regulation of hepatic drug-metabolizing enzymes in germ-free mice by conventionalization and probiotics. *Drug Metab Disp*. 2016;44:2, 262–274.
32. MacLaren R, Devlin JW. The bedside critical care pharmacist: a mandatory ICU team member essential for patient care. *Crit Care Med*. 2019;47:9, 1276-1278.
33. Sohrevardi SM, Jarahzadeh MH, Mirzaei E, et al. Medication errors in patients with enteral feeding tubes in the intensive care unit. *J Res Pharm Pract*. 2017;6:100–105.
34. Tully AP, Hammond DA, Li C, Jarrell AS, Kruer RM. Evaluation of medication errors at the transition of care from an ICU to non-ICU location. *Crit Care Med*. 2019;47:4, 543-549.
35. Boullata JI. Drug and nutrition interactions: not just food for thought. *J Clin Pharm Ther*. 2013;38:4, 269–271.
36. Boullata JI, Hudson LM. Drug-nutrient interactions: a broad view with implications for practice. *J Acad Nutr Diet*. 2012;112:4, 506–517.
37. Chan LN. Drug-nutrient interactions. *JPEN J Parenter Enteral Nutr*. 2013;37:4, 450–459.
38. Boullata JI, Armenti VT, eds. *Handbook of Drug-Nutrient Interactions*. 2nd ed. New York, NY: Humana Press; 2010.
39. Boullata JI. Drug-nutrition interactions and the brain: it's not all in your head. *Curr Nutr Rep*. 2019;8(2):92-98.
40. Boullata JI. Drug-nutrition interactions in infectious diseases. In: Humphries D, Scott M, Vermund SH, eds. *Nutrition and Infectious*

Diseases: Shifting the Clinical Paradigm. Switzerland AG: Springer Nature, 2021:367-410.
41. Yu J, Petrie ID, Levy RH, Ragueneau-Majlessi I. Mechanisms and clinical significance of pharmacokinetic-based drug-drug interactions with drugs approved by the U.S. Food and Drug Administration in 2017. *Drug Metab Disp*. 2019;47:2, 135-144.
42. Lincoln J, Stewart ME, Preskorn SH. How sequential studies inform drug development: evaluating the effect of food intake on optimal bioavailability of ziprasidone. *J Psychiatr Pract*. 2010;16:2, 103–114.
43. Sutton SC, Nause R, Gandelman K. The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption. *AAPS J*. 2017;19:4, 1084–1090.
44. Deng J, Zhu X, Chen Z, et al. A review of food-drug interactions on oral drug absorption. *Drugs*. 2017;77:17, 1833-1855.
45. Kim SHJ, Jackson AJ, Hunt CA. In silico, experimental, mechanistic model for extended-release felodipine disposition exhibiting complex absorption and a highly variable food interaction. *PLoS One*. 2014;9:9, e108392.
46. Rubbens J, Brouwers J, Tack J, Augustijns P. Gastric and duodenal diclofenac concentrations in healthy volunteers after intake if the FDA standard meal: in vivo observations and in vitro explorations. *Mol Pharmaceutics*. 2019;16:2, 573-582.
47. Schick P, Sager M, Wegner F, et al. Application of the GastroDuo as an in vitro dissolution tool to simulate gastric emptying of the postprandial stomach. *Mol Pharmaceutics*. 2019;16:11, 4651-4660.
48. Gleeson JP, McCartney F. Striving towards the perfect in vitro oral drug absorption model. *Trends Pharmacol Sci*. 2019;40:10, 720-724.
49. Kataoka M, Ohi Y, Sakanoue K, et al. Impact of dietary intake of medium-chain triacylglycerides on the intestinal absorption of poorly permeable compounds. *Mol Pharmaceutics*. 2020;17:1, 212-218.
50. Ronis MJJ, Chen Y, Liu X, et al. Enhanced expression and glucocorticoid-inducibility of hepatic cytochrome P450 3A involve recruitment of the pregnane-X-receptor promoter elements in rats fed soy protein isolate. *J Nutr*. 2011;141:1, 10–16.
51. Ando H, Tsuruoka S, Yanagihara H, et al. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br J Clin Pharmacol*. 2005;60:5, 494–497.
52. Dolton MJ, Roufogalis BD, McLachlan AJ. Fruit juices as perpetrators of drug interactions: the role of organic anion-transporting polypeptides. *Clin Pharmacol Ther*. 2012;92:5, 622–630.
53. Bailey DG, Dresser G, Arnold MO. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ*. 2013;185:4, 309-316.
54. Hyewon J, In-Jin J, Hwan LS, et al. Apple juice greatly reduces systemic exposure to atenolol. *Br J Clin Pharmacol*. 2013;75(1):172-179.
55. Fleisher B, Unum J, Shao J, An G. Ingredients in fruit juices interact with dasatinib through inhibition of BCRP: a new mechanism of beverage-drug interaction. *J Pharm Sci*. 2015;104:1, 266–275.
56. Sand PG, Dreiseitel A, Stang, M, et al. Cytochrome P450 2C19 inhibitory activity of common berry constituents. *Phytother Res*. 2010;24:2, 304–307.
57. Dreiseitel A, Oosterhuis B, Vukman KV, et al. Berry anthocyanins and anthocyanidins exhibit distinct affinities for the efflux transporters BCRP and MDR1. *Br J Pharmacol*. 2009;158:8, 1942–1950.
58. Egert S, Rimbach G. Which sources of flavonoids: complex diets or dietary supplements? *Adv Nutr*. 2011;2:1, 8–14.
59. Funai Y, Shirasaka Y, Ishihara M, et al. Effect of osmolality on the pharmacokinetic interaction between apple juice and atenolol in rats. *Drug Metab Disp*. 2019;47:4, 386-391.
60. Benet LZ. The role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in drug development. *J Pharm Sci*. 2013;102:1, 34–42.
61. Varma MV, Steyn SJ, Allerton C, El-Kattan AF. Predicting clearance mechanism in drug discovery: extended clearance classification system (ECCS). *Pharm Res*. 2015;32:12, 3785-3802.
62. Sugihara M, Takeuchi S, Sugita M, et al. Analysis of intra- and intersubject variability in oral drug absorption in human bioequivalence studies of 113 generic products. *Mol Pharmaceutics*. 2015;12:12, 4405–4413.
63. Cornish P. "Avoid the Crush": hazards of medication administration in patients with dysphagia or a feeding tube. *CMAJ*. 2005;172:7, 871-872.
64. Paparella S. Identified safety risks with splitting and crushing oral medications. *J Emerg Nurs*. 2010;36:2, 156–158.
65. Arimanickam G. Tube feeding and drugs in intensive care unit. *Anaesth Intensive Care*. 2011;39(4):776.
66. Stegemann S. Drug administration via enteral tubing: an unresolved but increasing challenge. *Expert Opin Drug Deliv*. 2015;12:2, 159–161.
67. Leff RD, Roberts RJ. Enteral drug administration practices: report of a preliminary survey. *Pediatrics*. 1988;81(4):549–551.
68. Mateo A. Nursing management of enteral tube feedings. *Heart Lung*. 1996;25:4, 318–323.
69. Schmieding NJ, Waldman RC. Nasogastric tube feeding and medication administration: a survey of nursing practices. *Gastroenterol Nurs*. 1997;20:4, 118–124.
70. Belknap DC, Seifert CF, Peterman M. Administration of medications through enteral feeding catheters. *Am J Crit Care*. 1997;6:5, 382–392.
71. Seifert CF, Johnston BA. Drug administration through enteral feeding catheters. *Am J Health Syst Pharm*. 2002;59:4, 378–379.
72. Hanssens Y, Woods D, Alsulaiti A, et al. Improving oral medicine administration in patients with swallowing problems and feeding tubes. *Ann Pharmacother*. 2006;40:12, 2142–2147.
73. Guenter P, Boullata J. Nursing2013 survey results: drug administration by enteral feeding tube. *Nursing*. 2013;43(12):26–35.
74. Schier JG, Howland MA, Hoffman RS, Nelson LS. Fatality from administration of labetalol and crushed extended-release nifedipine. *Ann Pharmacother*. 2003;37:10, 1420–1423.
75. Dickerson RN, Tidwell AC, Brown RO. Adverse effects from inappropriate medication administration via a jejunostomy feeding tube. *Nutr Clin Pract*. 2003;18:5, 402-405.
76. Madigan SM, Courtney DE, MaCauley D. The solution was the problem. *Clin Nutr*. 2002;21:6, 531-532.
77. Emami S, Hamishehkar H, Mashayekhi, S, et al. Errors of oral medication administration in a patient with enteral feeding tube. *J Res Pharm Pract*. 2012;1(1):37–40.
78. *Institute for Safe Medication Practices. Willingness of staff to give oral meds IV is disconcerting. ISMP Acute Care Med Safety Alert Newsletter*. May 20, 1998. Accessed XXXX. https://www.ismp.org/newsletters/acute-care and then enter search terms for issue.
79. Guenter P, Hicks RW, Simmons D, et al. Enteral feeding misconnections: a consortium position statement. *Jt Comm J Qual Patient Saf*. 2008;34(5):285–292.
80. Institute for Safe Medication Practices. Avoiding inadvertent IV injection of oral liquids. *ISMP Acute Care Med Safety Alert Newsletter*. August 23, 2012. Accessed 1 August 2020. https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=29.
81. Institute for Safe Medication Practices. A successful ENFit launch still won't stop all incidents of oral medications given intravenously. ISMP Acute Care Med Safety Alert Newsletter. August 13, 2015. Accessed 1 August 2020. https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=115.
82. Bertsche T, Nieman D, Mayer Y, et al. Prioritizing the prevention of medication handling errors. *Pharm World Sci*. 2008;30:6, 907–915.

83. Joos E, Mehuys E, Van Bocxlaer J, et al. Drug administration via enteral feeding tubes in residential care facilities for individuals with intellectual disability: an observational study. *J Intellect Disab Res*. 2015;59:3, 215–225.
84. Institute for Safe Medication Practices. Preventing errors when administering drugs via an enteral feeding tube. ISMP Acute Care Med Safety Alert Newsletter. May 6, 2010. Accessed 1 August 2020. https://www.ismp.org/newsletters/acutecare/articles/20100506.asp.
85. Boullata JI. Safe practices for enteral and parenteral nutrition. In: Seres DS, Van Way CW, eds. *Nutrition Support for the Critically Ill*. New York: Humana Press; 2016:229–241.
86. Boullata JI, Carrera AL, Banchik LH, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr*. 2017;41:1, 15–103.
87. Boullata JI. *Guidebook on Enteral Medication Administration*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2019.
88. Niemiec PW, Vanderveen TW, Morrison JI, Hohenwarter MW. Gastrointestinal disorders caused by medication and electrolyte solution osmolality during enteral nutrition. *JPEN J Parenter Enteral Nutr*. 1983;7:4, 387–389.
89. Atakent Y, Ferrara A, Bhoqal M, Klupsteen M. The adverse effects of high oral osmolal mixtures in neonates: a review and study of the osmolality of calcium preparations. *Clin Pediatr*. 1984;23:9, 487–491.
90. Obladen M, Mutz A. Oral medication in preterm infants? Physical properties of liquid drugs. Article in German. *Montasschr Kinderheilkd*. 1985;133: 669–674.
91. Dickerson RN, Melnik G. Osmolality of oral drug solutions and suspensions. *Am J Hosp Pharm*. 1988;45:832–834.
92. Fernández Polo A, Cabañas Poy MJ, Clemente Bautista S, et al. Osmolality of oral liquid dosage forms to be administered to newborns in a hospital. *Farm Hosp*. 2007;31:5, 311–314.
93. *Institute for Safe Medication Practices. Oral dosage forms that should not be crushed*. 21 February 2020. Accessed 1 August 2020. http://www.ismp.org/tools/DoNotCrush.pdf.
94. Salmon D, Pont E, Chevallard H, et al. Pharmaceutical and safety considerations of tablet crushing in patients undergoing enteral intubation. *Int J Pharmaceut*. 2013;443:1-2, 146–153.
95. Institute for Safe Medication Practices. Safety briefs: should the PillCrusher syringe be used for crushing tablets? *Acute Care ISMP Medication Safety Alert Newsletter*. February 27, 2020.
96. Martin TP, Hayes P, Collins DM. Tablet dispersion as an alternative to formulation of oral liquid dosage forms. *Aust J Hosp Pharm*. 1993;23:378–386.
97. Jew RK, Soo-Hoo W, Erush SC. *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients*. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010.
98. Allen LV, ed. *The Art, Science, and Technology of Pharmaceutical Compounding*. 5th ed. Washington, DC: American Pharmacists Association; 2016.
99. Trissel LA, Ashworth LD, Ashworth J. *Trissel's Stability of Compounded Formulations*. 6th ed. Washington, DC: American Pharmacists Association; 2018.
100. Nahata MC, Pai VB, eds. *Pediatric Drug Formulations*. 6th ed. Cincinnati, OH: Harvey Whitney Books; 2014.
101. *United States Pharmacopeia. USP <795> Pharmaceutical compounding—nonsterile preparations*. http://www.usp.org.
102. Glass BD, Haywood A. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *J Pharm Pharmaceut Sci*. 2006;9(3):398–426.
103. Haywood A, Glass BD. Liquid dosage forms extemporaneously prepared from commercially available products – considering new evidence on stability. *J Pharm Pharmaceut Sci*. 2013;16(3): 441–455.
104. Crawford SY. Anaizi NH, Swenson C. Tam YK, Pereira CM. Tap water should not be used. *Am J Hosp Pharm*. 1993;50(8):1579.
105. Cacek AT, DeVito JM, Koonce JR. In vitro evaluation of nasogastric administration methods for phenytoin. *Am J Hosp Pharm*. 1986;43(3):689–692.
106. Clark-Schmidt AL. Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm*. 1990;47(9):2034–2037.
107. Dodds Ashley ES, Varkey JB, Krishna G, et al. Pharmacokinetics of posaconazole administration orally or by nasogastric tube in healthy volunteers. *Antimicrob Agents Chemother*. 2009;53:7, 2960–2964.
108. Störzinger D, Borghorst S, Hofer S, et al. Plasma concentrations of posaconazole administered via nasogastric tube in patients in a surgical intensive care unit. *Antimicrob Agents Chemother*. 2012;56:8, 4468–4470.
109. Boullata JI. Drug administration through an enteral feeding tube: the rationale behind the guidelines. *Am J Nurs*. 2009;109(10):34-42.
110. Williams NT. Medication administration though enteral feeding tubes. *Am J Health Syst Pharm*. 2008;65:24, 2347–2357.
111. Wohlt PD, Zheng L, Gunderson S, et al. Recommendations for the use of medications with continuous enteral nutrition. *Am J Health Syst Pharm*. 2009;66:16, 1458–1467.
112. Holtz L, Milton J, Sturek JK. Compatibility of medications with enteral feedings. *JPEN J Parenter Enteral Nutr*. 1987;11:2, 183–186.
113. Burns PE, McCall L, Wirsching R. Physical compatibility of enteral formulas with various common medications. *J Am Diet Assoc*. 1988;88(9):1094–1096.
114. Strom JG, Miller SW. Stability of drugs with enteral nutrient formulas. *DICP Ann Pharmacother*. 1990;24(2):130–134.
115. Magnuson BL, Clifford TM, Hoskins LA, Bernard AC. Enteral nutrition and drug administration, interactions, and complications. *Nutr Clin Pract*. 2005;20:6, 618-624.
116. Matysiak-Luśnia K, Łysenko L. Drug administration via enteral feeding tubes in intensive therapy—terra incognita? *Anaesthesiol Intens Ther*. 2014;46:4, 307–311.
117. Silva RF, Novaes CG, Rita M. Interactions between drugs and drug-nutrient in enteral nutrition: a review based on evidence. *Nutr Hosp*. 2014;30:514–518.
118. White R, Bradnam V. *Handbook of Drug Administration via Enteral Feeding Tubes*. 3rd ed. London, UK: Pharmaceutical Press; 2015.
119. Cutie AJ, Altman E, Lenkel L. Compatibility of enteral products with commonly employed drug additives. *JPEN J Parenter Enteral Nutr*. 1983;7:2, 186–191.
120. Ortega de la Cruz C, Fernández Gallardo LC, Damas Fernández-Figares M, García Martínez E. Compatibilidad físico-química de medicamentos con nutrición enteral. *Nutr Hosp*. 1993;8:105-108.
121. Udeani GO, Bass J, Johnston TP. Compatibility of oral morphine sulfate solution with enteral feeding products. *Ann Pharmacother*. 1994;28:4, 451–455.
122. Crowther RS, Bellanger R, Szauter KEM. In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother*. 1995;29:9, 859–862.
123. Klang M, McLymont V, Ng N. Osmolality, pH, and compatibility of selected oral liquid medications with an enteral nutrition product. *JPEN J Parenter Enteral Nutr*. 2013;37:5, 689-694.
124. Gu C-H, Li H, Levons J, et al. Predicting effect of food on extent of drug absorption based on physicochemical properties. *Pharmaceut Res*. 2007;24:6, 1118–1130.
125. Kassam RM, Friesen E, Locock RA. In vitro recovery of carbamazepine from Ensure. *JPEN J Parenter Enteral Nutr*. 1989;13:3, 272–276.

126. Bass J, Miles MV, Tennison MB, Holcombe BJ, Thorn MD. Effects of enteral tube feeding on the absorption and pharmacokinetic profile of carbamazepine suspension. *Epilepsia*. 1989;30:3, 364–369.
127. Riss JR, Kriel RL, Kammer NM, Judge MK, Montgomery MJ. Administration of Carbatrol to children with feeding tubes. *Pediatr Neurol*. 2002;27:3, 193–195.
128. Bauer LA. Interference of oral phenytoin absorption by continuous nasogastric feedings. *Neurology*. 1982;32:5, 570–572.
129. Bauer LA, Edwards WA, Dellinger EP, et al. Importance of unbound phenytoin serum levels in head trauma patients. *J Trauma*. 1983;23:12, 1058–1060.
130. Saklad JJ, Graves RH, Sharp WP. Interaction of oral phenytoin with enteral feedings. *JPEN J Parenter Enteral Nutr*. 1986;10:3, 322–323.
131. Guidry JR, Eastwood TF, Curry SC. Phenytoin absorption in volunteers receiving selected enteral feedings. *West J Med*. 1989;150:659–661.
132. Au Yeung SCS, Ensom MHH. Phenytoin and enteral feedings: does evidence support an interaction? *Ann Pharmacother*. 2000;34:7-8, 896–905.
133. Ozuna J, Friel P. Effects of enteral tube feeding on serum phenytoin levels. *J Neurosurg Nurs*. 1984;16:6, 289–291.
134. Faraji B, Yu PP. Serum phenytoin levels of patients on gastrostomy tube feeding. *J Neurosci Nurs*. 1998;30:1, 55–59.
135. Gilbert S, Hatton J, Magnuson B. How to minimize interaction between phenytoin and enteral feedings: two approaches. *Nutr Clin Pract*. 1996;11:1, 28–31.
136. Bader MK. Case study of two methods for enteral phenytoin administration. *J Neurosci Nurs*. 1993;25:4, 233–242.
137. Splinter MY, Seifert CF, Bradberry JC, et al. Recovery of phenytoin suspension after in vitro administration through percutaneous endoscopic gastrostomy Pezzer catheters. *Am J Hosp Pharm*. 1990;47(2):373–377.
138. Splinter MY, Seifert CF, Bradberry JC, et al. Effect of pH on the equilibrium dialysis of phenytoin suspension with and without enteral feeding formula. *JPEN J Parenter Enteral Nutr*. 1990;14:3, 275–278.
139. Doak KK, Haas CE, Dunnigan KJ, et al. Bioavailability of phenytoin acid and phenytoin sodium with enteral feedings. *Pharmacotherapy*. 1998;18(3):637–645.
140. Krueger KA, Garnett WR, Cornstock TJ, et al. Effect of two administration schedules of an enteral nutrient formula on phenytoin bioavailability. *Epilepsia*. 1987;28:6, 706–712.
141. Marvel ME, Bertino JS. Comparative effects of an elemental and a complex enteral feeding formulation on the absorption of phenytoin suspension. *JPEN J Parenter Enteral Nutr*. 1991;15:3, 316–318.
142. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:3, 269-271.
143. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Anticmicrob Agents*. 2020;56(1):105949.
144. Read SA. The role of zinc in antiviral immunity. *Adv Nutr*. 2019;10:4, 696-710.
145. Derwand R, Scholz M. *Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19? Med Hypoth*. 2020;142:109815.
146. Shittu MO, Afolami OI. Improving the efficacy of chloroquine and hydroxchloroquine against SARS-CoV-2 may require zinc additives: a better synergy for future COVID-19 clinical trials. *Infez Med*. 2020;28(2):192-197.
147. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. *Am J Med*. 1989;87(5):76S–81S.
148. Lomaestro BM, Bailie GR. Quinolone-cation interaction: a review. *Ann Pharmacother*. 1991;25(11):1249–1258.
149. Lomaestro BM, Bailie GR. Effect of staggered dose of calcium on the bioavailability of ciprofloxacin. *Antimicrob Agents Chemother*. 1991;35:5, 1004–1007.
150. Mueller BA, Brierton DG, Abel SR, et al. Effect of enteral feeding with Ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrob Agents Chemother*. 1994;38:9, 2101–2105.
151. Cohn SM, Sawyer MD, Burns GA, et al. Enteric absorption of ciprofloxacin during tube feeding in the critically ill. *J Antimicrob Chemother*. 1996;38:5, 871–876.
152. Wright DH, Pietz SL, Konstantinides FN, Rotschafer JC. Decreased in vitro fluoroquinolone concentrations after admixture with an enteral feeding formulation. *JPEN J Parenter Enteral Nutr*. 2000;24:1, 42–48.
153. de Marie S, VandenBergh MFQ, Bujik SLCE, et al. Bioavailability of ciprofloxacin after multiple enteral and intravenous doses in ICU patients with severe Gram-negative intra-abdominal infections. *Intens Care Med*. 1998;24:4, 343–346.
154. Mimoz O, Binter V, Jacolot A, et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients. *Intens Care Med*. 1998;24:10, 1047–1051.
155. Chui D, Cheng L, Tejani A. Clinical equivalency of ciprofloxacin 750 mg enterally and 400 mg intravenously for patients receiving enteral feeding: systematic review. *CJHP*. 2009;62(2):127–134.
156. Song I, Borland J, Chen S, et al. Effect of food on the pharmacokinetics of the integrase inhibitor dolutegravir. *Antimicrob Agents Chemother*. 2012;56:3, 1627-1629.
157. Patel P, Song I, Borland J, et al. Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers. *J Antimicrob Chemother*. 2011;66:7, 1567-1572.
158. Roskam-Kwint M, Bollen P, Colbers A, et al. Crushing of dolutegravir fixed-dose combination tablets increases dolutegravir exposure. *J Antimicrob Chemother*. 2018;73:9, 2430-2434.
159. Turley SL, Fulco PP. Enteral administration of twice-daily dolutegravir and rilpivirine as a part of a triple-therapy regimen in a critically ill patient with HIV. *J Int Assoc Provid AIDS Care*. 2017;16(2):117-119.
160. Chrdle A, Jerhotová Z, Vacík M, Linka M, Chmelík V. Crushed dolutegravir/abacavir/lamivudine given via nasogastric tube in gastric outlet obstruction caused by cancer resulted in rapid viral load suppression. *Int J STD AIDS*. 2019;30:1, 94-98.
161. Brooks KM, Garrett KL, Kuriakose SS, et al. Decreased absorption of dolutegravir and tenofovir disoproxil fumurate, but not emtricitabine, in an HIV-infected patient following oral and jejunostomy-tube administration. *Pharmacotherapy*. 2017;37:8, e82-e89.
162. Kumar AKH, Chandrasekaran V, Kumar AK, et al. Food significantly reduces plasma concentrations of first-line anti-tuberculosis drugs. *Indian J Med Res*. 2017;145(4):530-535.
163. Koegelenberg CFN, Nortje A, Lalla U, et al. The pharmacokinetics of enteral antituberculosis drugs in patients requiring intensive care. *S Afr Med J*. 2013;103:6, 394-398.
164. Dodds Ashley ES, Zaas AK, Fang AF, Damle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. *Antimicrob Agents Chemother*. 2007;51:3, 877-880.
165. Mohammedi I, Piens MA, Padoin C, Robert D. Plasma levels of voriconazole administered via a nasogastric tube to critically ill patients. *Eur J Clin Microbiol Infect Dis*. 2005;24:5, 358-360.
166. Martinez V, Le Guillou J-L, Lamer C, et al. Serum voriconazole levels following administration via percutaneous jejunostomy tube. *Antimicrob Agents Chemother*. 2003;47:3375.

167. Williams D. The effect of enteral nutrition supplements on serum voriconazole levels. *J Oncol Pharm Pract*. 2011;18:1, 128-131.
168. Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. *Br J Clin Pharmacol*. 2003;56(Suppl 1):17-23.
169. Casier I, Jeanjean A, Hantson P. Postoperative hyperthermic syndrome following antiparkinsonian drugs withdrawal: the pitfalls of enteral refeeding. *Anaesth Intens Care*. 2013;41(6):814–815.
170. Whitman CB, Ablordeppey E, Taylor B. Levodopa withdrawal presents as fever in a critically ill patient receiving concomitant enteral nutrition. *J Pharm Pract*. 2016;29:6, 574–578.
171. Cooper MK, Brock DG, McDaniel CM. Interaction between levodopa and enteral nutrition. *Ann Pharmacother*. 2008;42:3, 439–442.
172. Bonnici A, Ruiner C-E, St-Laurent L, Hornstein D. An interaction between levodopa and enteral nutrition resulting in neuroleptic malignant-like syndrome and prolonged ICU stay. *Ann Pharmacother*. 2010;44:9, 1504–1507.
173. Cucca A, Mazzucco S, Bursomanno A, et al. Amino acid supplementation in L-dopa treated Parkinson's disease patients. *Clin Nutr*. 2015;34:6, 1189–1194.
174. O'Reilly RA, Rytand DA. Resistance to warfarin due to unrecognized vitamin K supplementation. *N Engl J Med*. 1980;303(3):160–161.
175. Landau J, Moulds RFW. Warfarin resistance caused by vitamin K in intestinal feeds. *Med J Aust*. 1982;2:6, 263–264.
176. Parr MD, Record KE, Griffith GL, Zeok JV, Todd EP. Effect of enteral nutrition on warfarin therapy. *Clin Pharm*. 1982;1(3): 274-276.
177. Watson AJM, Pegg M, Green JRB. Enteral feeds may antagonize warfarin. *BMJ*. 1984;288:6416, 6416.
178. Martin JE, Lutomski DM. Warfarin resistance and enteral feedings. *JPEN J Parenter Enteral Nutr*. 1989;13:2, 206–208.
179. Violi F, Lip GYH, Pignatelli P, Pastori D. Interaction between dietary vitamin K intake and anticoagulation by vitamin K antagonists: is it really true? *Medicine*. 2016;95:10, e2895.
180. Kuhn TA, Garnett WR, Wells BK, et al. Recovery of warfarin from an enteral nutrient formula. *Am J Hosp Pharm*. 1989;46(7):1395–1399.
181. Petretich DA. Reversal of Osmolite warfarin interaction by changing administration time. *Clin Pharm*. 1990;9(2):93.
182. Penrod LE, Allen JB, Cabacungan LR. Warfarin resistance and enteral feedings: 2 case reports and a supporting in vitro study. *Arch Phys Med Rehab*. 2001;82:9, 1270–1273.
183. Krajewski KC, Butterfoss K. Achievement of therapeutic international normalized ratio following adjustment of tube feeds. *J Clin Pharmacol*. 2011;51:3, 440–443.
184. Dickerson RN, Garmon WM, Kuhl DA, et al. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. *Pharmacotherapy*. 2008;28:3, 308–313.
185. Dickerson RN. Warfarin resistance and enteral tube feeding: a vitamin K-independent interaction. *Nutrition*. 2008;24:10, 1048–1052.
186. Klang M, Graham D, McLymont V. Warfarin bioavailability with feeding tubes and enteral formula. *JPEN J Parenter Enteral Nutr*. 2010;34:3, 300–304.
187. Wensel TM. Administration of proton pump inhibitors in patients requiring enteral nutrition. *P T*. 2009;34(3):143–160.
188. Ren P, Cui M, Anand O, et al. In vitro approaches to support bioequivalence and substitutability of generic proton pump inhibitors via nasogastric tube administration. *AAPS J*. 2017;19:6, 1593-1599.
189. Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med*. 2005;33:4, 760–765.
190. Yu Z, Fan W, Wang L, et al. Effect of surface charges on oral absorption of intact solid lipid nanoparticles. *Mol Pharmaceutics*. 2019;16:12, 5013-5024.
191. Stewart AM, Grass ME. Practical approach to modeling the impact of amorphous drug nanoparticles on the oral absorption of poorly soluble drugs. *Mol Pharmaceutics*. 2020;17:1, 180-189.

REVIEW

Preventing Aspiration Pneumonia by Addressing Three Key Risk Factors: Dysphagia, Poor Oral Hygiene, and Medication Use

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Abstract: Aspiration, which is a common problem among long-term care (LTC) residents, occurs upon inhalation of oropharyngeal or gastric contents into the lower respiratory tract. This can lead to aspiration pneumonia, and, subsequently, an increased risk of hospital transfers, morbidity, and mortality. Although various treatment guidelines for adults with lower respiratory tract infections exist, a greater emphasis on prevention of aspiration should be considered for older adults, as the mortality associated with this disease process can be staggering in this vulnerable population. This article provides an overview of three key risk factors all healthcare providers need to carefully consider when developing aspiration prevention strategies for their at-risk LTC residents: dysphagia, poor oral hygiene, and the use of certain medications.

Key words: Aspiration, aspiration pneumonia, aspiration prevention, dysphagia, lower respiratory tract infections, medication use, oral hygiene.

Citation: *Annals of Long-Term Care: Clinical Care and Aging*. 2014;22(10):42-48.

Aspiration can be defined as the inhalation of oropharyngeal or gastric contents into the lower respiratory tract. Patients residing in long-term care (LTC) facilities have been shown to have a threefold increased risk of aspiration compared with their community-dwelling counterparts.[1] This is likely attributed, at least in part, to the high prevalence of major risk factors for aspiration pneumonia in this population, including dysphagia, poor oral hygiene, and use of certain medications. Many subsequent syndromes can occur following aspiration, including pneumonitis, abscess, obstruction, and pneumonia. Pneumonia typically arises when the aspirated material contains bacteria and other microorganisms, precipitating an inflammatory reaction.

In the LTC setting, aspiration pneumonia is the second most common cause of infection, hospital transfer, and mortality.[2] It is also one of the most common causes of nursing home–acquired pneumonia (NHAP), with one study finding that 18% of patients with NHAP had aspiration pneumonia versus 5% of community-dwelling patients with community-acquired pneumonia (CAP; $P<.001$).[3] In another study, the odds ratio (OR) of witnessed aspiration developing into pneumonia among nursing home residents was 13.9 (95% confidence interval [CI], 1.7-111.0; $P=.01$).[4]

Mortality associated with pneumonia in the LTC population has been studied with discouraging results. A prospective study of 108 consecutive patients who acquired pneumonia in an LTC facility over the course of 1 year found mortality to be 19% at 14 days, 59% at 1 year, and 75% at 2 years.[5] Another study that included 104 case-control residents of a Veterans Affairs LTC facility showed similar results.[4] In this study, mortality due to pneumonia was 23% at 14 days, and patients with pneumonia had a significantly higher mortality at 1 year than controls (75% vs 40%; $P<.001$), with survival curves only converging

at 2 years.[4] As these data show, reducing the risks associated with aspiration is clearly an opportunity for healthcare providers to reduce pneumonia-associated mortality.

Although treatment guidelines for adults with lower respiratory tract infections have been previously outlined by expert committees in both infectious diseases and critical care medicine,[6] a greater emphasis on prevention of aspiration should be considered in the older adult population, as the mortality associated with this disease process is staggering. In this article, we review three common risk factors associated with aspiration pneumonia: dysphagia, poor oral hygiene, and the use of certain medications. Recognizing and promptly addressing these risk factors is essential to protecting the health and wellbeing of our most vulnerable residents.

Dysphagia

Dysphagia is defined as a subjective sensation of difficulty or abnormality of swallowing. It is a common problem in the older adult population and a known cause of aspiration.[7] Approximately 15% of older adults are affected by dysphagia,[8] with an estimated 70% of referrals to otolaryngologists for dysphagia being for persons older than 60 years.[9] The rate of referral for dysphagia increases twofold for patients aged 80 to 89 years and threefold for those older than 90 years.[9]

A variety of health conditions can contribute to the development of dysphagia, [including] neurologic diseases, stroke, dementia, cerebral palsy, traumatic brain injury, Parkinson's disease, and achalasia.

Advancing age represents an independent risk factor for dysphagia, as even with healthy aging there is physical toll on head and neck anatomy and changes to the physiologic and neural mechanisms that support swallowing.[10] One study that surveyed elderly patients in the community found the prevalence of dysphagia to be 13.8%.[11] This percentage is considerably higher in nursing homes. A 2013 South Korean study reported a prevalence of 52.7% among 395 older adults residing in two urban nursing homes.[12] This finding is in keeping with the general medical literature, which suggests a prevalence rate between 40% and 60%.[13]

In addition to older age, a variety of other health conditions can contribute to the development of dysphagia, with the most common being neurologic diseases, stroke, dementia, cerebral palsy, traumatic brain injury, Parkinson's disease, tumors arising from the nasopharyngeal tract, and achalasia.[7,14-17] For example, as many as 50% of patients have swallowing abnormalities following a stroke.[7] An increased risk of pneumonia in poststroke patients with dysphagia was documented in a retrospective analysis of database records from 1966 to 2005, which found a relative risk (RR) of 3.17 (95% CI, 2.07-4.87).[14] This same study also found that RR increased to 11.56 (95% CI, 3.36-39.77) for patients who aspirated.

Dysphagia is also common in persons with dementia. Oropharyngeal swallowing abnormalities, including aspiration, have been reported to be as high as 45% among institutionalized persons with dementia.[18] In patients with Alzheimer's disease, there is gradual regression in appetite, food intake, and feeding and alimentation skills in addition to cognitive and physical decline, placing these individuals at increased risk for aspiration.[15,16]

Management of Dysphagia

Dysphagia in the elderly is most successfully managed via an interdisciplinary approach that involves nursing staff and assistants, speech-language pathologists, dieticians, and physicians working in tandem. The goal of most interventions is to maximize the safety of oral feeding when it has been compromised.[10] Several interventions that have been used to manage dysphagia include posture changes and swallowing therapy, dietary modification, and tube feeding.

Posture changes and swallowing therapy. Changes in the posture of patients and speech/language pathology–led swallowing maneuvers performed in swallowing rehabilitation have been shown in small studies to help improve swallowing function.[19,20] In one study, behavioral interventions (ie, standard swallowing compensation strategies and diet prescription three times weekly for up to 1 month) resulted in a 41% increase in the proportion of patients with dysphagia who regained swallowing function by 6 months.[19] Another study reported a 67% improvement in swallowing function following 15 weeks of swallowing therapy after removal of a feeding tube.[20]

Dietary modification. Dietary modification to facilitate swallowing is another major management strategy for dysphagia. A 2008 videofluorographic swallowing study that assessed the effects of the chin-down posturing approach with thin liquids, nectar-thickened liquids, and honey-thickened liquids on the rates of aspiration in patients with Parkinson's disease and dementia found that honey-thick liquids were less likely to be aspirated than nectar-thick or thin liquids (53% vs 63% vs 68%, respectively).[21] To achieve a honey-like viscosity, starch- and gum-based commercial thickening agents are often added to fluids to prevent aspiration in patients with dysphagia; however, a recent study showed that the fluid these thickeners are added to can affect viscosity.[22] The study assessed apple, orange, grape, peach-grape, and pineapple juices; black and chamomile teas; whole, skim,

and a vegetable (tigernut) milk; and instant coffee. All of these fluids were separately thickened using a starch- and a gum-based thickening agent and compared with thickened water and assessed against the National Dysphagia Diet (NDD) reference limits. Compared with thickened water, the investigators observed significant changes in viscosity for all beverages except apple juice when using starch- and gum-based thickeners, and orange juice, pineapple juice, and chamomile tea when using the gum-based thickener. However, changes in viscosity per the NDD reference limits were only significant for peach-grape juice and pineapple juice with the starch-based thickener.[22] This study indicates that healthcare providers need to be mindful that thickening agents will not provide the same viscosity for all fluids and that some adjustments may be needed to ensure the proper viscosity is achieved.

Tube feeding. Enteral tube feeding is often used to prevent aspiration,[23] but it is not without significant risk and should generally be used as a last resort. While trying to prevent anterograde aspiration (normal swallowing process), tube feeding can lead to retrograde aspiration due to loss of upper esophageal sphincter and lower esophageal sphincter (LES) integrity, transient LES relaxation, and loss of swallowing reflex over time.[24] A difference in aspiration risk dependent on the location of the feeding tube has been reported, with one study finding a reduction in pneumonia with postpyloric feeding as compared with gastric feeding (RR, 0.63; 95% CI, 0.48-0.83; *P*=.001).[25]

Despite the risks associated with tube feeding, this intervention may be needed for certain elderly persons with dysphagia. A healthcare provider tip sheet (see page 49) from The Hartford Institute for Geriatric Nursing notes that short-term tube feeding may be beneficial for managing severe dysphagia and aspiration in elderly patients who are expected to recover their swallowing function.[26] It also notes that tube feeding may be an appropriate early intervention for patients with dysphagia following a stroke, with a goal of transitioning these patients to oral feeding as their dysphagia resolves. Finally, it suggests that patients with persistent dysphagia may warrant placement of a percutaneous gastrostomy tube.[26]

Many persons with dementia will require assistance with oral feeding as their cognitive impairment progresses. In such cases, placement of feeding tubes is often considered, particularly when dysphagia is present; however, the literature has not shown tube feeding to improve quality of life or to reduce mortality rates in persons with dementia, and continued assistance with oral feedings is often recommended.[27] Yet assisted oral feedings are not without risk. In a prospective outcomes study of 189 elderly patients recruited from outpatient clinics, inpatient acute care wards, and a nursing home care center, Langmore and colleagues[28] identified dependency upon others for feeding, and not necessarily dysphagia alone, as the dominant risk factor for aspiration pneumonia, with an OR of 19.98 in a logistic regression model that excluded tube-fed patients. As these findings indicate, healthcare providers need to carefully assess the risks and benefits of both tube feedings and assisted oral feedings for their patients. In either case, the risks of aspiration can be reduced by employing various safety strategies (**Table 1**).[26]

Table 1. Strategies for Preventing Aspiration in Patients With Feeding Tubes and Those Receiving Oral-Assisted Feedings[a]

With Feeding Tubes

- Keep bed backrest elevated to at least 30 degrees during continuous feedings
- Ask patients who are able to communicate whether they are experiencing any nausea, fullness, abdominal pain, or abdominal cramping, which may indicate slowed gastric emptying and lead to regurgitation and subsequent aspiration of gastric contents
- Measure gastric residual volumes every 4 to 6 hours during continuous feedings and immediately before each intermittent feeding, particularly if the patient is unable to communicate
- Consider using a prokinetic agent when the patient has two or more gastric residual volumes ≥250 mL

During Oral-Assisted Feedings

- Enable patient to rest 30 minutes before feeding him/her
- Ensure patient is seated upright in a chair or elevate the backrest to a 90-degree angle if patient is bedbound
- Try using chin-down posture during feeding; this posture has been shown to prevent aspiration in some patients
- Adjust the rate of feeding and size of bites to match the patient's tolerance
- Alternate solids and liquids
- Consider the patient's deficit and place food in his/her mouth accordingly; for example, placing food on the right side of the mouth if there is left facial weakness
- Pay attention to the viscosity of foods and liquids and try to match viscosity to the patient's tolerance
- Avoid use of certain medications, including sedatives, hypnotics, and any other agents that may impair the cough reflex and/or swallowing, as well as those that dry up secretions (eg, calcium channel blockers, diuretics)
- Minimize distractions during feedings

[a]Table based on information from reference 26 in the citation list.

Poor Oral Hygiene

Dental care is often neglected in LTC residents. In one cross-sectional study of 260 LTC patients aged 60 years and older (mean age, 83 years), 70% had not seen a dentist in more than 5 years.[29] Of those wearing dentures, 82% were unable to clean their dentures themselves. Only 19% of patients who wore dentures were described as having good denture hygiene, while 37% were described as having poor denture hygiene. Of dentate patients, 75% were reported to be unable to clean their own teeth, but none received regular assistance.[29] Yet poor dental hygiene has a significant impact on overall health,

including risk for aspiration and associated pneumonia. Poorly fitting dentures and edentulism can lead to chewing and swallowing difficulties, increasing the risk of aspiration, and poor oral hygiene and periodontal disease may enable respiratory pathogens to proliferate in the oropharyngeal region, which, if aspirated, can lead to pneumonia.[30]

A key strategy that has been proposed to reduce the risk of precipitating [mouth care–resistant] behaviors is to properly communicate with residents before attempting oral care.

One study randomly assigned 417 elderly patients across 11 nursing homes in Japan to receive standard oral care versus no oral care.[31] The standard oral care group was provided daily toothbrushing after meals by trained nurses and also saw dentists/hygienists every week for the duration of the study. Patients randomly assigned to standard oral care showed significant reduction in pneumonia, febrile days, and death compared with the no oral care group. In contrast, in the no-care group the RR was 2.45 for fever and 1.67 for pneumonia.[31]

Evidence of an association between poor dental hygiene and aspiration pneumonia was also demonstrated in a systematic review of studies including patients with pneumonia or chronic obstructive pulmonary disease and periodontal disease, as measured by assessing level of gingival inflammation, probing depth, clinical attachment, and/or radiographic bone loss or oral hygiene indices.[30] The study authors found the OR for pneumonia to be 1.2 for tooth decay, 2.8 for dependency on others for oral care, and 4.2 for the presence of dental plaque.[30] There was an overall RR of 9.6 for pneumonia if dental plaques were found to be colonized.

Another study of 697 adults older than 80 years found that those with 10 or more teeth containing a periodontal pocket had 3.9-times the adjusted mortality risk due to pneumonia than those without pocketing.[32] Periodontal pockets are associated with severe gum disease and are thought to be a potent source of infection.[32] As these data collectively show, a comprehensive oral hygiene program is crucial in preventing pneumonia in nursing home residents. Successful implementation of such programs requires addressing barriers to oral care.

Addressing Barriers to Oral Care

Several key barriers that prevent oral care from being provided to residents include mouth care–resistant behaviors by residents, lack of staff education on providing oral care to LTC residents, and lack of accountability for providing oral care to LTC residents.[33] To overcome these barriers, a multidisciplinary approach that includes dentists, hygienists, and certified nursing assistants (CNAs) is essential.

Managing mouth care–resistant behaviors. Residents may display a variety of mouth care–resistant behaviors, including refusing to open their mouths, biting toothbrushes or fingers inserted in or near the oral cavity, and kicking or hitting the oral care provider. These behaviors are more common among residents with dementia and other cognitive impairments, with one study reporting an eightfold increase in mouth care–resistant behaviors when dementia has become severe.[34] Yet even when dementia is present, a key strategy that has been proposed to reduce the risk of precipitating these behaviors is to properly communicate with residents before attempting oral care.[35] When communicating with residents, elderspeak should be avoided. *Elderspeak* is a speech style that resembles "baby talk," often using fragmented sentences, simple vocabulary, repetition, and a higher pitch tone. It is perceived as patronizing and underestimates the abilities of the older person.[35]

Other strategies that can prevent or reduce mouth care–resistant behaviors include positioning oneself at or below eye level with the resident; maintaining a friendly disposition; using gestures and pantomime, as needed; ensuring the resident is as upright as possible to prevent aspiration and discomfort; and encouraging the resident to perform his or her own oral care as much as possible.[35] A resident with dementia, for instance, might instinctively start brushing his or her own teeth if handed a prepared toothbrush, despite not being able to name what a toothbrush is, or may be successfully guided through the task, with the care provider gently placing his or her hands over the resident's hands and guiding them along.[35]

Educating LTC staff about oral care and addressing accountability. Nursing home staff often receive little education on how to provide oral care to their residents or on the importance of providing such care. A questionnaire distributed to 169 caregivers in 13 nursing homes revealed that the majority had received no education on how to provide oral care to their residents, and these individuals did not accept responsibility for oral care, deferring the responsibility to the residents' regular dentist.[36] Furthermore, only 33% of the surveyed physicians indicated that they carried out a systematic examination of their residents' oral cavities.[36]

Studies have shown that education of nursing home staff can significantly improve oral care among nursing home residents.[37,38] One study reported a reduction in gingival bleeding scores ($P<.001$) and in plaque scores ($P<.001$)

following a repeated education program for nursing home staff.[37] In another study, the residents who received oral care from caregivers who had received 6 weeks of oral care education had a lower plaque index (P=.004) and less halitosis (P=.002) than residents who received usual oral care from a control group of caregivers who had not been educated.[38] In addition, scores on caregivers' knowledge (P<.001), behavior (P<.001), and attitudes (P<.001) for oral care were higher in the educated group than the control group, and the investigators concluded that "oral care education programs for caregivers are effective in improving the oral hygiene of elderly residents in nursing homes through enhancement of caregivers' knowledge, attitude, and behavioral change."[38]

When implementing an oral care program and educating staff on the importance of oral care, it is essential for healthcare providers to understand that all LTC residents require regular oral care, including those on feeding tubes. In fact, tube feeding in elderly persons has been associated with significant pathogenic colonization of the mouth, with these individuals having even more colonization than those receiving oral feedings, placing them at particularly high risk of aspiration pneumonia.[26]

Numerous strategies have been used to train nursing home staff on oral care. One model specifically trained one CNA to be the facility's oral health specialist, with this individual becoming responsible for the daily oral hygiene of the residents and having minimal other care responsibilities.[33] This specialist then carried out a standardized care plan, which was developed by a dental team and informed by a literature review of best practices in oral hygiene, taking into account barriers such as mouth care–resistant behaviors. The toolkit for this model is available at **www.uky.edu/NursingHomeOralHealth**.

AMDA – The Society for Post-Acute and Long-Term Care Medicine (formerly the American Medical Directors Association) also offers a variety of oral health resources to healthcare providers in LTC settings via its Oral Health in the Long Term Care Information Series Tool Kit. These resources, which can be customized and used to train staff, are available at **www.amda.com/tools/clinical/oralhealth.cfm**.

Medication and Polypharmacy

Approximately 95% of older persons take at least one medication.[39] In contrast, an estimated 46% of LTC residents take more than nine medications,[40] significantly increasing their risk of a variety of complications. Therefore, it is important for healthcare providers to consider the side effects of some of the commonly prescribed medications in this population and their potential to contribute to aspiration pneumonia. At the same time, several medications may protect against aspiration pneumonia, which is another important consideration. Medications that increase and reduce risk are reviewed in the sections that follow.

Medications That Increase Risk

Medications may increase the risk of aspiration pneumonia through numerous mechanisms. For example, some may increase the risk of bacterial overgrowth (eg, proton pump inhibitors [PPIs], H_2 blockers), others may impair the ability to swallow (eg, neuroleptics, sedatives, hypnotics, antiepileptics, skeletal muscle relaxants), and yet others may lead to dry mouth and make swallowing more difficult (eg, diuretics, antiemetics). Outlining every medication that has the propensity to affect swallowing and aspiration is well beyond the scope of this article, but what follows are the findings associated with a few of the aforementioned medications. A more comprehensive list of medication classes that can contribute to dysphagia are listed in **Table 2**.[41]

Proton pump inhibitors and H_2 blockers. A Norwegian retrospective study linked recent treatment with a PPI (<30 days) with an increased risk of developing CAP (OR, 3.1; 95% CI, 1.4-7.1).[42] Laheij and associates[43] conducted a retrospective study of development of CAP and use of either a PPI or an H_2 blocker. The RR of CAP in patients using a PPI was 1.89 versus nonusers, while H_2 blockers carried an RR of 1.63 versus nonusers (95% CI, 1.36-2.62). The incidence rate of developing pneumonia while on either medication was four times that of nonusers.[43]

Even in patients without dementia, neuroleptics can increase the risk of aspiration pneumonia, as these medications may cause extrapyramidal symptoms that can affect swallowing.

Neuroleptics, sedatives, and hypnotics. Neuroleptic medications are often prescribed to patients with dementia. Although dementia alone is a known risk factor for aspiration, with one study citing an OR of 6.75 for aspiration among patients with dementia,[44] adding a neuroleptic to manage behavior and mood disorders is not without risks. Use of neuroleptics and benzodiazepines, the latter of which has sedative and hypnotic properties, in a subset of patients with Alzheimer's disease was associated with an OR of 3.1 for development of aspiration pneumonia.[44] Even in patients without dementia, neuroleptics can increase the risk of aspiration pneumonia, as these medications may cause extrapyramidal symptoms that can affect swallowing.

Table 2. Medication Classes That May Increase the Risk of Dysphagia and Subsequent Aspiration[a]

Medication Class	Potential Mechanism Behind Dysphagia
Angiotensin-converting enzyme inhibitors[b]	May cause dry mouth
Antiarrhythmic agents	May cause dry mouth
Anticholinergic agents	May affect esophageal muscles
Antiemetic agents	May cause dry mouth
Antiepileptic agents	Affect on the central nervous system may impair voluntary muscle control
Antihistamines	May cause dry mouth
Antimuscarinic agents	May affect esophageal muscles
Benzodiazepines	Affect on the central nervous system may impair voluntary muscle control
Bisphosphonates	May cause esophageal injury if not taken properly
Calcium channel blockers	May cause dry mouth
Decongestants	May cause dry mouth
Diuretics	May cause dry mouth
H_2 blockers	May contribute to bacterial overgrowth by suppressing gastric acid production
Narcotics	Affect on the central nervous system may impair voluntary muscle control
Neuroleptics	May cause extrapyramidal symptoms
Nonsteroidal anti-inflammatory drugs	May cause esophageal injury if not taken properly
Proton pump inhibitors	May contribute to bacterial overgrowth by suppressing gastric acid production
Selective serotonin reuptake inhibitors	May cause dry mouth
Skeletal muscle relaxants	Affect on the central nervous system may impair voluntary muscle control

[a]Table based on information from reference 41 in the citation list.
[b]Angiotensin-converting enzyme inhibitors may also provide protective effects.

Potentially Protective Medications

Some medications may be protective for certain patients. Dopamine levels and swallowing function share a direct relationship, as low dopamine levels can lead to motor impairments of the muscles in the throat, leading to swallowing difficulties and an increased risk for aspiration pneumonia. Patients who have had basal ganglia infarctions often have delayed triggering of the swallowing reflex, which has been associated with an impairment of dopamine metabolism in their basal ganglia. One study investigating whether the dopamine-inducing drug levodopa, which is typically used to treat Parkinson's disease, improved the swallowing reflex in patients with basal ganglia infarctions and a history of aspiration pneumonia found that an infusion of levodopa in these patients led to a statistically significant improvement in swallowing reflex time.[45] This finding implies that use of levodopa in this population may reduce aspiration risk, but further studies are needed.

Although angiotensin-converting enzyme (ACE) inhibitors can contribute to dysphagia by causing dry mouth (Table 2), they have also emerged as possibly playing a role in reducing the incidence of aspiration pneumonia. In a large retrospective study of patients poststroke who were subsequently hospitalized for pneumonia, use of an ACE inhibitor reduced pneumonia risk by 30% (OR, 0.70; 95% CI, 0.68-0.87), and there was a significant dose-response relationship ($P<.01$).[46] This study considered both the enhancement of the cough reflex and a reduction in proinflammatory cytokine activity to contribute to reduced aspiration rates.[46] Similarly, a meta-analysis of several studies showed an overall RR of 0.61 (95% CI, 0.51-0.75; $P<.001$) for pneumonia in patients prescribed ACE inhibitors versus those not receiving these agents.[47] The findings were greater in the Asian population with an RR of 0.42 (95% CI, 0.32-0.56; $P<.001$), implying that perhaps there is a greater effect seen in this demographic.[47]

Conclusion

Aspiration pneumonia is a major concern in the elderly population, especially those living in LTC settings, as it is associated with a high risk of morbidity and mortality, even following successful treatment. Therefore, prevention of aspiration is essential in this population. Although aspiration pneumonia has a multifactorial etiology, there are three major risk factors that can significantly lower risk when properly addressed: dysphagia, dental hygiene, and concomitant medication use. Comprehensive interventions for these risk

factors is best achieved using a multidisciplinary approach that incorporates the efforts of healthcare professionals within nursing, nutrition, speech-language pathology, dentistry, pharmacy, and medical concentrations. ◆

References

1. Reza Shariatzadeh M, Huang JQ, Marrie TJ. Differences in the features of aspiration pneumonia according to site of acquisition: community or continuing care facility. *J Am Geriatr Soc*. 2006;54(2):296-302.
2. Oh E, Weintraub N, Dhanani S. Can we prevent aspiration pneumonia in the nursing home? *J Am Med Dir Assoc*. 2005;6(3 suppl):S76-S80.
3. Marrie TJ, Durant H, Kwan C. Nursing home-acquired pneumonia. A case-control study. *J Am Geriatr Soc*. 1986;34(10):697-702.
4. Vergis EN, Brennen C, Wagener M, Muder RR. Pneumonia in long-term care: a prospective case-control study of risk factors and impact on survival. *Arch Intern Med*. 2001;161(19):2378-2381.
5. Muder RR, Brennen C, Swenson DL, Wagener M. Pneumonia in a long-term care facility. A prospective study of outcome. *Arch Intern Med*. 1996;156(20):2365-2370.
6. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect*. 2011;17(6 suppl):E1-E59.
7. Mann G, Hankey GJ, Cameron D. Swallowing function after stroke: prognosis and prognostic factors at 6 months. *Stroke*. 1999;30(4):744-748.
8. Barczi SR, Sullivan PA, Robbins J. How should dysphagia care of older adults differ? Establishing optimal practice patterns. *Semin Speech Lang*. 2000;21(4):347-361.
9. Leder SB, Suiter DM. An epidemiologic study on aging and dysphagia in the acute care hospitalized population: 2000-2007. *Gerontology*. 2009;55(6):714-718.
10. Ney DM, Weiss JM, Kind AJ, Robbins J. Senescent swallowing: impact, strategies, and interventions. *Nutr Clin Pract*. 2009;24(3):395-413.
11. Kawashima K, Motohashi Y, Fujishima I. Prevalence of dysphagia among community-dwelling elderly individuals as estimated using a questionnaire for dysphagia screening. *Dysphagia*. 2004;19(4):266-271.
12. Park YH, Han HR, Oh BM, et al. Prevalence and associated factors of dysphagia in nursing home residents. *Geriatr Nurs*. 2013;34(3):212-217.
13. Shanley C, O'Loughlin G. Dysphagia among nursing home residents: an assessment and management protocol. *J Gerontol Nurs*. 2000;26(8):35-48.
14. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke*. 2005;36(12):2756-2763.
15. Horner J, Alberts MJ, Dawson DV, Cook GM. Swallowing in Alzheimer's disease. *Alzheimer Dis Assoc Disord*. 1994;8(3):177-189.
16. Claggett MS. Nutritional factors relevant to Alzheimer's disease. *J Am Diet Assoc*. 1989;89(3):392-396.
17. Morley JE. Nutrition in the elderly. *Curr Opin Gastroenterol*. 2002;18(2):240-245.
18. Easterling CS, Robbins E. Dementia and dysphagia. *Geriatr Nurs*. 2008;29(4):275-285.
19. Carnaby G, Hankey GJ, Pizzi J. Behavioural intervention for dysphagia in acute stroke: a randomised controlled trial. *Lancet Neurol*. 2006;5(1):31-37.
20. Neumann S. Swallowing therapy with neurologic patients: results of direct and indirect therapy methods in 66 patients suffering from neurological disorders. *Dysphagia*. 1993;8(2):150-153.
21. Logemann JA, Gensler G, Robbins J, et al. A randomized study of three interventions for aspiration of thin liquids in patients with dementia or Parkinson's disease. *J Speech Lang Hear Res*. 2008;51(1):173-183. www.ncbi.nlm.nih.gov/pmc/articles/PMC2894528. Accessed April 25, 2014.
22. Garin N, De Pourcq JT, Martín-Venegas R, Cardona D, Gich I, Mangues MA. Viscosity differences between thickened beverages suitable for elderly patients with dysphagia. *Dysphagia*. www.ncbi.nlm.nih.gov/pubmed/24842337. Accessed July 29, 2014.
23. Kirby DF, Delegge MH, Fleming CR. American Gastroenterological Association technical review on tube feeding for enteral nutrition. *Gastroenterology*. 1995;108(4):1282-1301. www.med.upenn.edu/gastro/documents/AGApositionstatemententeralnutrition.pdf. Accessed April 25, 2014.
24. DeMeo MT, Bruninga K. Physiology of the aerodigestive system and aberrations in that system resulting in aspiration. *JPEN J Parenter Enteral Nutr*. 2002;26(6 suppl):S9-S17.
25. Jiyong J, Tiancha H, Huiqin W, Jingfen J. Effect of gastric versus post-pyloric feeding on the incidence of pneumonia in critically ill patients: observations from traditional and Bayesian random-effects meta-analysis. *Clin Nutr*. 2013;32(1):8-15.
26. Metheny NA. Preventing aspiration in older adults with dysphagia. Try this: general assessment series. http://consultgerirn.org/uploads/File/trythis/try_this_20.pdf. Published 2012. Accessed July 29, 2014.
27. Hanson LC. Tube feeding versus assisted oral feeding for persons with dementia: using evidence to support decision-making. *Annals of Long-Term Care: Clinical Care and Aging*. 2013;21(1):36-39.
28. Langmore SE, Terpenning MS, Schork A, et al. Predictors of aspiration pneumonia: how important is dysphagia? *Dysphagia*. 1998;13(2):69-81.
29. Peltola P, Vehkalahti MM, Wuolijoki-Saaristo K. Oral health and treatment needs of the long-term hospitalised elderly. *Gerodontology*. 2004;21(2):93-99.
30. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Ann Periodontol*. 2003;8(1):54-69.
31. Yoneyama T, Yoshida M, Ohrui T, et al. Oral care reduces pneumonia in older patients in nursing homes. *J Am Geriatr Soc*. 2002;50(3):430-433.
32. Awano S, Ansai T, Takata Y, et al. Oral health and mortality risk from pneumonia in the elderly. *J Dent Res*. 2008;87(4):334-339.
33. Stein P, Aalboe A, Skelton J, Bright BM, Housley M. Meeting oral health challenges in long-term care facilities. *Annals of Long-Term Care: Clinical Care and Aging*. 2012;20(9):30-34.
34. Volicer L, Bass EA, Luther SL. Agitation and resistiveness to care are two separate behavioral syndromes of dementia. *J Am Med Dir Assoc*. 2007;8(8):527-532.
35. Jablonski RA. Examining oral health in nursing home residents and overcoming mouth care–resistive behaviors. *Annals of Long-Term Care: Clinical Care and Aging*. 2010;18(1):21-26.
36. Chung JP, Mojon P, Budtz-Jørgensen E. Dental care of elderly in nursing homes: perceptions of managers, nurses, and physicians. *Spec Care Dentist*. 2000;20(1):12-17.
37. Kullberg E, Sjögren P, Forsell M, Hoogstraate J, Herbst B, Johansson O. Dental hygiene education for nursing staff in a nursing home for older people. *J Adv Nurs*. 2010;66(6):1273-1279.
38. Park MS, Choi-Kwon S. The effects of oral care education on caregivers' knowledge, attitude, & behavior toward oral hygiene for elderly residents in a nursing home [in Korean]. *J Korean Acad Nurs*. 2011;41(5):684-693.
39. Franceschi M, Scarcelli C, Niro V, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf*. 2008;31(6):545-556.
40. Tamura BK, Bell CL, Lubimir K, Iwasaki WN, Ziegler LA, Masaki KH. Physician intervention for medication reduction in a nursing home: the polypharmacy outcomes project. *J Am Med Dir Assoc*. 2011;12(5):326-330.
41. CT.gov. Medications and dysphagia/swallowing risks. www.ct.gov/dds/lib/dds/health/attacha_med_dsyphagia_swallowing_risks.pdf. Accessed July 31, 2014.
42. Meijvis SC, Cornips MC, Voorn GP, et al. Microbial evaluation of proton-pump inhibitors and the risk of pneumonia. *Eur Respir J*. 2011;38(5):1165-1172.
43. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16):1955-1960.
44. Wada H, Nakajoh K, Satoh-Nakagawa T, et al. Risk factors of aspiration pneumonia in Alzheimer's disease patients. *Gerontology*. 2001;47(5):271-276.
45. Kobayashi H, Nakagawa T, Sekizawa K, Arai H, Sasaki H. Levodopa and swallowing reflex. *Lancet*. 1996;348(9037):1320-1321.
46. Liu CL, Shau WY, Wu CS, Lai MS. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and pneumonia risk among stroke patients. *J Hypertens*. 2012;30(11):2223-2229.
47. Shinohara Y, Origasa H. Post-stroke pneumonia prevention by angiotensin-converting enzyme inhibitors: results of a meta-analysis of five studies in Asians. *Adv Ther*. 2012;29(10):900-912.