DIARRHEA

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Non-Infectious Symptomatic Treatment of Diarrhea Clinical Guidance- Issued January 2020

Table of Contents

List of Figures

List of Tables

Related Documents

Related SOPs

IDF-FR-P-02-01-IndicationsReview&IDFUpdates
IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterology Association
BAD	Bile Acid Diarrhea
BEZ	Bezlotoxumab
CDI	Clostridium difficile infection
CHI	Council of Health Insurance
COVID-19	Coronavirus Disease 2019
CPGs	Clinical Practice Guidelines
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FMT	Fecal Microbiota Transplantation
G-CSFs	Granulocyte Colony-Stimulating Factors
i.v.	Intravenous
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IBS-D	Irritable Bowel Syndrome with Diarrhea
IDF	CHI Drug Formulary (International Drug Formulary)
IMRT	Intensity-Modulated Radiotherapy
NICE	National Institute for Health and Care Excellence (UK)
ORS	Oral Rehydration Solution
PPIs	Proton Pump Inhibitors
RT	Radiotherapy
s.c.	Subcutaneous
SeHCAT	Sehcat Test
SFDA	Saudi Food and Drug Authority
SIBO	Small Intestinal Bacterial Overgrowth
VDZ	Vedolizumab

Executive Summary

Diarrhea is a common problem characterized by loose and watery stools, often accompanied by other symptoms. It typically resolves on its own within a few days, but if it persists beyond that timeframe, it may indicate a more serious underlying condition. Symptoms may vary from one person to another, and may include: abdominal cramps, dehydration, bowel incontinence, nausea, and/or bloating.

Short-term or acute diarrhea is one that may last up to two weeks or less and then resolves. It is typically caused by infected food or water, or a viral infection. Long-term or chronic diarrhea is one that lasts several weeks. It may be caused by intestinal disease such as Crohn's disease or celiac disease. Other health problems include irritable bowel syndrome.

Left untreated, the patient is left at risk of dehydration; and severe dehydration can lead to shock, organ damage, loss of consciousness, or coma.

In 2016, diarrhea ranked as the eighth leading cause of death, claiming over 1.6 million lives[1]. Children under the age of 5 accounted for more than a quarter (26.93%) of these deaths, and the majority (89.37%) occurred in south Asia and sub-Saharan Africa[1]. In Saudi Arabia, the average prevalence rate is approximately two episodes of diarrhea per child per year, in the vicinity of the global average[2].

CHI issued Non-Infectious Symptomatic Treatment of Diarrhea clinical guidelines after thorough review of renowned international and national clinical guidelines in January 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Non-Infectious Symptomatic Treatment of Diarrhea clinical guidance and seeks to offer guidance for the effective management of Diarrhea. It provides an **update on the Non-Infectious Symptomatic Treatment of Diarrhea Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update were summarized, being **the issuance updated versions of previously reviewed guidelines** namely the American College of Gastroenterology's IBS Guidelines (2020)[3], and the American Gastroenterology Association Guidelines on pharmacological management of IBS (2022)[4]. The NICE Guidelines for Eluxadoline for Irritable bowel syndrome with diarrhea (2017) were **withdrawn**. Moreover, **new guidelines are added to the report** such as British Society of Gastroenterology guidelines on the management of irritable bowel syndrome (2021)[5], the ESMO Clinical Practice Guidelines on the management of Diarrhoea in adult cancer patients (2018)[6], the ACG Clinical Guidelines on the

Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections (2021)[7], the Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea (2020)[8], the Management of Digestive Disorders and Procedures Associated With COVID-19 (2020)[9], and A practice management guideline from the Eastern Association for the Surgery of Trauma on Antimotility agents for the treatment of acute noninfectious diarrhea in critically ill patients: (2019)[10].

After carefully examining clinical guidelines and reviewing the SFDA drug list, the following new drugs are to be added to the CHI formulary: Rifaximin, Telotristat Ethyl, Octreotide, Colestyramine, Racecadotril, Infliximab, Vedolizumab, Vancomycin, and Fidaxomicin. FDA has also approved the following new drugs: Vowst (fecal microbiota spores, live), Rebyota (fecal microbiota, live), Zinplava (bezlotoxumab), and Mytesi (crofelemer).

The following drugs had not been, and still are not SFDA registered: Bismuth Subcitrate, the combination of "Vitamins, Folic Acid, Pantothenic Acid, Calcium, and Lactic Ferments (Lactobacillus Acidophilus & Sporogenes, Bifidobacterium Bifidum, Longum & Infantis)", Vitamins, Zinc, Zinc (As Zinc Bisglycinate), Zinc Gluconate, and Zinc Orotate Dihydrate. The following drug is no longer SFDA-registered: the combination of Dextrose, Sodium Chloride, Sodium Citrate, and Potassium Chloride. It is advisable to delist the above medications from CHI formulary.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Non-Infectious Symptomatic Treatment of Diarrhea therapeutic management.

Below is a table summarizing the major changes based on the different Diarrhea guidelines used to issue this report:

Table 1. General Recommendations for the Management of Diarrhea

Symptomatic Treatment of Diarrhea		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
Bile acid sequestrants		
Not recommended for treating IBS-D symptoms	Conditional recommendation; very low quality of evidence	ACG[3]
Limited use due to potential gastrointestinal side effects	Level III, Grade B	ESMO[6]

Can be used for BAD, with gradual daily dose titration to minimize side effects	Conditional recommendation, very-low-certainty evidence	Canadian Association of Gastroenterology (Bile Acid Diarrhea)[8]
Rifaximin		
Strongly recommended for treating overall symptoms of IBS-D	Strong recommendation; moderate quality of evidence	ACG[3]
Suggested for use in patients with IBS-D and for retreatment in patients with recurrent symptoms	Conditional recommendation; moderate certainty in evidence	AGA[4]
Recommended second-line treatment for IBS with diarrhea	Recommendation: weak, quality of evidence: moderate	BSG[5]
Alosetron		
Conditionally recommended for relieving overall symptoms of IBS-D in women with severe symptoms who have not responded to conventional therapy	Conditional recommendation; low quality of evidence	ACG[3]
Suggested for use in patients with IBS-D	Conditional recommendation; moderate certainty in evidence	AGA[4]
Effective second-line drug for IBS with diarrhea	Recommendation: weak, quality of evidence: moderate to high	BSG[5]
Eluxadoline		
Suggested for use in patients with IBS-D, with contraindications in certain patient populations (patients with no gallbladder or	Conditional recommendation; moderate certainty in evidence	AGA[4]

who have more than 3 alcohol drinks a day)		
Effective second-line treatment for IBS with diarrhea	Recommendation: weak, quality of evidence: moderate	BSG[5]
Loperamide		
Suggested for use in patients with IBS-D	Conditional recommendation; very low certainty in evidence	AGA[4]
Can be effective for treating diarrhea in IBS, but common side effects may limit its tolerability	Recommendation: strong; quality of evidence: very low	BSG[5]
Recommended for uncomplicated diarrhea, and for the treatment of severe diarrhea	Level V, Grade A, Level II, Grade B	ESMO[6]
To improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults in non-infectious diarrhea	Conditionally recommended	Eastern Association for the Surgery of Trauma[10]
Oral vancomycin		
Recommended for non-severe and severe CDI	Strong recommendation, low quality of evidence	ACG (Clostridium difficile Infection)[7]
Recommended for fulminant CDI, and for long-term suppressive treatment for recurrent CDI	Conditional recommendation, very low quality of evidence	ACG (Clostridium difficile Infection)[7]
Fidaxomicin		
Recommended for non-severe CDI and for first recurrence after an initial course of vancomycin or metronidazole	Strong recommendation, moderate quality of evidence	ACG (Clostridium difficile Infection)[7]
Recommended in severe initial CDI.	Conditional recommendation, very low quality of evidence	ACG (Clostridium difficile Infection)[7]
Metronidazole		

Oral Metronidazole is considered in low-risk patients for non-severe CDI.	Strong recommendation, moderate quality of evidence	ACG (Clostridium difficile Infection)[7]
Parenteral Metronidazole is considered for fulminant CDI in combination with oral vancomycin.	Conditional recommendation, very low quality of evidence	ACG (Clostridium difficile Infection)[7]
Sodium Bicarbonate		
Severe diarrhea might include complications such as metabolic acidosis. Treatment of acidosis mainly includes sodium bicarbonate.	N/A	Sodium Bicarbonate, 2023[11]

At the end of the report, a key recommendation synthesis section is added highlighting the latest updates in **Diarrhea clinical and therapeutic management**.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Non-Infectious Symptomatic Treatment of Diarrhea report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the January 2020 CHI Non-Infectious Symptomatic Treatment of Diarrhea Report and the corresponding recommendations:

Table 2. Clinical Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated Versions**
Section 1.1 **American College of Gastroenterology Guidelines for Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)**[12]	N/A*
Section 1.2 **European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European society for pediatric infectious diseases guidelines Evidence based Guidelines for the management of acute Gastro-enteritis in children in Europe (2014)**[13]	N/A*
Section 1.3 **World Gastroenterology Organization Global Guidelines (2013)**[14]	N/A*
Section 1.4 **NICE Guidelines for Eluxadoline for Irritable bowel syndrome with diarrhea (2017)**	Guideline Withdrawn
Section 1.5 **World Gastroenterology Organization Guidelines on IBS-Induced diarrhea (2012)**	**World Gastroenterology Organization Guidelines on Irritable Bowel**

	Syndrome: A Global Perspective (2015)[14]
Section 1.6 **American College of Gastroenterology IBS Guidelines (2018)**	**ACG Clinical Guideline: Management of Irritable Bowel Syndrome (2020)**[3]
Section 1.7 **American Gastroenterology Association Guidelines on pharmacological management of IBS: 2014**	**AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea (2022)**[15]

*: No updated versions available

1.1.1 American College of Gastroenterology Guidelines for Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)

*Please refer to **Section 1.1** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

There are no new updates. The recommendations of this guideline remain unchanged[12].

1.1.2 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European society for pediatric infectious diseases guidelines Evidence based Guidelines for the management of acute Gastro-enteritis in children in Europe (2014)

*Please refer to **Section 1.2** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

There are no new updates. The recommendations of this guideline remain unchanged[13].

1.1.3 World Gastroenterology Organization Global Guidelines (2013)

*Please refer to **Section 1.3** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

There are no new updates. The recommendations of this guideline remain unchanged[14].

1.1.4 NICE Guidelines for Eluxadoline for Irritable bowel syndrome with diarrhea (2017)

*Please refer to **Section 1.4** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

The guideline had been withdrawn since the medication was withdrawn. “Allergan has stopped marketing eluxadoline (Truberzi) for commercial reasons and its marketing authorization has been withdrawn.”

1.1.5 World Gastroenterology Organization Guidelines on Irritable Bowel Syndrome: A Global Perspective (2015)

*Please refer to **Section 1.5** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

This guideline is outdated- there are more recent guidelines to follow[14].

1.1.6 ACG Clinical Guideline: Management of Irritable Bowel Syndrome (2020)

*Please refer to **Section 1.6** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

The 2020 revised edition of the 2018 ACG Clinical Guidelines on the Management of Irritable Bowel Syndrome has introduced a new set of recommendation accompanied by a grading schema, outlined as follows:

Table 3. Summary of Quality of Evidence

Summary of Quality of Evidence	
Recommendation	**Quality of Evidence**
Strong: The strength of recommendation is given as strong if most patients should receive the recommended course of action.	High—the estimate of effect is unlikely to change with new data
Conditional: The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients.	Moderate; low; very low—estimate of effect is very uncertain

The following recommendations are provided by ACG on the management of irritable bowel syndrome[3]:

- Bile acid sequestrants are not recommended to treat global IBS-D symptoms. (Conditional recommendation; very low quality of evidence)
- Rifaximin is strongly recommended for treating overall symptoms of IBS-D (Strong recommendation, moderate quality of evidence)
- Alosetron is conditionally recommended for relieving overall symptoms of IBS-D in women with severe symptoms who have not responded to conventional therapy. (Conditional recommendation; low quality of evidence).
- Mixed opioid agonists/antagonists are suggested for treating overall symptoms of IBS-D (Conditional recommendation; moderate quality of evidence).

1.1.7 AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea (2022)

*Please refer to **Section 1.7** of CHI Non-Infectious Symptomatic Treatment of Diarrhea Report.*

The 2022 revised edition of the 2014 AGA Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea has introduced a new set of recommendation accompanied by a grading schema, outlined as follows:

Table 4. Interpretation of Strong and Conditional Recommendations

Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessments, Development and Evaluation Approach		
Implications	**Strong Recommendation**	**Conditional Recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions

		consistent with their individual risks, values, and preferences
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.
Strong recommendations are indicated by statements that lead with "we recommend" and conditional recommendations are indicated by statements that lead with "we suggest."		

Table 5. Interpretation of the Certainty in Evidence of Effects

Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations Assessments, Development and Evaluation Approach	
Certainty of Evidence	**Definition**
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

The following recommendations are provided by AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea[4]:

- Eluxadoline is suggested for use in patients with IBS-D. However, it is contraindicated in patients without a gallbladder or those who consume more than 3 alcoholic beverages per day. (Conditional recommendation, moderate certainty in evidence)
- Rifaximin is suggested for use in patients with IBS-D (Conditional recommendation, moderate certainty in evidence)
- For patients with IBS-D who initially respond to rifaximin but experience recurrent symptoms, retreatment with rifaximin is suggested (Conditional recommendation, moderate certainty in evidence)

- Alosetron is suggested for use in patients with IBS-D (Conditional recommendation, moderate certainty in evidence)
- Loperamide is suggested for use in patients with IBS-D (Conditional recommendation, very low certainty in evidence)
- Tricyclic antidepressants (TCAs) are suggested for use in patients with IBS (Conditional recommendation, low certainty in evidence)
- Selective serotonin reuptake inhibitors (SSRIs) are not recommended for use in patients with IBS (Conditional recommendation, low certainty in evidence)
- Antispasmodics are suggested for use in patients with IBS (Conditional recommendation, low certainty in evidence)

1.2 New Guidelines

This section includes the added guidelines to the previous CHI Non-Infectious Symptomatic Treatment of Diarrhea report, along with their recommendations.

Table 6. List of Additional Guidelines

Additional Guidelines
Non-Infectious Diarrhea
British Society of Gastroenterology guidelines on the management of irritable bowel syndrome (2021)[5]
Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines (2018)[6]
Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea (2020)[8]
Antimotility agents for the treatment of acute noninfectious diarrhea in critically ill patients: A practice management guideline from the Eastern Association for the Surgery of Trauma (2019)[10]
Infectious Diarrhea
ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections (2021)[7]
Management of Digestive Disorders and Procedures Associated With COVID-19 (2020)[9]

1.2.1 Non-Infectious Diarrhea

1.2.1.1 British Society of Gastroenterology Guidelines on the Management of Irritable Bowel Syndrome (2021)

Evidence levels and recommendation grades are outlined below[16]:

Table 7. GRADE Certainty Rating

GRADE Certainty Rating	
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Table 8. Quality of Recommendations

Recommendation		
GRADE	**Description**	**Implication**
Strong	Suggests that all or almost all persons would choose that intervention.	It is likely that the majority of informed individuals will agree on this intervention without the need for extensive discussion.
Weak	Implies that there is likely to be an important variation in the decision that informed persons are likely to make.	Engaging in a shared decision-making process is essential since informed individuals may have differing preferences or considerations that need to be considered before choosing the intervention.
The strength of recommendations is actionable: a weak recommendation indicates that engaging in a shared decision-making process is essential, while a strong recommendation suggests that it is not usually necessary to present both options.		

The following recommendations are provided by the British Society of Gastroenterology Guidelines on the management of irritable bowel syndrome[5]:

- Loperamide can be effective for treating diarrhea in IBS, but common side effects like abdominal pain, bloating, nausea, and constipation may limit its tolerability. Careful dose adjustment can help manage these side effects (recommendation: strong; quality of evidence: very low).
- Eluxadoline, a mixed opioid receptor drug, is considered an effective second-line treatment for IBS with diarrhea in secondary care. However, there are contraindications to its use, such as prior sphincter of Oddi problems or cholecystectomy, alcohol dependence, pancreatitis, or severe liver impairment. Limited availability may also restrict its use. (Recommendation: weak, quality of evidence: moderate).
- 5-Hydroxytryptamine 3 (5-HT3) receptor antagonists are effective second-line drugs for IBS with diarrhea in specialized healthcare settings. Medications like alosetron and ramosetron may not be available in many countries, so titrating ondansetron can be a reasonable alternative. Constipation is a common side effect of this drug class. Overall, 5-HT3 receptor antagonists are likely the most effective treatment option for IBS with diarrhea. (Recommendation: weak, quality of evidence: moderate to high).
- Rifaximin, a non-absorbable antibiotic, is a recommended second-line treatment for IBS with diarrhea in specialized healthcare settings. It has been found to be effective, although its impact on abdominal pain is somewhat limited. While rifaximin is approved for this use in the United States, its availability for this specific indication may be limited in other countries. (Recommendation: weak, quality of evidence: moderate)

1.2.1.2 Diarrhoea in Adult Cancer Patients: ESMO Clinical Practice Guidelines (2018)

Evidence levels and recommendation grades are outlined below[6]:

Table 9. Levels of Evidence and Grades of Recommendation. Retrieved from the ESMO Clinical Practice Guidelines on the Management of Diarrhea in Adult Cancer Patients (2018)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [50].

The following recommendations are provided by the ESMO Clinical Practice Guidelines on the management of diarrhea in adult cancer patients[6]:

Management of chemotherapy-related (ChT-related) diarrhea

Approach to uncomplicated diarrhea:

- Manage conservatively using oral hydration and loperamide [V, A].
- For mild to moderate diarrhea, start with dietary changes (remove lactose-containing products and high-osmolar dietary supplements). Keep track of stool frequency and watch for serious symptoms (fever, dizziness upon standing).
- Begin loperamide at 4 mg, then take 2 mg every 4 hours or after each loose stool (maximum 16 mg/day) [V, A].

Approach to complicated diarrhea (moderate-severe cramping, nausea, vomiting, diminished performance status, fever, sepsis, neutropaenia, bleeding or dehydration)

- Severe diarrhea is considered 'complicated,' requiring hospitalization and intensive evaluation and treatment [V, A].
- In complicated cases, hospital admission is usually necessary. Treatment involves intravenous (i.v.) fluids, starting octreotide at 100–150 mg s.c. three times a day (tid) or i.v. (25–50 mg/h) for severely dehydrated patients.

Octreotide dose can be increased up to 500 mg s.c. tid until diarrhea is controlled, along with administering antibiotics (e.g., fluoroquinolone) [V, A].

- Patients should undergo evaluation with a complete blood count, electrolyte profile, and stool analysis to check for blood, Clostridium difficile, Salmonella, Escherichia coli, Campylobacter, and infectious colitis [V, A].

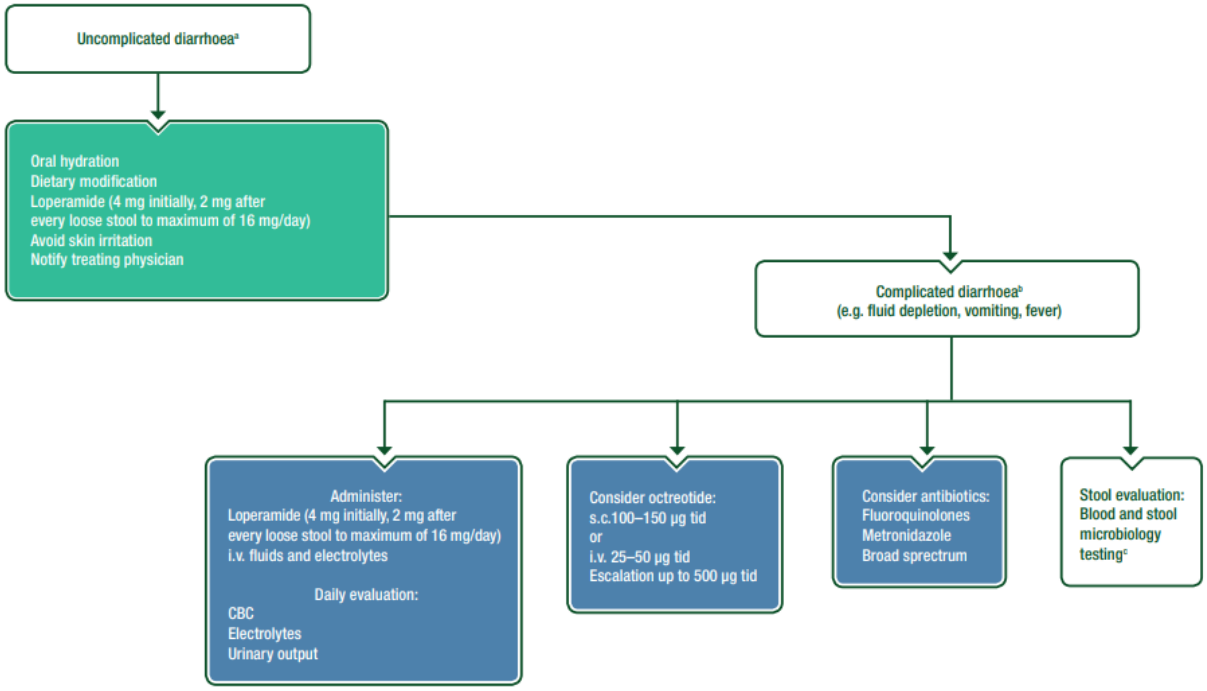


Figure 1. *Treatment Algorithm for Therapeutic Approach of Uncomplicated and Complicated Diarrhea. Retrieved from the ESMO Clinical Practice Guidelines on the Management of Diarrhea in Adult Cancer Patients (2018).*

Special case - Management of neutropenic enterocolitis:

- Neutropenic enterocolitis is initially treated medically, involving broad-spectrum antibiotics, granulocyte colony-stimulating factors (G-CSFs), nasogastric decompression, intravenous (i.v.) fluids, bowel rest, and regular abdominal examinations [V, A].
- The antibiotics administered should cover enteric gram-negative organisms, gram-positive organisms, and anaerobes [V, A].
- Initial antibiotic choices may include piperacillin-tazobactam or imipenem-cilastatin monotherapy, or combination therapy with cefepime or ceftazidime along with metronidazole [V, A]. If bacterial treatment fails, amphotericin should be considered due to the common occurrence of fungemia [V, A].
- Blood transfusions may be necessary as diarrhea often contains blood [V, A].

- Avoid the use of anticholinergic, antidiarrheal, and opioid agents as they can worsen ileus [V, A].
- The indications and timing for surgical intervention are debated. The mortality rate is high for patients who do not respond to medical treatment, and not all patients may be salvageable. However, surgery may be beneficial in select cases to prevent progressive bowel necrosis, perforation, and sepsis. Common indications for surgery include: (i) ongoing gastrointestinal bleeding despite correction of thrombocytopenia and coagulopathy, (ii) evidence of intraperitoneal perforation, (iii) abscess formation, (iv) clinical deterioration despite aggressive measures, (v) radiological exams to rule out other intra-abdominal issues such as bowel obstruction or acute appendicitis [V, A].
- If exploratory surgery is performed, resection of visibly affected bowel is necessary. Complete removal of necrotic tissue, typically through a right hemicolectomy, ileostomy, and mucous fistula, is crucial. Failure to remove the necrotic area in these severely immunocompromised patients often leads to fatality [V, A].
- Primary anastomosis is generally not recommended in severely immunocompromised patients due to the increased risk of anastomotic leakage [V, A].

Treatment approaches for diarrhea

Fluids and electrolytes

- Oral rehydration therapy (ORT) is suitable for mild diarrhea [I, A].
- For mild cases, diluted fruit juices, flavored soft drinks, saltine crackers, broths, or soups may provide adequate fluid and salt. In more severe cases, standard World Health Organization (WHO) ORSs or commercial ORSs are more appropriate [II, A].
- Rapid fluid resuscitation is not necessary for patients with mild to moderate hypovolemia [I, A]. The fluid administration rate should exceed the rate of fluid losses, which includes urine output, estimated insensible losses (usually 30-50 mL/h), and gastrointestinal losses, to prevent worsening of the volume deficit [I, A].

IV rehydration

- Most patients receive isotonic saline or balanced salt solution, but the choice may vary based on serum sodium, potassium levels, or metabolic acidosis [I, A].
- If a patient has tachycardia and potential sepsis, an initial fluid bolus of 20 mL/kg is recommended [I, A].

- Concurrent potassium replacement is necessary for those with potassium depletion. Fluid replacement continues rapidly until signs of hypovolemia improve (e.g., low blood pressure, low urine output, impaired mental status) [I, A].
- Consider monitoring with a central venous pressure line and urinary catheter to measure urinary output but be cautious of infection and bleeding risks [V, B].
- Aim for adequate central venous pressure and urine output > 0.5 mL/kg/h for fluid balance [I, A].
- Patients with oliguric acute kidney injury (< 0.5 mL/kg/h) despite adequate volume resuscitation, as indicated by central venous pressure, are at risk of pulmonary edema. Immediate consultation with intensive-care experts or nephrologists is essential [V, B].

Opioids (loperamide)

- Loperamide can be initiated at 4 mg, followed by 2 mg every 2-4 hours or after each unformed stool [II, B]. The maximum daily dose is 16 mg.
- Other opioids like tincture of opium, morphine, or codeine can be used as antidiarrheal agents [V, C].
- Deodorized tincture of opium is commonly used and recommended as an alternative to loperamide. It contains the equivalent of 10 mg/mL morphine, and the suggested dose is 10-15 drops in water every 3-4 hours [V, C].
- Be cautious not to confuse it with paregoric, a camphorated (alcohol-based) tincture. Paregoric is less concentrated and contains the equivalent of 0.4 mg/mL morphine. The recommended dose is 5 mL in water every 3-4 hours [V, C].

Somatostatin analogues (octreotide)

- For severe or persistent diarrhea, consider using the somatostatin analogue octreotide along with continuing loperamide for the first 48 hours, starting at a usual dose of 100-150 mcg s.c./i.v. tid [IV, B] and titrating up to 500 mcg s.c./i.v. tid or 25-50 mcg/h by continual i.v. infusion due to its multiple antidiarrheal actions [V, B].

Uridine triacetate (for 5-FU/capecitabine-induced diarrhea)

- In cases of severe diarrhea occurring within 96 hours after completing treatment with 5-FU or capecitabine, consider administering uridine triacetate, an orally administered prodrug of uridine, which serves as a specific pharmacological antidote to fluoropyrimidines and is a potentially life-saving

treatment for overdoses of these agents. The recommended dose for adults is 10 g orally every 6 hours for 20 doses [II, A].

Steroids

- Budesonide, an orally administered, topically active steroid with high activity in inflammatory bowel disease (IBD), is commonly used to manage diarrhea in patients with low- to medium-grade IBD, and it has shown efficacy in managing chemotherapy-induced diarrhea that did not respond to loperamide [IV, C].
- Prophylactic budesonide is not recommended [II, B].

Antibiotics

- Antibiotics should only be used in patients with specific symptoms, including fever, hypotension, peritoneal signs, neutropenia, small intestinal bacterial overgrowth, perianal sepsis, or bloody diarrhea, which may suggest conditions like neutropenic enterocolitis, Clostridium difficile infection, or other infectious causes (refer to relevant sections).

Bile acid sequestrants

- Bile acid sequestrants use is limited because they can cause gastrointestinal side effects such as bloating, flatulence, abdominal discomfort, and constipation [III, B].

Treatment of immunotherapy-induced diarrhea and colitis

- Grade 1 diarrhea is managed with symptomatic treatment, including oral rehydration and antidiarrheal medications like racecadotril or loperamide [III, A].
- Grade 2 Diarrhea: Stop immunotherapy treatment. Add budesonide 9 mg once daily if no bloody diarrhea [V, C]. Use oral corticosteroids (0.5–1 mg/kg/day prednisone equivalent) for diffuse ulceration, bleeding under endoscopic evaluation, or persistent symptoms after 3 days with symptomatic treatment and budesonide [III, A].
- Grade 3 and 4 Diarrhea and Colitis: Administer 1–2 mg/kg/day prednisone equivalent via i.v. injections [III, A]. Avoid loperamide and opioids. Consider non-steroidal immunosuppressive medication (e.g., infliximab) if symptoms persist for > 3–5 days or recur after improvement [III, A]. Vedolizumab may be an alternative to infliximab; further studies needed for confirmation [V, C]. Empirical antibiotics are to be considered for patients with fever or leukocytosis.
- Pneumocystosis Antibiotic Prophylaxis: Add oral trimethoprim/ sulfamethoxazole (400 mg once a day) for prolonged immune suppression.

- Rare cases may lead to bowel perforation, necessitating colectomy.
- Subtotal colectomy is preferred due to extensive colonic lesions and potential postoperative flare-ups.
- Immunotherapy can be resumed when symptoms disappear, or diarrhea recovers to grade 1.
- Immunotherapy should be definitively discontinued for grade 4 or recurrent grade 3 diarrhea, or grade 2 that does not resolve after 3 months despite appropriate treatment.

Prevention and treatment of acute RT-induced diarrhea

- Technical RT measures:
    - Utilizing RT techniques like IMRT (intensity-modulated radiotherapy) [IV, B].
    - Implementing physical measures such as the belly board device, bladder distension, and surgical approaches to displace small bowel volume [IV, C].
- Nutritional status and prophylactic measures:
    - Providing dietary counseling, which includes reducing fatty foods, adopting a lactose-free diet for lactose intolerance, and avoiding caffeine, alcohol, and tobacco [III, B].
    - Incorporating a high-fiber diet [II, B].
    - Administering oral supplements like colesevelam for patients with bile salt malabsorption [IV, B].
    - Considering probiotics (Lactobacillus, Bifidobacterium, and cocci) with caution and emphasizing the need for further safety analysis in immunocompromised patients [II, B].
- Treatment approaches:
    - Managing caloric and fluid intakes [IV, B].
    - Using loperamide with an initial dose of 4 mg, followed by 2 mg every 4 hours or after each unformed stool, while ensuring the total daily dose does not exceed 16 mg [I, A].
    - Administering octreotide (100 mcg three times daily) for patients who do not respond to loperamide and have severe toxicity [II, B].
    - Employing anticholinergic antispasmodic agents to alleviate bowel cramping [IV, B]

Treatment of chronic RT-induced diarrhea

- After completing a 7-day dietary diary, referral to an expert dietician is recommended [IV, C].
- Lifestyle advice, such as smoking cessation, is also important [IV, C].

- Considering referral for psychological support can be beneficial [IV, C].
- Highly caloric nutritional supplements containing essential nutrients like iron, folic acid, vitamin B12, vitamin D, magnesium, calcium, trace elements, and fat-soluble vitamins are recommended [IV, B].
- Colesevelam is preferred over colestyramine for the treatment of bile salt malabsorption due to better tolerance [IV, B].
- Broad-spectrum antimicrobial therapy (often empirical) may be required, with some cases necessitating prolonged and cyclical courses [V, C].
- The use of antidiarrheal agents (e.g., loperamide) is beneficial [IV, B].
- Pelvic floor and toileting exercises are suggested if evidence of radiation proctopathy and increased defecation frequency is present [IV, C].

Diarrhoea in advanced care patients not receiving oncological treatments: practical management:

- Patients must be rehydrated either orally or, when suitable, through parenteral infusion.
- Special attention should be provided to patients who are incontinent of stool, as they are at risk of pressure ulcer formation. The use of skin barriers is essential to prevent skin irritation caused by fecal material.
- Cause and Management:
    - Drugs: laxatives, antibiotics, antacids, PPIs, NSAIDs, iron, antidiabetics: adjust medication.
    - Overflow diarrhea (incomplete obstruction or constipation and impacted stools); Enema
    - Resections, fistulae, or manifestations of tumor which reduce absorptive surfaces: Symptomatic therapy with loperamide.
    - Exocrine pancreatic insufficiency; Enzyme therapy
    - Immune: Late effects of immunotherapy GvHD: Immunosuppression

Role of diet in managing diarrhea:

- Avoid spices, coffee, and alcohol, as well as consider reducing intake of insoluble fiber, as they may exacerbate symptoms [V, C].
- For patients experiencing diarrhea during chemotherapy (ChT), it is recommended to avoid milk and most dairy products, except for yogurt and firm cheeses, to potentially alleviate the intensity and duration of symptoms [V, C].

1.2.1.3 Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea (2020)

Evidence levels and recommendation grades are outlined below[17]:

Table 10. Quality of Evidence and Definitions

Quality of Evidence and Definitions	
Recommendation	**Quality of Evidence**
High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

The following recommendations are provided by the Canadian Association of Gastroenterology Clinical Practice Guidelines on the Management of Bile Acid Diarrhea[8]:

Diagnosis of BAD:

- Use risk factors (history of terminal ileal resection, cholecystectomy, or radiotherapy) to identify possible BAD in patients with chronic nonbloody diarrhea. (Strong recommendation, very low-certainty evidence).
- Do not rely on symptom presentation as the initial assessment to identify possible BAD in patients with chronic nonbloody diarrhea. (Conditional recommendation, very-low-certainty evidence).
- Consider SeHCAT testing to identify BAD in patients with chronic diarrhea, including irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea. (Conditional recommendation, very-low-certainty evidence).
- Consider SeHCAT testing in patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea. (Conditional recommendation, very-low-certainty evidence).
- Consider using a C4 assay to identify possible BAD in patients with chronic diarrhea, including IBS-D and functional diarrhea. (Conditional recommendation, very-low-certainty evidence).

- Avoid initiating empiric bile acid sequestrants (BAST) without performing SeHCAT testing to diagnose BAD. (Conditional recommendation, very-low-certainty evidence).

Induction Therapy for BAD (BAST):

- For patients with type 1 or type 3 BAD, use treatments for remediable causes (e.g., Crohn's disease, microscopic colitis, SIBO) in addition to treatment for BAD to induce a clinical response. (Conditional recommendation, very-low-certainty evidence).
- Use cholestyramine over no treatment to induce a clinical response in patients with BAD. (Conditional recommendation, very-low-certainty evidence).
- Consider cholestyramine as the initial therapy over other BASTs to induce a clinical response in patients with BAD. (Conditional recommendation, very-low-certainty evidence).
- Use an alternative BAST if patients with BAD are unable to tolerate cholestyramine for induction of clinical response. (Conditional recommendation, low-certainty evidence).
- Employ gradual daily dose titration of BAST in patients with BAD to minimize side effects. (Good practice statement).
- Avoid using BAST in patients with Crohn's disease with extensive ileal involvement or resection. (Conditional recommendation, very-low-certainty evidence).

Maintenance Therapy for BAD (BAST):

- Consider intermittent, on-demand dosing of BAST in patients with BAD who respond to treatment. (Conditional recommendation, very-low-certainty evidence).
- In patients unable to tolerate BAST for long-term symptomatic therapy, consider using alternative antidiarrheal agents over no treatment. (Conditional recommendation, very-low-certainty evidence).
- Use the lowest effective dose of BAST in patients with BAD for maintenance therapy to minimize symptoms. (Good practice statement).
- Conduct diagnostic re-evaluation in patients with BAD and recurrent or worsening symptoms despite stable BAST. (Good practice statement).
- Review concurrent medications in patients being considered for BAST to minimize potential drug interactions. (Good practice statement).

Statements with No Recommendations:

- No recommendation A. The use of FGF19 assay to identify possible BAD in patients with chronic diarrhea, including IBS-D and functional diarrhea. (Very-low-certainty evidence).
- No recommendation B. The measurement of fat-soluble vitamin levels at baseline and annually in patients receiving long-term maintenance therapy with BAST. (Very-low-certainty evidence).

1.2.1.4 Antimotility Agents for the Treatment of Acute Noninfectious Diarrhea in Critically Ill Patients: A Practice Management Guideline from the Eastern Association for the Surgery of Trauma (2019)

Evidence levels and recommendation grades are outlined below[18]:

Table 11. GRADE Approach to Rating Quality of Evidence. Retrieved from the Eastern Association for the Surgery of Trauma on Antimotility Agents for the Treatment of Acute Noninfectious Diarrhea in Critically Ill Patients (2019)

A Summary of GRADE's Approach to Rating Quality of Evidence				
Study Design	**Initial Quality of a Body of Evidence**	**Lower If**	**Higher If**	**Quality of a Body of Evidence**
Randomized trials	High ⇒	Risk of bias −1 Serious −2 Very serious Inconsistency −1 Serious −2 Very serious Indirectness −1 Serious −2 Very serious Imprecision −1 Serious −2 Very serious Publication bias −1 Likely −2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	High (four pluses: ⊕⊕⊕⊕) Moderate (three pluses: ⊕⊕⊕○) Low (two pluses: ⊕⊕○○) Very low (one plus: ⊕○○○)
Observational studies	Low ⇒			

The following recommendations are provided by the Eastern Association for the Surgery of Trauma on Antimotility agents for the treatment of acute noninfectious diarrhea in critically ill patients[10]:

- Conditionally recommend administering loperamide to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults.
- Conditionally recommend administering diphenoxylate/atropine to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults.

- No specific recommendations can be made regarding the use of an elemental diet to treat diarrhea in critically ill adult patients due to the lack of relevant studies.

1.2.2 Infectious Diarrhea

1.2.2.1 ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides Difficile Infections (2021)

Evidence levels and recommendation grades are outlined below[7]:

Table 12. Strength of Recommendation and Quality of Evidence. Retrieved from the ACG Clinical Guidelines on the Prevention, Diagnosis, and Treatment of Clostridioides Difficile Infections (2021)

Table 1. Quality assessment criteria (6)

Study design	Quality of evidence	Lower if	Higher if
Randomized trial	High	Risk of bias	Large effect
		−1 serious	+1 large
		−2 very serous	+2 very large
	Moderate	Inconsistency	Dose response
		−1 serious	+1 evidence of a gradient
		−2 very serious	
		Indirectedness	All plausible confounding
		−1 serious	+1 would reduce demonstrated effect or
		−2 very serious	+1 would suggest a spurious effect when results show no effect
Observational trial	Low	Imprecision	
		−1 serious	
		−2 very serious	
	Very low	Publication bias	
		−1 likely	
		−2 very likely	

The following recommendations are provided by the ACG Clinical Guidelines on the Prevention, Diagnosis, and Treatment of Clostridioides difficile infections[7]:

Prevention

- Probiotics are not recommended for the prevention of Clostridium difficile infection (CDI) in patients being treated with antibiotics (primary prevention) (Conditional recommendation, moderate quality of evidence).
- Probiotics are not recommended for the prevention of CDI recurrence (secondary prevention) (Strong recommendation, very low quality of evidence).

Diagnosis

- CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (Conditional recommendation, low quality of evidence).

Treatment

- Initial treatment of non-severe CDI:
    - Oral vancomycin 125 mg 4 times daily for 10 days is recommended (Strong recommendation, low quality of evidence).
    - Oral fidaxomicin 200 mg twice daily for 10 days is recommended (Strong recommendation, moderate quality of evidence).
    - Oral metronidazole 500 mg 3 times daily for 10 days may be considered in low-risk patients (Strong recommendation, moderate quality of evidence).
- Initial therapy for severe CDI:
    - Vancomycin 125 mg 4 times a day for 10 days is recommended (Strong recommendation, low quality of evidence).
    - Fidaxomicin 200 mg twice daily for 10 days can be considered (Conditional recommendation, very low quality of evidence).
- Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hours daily for the first 48-72 hours. Combination therapy with parenteral metronidazole 500 mg every 8 hours can be considered (Conditional recommendation, very low quality of evidence).
- For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (Conditional recommendation, very low quality of evidence).
- Fecal microbiota transplantation (FMT) should be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, especially when they are poor surgical candidates (Strong recommendation, low quality of evidence).
- Tapering/pulsed-dose vancomycin is suggested for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (Strong recommendation, very low quality of evidence).
- Fidaxomicin is recommended for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (Strong recommendation, moderate quality of evidence).

Prevention of Recurrence

- FMT is recommended for patients experiencing their second or further recurrence of CDI to prevent further recurrences (Strong recommendation, moderate quality of evidence).
- FMT should be delivered through colonoscopy (Strong recommendation, moderate quality of evidence) or capsules (Strong recommendation, moderate quality of evidence) for the treatment of recurrent CDI. Enema delivery can be considered if other methods are unavailable (Conditional recommendation, low quality of evidence).
- Repeat FMT is suggested for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (Conditional recommendation, very low quality of evidence).
- For patients with recurrent CDI (rCDI) who are not candidates for FMT, relapsed after FMT, or require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences (Conditional recommendation, very low quality of evidence).
- Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (Conditional recommendation, low quality of evidence).
- Bezlotoxumab (BEZ) may be considered for the prevention of CDI recurrence in patients who are at high risk of recurrence (Conditional recommendation, moderate quality of evidence).
- Antisecretory therapy should not be discontinued in patients with CDI, provided there is an appropriate indication for their use (Strong recommendation, very low quality of evidence).

Special Populations

- C. difficile testing is recommended in patients with inflammatory bowel disease (IBD) presenting with an acute flare associated with diarrhea (Strong recommendation, low quality of evidence).
- Vancomycin 125 mg p.o. 4 times a day for a minimum of 14 days is suggested for CDI treatment in patients with IBD (Strong recommendation, very low quality of evidence).
- FMT should be considered for recurrent CDI in patients with IBD (Strong recommendation, very low quality of evidence).

1.2.2.2 Management of Digestive Disorders and Procedures Associated With COVID-19 (2020)

Evidence levels and recommendation grades were not outlined in the article.

The following recommendations were provided by the American College of Gastroenterology on the Management of Digestive Disorders and Procedures associated with COVID-19[9]:

Management of Diarrhea

- COVID-19-associated diarrhea is usually mild or moderate and resolves on its own.
- Antiviral drug-induced diarrhea typically resolves spontaneously without treatment.
- Adjust the dosage of antiviral agents for patients experiencing frequent diarrhea (≥4 times/day) or drug intolerance.
- There is no specific therapy for diarrhea caused by SARS-CoV-2.
- Dioctahedral montmorillonite and probiotics may provide benefits for COVID-19-associated diarrhea.
- Certain Lactobacillus probiotics have been effective in relieving animal coronavirus-associated diarrhea.
- The effectiveness of these probiotics on human coronavirus-associated diarrhea is still uncertain.
- Probiotic preparations containing Lactobacillus can be considered for clinical trials in patients with COVID-19 diarrhea.
- Clinicians should be vigilant for antibiotic-associated diarrhea or Clostridium difficile infection (CDI) in critical COVID-19 patients.
- CDI tests should be performed, and probiotics should be given to prevent or control the occurrence of CDI in severe COVID-19 patients.

Section 2.0 Drug Therapy in the Treatment of Diarrhea

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drug that have been approved by the FDA and/or EMA, but are not currently SFDA registered.

2.1 Additions

After January 2020, there have been a few new drugs that have received FDA approval. Moreover, other drugs had been registered in the SFDA list and submitted to CHI for evaluation. Relevant information pertaining to the drugs can be found below:

2.1.1 Rifaximin

This section includes pertinent information regarding the use of Rifaximin (Xifaxan®) in diarrhea (Lexicomp 2023):

Table 13. Drug Information Rifaximin

RIFAXIMIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K58. 1 (IBS-D), A04. 7 (CDI), A09.0 (Traveler's Diarrhea)
Drug Class	Rifamycin, Antibiotic
Drug Sub-class	
ATC Code	A07AA11
Pharmacological Class (ASHP)	8:12.28.30 Rifamycins
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**CDI recurrence:** 400 mg 3 times daily for 20 days- after a 10-day course of oral vancomycin

	IBS-D: 550 mg 3 times daily for 14 days **Traveler's Diarrhea:** **Prophylaxis:** 200 mg 1 to 3 times daily for the duration of travel **Treatment:** 200 mg 3 times daily for 3 days
Maximum Daily Dose Adults*	1,200 mg/day
Dose (pediatrics)	**CDI recurrence:** **<12 years:** 15 to 30 mg/kg/day in divided doses 3 times daily for 20 days; after a 10-day course of oral vancomycin **≥12 years:** 400 mg 3 times daily for 20 days; after a 10-day course of oral vancomycin **Traveler's Diarrhea:** **<12 years**: 100 mg 4 times daily for up to 5 days has been used in 38 children (age range: 3 to 8 years) to treat infectious diarrhea (limited data available) **≥12 years**: Oral: 200 mg 3 times daily for 3 days
Maximum Daily Dose Pediatrics*	600mg
Adjustment	No dose adjustment recommendation in altered kidney function. Use with caution in severe liver impairment (Child-Pugh Class C).
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (Most common and most serious)	**Most common:** peripheral edema, ascites, nausea, dizziness, fatigue **Most serious:** Infection due to inappropriate use/unexpected failure of therapy, Increased risk of resistant infections
Drug Interactions*	X- Cholera Vaccine X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal) D- Bacillus clausii D- Sodium Picosulfate
Special Population	**N/A**
Pregnancy	Adverse events have been observed in some animal reproduction studies. Due to the limited oral absorption of rifaximin in patients with normal hepatic function, exposure to the fetus is expected to be low.
Lactation	It is not known if rifaximin is excreted in human milk. According to the manufacturer, the decision to breast-feed during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother. Because of the limited oral absorption of rifaximin in patients with normal hepatic function, exposure to the nursing infant is expected to be low.
Contraindications	Hypersensitivity to rifaximin, other rifamycin antibiotics, or any component of the formulation.
Monitoring Requirements	Monitor for severe or bloody diarrhea and send a specimen to the lab for C. difficile. Monitor for and educate patient to report signs of hypersensitivity reactions, fever, or blood in the stool.
Precautions	• Hypersensitivity reactions (eg, exfoliative dermatitis, rash, urticaria, flushing, angioneurotic edema, pruritus, anaphylaxis) have occurred

	as early as within 15 minutes of drug administration. • Fungal or bacterial superinfection with prolonged use, including Clostridioides difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. • Diarrhea: Appropriate use: Avoid use in diarrhea with fever and/or blood in the stool and in the treatment of diarrhea due to pathogens other than Escherichia coli, including Campylobacter jejuni, Shigellal spp., and Salmonella spp. (efficacy has not been established). Consider alternative therapy if symptoms persist or worsen after 24 to 48 hours of treatment. • Hepatic impairment: Efficacy for prevention of encephalopathy has not been established in patients with a Model for End-Stage Liver Disease (MELD) score >25; use caution in patients with severe hepatic impairment (Child-Pugh class C). • Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. • Appropriate use: Not for treatment of systemic infections; <1% is absorbed orally.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Rifaximin.**

Table 14. Rifaximin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Rifaximin	NICE	Recommendations are provided for another indication (hepatic encephalopathy).
	CADTH	Recommendations are provided for another indication (hepatic encephalopathy).
	HAS	Recommendations are provided for another indication (hepatic encephalopathy).
	IQWIG	No recommendations for this medication.
	PBAC	Recommendations are provided for another indication (hepatic encephalopathy).

CONCLUSION STATEMENT- RIFAXIMIN

The different HTA bodies do not provide any information on the use of Rifaximin in diarrhea.

2.1.2 Telotristat Ethyl

This section includes pertinent information regarding the use of Telotristat Ethyl (Xermelo®) in diarrhea (Lexicomp 2023):

Table 15. Drug Information Telotristat Ethyl

TELOTRISTAT ETHYL	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No

Indication (ICD-10)	E34. 0 (Carcinoid syndrome)
Drug Class	Tryptophan Hydroxylase Inhibitor
Drug Sub-class	
ATC Code	A16AX
Pharmacological Class (ASHP)	56:08 - Antidiarrhea Agents
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	250 mg 3 times daily
Maximum Daily Dose Adults*	750 mg
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dose adjustments recommended in altered kidney function. Use is not recommended in moderate to severe hepatic impairment (Child-Pugh class B and C). Gastrointestinal toxicity: Discontinue for severe constipation or for development of severe, persistent, or worsening abdominal pain
Prescribing edits*	AGE
AGE (Age Edit): Given to adult patients.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** nausea and headache **Most serious:** Increased gamma-glutamyl transferase, fecaloma, hypertension
Drug Interactions*	D- Algestone Acetophenide

	D- Chlormadinone D- Desogestrel D- Drospirenone D- Estetrol D- Estradiol and Dienogest D- Estradiol Enthanate D- Ethinyl Estradiol D- Ethynodiol Diacetate D- Etonogestrel D- Gestodene D- Levonorgestrel (Systemic) D- Lynestrenol D- MedroxyPROGESTERone D- Mestranol D- Norelgestromin D- Norethindrone D- Norgestimate D- Norgestrel D- Octreotide (Depends on Dosage Form) D- Segesterone Acetate D- Ubrogepant
Special Population	Very few older adults were included in the clinical trials, but age did not appear to influence the pharmacokinetics of telotristat. Efficacy and toxicity were similar in older and younger patients.
Pregnancy	Adverse events were observed in some animal reproduction studies.
Lactation	It is not known if telotristat ethyl is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Breastfed infants should be monitored for constipation.

Contraindications	Hypersensitivity (eg, angioedema, rash, pruritus) to telotristat ethyl or any component of the formulation.
Monitoring Requirements	Monitor for symptoms of constipation and/or severe, persistent, or worsening abdominal pain.
Precautions	• Gastrointestinal toxicity: Constipation has been reported in clinical trials. Although rarely serious, some events resulted in hospitalization, intestinal perforation, or bowel obstruction (these events occurred at a dose higher than the recommended dose). Patients with advanced carcinoid tumors may be at risk for altered gastrointestinal tract wall integrity; monitor closely for constipation and/or severe, persistent, or worsening abdominal pain. Discontinue for severe constipation and/or the development of severe persistent or worsening abdominal pain. • Hepatic impairment: Additional monitoring for GI effects (eg, constipation) recommended in patients with mild impairment. Use not recommended in moderate to severe impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Telotristat Ethyl.**

Table 16. Telotristat Ethyl HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Telotristat Ethyl	NICE	No recommendations for this medication.
	CADTH	Does not recommend the reimbursement of this drug the treatment of refractory carcinoid syndrome diarrhea, in combination SSA therapy, in patients inadequately controlled by SSA therapy alone. There was uncertain clinical relevance (TELESTAR trial) in the magnitude of the difference between telotristat and placebo in reducing the number of daily bowel movements. Telotristat did not improve symptoms of urgency, abdominal pain, flushing, or quality of life. Moreover, since patients received concomitant SSA therapy (octreotide and lanreotide), the effects of telotristat are unclear in patients inadequately controlled by optimized SSA therapy.
	HAS	No recommendations for this medication.
	IQWIG	There was proven medical benefit of the drug, and it was approved. However, the detailed report is provided in German.
	PBAC	No recommendations for this medication.

CONCLUSION STATEMENT- TELOTRISTAT ETHYL

The use of Telotristat Ethyl is not recommended for reimbursement by CADTH, whereas IQWIG did prove the medical benefit of the medication. There were no recommendations provided by the other organizations: NICE, HAS, and PBAC.

2.1.3 Octreotide

This section includes pertinent information regarding the use of Octreotide in diarrhea (Lexicomp 2023):

Table 17. Drug Information Octreotide

OCTREOTIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes, under European Commission final decision
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K52. 1
Drug Class	Antidiarrheal
Drug Sub-class	Somatostatin Analog
ATC Code	H01CB02 QH01CB02
Pharmacological Class (ASHP)	68:29.04 - Somatostatin Agonists
DRUG INFORMATION	
Dosage Form	Solution for injection/infusion Powder and solvent for suspension for injection Powder and solvent for prolonged-release suspension for injection
Route of Administration	Subcutaneous use Intramuscular use Intravenous
Dose (Adult) [DDD]*	**Low grade:** **SQ:** 100-150mcg 3 times daily **Severe:** **IV/SQ:** 100-150mcg 3 times, may increase to 500 to 2,000 mcg IV or SubQ 3 times daily **or** **IV infusion:** 25 to 50 mcg/hour **Discontinue therapy within 24 hours of resolution of diarrhea to reduce the risk of ileus**
Maximum Daily Dose Adults*	**2,000 mcg IV or SQ three times daily**
Dose (pediatrics)	**Intermittent SubQ:** Usual initial dose: 1 to 10 mcg/kg/dose every 8 to 12 hours,

	higher dose of 60 mcg/kg/day has been reported. **Continuous IV infusion:** 1 mcg/kg/hour, doses up to 49 mcg/kg/day have been reported
Maximum Daily Dose Pediatrics*	**Intermittent SQ:** 60 mcg/kg/day **Continuous IV inf:** 49 mcg/kg/day
Adjustment	No initial or maintenance dosage adjustments are likely necessary for any degree of kidney dysfunction, although clearance is reduced, and dosage modifications may be necessary in patients with end-stage kidney disease (ESKD) receiving dialysis. In hepatic impairment, and using the LAR depot suspension: Patients with established cirrhosis of the liver: IM: Initial: 10 mg IM every 4 weeks; titrate based upon response.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most serious:** Cholelithiasis and related complications, Glucose dysregulation, Necrotizing enterocolitis **Most common:** sinus bradycardia, diaphoresis, hyperglycemia, abdominal pain, cholelithiasis, diarrhea, nausea, anemia
Drug Interactions*	X- Fexinidazole X- Macimorelin

	D- Algestone Acetophenide D- Ceritinib D- Chlormadinone D- Copper Cu 64 Dotatate D- Desogestrel D- Drospirenone D- Estetrol D- Estradiol and Dienogest D- Estradiol Enthanate D- Ethinyl Estradiol D- Ethynodiol Diacetate D- Etonogestrel D- Fingolimod D- Gallium Ga 68 Dotatate D- Gallium Ga 68 Dotatoc D- Gestodene D- Levonorgestrel (Systemic) D- Lutetium Lu 177 Dotatate D- Lynestrenol D- MedroxyPROGESTERone D- Mestranol D- Norelgestromin D- Norethindrone D- Norgestimate D- Norgestrel D- Ponesimod D- Segesterone Acetate D- Sincalide D- Siponimod D- Telotristat Ethyl (Depends on Dosage Form)
Special Population	Serious and some fatal adverse effects have been reported in pediatric patients including NEC, hypoxia, and pancreatitis, and during administration of IV doses bradycardia has been reported; most severe adverse events or death were observed in neonates, infants, and children <2 years of age;

	direct causality with octreotide was not established due to complex patient comorbidities. Use in neonates, including term and preterm, should be done with extreme caution and reserved for refractory cases; consider avoiding use if patient has other risk factors for NEC.
Pregnancy	Octreotide crosses the placenta and can be detected in the newborn at delivery.
Lactation	Octreotide is present in breast milk. Information related to octreotide use in breastfeeding women is limited.
Contraindications	Hypersensitivity to octreotide or any component of the formulation.
Monitoring Requirements	Check ordered lab and report any abnormalities. Educate patient on proper administration and disposal of syringes. Educate patient with diabetes to monitor glucose closely. Monitor for and educate patient to report signs of pancreatitis (severe abdominal pain, severe back pain, nausea, or vomiting) or signs of gallbladder problems (pain in upper right abdomen, right shoulder pain, jaundice, bloating, nausea, or vomiting).
Precautions	• Abnormal Schillings test: Chronic treatment has been associated with abnormal Schillings test; monitor vitamin B12 levels. • Cardiovascular events: Complete atrioventricular block has been reported in patients receiving IV therapy during surgical procedures; most causes occurred with continuous IV infusion at higher than recommended doses. Safety of continuous IV infusion has not been

	established in patients receiving octreotide for approved indications. • Hypothyroidism: Suppresses secretion of TSH; monitor for hypothyroidism.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Octreotide.**

Table 18. Octreotide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Octreotide	NICE	No recommendations found for this medication.
	CADTH	No recommendations found for this medication.
	HAS	Recommendation provided for another indication.
	IQWIG	Recommendation provided for another indication.
	PBAC	The PBAC does recommend octreotide, and that it should be available only under special arrangements.

CONCLUSION STATEMENT- OCTREOTIDE

The use of Octreotide is recommended by the PBAC- to be available under special arrangements.

2.1.4 Colestyramine

This section includes pertinent information regarding the use of Colestyramine in diarrhea (Lexicomp 2023):

Table 19. Drug Information Colestyramine

COLESTYRAMINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	No
Indication (ICD-10)	K52. 1, 70
Drug Class	Antilipemic Agent
Drug Sub-class	Bile Acid Sequestrant
ATC Code	C10AC01
Pharmacological Class (ASHP)	
DRUG INFORMATION	
Dosage Form	Powder
Route of Administration	Oral use
Dose (Adult) [DDD]*	2 to 4 g/day as single dose or in 1-4 divided doses; increase gradually (e.g., by 4 g at weekly intervals) based on response and tolerability
Maximum Daily Dose Adults*	24 g/day
Dose (pediatrics)	240 mg/kg/day in 2 to 3 divided doses
Maximum Daily Dose Pediatrics*	8 g/day
Adjustment	There are no dosage adjustments provided for renal or hepatic dysfunction.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most serious:** Fat-soluble vitamin/folate deficiency, Hemorrhage, Hyperchloremic metabolic acidosis, **Most common:** Constipation, hypertriglyceridemia
Drug Interactions*	X - Mycophenolate X - Taurursodiol D - Acenocoumarol D - Alfacalcidol (Depends on Route) D - Amiodarone D - Bendroflumethiazide (Depends on Route) D - Bezafibrate D - Calcifediol (Depends on Route) D - Calcitriol (Systemic) (Depends on Route) D - Chenodiol D - Chlorothiazide (Depends on Route) D - Chlorthalidone (Depends on Route) D - Cholecalciferol (Depends on Route) D - Cholic Acid D - Ciprofibrate D - Cyclopenthiazide (Depends on Route) D - Cyproterone and Ethinyl Estradiol (Depends on Route) D - Deferasirox D - Doxercalciferol (Depends on Route) D - Ergocalciferol (Depends on Route) D - Ethinyl Estradiol (Depends on Route) D - Ezetimibe D - Fenofibrate and Derivatives D - Fluvastatin D - Gemfibrozil D - HydroCHLOROthiazide (Depends on Route) D - Hydroflumethiazide (Depends on Route)

	D - Indapamide (Depends on Route) D - Leflunomide D - Levothyroxine (Depends on Route) D - Liothyronine (Depends on Route) D - Lomitapide D - Maralixibat D - Mestranol (Depends on Route) D - MetOLazone (Depends on Route) D - Multivitamins/Fluoride (with ADE) (Depends on Route) D - Multivitamins/Minerals (with ADEK, Folate, Iron) D - Multivitamins/Minerals (with AE, No Iron) D - Niacin (Depends on Route) D - Obeticholic Acid D - Odevixibat D - Paricalcitol (Depends on Route) D - Phenindione D - PHENobarbital D - Phenprocoumon [INT] D - Pravastatin D - Raloxifene D - Rosiglitazone D - Sincalide D - Teicoplanin (Depends on Route) D - Teriflunomide D - Thyroid, Desiccated (Depends on Route) D - Ursodiol D - Valproic Acid and Derivatives D - Warfarin D - Xipamide (Depends on Route)
Special Population	Pediatric Considerations: prolonged use may potentially cause hyperchloremic acidosis due to the exchange of organic anions for chloride; (eg, ages reported: 1.5 days, 4 weeks, 5 weeks, 6 months, 5 years, 10 years); reported precipitating

	factors include renal failure or volume depletion in setting of diarrhea or infection and cholestatic jaundice. Prolonged exposure to tooth enamel may result in discoloration or erosion; patients should be instructed to avoid sipping or slowly swallowing cholestyramine doses and to maintain good dental hygiene practices. May increase serum triglyceride concentrations; in a trial of children and adolescents (>10 years of age); the serum triglycerides increased 6% to 9% from baseline (not statistically significant)
Pregnancy	Cholestyramine is not absorbed systemically, but may interfere with maternal vitamin absorption; therefore, regular prenatal supplementation may not be adequate.
Lactation	Due to lack of systemic absorption, cholestyramine is not expected to be present in breast milk.
Contraindications	Hypersensitivity to bile acid sequestering resins or any component of the formulation; complete biliary obstruction
Monitoring Requirements	Check ordered labs and report any abnormalities. Instruct patient on proper administration and taking with other medicines. Monitor for and educate patient to report any signs and symptoms of constipation or abdominal pain.
Precautions	• Bleeding: Chronic use may be associated with bleeding problems (especially in high doses); may be prevented with use of oral vitamin K therapy. • Constipation: May produce or exacerbate constipation problems;

	initiate therapy at a reduced dose in patients with a history of constipation. Hemorrhoids may be worsened. • Bleeding: Chronic use may be associated with bleeding problems (especially in high doses); may be prevented with use of oral vitamin K therapy. • Decreased absorption (orally administered drugs): Not to be taken simultaneously with many other medicines (decreased absorption). • Patients susceptible to fat-soluble vitamin deficiencies: Use with caution. Absorption of fat-soluble vitamins A, D, E, and K and folic acid may be decreased; patients should take vitamins 1 hour before or ≥4 hours after cholestyramine. • Some products may contain phenylalanine. • Hyperlipidemia: Secondary causes should be ruled out prior to therapy.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Cholestyramine.**

Table 20. Colestyramine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cholestyramine	NICE	No recommendation for this medication.
	CADTH	No recommendation for this medication.
	HAS	No recommendation for this medication.
	IQWIG	No recommendation for this medication.
	PBAC	Restricted benefit for primary hypercholesterolemia.

CONCLUSION STATEMENT- CHOLESTYRAMINE

The different HTA bodies do not provide any information on the use of Cholestyramine in diarrhea.

2.1.5 Racecadotril

This section includes pertinent information regarding the use of Racecadotril in diarrhea (Lexicomp 2023):

Table 21. Drug Information Racecadotril

RACECADOTRIL	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	K52. 1
Drug Class	Antidiarrheal
Drug Sub-class	
ATC Code	A07XA04
Pharmacological Class (ASHP)	
DRUG INFORMATION	
Dosage Form	Capsule, hard Granules for oral suspension
Route of Administration	Oral use

Dose (Adult) [DDD]*	100 mg 3 times daily until symptoms improve (2 normal bowel movements) for up to 7 days
Maximum Daily Dose Adults*	300 mg
Dose (pediatrics)	1.5 mg/kg/dose 3 times daily
Maximum Daily Dose Pediatrics*	6 mg/kg/day
Adjustment	There are no dosage adjustments for hepatic or renal impairment.
Prescribing edits*	AGE
AGE (Age Edit): Infants >3 months	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Headache
Drug Interactions*	C - Alacepril C - Benazepril C - Captopril C - Cilazapril C - Enalapril C - Enalaprilat C - Fosinopril C - Imidapril C - Lisinopril C - Moexipril C - Perindopril C - Quinapril C - Ramipril C - Trandolapril C - Zofenopril
Special Population	

Pregnancy	Some product labeling contraindicates use with pregnancy. There is no adequate data on use of racecadotril in pregnant patients; manufacturers recommend avoiding use. If treatment for acute diarrhea is needed, agents other than racecadotril are recommended for use in pregnant patients.
Lactation	Some product labeling contraindicates use with breastfeeding. It is unknown if racecadotril is present in breast milk; manufacturers recommend avoiding use in breastfeeding patients.
Contraindications	• Angioedema: Angioedema has been reported with use and may occur at any time during treatment. Risk may be increased in patients with a history of angioedema (of any etiology) or with concurrent ACE inhibitor use. Administer emergency therapy if associated with tongue, glottis, or larynx as they are associated with airway obstruction. • Skin reaction: Mild to severe, life-threatening (rare) skin reactions have been reported with use; discontinue use if a severe skin reaction occurs. • Hepatic impairment: Use with caution in patients with hepatic impairment; only limited data available. Avoid use in pediatric patients with hepatic impairment. • Kidney impairment: Use with caution in patients with kidney impairment; only limited data available. Avoid use in pediatric patients with kidney impairment. • Prolonged vomiting may reduce the bioavailability of racecadotril; avoid use.

	• Pediatric: Concurrent rehydration therapy is crucial in pediatric patients, especially infants, and should be based on age, weight, and severity of condition including duration of diarrhea, concurrent vomiting, and appetite. Avoid use in pediatric patients with hepatic or renal impairment. • Lactose/Sucrose: Some formulations may contain lactose or sucrose; avoid use in patients with rare hereditary disorders including galactose or fructose intolerance, congenital lactase deficiency, glucose-galactose malabsorption syndrome, or saccharase-isomaltase deficiency. Use caution in patients with diabetes. • Appropriate use: Administer in conjunction with rehydration therapy. Do not administer to patients with diarrhea due to invasive disease (eg, fever, pus, or blood in stool) or antibiotic use. Rehydration requirements vary on age and weight of the patient, stage and severity of the condition, and the duration of diarrhea, vomiting, and/or lack of appetite, but are particularly important in infants. Use has not been sufficiently studied in patients with chronic diarrhea.
Monitoring Requirements	None listed
Precautions	• Angioedema: Angioedema has been reported with use and may occur at any time during treatment. Risk may be increased in patients with a history of angioedema (of any etiology) or with concurrent ACE inhibitor use. Administer emergency therapy if associated with tongue, glottis, or

	larynx as they are associated with airway obstruction. • Skin reaction: Mild to severe, life-threatening (rare) skin reactions have been reported with use; discontinue use if a severe skin reaction occurs. • Use with caution in patients with hepatic impairment; only limited data available. Avoid use in pediatric patients with hepatic impairment. • Use with caution in patients with kidney impairment; only limited data available. Avoid use in pediatric patients with kidney impairment. • Prolonged vomiting may reduce the bioavailability of racecadotril; avoid use. • Concurrent rehydration therapy is crucial in pediatric patients, especially infants, and should be based on age, weight, and severity of condition including duration of diarrhea, concurrent vomiting, and appetite. Avoid use in pediatric patients with hepatic or renal impairment. • Lactose/Sucrose: Some formulations may contain lactose or sucrose; avoid use in patients with rare hereditary disorders including galactose or fructose intolerance, congenital lactase deficiency, glucose-galactose malabsorption syndrome, or saccharase-isomaltase deficiency. Use caution in patients with diabetes. • Appropriate use: Administer in conjunction with rehydration therapy. Do not administer to patients with diarrhea due invasive disease (eg, fever, pus or blood in stool) or antibiotic use. Rehydration requirements vary on age and weight

	of the patient, stage and severity of the condition, and the duration of diarrhea, vomiting, and/or lack of appetite, but are particularly important in infants. Use has not been sufficiently studied in patients with chronic diarrhea.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Racecadotril.**

Table 22. Racecadotril HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Racecadotril	NICE	The product has been withdrawn from the UK and the evidence has been withdrawn.
	CADTH	No recommendation provided for this medication.
	HAS	No recommendation provided for this medication.
	IQWIG	No recommendation provided for this medication.
	PBAC	No recommendation provided for this medication.

CONCLUSION STATEMENT- Racecadotril

The different HTA bodies do not provide any information on the use of Racecadotril in diarrhea.

2.1.6 Infliximab

This section includes pertinent information regarding the use of Infliximab in diarrhea (Lexicomp 2023):

Table 23. Drug Information Infliximab

INFLIXIMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K52. 1
Drug Class	Immunosuppressant Agent, Monoclonal Antibody
Drug Sub-class	Tumor Necrosis Factor (TNF) Blocking Agent
ATC Code	L04AB02
Pharmacological Class (ASHP)	92:36 - Disease-modifying Antirheumatic Drugs; 92:20 - Immunomodulatory Agents; 56:92 - GI Drugs, Misc; 84:92 - Skin and Mucous Membrane Agents, Misc
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion. Solution for injection
Route of Administration	Intravenous use Subcutaneous use
Dose (Adult) [DDD]*	5 mg/kg at week 0, a second dose may be repeated 2 weeks later, and a third dose may be considered at 6 weeks if needed; use in combination with a corticosteroid
Maximum Daily Dose Adults*	5 mg/kg
Dose (pediatrics)	5 mg/kg/dose at 0, 2, and 6 weeks, followed by maintenance: 5 mg/kg/dose every 8 weeks thereafter. Note: Therapeutic drug monitoring and dose adjustment as appropriate are recommended. Patients with low body

	weight (eg, <30 kg), high BMI, high inflammatory burden, or low albumin may need higher dosing (eg, 10 mg/kg/dose) or shorter intervals (eg, every 4 weeks)
Maximum Daily Dose Pediatrics*	10 mg/kg/dose
Adjustment	No dosage adjustments recommended in renal impairment. For infliximab-induced hepatic impairment, AST/ALT ≥5 times ULN: Discontinue infliximab therapy and consult hepatologist. May be indicative of infliximab-induced autoimmune hepatitis, which may cause severe liver injury and can be fatal or lead to liver transplantation.
Prescribing edits*	AGE, CU, MD
AGE (Age Edit): Not to be given to patients less than 3 months old.	
CU (Concurrent Use Edit): Premedication with antihistamines (H1-antagonist +/- H2-antagonist), acetaminophen, and/or corticosteroids may be considered to prevent and/or manage infusion-related reactions.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be used under the supervision of a specialized physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** abdominal pain, nausea, anemia, infusion-related reaction, antibody development, abscess, upper respiratory tract infection **Most serious:** autoimmune disorder, demyelinating disease, dermatologic reactions, heart failure, hepatitis B virus reactivation, hepatotoxicity, infection,

	infusion-related reactions, malignancy, tuberculosis
Drug Interactions*	X - Abatacept X - Abrocitinib X - Adalimumab X - Adenovirus (Types 4, 7) Vaccine X - Anakinra X - Anifrolumab X - Baricitinib X- BCG (Intravesical) X - BCG Vaccine (Immunization) X - Bimekizumab X - Brivudine X - Brodalumab X - Canakinumab X - Certolizumab Pegol X - Cholera Vaccine X - Cladribine X - Dengue Tetravalent Vaccine (Live) X- Deucravacitinib X - Ebola Zaire Vaccine (Live) X - Etanercept X - Filgotinib X - Golimumab X - Guselkumab X - Influenza Virus Vaccine (Live/Attenuated) X - Ixekizumab X - Japanese Encephalitis Virus Vaccine (Live/Attenuated) X - Measles, Mumps, and Rubella Virus Vaccine X - Measles, Mumps, Rubella, and Varicella Virus Vaccine X - Mumps Virus Vaccine X - Nadofaragene Firadenovec X - Natalizumab X - Pimecrolimus

	X - Poliovirus Vaccine (Live/Bivalent/Oral) X - Poliovirus Vaccine (Live/Trivalent/Oral) X - Rilonacept X - Risankizumab X - Ritlecitinib X - RiTUXimab X - Rotavirus Vaccine X - Ruxolitinib (Topical) X - Sarilumab X - Secukinumab X - Smallpox Vaccine Live X - Tacrolimus (Topical) X - Talimogene Laherparepvec X - Tertomotide X - Tildrakizumab X - Tocilizumab X - Tofacitinib X - Typhoid Vaccine X - Upadacitinib X - Ustekinumab X - Varicella Virus Vaccine X - Vedolizumab X - Yellow Fever Vaccine X - Zoster Vaccine (Live/Attenuated)
Special Population	• Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing cycle (eg, for medications administered every 4 weeks, schedule surgery 5 weeks from last administered dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling,

	erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications. • Pediatric: Malignancies have been reported among children and adolescents receiving TNF-blocking agents.
Pregnancy	Inflammatory bowel disease is associated with adverse pregnancy outcomes including an increased risk of miscarriage, premature delivery, delivery of a low birth weight infant, and poor maternal weight gain. Management of maternal disease should be optimized prior to pregnancy. Treatment decreases disease flares, disease activity, and the incidence of adverse pregnancy outcomes. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of infliximab may be altered. Clearance may be decreased as pregnancy progresses leading to an increase in maternal plasma concentrations; therapeutic drug monitoring may be required in some patients. Infliximab may be continued during the first and second trimesters of pregnancy in patients with rheumatic and musculoskeletal diseases. Use should be discontinued during the third trimester in patients with well-controlled disease. Newborn exposure

	should be considered if treatment cannot be discontinued due to active disease. Data collection to monitor pregnancy and infant outcomes following exposure to infliximab is ongoing. Health care providers are also encouraged to enroll females exposed to infliximab during pregnancy in the MotherToBaby Autoimmune Diseases Study by contacting the Organization of Teratology Information Specialists.
Lactation	Infliximab is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα)-blocking agents, including infliximab, are considered compatible with breastfeeding.
Contraindications	Previous severe hypersensitivity (eg, anaphylaxis, hypotension, serum sickness) to infliximab, murine proteins, or any component of the formulation; doses >5 mg/kg in patients with moderate or severe heart failure (NYHA class III/IV). Canadian labeling: Additional contraindications (not in US labeling): Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections); use in patients with moderate or severe heart failure (NYHA class III/IV).
Monitoring Requirements	At baseline and periodically: CBC with differential, complete metabolic panel, liver function tests. Prior to initiation: tuberculosis screening, hepatitis B/C virus screening

Precautions	• Antibody formation: Formation of neutralizing anti-drug antibodies may occur with biologic tumor necrosis factor (TNF) inhibitors and may be associated with loss of efficacy • Autoimmune disorder: Positive antinuclear antibody titers have been detected in patients (with negative baselines). Rare cases of autoimmune disorder, including lupus-like syndrome, have been reported; monitor and discontinue if symptoms develop. • Cardiovascular/cerebrovascular reactions during and following infusion: Cerebrovascular accidents, MI (some fatal), hypotension, hypertension, and arrhythmias have been reported within 24 hours of infusion. Transient vision loss has also been reported during or within 2 hours of infusion. Discontinue therapy if serious reaction occurs. • Hematologic disorders: (eg, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported (may be fatal). Patients must be advised to seek medical attention if they develop signs and symptoms suggestive of blood dyscrasias (eg, persistent fevers); discontinue if significant hematologic abnormalities are confirmed. Use with caution in patients with a history of hematologic abnormalities. • Hepatic reactions: (including hepatitis, jaundice, acute hepatic failure, and cholestasis) have been reported during treatment; reactions

	occurred between 2 weeks to >1 year after initiation of therapy and some cases were fatal or necessitated liver transplantation; discontinue with jaundice and/or marked increase in liver enzymes (≥5 times ULN). • Hepatitis B: Reactivation of has occurred in chronic carriers of the virus, usually in patients receiving concomitant immunosuppressants (may be fatal); evaluate for HBV prior to initiation in all patients. Monitor during and for several months following discontinuation of treatment in HBV carriers; interrupt therapy if reactivation occurs and treat appropriately with antiviral therapy; if resumption of therapy is deemed necessary, exercise caution and monitor patient closely. • Hypersensitivity or infusion reactions: including anaphylaxis, may occur within 2 hours of infusion. Medication and equipment for management of hypersensitivity reaction should be available for immediate use. Interruptions and/or reinstitution at a slower rate may be required (consult protocols). Pretreatment may be considered and may be warranted in all patients with prior infusion reactions. Serum sickness-like reactions have occurred; may be associated with a decreased response to treatment. The development of antibodies to infliximab may increase the risk of hypersensitivity and/or infusion reactions; concomitant use of immunosuppressants may lessen the development of anti-infliximab

	antibodies. The risk of infusion reactions may be increased with re-treatment after an interruption (> 8 weeks) or discontinuation of prior maintenance therapy. Re-treatment in psoriasis patients should be resumed as a scheduled maintenance regimen without any induction doses; use of an induction regimen should be used cautiously for re-treatment of all other patients. • Infections: [US Boxed Warning]: Patients receiving infliximab are at increased risk for serious infections which may result in hospitalization and/or fatality; infections usually developed in patients receiving concomitant immunosuppressive agents (eg, methotrexate or corticosteroids) and may present as disseminated (rather than local) disease. Active tuberculosis (or reactivation of latent tuberculosis), invasive fungal (including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and pneumocystosis) and bacterial, viral or other opportunistic infections (including legionellosis and listeriosis) have been reported. Monitor closely for signs/symptoms of infection. Discontinue for serious infection or sepsis. Consider risks versus benefits prior to use in patients with a history of chronic or recurrent infection. Consider empiric antifungal therapy in patients who are at risk for invasive fungal infection and develop severe systemic illness. Caution should be exercised when considering use in

	the elderly or in patients with conditions that predispose them to infections (eg, diabetes) or residence/travel from areas of endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis), or with latent or localized infections. Do not initiate infliximab therapy in patients with an active infection, including clinically important localized infection. Patients who develop a new infection while undergoing treatment should be monitored closely. • Malignancy: [US Boxed Warning]: Lymphoma and other malignancies (may be fatal) have been reported in children and adolescent patients receiving TNF-blocking agents including infliximab. Half the cases are lymphomas (Hodgkin's and non-Hodgkin's) and the other cases are varied but include malignancies not typically observed in this population. [US Boxed Warning]: Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab. Almost all patients had received concurrent or prior treatment with azathioprine or mercaptopurine at or prior to diagnosis and the majority of reported cases occurred in adolescent and young adult males with Crohn disease or ulcerative colitis. Malignancies occurred after a median of 30 months (range: 1 to 84 months) after the first dose of TNF blocker therapy; most patients were receiving concomitant immunosuppressants. The impact of

	infliximab on the development and course of malignancies is not fully defined. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis alone has been previously associated with an increased rate of lymphoma. Use caution in patients with a history of COPD, higher rates of malignancy were reported in COPD patients treated with infliximab. Psoriasis patients with a history of phototherapy had a higher incidence of nonmelanoma skin cancers. Melanoma and Merkel cell carcinoma have been reported in patients receiving TNF-blocking agents including infliximab. Perform periodic skin examinations in all patients during therapy, particularly those at increased risk for skin cancer. Women with rheumatoid arthritis had a higher incidence of invasive cervical cancer; periodic screening should be continued in women treated with infliximab. • Tuberculosis: [US Boxed Warning]: Infliximab treatment has been associated with active tuberculosis (may be disseminated or extrapulmonary) or reactivation of latent infections. Evaluate patients for tuberculosis risk factors and latent tuberculosis infection (with a tuberculin skin test) prior to and during therapy. Treatment of latent tuberculosis should be initiated before use. Patients with initial negative tuberculin skin tests should receive continued monitoring for

	tuberculosis throughout treatment. Most cases of reactivation have been reported within the first couple months of treatment. Caution should be exercised when considering the use in patients who have been exposed to tuberculosis. • Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of optic neuritis and demyelinating disease (including multiple sclerosis, systemic vasculitis, and Guillain-Barré syndrome) have been reported; consider discontinuation of therapy if patient develops significant CNS reactions. • Heart failure: Use with caution in patients with mild heart failure (NYHA class I, II) or decreased left ventricular function; worsening and new-onset heart failure (with and without identifiable precipitating factors [eg, preexisting cardiovascular disease]) has been reported; doses >5 mg/kg are contraindicated in patients with moderate to severe heart failure (NYHA class III/IV). Monitor patients closely if doses ≤5 mg/kg are administered to patients with moderate or severe heart failure or any approved dose is administered to patients with mild heart failure and discontinue therapy with onset of new or worsening symptoms. In a scientific statement from the American Heart Association, TNF blockers have been determined to be agents that may either cause

	direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: major). • HIV: Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided they have normal CD4 counts, no viral load, and no recent opportunistic infections. • Seizure disorders: Use with caution in patients with a history of seizures; discontinue if significant CNS adverse reactions develop. • Solid organ transplant: Consider holding infliximab prior to living donor solid organ transplant (eg, hold IV infliximab for at least 4 weeks; hold SUBQ infliximab for 1 week) • Polysorbate 80: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported. • Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there are no data available concerning secondary transmission of live vaccines in patients receiving therapy. A fatal outcome has been reported in an infant who received a live vaccine (BCG) after in utero exposure to infliximab. It is recommended to wait ≥6 months following birth before administering any live vaccine to infants exposed to infliximab in utero (Remsima

	[Canadian product] recommends waiting until 12 months of age).
Black Box Warning	- **Serious infections** - **Malignancy**
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Infliximab.**

Table 24. Infliximab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Infliximab	NICE	Infliximab has a market authorization for the treatment of acute exacerbations of severely active ulcerative colitis. Otherwise, it is to be used only in clinical trials. Drug cost varies from patient to patient since the dose is adjusted based on body weight. It may also differ based on setting according to negotiated procurement discounts. NICE does recommend this treatment "as an option" if the doctor responsible of the patient's care believes that it is the right treatment.
	CADTH	Remicade® (Infliximab) is not recommended by CEDAC to be listed for the treatment of moderately-severely active ulcerative colitis who had inadequate response to conventional therapy. It was not deemed to be a cost-effective treatment, and there was still some uncertainty regarding the durability of effect. Renflexis® (Infliximab) and Inflectra® (Infliximab) are recommended to be reimbursed when Infliximab is the most appropriate treatment option. They have been shown to have similar pharmacokinetics, efficacy, safety, and immunogenicity as Remicade®- and exploration of data from trials have demonstrated to role of tumor

		necrosis alpha drugs in the indication of ulcerative colitis. They are also less costly than Remicade®. Moreover, Renflexis® is the first biosimilar approved for pediatric indications of Remicade®.
	HAS	The recommendation is favorable for the reimbursement of infliximab for the treatment of moderately-severely active ulcerative colitis in patients who have had inadequate response to conventional therapy. The clinical benefit of infliximab is substantial in ulcerative colitis.
	IQWIG	No recommendation provided for this medication.
	PBAC	"Infliximab is TGA registered for use in adults and in children and adolescents (6 to 17 years) for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy (May 2012)". It is recommended by the PBAC as it was shown to be non-inferior to cyclosporin in terms of comparative effectiveness and safety. It has also shown benefits in improving quality of life, lowering community indirect costs, and avoidance of surgery.

CONCLUSION STATEMENT- Infliximab

The use of Infliximab is recommended by different HTA bodies for the treatment of moderately-severely active ulcerative colitis. NICE does recommend infliximab as a treatment option if the physician deems the treatment right. Renflexis® and Inflectra®, who are biosimilars of Infliximab, were deemed to be cost-effective by CADTH, whereas Remicade® was not. Both HAS and PBAC have recommended Infliximab due to its clinical benefits. No recommendation was provided by IQWIG.

2.1.7 Vedolizumab

This section includes pertinent information regarding the use of Vedolizumab in diarrhea (Lexicomp 2023):

Table 25. Drug Information Vedolizumab

VEDOLIZUMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K52. 1
Drug Class	Monoclonal Antibody
Drug Sub-class	Selective Adhesion-Molecule Inhibitor
ATC Code	L04AA33 QL04AA33
Pharmacological Class (ASHP)	56:92 - GI Drugs, Miscellaneous
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion Solution for injection
Route of Administration	Intravenous use Subcutaneous use
Dose (Adult) [DDD]*	**IV:** 300 mg at 0, 2, and 6 weeks and then every 8 weeks thereafter. Discontinue therapy in patients who show no evidence of therapeutic benefit by week 14. **SUBQ [Canadian product]:** Maintenance: 108 mg once every 2 weeks beginning after at least 2 IV infusions; administer in place of next scheduled IV dose and then every 2 weeks thereafter.
Maximum Daily Dose Adults*	300 mg IV and 108 mg SUBQ
Dose (pediatrics)	

Maximum Daily Dose Pediatrics*	
Adjustment	There are no dosage adjustments recommended in hepatic or renal impairment.
Prescribing edits*	AGE, MD
AGE (Age Edit): Treatment in adults	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be used under the supervision of a specialized physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most serious:** Infusion-related hypersensitivity and/or cutaneous reactions, liver injury, progressive multifocal leukoencephalopathy, serious infections **Most common**: antibody development, liver injury, progressive multifocal leukoencephalopathy, serious infections
Drug Interactions*	X- Abrocitinib X - Adalimumab X - Adenovirus (Types 4, 7) Vaccine X - Baricitinib X - BCG (Intravesical) X - BCG Vaccine (Immunization) X - Brivudine X - Certolizumab Pegol X - Cholera Vaccine X - Cladribine X - Dengue Tetravalent Vaccine (Live) X - Deucravacitinib X - Ebola Zaire Vaccine (Live) X - Etanercept

	X - Filgotinib X - Golimumab X - InFLIXimab X - Influenza Virus Vaccine (Live/Attenuated) X - Japanese Encephalitis Virus Vaccine (Live/Attenuated) X - Lenalidomide X - Measles, Mumps, and Rubella Virus Vaccine X - Measles, Mumps, Rubella, and Varicella Virus Vaccine X - Mumps Virus Vaccine X - Nadofaragene Firadenovec X - Natalizumab X - Pimecrolimus X - Poliovirus Vaccine (Live/Bivalent/Oral) X - Poliovirus Vaccine (Live/Trivalent/Oral) X - Pomalidomide X - Ritlecitinib X - Rotavirus Vaccine X - Ruxolitinib (Topical) X - Smallpox Vaccine Live X - Tacrolimus (Topical) X - Talimogene Laherparepvec X - Tertomotide X - Thalidomide X - Tofacitinib X - Typhoid Vaccine X - Upadacitinib X - Varicella Virus Vaccine X - Yellow Fever Vaccine X - Zoster Vaccine (Live/Attenuated) D - Anthrax Vaccine Adsorbed D - Coccidioides immitis Skin Test D - COVID-19 Vaccine (Adenovirus Vector)

	D - COVID-19 Vaccine (mRNA) D - Denosumab D - Diphtheria and Tetanus Toxoids D - Diphtheria and Tetanus Toxoids, Acellular Pertussis, and Poliovirus Vaccine D - Diphtheria and Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), Poliovirus (Inactivated), and Haemophilus influenzae B Conjugate (Adsorbed) Vaccine D - Diphtheria and Tetanus Toxoids, Acellular Pertussis, Poliovirus and Haemophilus b Conjugate Vaccine D - Diphtheria and Tetanus Toxoids, and Acellular Pertussis Vaccine D - Diphtheria and Tetanus Toxoids, Whole-Cell Pertussis, Hepatitis B (Recombinant), and Haemophilus influenzae b Conjugate Vaccine D - Diphtheria, Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), and Poliovirus (Inactivated) Vaccine D - Haemophilus b Conjugate Vaccine D - Hepatitis A and Hepatitis B Recombinant Vaccine D - Hepatitis A Vaccine D - Hepatitis B Vaccine (Recombinant [Adjuvanted]) D - Hepatitis B Vaccine (Recombinant) D - Hepatitis B Vaccine (Trivalent [Recombinant]) D - Human Papillomavirus Vaccine (9-Valent) D - Human Papillomavirus Vaccine (Bivalent) D - Human Papillomavirus Vaccine (Quadrivalent) D - Influenza A Virus Vaccine (H5N1)

	D - Influenza Virus Vaccine (Inactivated) D - Influenza Virus Vaccine (Recombinant) D - Japanese Encephalitis Virus Vaccine (Inactivated) D - Leflunomide D - Meningococcal (Groups A / C / Y and W-135) Conjugate Vaccine D - Meningococcal Group B Vaccine D - Meningococcal Group C Conjugate Vaccine D - Poliovirus Vaccine (Inactivated) D - Polymethylmethacrylate D - Q Fever Vaccine D - Rabies Vaccine D - Respiratory Syncytial Virus Vaccine (Recombinant [Adjuvanted]) D - Respiratory Syncytial Virus Vaccine (Recombinant) D - Sipuleucel-T D - Smallpox and Monkeypox Vaccine (Live) D - Tetanus Toxoid (Adsorbed) D - Tick-Borne Encephalitis Vaccine D - Travelers' Diarrhea and Cholera Vaccine D - Typhoid and Hepatitis A Vaccine D - Zoster Vaccine (Recombinant)
Special Population	Clinical studies to date have not identified any differences in safety and efficacy when vedolizumab was administered to elderly patients compared to younger patients; however, clinical trials did not include a sufficient number of older adults ≥65 years of age.
Pregnancy	Vedolizumab crosses the placenta. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of vedolizumab may be

	altered. Maternal serum levels may decrease as pregnancy progresses due increased clearance; however, this may not be clinically significant. Inflammatory bowel disease is associated with adverse pregnancy outcomes including an increased risk of miscarriage, premature delivery, delivery of a low-birth-weight infant, and poor maternal weight gain. Management of maternal disease should be optimized prior to pregnancy. Treatment decreases disease flares, disease activity, and the incidence of adverse pregnancy outcomes. When treatment for inflammatory bowel disease is needed in pregnant patients, appropriate biologic therapy can be continued without interruption. Serum levels should be evaluated prior to conception and optimized to avoid subtherapeutic concentrations or high levels which may increase placental transfer. Dosing can be adjusted so delivery occurs at the lowest serum concentration. For vedolizumab, the final injection can be given 6 to 10 weeks prior to the estimated date of delivery (4 to 5 weeks before delivery if every-4-week dosing), then continued 48 hours' postpartum. Data collection to monitor pregnancy and infant outcomes following exposure to vedolizumab is ongoing. Health care providers are encouraged to enroll patients exposed to vedolizumab during pregnancy in a pregnancy exposure registry.
Lactation	It is expected that any vedolizumab ingested via breast milk would be degraded in the infant GI tract and have

	minimal impact to the breastfed infant. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother; however, available guidelines note maternal use of vedolizumab is considered compatible with breastfeeding.
Contraindications	• Serious or severe hypersensitivity to vedolizumab or any component of the formulation • Canadian labeling: Additional contraindications (not in US labeling): Patients with active severe infections or opportunistic infections.
Monitoring Requirements	Monitor vital signs, as well as signs of infection especially respiratory or nasal ones, impaired liver function, changes in mental status or neurological status. Instruct patients to report signs and symptoms of infection and changes in mentation.
Precautions	• Hypersensitivity/infusion-related reactions: including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased BP and heart rate. Reactions may occur with the first or subsequent infusions; onset may vary from during the infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration immediately and initiate appropriate treatment. • Use may be associated with an increased risk for developing infections; most commonly reported infections included upper respiratory

	and nasal mucosa. Serious infections have also been reported in patients treated, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. Therapy is not recommended in patients with uncontrolled, active, severe infections. If a patient develops a serious infection, consider discontinuing therapy. Use with caution in patients with a history of recurring severe infections. Screening for tuberculosis should be considered. • Liver injury: Elevations of transaminase and/or bilirubin have been reported in patients receiving vedolizumab. Discontinue therapy in patients with jaundice or other evidence of significant liver injury such as fatigue, anorexia, right upper abdominal discomfort, or dark urine. • Progressive multifocal leukoencephalopathy: Progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the CNS caused by the John Cunningham virus, has been reported with integrin receptor antagonists, including vedolizumab. The case with vedolizumab occurred in a patient with multiple risk factors for PML (ie, HIV, CD4 count 300 cells/mm3, prolonged prior and concurrent immunosuppression) (Lotus 2020). Monitor patients for any new onset or worsening of neurological signs and symptoms including progressive weakness on one side of the body or

	clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. Symptoms may progress over days to weeks and can lead to death or severe disability in weeks to months. If PML is suspected, withhold therapy and refer to a neurologist; if confirmed, discontinue therapy permanently. • Immunizations: Patients should be brought up to date with all immunizations according to immunization guidelines before initiating therapy. Live vaccines should not be given concurrently unless the benefits outweigh the risks; there are no data on the secondary transmission of infection by live vaccines with vedolizumab. Non-live vaccines may be given concurrently.
Black Box Warning	**N/A**
REMS*	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Vedolizumab.**

Table 26. Vedolizumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Vedolizumab	NICE	Vedolizumab is recommended within its marketing authorization for the treatment of moderately-severely active ulcerative colitis in adults, if the company provides the discount agreed patient access scheme (level of discount is commercial in confidence). To be reassessed 12 months after start of

		treatment, to check if it is to be continued. It is to be given until it stops working or until surgery is needed.
	CADTH	CADTH recommends the reimbursement of SC Vedolizumab for the treatment of adult patients with moderately-severely active ulcerative colitis who have had inadequate response to conventional therapy or infliximab- to be reimbursed in a similar manner of the IV formulation. Before starting therapy with vedolizumab SC, patients should have achieved a clinical response after receiving the induction therapy with vedolizumab IV 300 mg. Additionally, the drug plan cost for the SC injection of vedolizumab should not exceed the cost of the least expensive biologic currently reimbursed for the treatment of ulcerative colitis.
	HAS	The recommendation is in favor of reimbursement of the drug in adult patients to be treated for moderately-severely active ulcerative colitis who have not responded to conventional therapy or 2nd/3rd line treatment with tumor necrosis factor alpha inhibitors. The clinical evidence was shown to be substantial. No added clinical value with respect to the IV formulation.
	IQWIG	No proven benefit for the drug in ulcerative colitis with respect to comparator therapy.
	PBAC	The PBAC suggested approving vedolizumab (VDZ) SC for treating moderate-to-severe ulcerative colitis and severe Crohn's disease, on a cost-minimization basis compared to the IV formulation. The recommendation is based on the equivalent effectiveness of VDZ SC at a dose of 108 mg every 2 weeks compared to VDZ IV at 300 mg every 8 weeks.

CONCLUSION STATEMENT- Vedolizumab

The use of Vedolizumab (VDZ) is recommended by different HTA bodies for the treatment of ulcerative colitis, except for IQWIG which found no proven benefit for VDZ in ulcerative colitis compared to comparator therapy. NICE recommends VDZ for moderately-severely active ulcerative colitis in adults with a patient access scheme discount, subject to reassessment after 12 months. CADTH recommends reimbursement of VDZ SC for adults with moderately-severely active ulcerative

colitis who had an inadequate response to conventional therapy or infliximab, at a cost similar to the IV formulation, following induction therapy with IV Vedolizumab 300 mg. HAS favors reimbursement for adult patients with ulcerative colitis who didn't respond to conventional or 2nd/3rd line therapy with tumor necrosis factor alpha inhibitors, citing substantial clinical evidence and no added value over the IV formulation. PBAC suggests approving VDZ SC for moderate-to-severe ulcerative colitis and severe Crohn's disease, on a cost-minimization basis compared to the IV formulation, based on equivalent effectiveness with different dosing intervals.

2.1.8 Vancomycin

This section includes pertinent information regarding the use of Vancomycin in diarrhea (Lexicomp 2023):

Table 27. Drug Information Vancomycin

VANCOMYCIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	A04. 7
Drug Class	Glycopeptide
Drug Sub-class	
ATC Code	A07AA09 J01XA01
Pharmacological Class (ASHP)	8:12.28.16 - Glycopeptides
DRUG INFORMATION	
Dosage Form	Solution for infusion Powder for solution for injection/infusion Lyophilisate for solution for injection Powder for solution for infusion Powder for concentrate for solution for infusion Powder for solution for injection/infusion Injection

Route of Administration	Parenteral use Intravenous use
Dose (Adult) [DDD]*	**Prevention:** 125mg once daily for 5-7 days after completing systemic antibiotic **Treatment:** *Initial/recurrent nonfulminant infection* (alternative agent Oral: 125 mg 4 times daily (for 10 days; if delayed response to treatment, a longer duration (eg, up to 14 days) may be considered. *Recurrent nonfulminant infection: Pulsed-tapered regimen*: Oral: 125 mg 4 times daily for 10 to 14 days, then 125 mg twice daily for 7 days, then 125 mg once daily for 7 days, then 125 mg every 2 or 3 days for 2 to 8 weeks. *Recurrent nonfulminant infection: Combination regimen with rifaximin*: Oral: 125 mg 4 times daily for 10 days followed by rifaximin. *Fulminant infection (ie, ileus, megacolon, and/or hypotension/shock):* Oral or via nasogastric tube: 500 mg 4 times daily with IV metronidazole; if ileus is present, may consider vancomycin retention enema. Usual duration is 10 days; if delayed response to treatment, a longer duration (eg, up to 14 days) may be considered. If antibiotic(s) for a primary infection are essential, some experts extend CDI treatment one week beyond other antibiotic(s). *Fulminant infection with ileus:* Rectal retention enema (off-label route): 500 mg in 100 mL NS; retained for as long as possible and replaced every 6 hours. Use in combination with oral vancomycin (if the ileus is partial) or in place of oral vancomycin (if the ileus is

	complete) plus IV metronidazole. Note: Optimal regimen not established. Use of rectal vancomycin should be reserved for patients who have not responded to standard therapy and performed by individuals with expertise in administration, as there is risk of colonic perforation. Usual duration is 10 days; if delayed response to treatment, a longer duration (eg, up to 14 days) may be considered. If antibiotic(s) for a primary infection are essential, some experts extend CDI treatment one week beyond other antibiotic(s).
Maximum Daily Dose Adults*	2000mg
Dose (pediatrics)	40 mg/kg/day divided every 6 to 8 hours for 7 to 10 days
Maximum Daily Dose Pediatrics*	2,000 mg/day
Adjustment	The renal dosing recommendations: • For oral administration, no dosage adjustments are provided by the manufacturer due to low systemic absorption. **There are no dosage adjustments for hepatic impairment.**
Prescribing edits*	PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): requires a positive test for Clostridium difficile antigen and toxins A and B prior to initiation	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	• Anaphylaxis • Clostridioides difficile infection

	• Drug-induced immune thrombocytopenia • Hypersensitivity reactions (delayed) • Nephrotoxicity • Neutropenia/pancytopenia • Ototoxicity • Vancomycin infusion reaction
Drug Interactions*	X - BCG (Intravesical) X - Cholera Vaccine X - Fecal Microbiota (Live) (Oral) X - Fecal Microbiota (Live) (Rectal) D - Amikacin (Systemic) Depends on Indication D - Arbekacin Depends on Indication D - Bacillus clausii D - Colistimethate D - Gentamicin (Systemic) Depends on Indication D - Isepamicin Depends on Indication D - Kanamycin Depends on Indication D - Neomycin (Systemic) Depends on Indication D - Netilmicin (Systemic) Depends on Indication D - Paromomycin Depends on Indication D - Plazomicin Depends on Indication D - Ribostamycin Depends on Indication D - Sisomicin Depends on Indication D - Sodium Picosulfate D - Streptomycin Depends on Indication D -Tobramycin (Systemic) Depends on Indication D - Typhoid Vaccine Depends on Route
Special Population	Older Adult Considerations: As a result of age-related changes in renal function

	and volume of distribution, accumulation and toxicity are a risk in the elderly with IV administration. Careful monitoring and dosing adjustment is necessary.
Pregnancy	Vancomycin crosses the placenta and can be detected in fetal serum, amniotic fluid, and cord blood. Adverse fetal effects, including sensorineural hearing loss or nephrotoxicity, have not been reported following maternal use during the second or third trimesters of pregnancy. The pharmacokinetics of vancomycin may be altered during pregnancy and pregnant patients may need a higher dose of vancomycin. Maternal half-life is unchanged, but the volume of distribution and the total plasma clearance may be increased. Individualization of therapy through serum concentration monitoring may be warranted. Vancomycin is recommended for the treatment of mild, moderate, or severe Clostridioides difficile infections in pregnant patients. Standard doses should be used. The formulation of vancomycin injection containing the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA) has caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during the first or second trimesters of pregnancy, use other available formulations of vancomycin.
Lactation	Vancomycin is present in breast milk following IV administration. Vancomycin exhibits minimal oral absorption; therefore, the amount available to pass into the milk would be limited following oral administration

	and unlikely to provide clinically relevant exposure to an infant exposed via breast milk. In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora. Monitor infants for GI disturbances, such as thrush or diarrhea. Vancomycin is recommended for the treatment of Clostridioides difficile infections in breastfeeding women and is considered compatible with breastfeeding when used for the treatment of airway diseases, such as cystic fibrosis. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to vancomycin or any component of the formulation
Monitoring Requirements	Periodic renal function tests, CBC, pregnancy test prior to use for formulation containing PEG 400 and NADA excipients, serial auditory function testing may be helpful to minimize risk of ototoxicity, serum trough vancomycin concentrations in select patients (eg, aggressive dosing, life-threatening infection, seriously ill, unstable renal function, concurrent nephrotoxins, prolonged courses). AUC monitoring: Frequency based on clinical judgement; frequent or daily monitoring may be appropriate for hemodynamically unstable patients; hemodynamically stable patients may only require once-weekly monitoring.

	Trough monitoring: Hemodynamically stable patients: Draw trough concentrations at least once weekly. Hemodynamically unstable patients: Draw trough concentrations more frequently or in some instances daily. Prolonged courses (>3 to 5 days): Draw at least one steady-state trough concentration; repeat as clinically appropriate. Note: Drawing >1 trough concentration prior to the fourth dose for short course (<3 days) or lower intensity dosing (target trough concentrations <15 mg/L) is not recommended. For patients with uncomplicated skin and soft tissue infections who are not obese and have normal renal function, serum trough monitoring is generally not needed. Oral/rectal therapy: Serum sample monitoring is not typically required; systemic absorption of enteral vancomycin may occur in patients with mucosal disruption due to colitis, especially in patients with renal failure. Monitoring serum vancomycin levels may be considered for patients with renal failure who have severe colitis and require a prolonged course of enteral vancomycin
Precautions	• Extravasation and thrombophlebitis: IV vancomycin is an irritant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. Pain, tenderness, and necrosis may occur with extravasation. If thrombophlebitis occurs, slow infusion rates, dilute

	solution (eg, 2.5 to 5 g/L) and rotate infusion sites. • Superinfection: Prolonged use may result in fungal or bacterial superinfection. • Inflammatory bowel disease: Clinically significant serum concentrations have been reported in patients with inflammatory disorders of the intestinal mucosa who have taken oral vancomycin (multiple doses) for the treatment of C. difficile-associated diarrhea. Although use may be warranted, the risk for adverse reactions may be higher in this situation; consider monitoring serum trough concentrations in patients with renal insufficiency, severe colitis, and a prolonged course. • Renal impairment: Use with caution in patients with renal impairment or those receiving other nephrotoxic drugs; dosage modification required and close monitoring is recommended in patients with preexisting renal impairment and those at high risk for renal impairment. Accumulation may occur after multiple oral doses of vancomycin in patients with renal impairment; consider monitoring serum concentrations in this circumstance**.** • Appropriate use: Oral vancomycin is only indicated for the treatment of CDI or enterocolitis due to S. aureus and is not effective for systemic infections; parenteral vancomycin is not effective for the treatment of enterocolitis.

	• Intraocular administration (off-label route): Hemorrhagic occlusive retinal vasculitis (HORV), including permanent visual loss, has been reported in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. • Intraperitoneal administration (off-label route): Use caution when administering intraperitoneally (IP); in some continuous ambulatory peritoneal dialysis (CAPD) patients, chemical peritonitis (cloudy dialysate, fever, severe abdominal pain) has occurred. Symptoms are self-limited and usually clear after vancomycin discontinuation.
Black Box Warning	Risk of embryo-fetal toxicity due to excipients
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Vancomycin.**

Table 28. Vancomycin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Vancomycin	NICE	Recommended for C. difficile treatment, but there is no data on clinical efficacy or cost effectiveness.
	CADTH	No cost-effectiveness studies related to therapeutic drug monitoring of vancomycin were found.
	HAS	No recommendation provided for this medication.
	IQWIG	No recommendation provided for this medication.

	PBAC	Recommended where the patient is unresponsive or intolerant to metronidazole.

CONCLUSION STATEMENT- Vancomycin

According to different bodies, NICE recommends vancomycin for C. difficile treatment, but there is a lack of data on clinical efficacy and cost-effectiveness. CADTH states that no cost-effectiveness studies related to therapeutic drug monitoring of vancomycin were found. HAS and IQWIG do not provide specific recommendations for this medication. However, PBAC recommends the use of vancomycin when the patient is unresponsive or intolerant to metronidazole.

2.1.9 Fidaxomicin

This section includes pertinent information regarding the use of Fidaxomicin in diarrhea (Lexicomp 2023):

Table 29. Drug Information Fidaxomicin

FIDAXOMICIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	A04. 7
Drug Class	Antibiotic
Drug Sub-class	Macrolide
ATC Code	A07AA12
Pharmacological Class (ASHP)	8:12.12.92 - Other Macrolides
DRUG INFORMATION	
Dosage Form	**Film-coated tablet**
Route of Administration	Oral
Dose (Adult) [DDD]*	**Initial infection:** Oral: 200 mg twice daily for 10 days. If delayed response to treatment, a longer duration (eg, up to 14 days) may be considered. **Recurrent infection:** Oral: 200 mg twice daily for 10 days or 200 mg twice daily

	for 5 days, followed by 200 mg once every other day for 20 days.
Maximum Daily Dose Adults*	400 mg
Dose (pediatrics)	*Weight-directed dosing*: Limited data available: Infants ≥6 months and Children: Oral: 16 mg/kg/dose twice daily for 10 days; maximum dose: 200 mg/dose. *Fixed dosing*: Infants ≥6 months, Children, and Adolescents: • 4 to <7 kg: Oral: Oral suspension: 80 mg twice daily for 10 days. • 7 to <9 kg: Oral: Oral suspension: 120 mg twice daily for 10 days. • 9 to <12.5 kg: Oral: Oral suspension: 160 mg twice daily for 10 days. • ≥12.5 kg: Oral: Oral suspension, tablets: 200 mg twice daily for 10 days
Maximum Daily Dose Pediatrics*	400 mg
Adjustment	Unlikely to be dialyzed by hemodialysis or peritoneal dialysis. No dosage adjustments recommended for renal or hepatic impairment.
Prescribing edits*	Age
AGE (Age Edit): infants ≥6 months	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** fever and nausea **Most serious:** GI hemorrhage, intestinal obstruction, non-Hirschsprung

	megacolon, decreased platelet count, anemia, increased liver enzymes
Drug Interactions*	X - Cholera Vaccine X - Fecal Microbiota (Live) (Oral) X - Fecal Microbiota (Live) (Rectal) X - Mizolastine D - Bacillus clausii D - Sodium Picosulfate D - Typhoid Vaccine Depends on Route
Special Population	Older adult considerations: Fifty percent of subjects in fidaxomicin's pivotal trials were ≥65 years; 31% were ≥75 years. A pooled analysis of clinical outcomes by age and treatment assignment did not find a difference in clinical cure between fidaxomicin and vancomycin, yet the odds of clinical cure decreased by 17% per decade increase in age for both treatments. The probability of sustained response was 1.86 times greater with fidaxomicin and was 13% lower per decade increase in age. The odds of recurrence were 54% lower with fidaxomicin while the odds of recurrence increased 17% per decade of age with both treatments. The clinical studies can be criticized for only following patients 36-40 days for recurrence as opposed to the recommended 90 days, and for excluding patients with life-threatening or fulminant *C. difficile* infections or a history of more than one recurrent *C. difficile*-associated diarrhea episode in the preceding 3 months; hence, its efficacy in these patients has not been established
Pregnancy	The limited systemic absorption of fidaxomicin may limit potential fetal exposure.

Lactation	It is not known if fidaxomicin is present in breast milk. The limited systemic absorption of fidaxomicin may limit potential distribution into breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to fidaxomicin or any component of the formulation
Monitoring Requirements	Check ordered labs and tests and report abnormalities. Monitor for signs and symptoms of hypersensitivity. Educate patients and family regarding infection prevention using contact precautions, and frequent hand hygiene using soap and water. Monitor for effectiveness of treatment. Educate patient on the importance of completing entire therapy.
Precautions	• Hypersensitivity: Hypersensitivity reactions (angioedema [mouth, face, throat], dyspnea, pruritus, and rash) to fidaxomicin have been reported. If a severe reaction occurs, discontinue drug and institute supportive care. • Macrolide allergy: Use with caution in patients with a history of macrolide allergy; may be at increased risk for hypersensitivity. • Appropriate use: Do not use for systemic infections; fidaxomicin systemic absorption is negligible. Use only in patients with proven or strongly suspected C. difficile infections.
Black Box Warning	N/A

REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diarrhea treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Fidaxomicin.**

Table 30. Fidaxomicin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Fidaxomicin	NICE	Recommended for C. difficile treatment, but there is no data on clinical efficacy or cost effectiveness.
	CADTH	Fidaxomicin was recommended not to be listed at the submitted price. It was shown to have similar clinical efficacy with respect to vancomycin but is more expensive. Fidaxomicin showed superiority to vancomycin in clinical recurrence and sustained cure over four weeks, but uncertainty in estimates of recurrence beyond the first recurrence makes the cost-effectiveness of fidaxomicin uncertain; considering more conservative estimates, the incremental cost of fidaxomicin compared with vancomycin exceeded $90,000 per quality-adjusted life-year (QALY). No HTA literature identified for fidaxomicin pulse therapy for the treatment of Clostridium difficile infections.
	HAS	The medication provides a significant benefit in the management of documented C. difficile infections, particularly when the presence of the toxin is demonstrated in stools, leading to a moderate improvement in actual patient outcomes.
	IQWIG	The medication is approved for the treatment of adults with Clostridium difficile, however there was no proven added benefit.
	PBAC	No recommendation provided for this medication.

CONCLUSION STATEMENT- Fidaxomicin

According to different bodies, NICE recommends fidaxomicin for C. difficile treatment, but there is a lack of data on clinical efficacy or cost-effectiveness. CADTH recommends against listing fidaxomicin due to its higher cost despite showing similar clinical efficacy compared to vancomycin. HAS acknowledges that fidaxomicin provides a significant benefit in managing documented C. difficile infections, especially with toxin presence in stools, resulting in a moderate improvement in patient outcomes. IQWIG approves the medication for C. difficile treatment in adults but found no proven added benefit. PBAC does not provide a specific recommendation for this medication.

2.2 Modifications

The NICE Guidelines for Eluxadoline for Irritable bowel syndrome with diarrhea (2017) had been withdrawn since the medication was withdrawn. “Allergan has stopped marketing eluxadoline (Truberzi) for commercial reasons and its marketing authorization has been withdrawn.”

2.3 Delisting

The medications below are no longer SFDA registered (SFDA Drug List, June 2023), therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drug Therapy in Non-Infectious Symptomatic Treatment of Diarrhea - Section 2*** *of CHI Non-Infectious Symptomatic Treatment of Diarrhea original clinical guidance:*

- Bismuth Subcitrate
- Dextrose, Sodium Chloride, Sodium Citrate, Potassium Chloride
- Vitamins, Zinc
- Zinc
- Zinc (As Zinc Bisglycinate)
- Zinc Gluconate
- Zinc Orotate Dihydrate
- Vitamins, Folic Acid, Pantothenic Acid, Calcium, Lactic Ferments (Lactobacillus Acidophilus & Sporogenes, Bifidobacterium Bifidum, Longum & Infantis)

2.4 Other Drugs

The following drugs are newly FDA-approved, but are not SFDA registered:

2.4.1 Vowst (fecal microbiota spores, live-brpk)

Vowst is a microbiota-based therapeutic indicated to prevent recurrent Clostridioides difficile infection (CDI) in individuals 18 years and older[20]. It is administered orally in capsule form, and the FDA approval was based on a study showing a lower CDI recurrence rate with Vowst compared to placebo through 8 weeks, 12 weeks, and 24 weeks after treatment[20].

2.4.2 Rebyota (fecal microbiota, live - jslm) suspension

Rebyota is a live biotherapeutic product indicated to prevent Clostridioides difficile infection (CDI) recurrence in individuals 18 and older, following antibiotic treatment[21]. The FDA approval was based on a phase 3 trial where Rebyota demonstrated superiority to placebo in reducing CDI recurrence after standard-of-care antibiotic treatment[21].

2.4.3 Zinplava (bezlotoxumab)

Zinplava (bezlotoxumab) is a human monoclonal antibody that neutralizes C. difficile toxin B's effects[22]. It is specifically indicated to reduce Clostridium difficile infection (CDI) recurrence in patients aged 18 years or older who are receiving antibacterial drug treatment for CDI and have a high risk of recurrence[22]. The FDA approval of Zinplava was based on two phase III trials, MODIFY I and MODIFY II, which demonstrated a significantly lower rate of CDI recurrence in patients receiving bezlotoxumab compared to placebo through 12 weeks after treatment in various patient subgroups known to be at high risk for CDI recurrence[22].

2.4.4 Mytesi (crofelemer)

Mytesi is specifically indicated for relieving non-infectious diarrhea symptoms in adult HIV/AIDS patients on anti-retroviral therapy[23]. The FDA approval was based on a randomized, double-blind, placebo-controlled, and placebo-free study involving HIV-positive patients on stable anti-retroviral therapy with a history of diarrhea[23]. The primary efficacy endpoint showed that a significantly higher proportion of patients in the crofelemer 125 mg twice daily group experienced a clinical response compared to the placebo group[23].

Section 3.0 Key Recommendations Synthesis

- Recommendations for IBS:
    - Bile acid sequestrants are not recommended for treating IBS-D symptoms. (ACG: Conditional recommendation; very low quality of evidence)
    - Rifaximin is strongly recommended for treating overall symptoms of IBS-D. (ACG: Strong recommendation; moderate quality of evidence)
    - 5-HT3 receptor antagonists (e.g., alosetron) are effective second-line drugs for IBS with diarrhea in specialized healthcare settings. (BSG: Recommendation: weak, quality of evidence: moderate to high)
    - Eluxadoline is considered an effective second-line treatment for IBS with diarrhea in specialized healthcare settings, with contraindications. (BSG: Recommendation: weak, quality of evidence: moderate)
    - Loperamide is suggested for use in patients with IBS-D. (AGA: Conditional recommendation; very low certainty in evidence)
    - Mixed opioid agonists/antagonists are suggested for treating overall symptoms of IBS-D. (ACG: Conditional recommendation; moderate quality of evidence)
    - Tricyclic antidepressants (TCAs) are suggested for use in patients with IBS. (AGA: Conditional recommendation; low certainty in evidence)
- ESMO (European Society for Medical Oncology) Recommendations for Diarrhea in Adult Cancer Patients:
    - Uncomplicated Diarrhea:
        - Manage conservatively using oral hydration and loperamide (Level V, Grade A).
        - Begin loperamide at 4 mg, then take 2 mg every 4 hours or after each loose stool, with a maximum 16 mg/day (Level V, Grade A).
    - Complicated Diarrhea:
        - Severe diarrhea requires hospitalization and intensive evaluation and treatment (Level V, Grade A).
        - Treatment involves intravenous (i.v.) fluids and starting octreotide at 100–150 mcg s.c. three times a day (tid) or i.v. (25–50 mcg/h) for severely dehydrated patients. Octreotide dose can be increased up to 500 mcg s.c. tid until diarrhea is controlled (Level V, Grade A).

- Treatment Approaches for Diarrhea in the management of Neutropenic Enterocolitis:
    - Oral rehydration therapy (ORT) is suitable for mild diarrhea (Level I, Grade A).
    - Most patients receive isotonic saline or balanced salt solution for IV rehydration, with concurrent potassium replacement if necessary (Level I, Grade A).
    - Loperamide can be initiated at 4 mg, followed by 2 mg every 2-4 hours or after each unformed stool (maximum daily dose is 16 mg) (Level II, Grade B).
    - Somatostatin analogues (octreotide) can be used for severe or persistent diarrhea, starting at a usual dose of 100-150 mcg s.c./i.v. tid and titrating up to 500 mcg s.c./i.v. tid or 25-50 mcg/h by continual i.v. infusion (Level IV, Grade B).
    - Uridine triacetate can be administered in cases of severe diarrhea occurring within 96 hours after completing treatment with 5-FU or capecitabine. The recommended dose for adults is 10 g orally every 6 hours for 20 doses (Level II, Grade A).
    - Budesonide is commonly used to manage diarrhea in patients with low- to medium-grade inflammatory bowel disease (Level IV, Grade C). Prophylactic budesonide is not recommended (Level II, Grade B).
    - Antibiotics should only be used in patients with specific indications (No specific level or grade provided).
    - Bile acid sequestrants' use is limited due to potential gastrointestinal side effects (Level III, Grade B).
- Canadian Association of Gastroenterology Clinical Practice Guidelines on Clostridium difficile Infection in Adults
    - Initial treatment of non-severe CDI:
        - Oral vancomycin 125 mg 4 times daily for 10 days is recommended. (Strong recommendation, low quality of evidence)
        - Oral fidaxomicin 200 mg twice daily for 10 days is recommended. (Strong recommendation, moderate quality of evidence)
        - Oral metronidazole 500 mg 3 times daily for 10 days may be considered in low-risk patients. (Strong recommendation, moderate quality of evidence)

- Initial therapy for severe CDI:
    - Vancomycin 125 mg 4 times a day for 10 days is recommended. (Strong recommendation, low quality of evidence)
    - Fidaxomicin 200 mg twice daily for 10 days can be considered. (Conditional recommendation, very low quality of evidence)
    - Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hours daily for the first 48-72 hours. Combination therapy with parenteral metronidazole 500 mg every 8 hours can be considered. (Conditional recommendation, very low quality of evidence)
    - For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial. (Conditional recommendation, very low quality of evidence)
    - Fecal microbiota transplantation (FMT) should be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, especially when they are poor surgical candidates. (Strong recommendation, low quality of evidence)
    - Tapering/pulsed-dose vancomycin is suggested for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole. (Strong recommendation, very low quality of evidence)
    - Fidaxomicin is recommended for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole. (Strong recommendation, moderate quality of evidence)
- **Prevention of Recurrence:**
- FMT is recommended for patients experiencing their second or further recurrence of CDI to prevent further recurrences. (Strong recommendation, moderate quality of evidence)
- FMT should be delivered through colonoscopy (Strong recommendation, moderate quality of evidence) or capsules (Strong recommendation, moderate quality of evidence) for the treatment of recurrent CDI. Enema delivery can be considered if other methods are unavailable. (Conditional recommendation, low quality of evidence)

    - Repeat FMT is suggested for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT. (Conditional recommendation, very low quality of evidence)
    - For patients with recurrent CDI (rCDI) who are not candidates for FMT, relapsed after FMT, or require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences. (Conditional recommendation, very low quality of evidence)
    - Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence. (Conditional recommendation, low quality of evidence)
    - Bezlotoxumab (BEZ) may be considered for the prevention of CDI recurrence in patients who are at high risk of recurrence. (Conditional recommendation, moderate quality of evidence)
    - Antisecretory therapy should not be discontinued in patients with CDI, provided there is an appropriate indication for their use. (Strong recommendation, very low quality of evidence)
    - **Special Populations:**
    - C. difficile testing is recommended in patients with inflammatory bowel disease (IBD) presenting with an acute flare associated with diarrhea. (Strong recommendation, low quality of evidence)
    - Vancomycin 125 mg p.o. 4 times a day for a minimum of 14 days is suggested for CDI treatment in patients with IBD. (Strong recommendation, very low quality of evidence)
    - FMT should be considered for recurrent CDI in patients with IBD. (Strong recommendation, very low quality of evidence)
- Canadian Association of Gastroenterology Clinical Practice Guidelines on the Management of Bile Acid Diarrhea
    - ***Induction Therapy for BAD (BAST):***
    - For patients with type 1 or type 3 BAD, use treatments for remediable causes (e.g., Crohn's disease, microscopic colitis, SIBO) in addition to treatment for BAD to induce a clinical response. (Conditional recommendation, very-low-certainty evidence)
    - Consider cholestyramine as the initial therapy over other BASTs to induce a clinical response in patients with BAD. (Conditional recommendation, very-low-certainty evidence)

    - Use an alternative BAST if patients with BAD are unable to tolerate cholestyramine for induction of clinical response. (Conditional recommendation, low-certainty evidence)
    - Employ gradual daily dose titration of BAST in patients with BAD to minimize side effects. (Good practice statement)
    - Avoid using BAST in patients with Crohn's disease with extensive ileal involvement or resection. (Conditional recommendation, very-low-certainty evidence)
    - ***Maintenance Therapy for BAD (BAST):***
    - Consider intermittent, on-demand dosing of BAST in patients with BAD who respond to treatment. (Conditional recommendation, very-low-certainty evidence)
    - In patients unable to tolerate BAST for long-term symptomatic therapy, consider using alternative antidiarrheal agents over no treatment. (Conditional recommendation, very-low-certainty evidence)
    - Use the lowest effective dose of BAST in patients with BAD for maintenance therapy to minimize symptoms. (Good practice statement)
    - Conduct diagnostic re-evaluation in patients with BAD and recurrent or worsening symptoms despite stable BAST. (Good practice statement)
    - Review concurrent medications in patients being considered for BAST to minimize potential drug interactions. (Good practice statement)
    - *Statements with No Recommendations:*
    - The use of FGF19 assay to identify possible BAD in patients with chronic diarrhea, including IBS-D and functional diarrhea. (Very-low-certainty evidence)
    - The measurement of fat-soluble vitamin levels at baseline and annually in patients receiving long-term maintenance therapy with BAST. (Very-low-certainty evidence)
- *Guidelines:* American College of Gastroenterology on the Management of Digestive Disorders and Procedures associated with COVID-19
    - **Management of Diarrhea in COVID-19:**
    - COVID-19-associated diarrhea is usually mild or moderate and resolves on its own.
    - Antiviral drug-induced diarrhea typically resolves spontaneously without treatment.

    - Adjust the dosage of antiviral agents for patients experiencing frequent diarrhea (≥4 times/day) or drug intolerance.
    - There is no specific therapy for diarrhea caused by SARS-CoV-2.
    - Dioctahedral montmorillonite and probiotics may provide benefits for COVID-19-associated diarrhea.
    - Certain Lactobacillus probiotics have been effective in relieving animal coronavirus-associated diarrhea.
    - The effectiveness of these probiotics on human coronavirus-associated diarrhea is still uncertain.
    - Probiotic preparations containing Lactobacillus can be considered for clinical trials in patients with COVID-19 diarrhea.
    - Clinicians should be vigilant for antibiotic-associated diarrhea or Clostridium difficile infection (CDI) in critical COVID-19 patients.
    - CDI tests should be performed, and probiotics should be given to prevent or control the occurrence of CDI in severe COVID-19 patients.
- Eastern Association for the Surgery of Trauma on Antimotility agents for **Management of Acute Noninfectious Diarrhea in Critically Ill Patients:**
    - Conditionally recommend administering loperamide to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults.
    - Conditionally recommend administering diphenoxylate/atropine to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults.
    - No specific recommendations can be made regarding the use of an elemental diet to treat diarrhea in critically ill adult patients due to the lack of relevant studies.

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Non-Infectious Symptomatic Treatment of Diarrhea report** and aims to provide recommendations to aid in the management of Diarrhea. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Diarrhea. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Published 2018. Accessed July 17, 2023. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30362-1/fulltext

2. Factors Associated with Diarrhoea Prevalence in Saudi Arabia. Accessed July 17, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437149/#:~:text=The%20Saudi%20climate%20is%20unfavourable,the%20vicinity%20of%20global%20average.

3. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. *American Journal of Gastroenterology*. 2021;116(1):17-44. doi:10.14309/ajg.0000000000001036

4. Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea. *Gastroenterology*. 2022;163(1):137-151. doi:10.1053/j.gastro.2022.04.017

5. Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut*. 2021;70(7):1214-1240. doi:10.1136/gutjnl-2021-324598

6. Bossi P, Antonuzzo A, Cherny NI, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2018;29:iv126-iv142. doi:10.1093/annonc/mdy145

7. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. *American Journal of Gastroenterology*. 2021;116(6):1124-1147. doi:10.14309/ajg.0000000000001278

8. Sadowski DC, Camilleri M, Chey WD, et al. Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea. *Clinical Gastroenterology and Hepatology*. 2020;18(1):24-41.e1. doi:10.1016/j.cgh.2019.08.062

9. Zhang X, Tang C, Tian D, Hou X, Yang Y. Management of Digestive Disorders and Procedures Associated with COVID-19. *American Journal of Gastroenterology*. 2020;115(8):1153-1155. doi:10.14309/ajg.0000000000000728

10. Bugaev N, Bhattacharya B, Chiu WC, et al. Antimotility agents for the treatment of acute noninfectious diarrhea in critically ill patients: A practice management guideline from the Eastern Association for the Surgery of Trauma. In: *Journal of Trauma and Acute Care Surgery*. Vol 87. Lippincott Williams and Wilkins; 2019:915-921. doi:10.1097/TA.0000000000002449

11. *Sodium Bicarbonate*.; 2023.

12. Riddle MS, Dupont HL, Connor BA. ACG clinical guideline: Diagnosis, treatment, and prevention of acute diarrheal infections in adults. *American Journal of Gastroenterology*. 2016;111(5):602-622. doi:10.1038/ajg.2016.126

13. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European society for pediatric gastroenterology, hepatology, and nutrition/european society for pediatric infectious diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: Update 2014. *J Pediatr Gastroenterol Nutr*. 2014;59(1):132-152. doi:10.1097/MPG.0000000000000375

14. Fried M, Kok-Ann S, Singapore G, et al. *World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: A Global Perspective*.

15. Lembo A, Sultan S, Chang L, Heidelbaugh JJ, Smalley W, Verne GN. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea. *Gastroenterology*. 2022;163(1):137-151. doi:10.1053/j.gastro.2022.04.017

16. What is GRADE? BMJ Best Practice. Accessed July 20, 2023. https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/#:~:text=GRADE%20has%20four%20levels%20of,data%20starts%20at%20low%20quality.

17. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Accessed July 20, 2023. https://www.sciencedirect.com/science/article/abs/pii/S0895435614005447

18. Kerwin AJ, Haut ER, Burns JB, et al. The eastern association of the surgery of trauma approach to practice management guideline development using Grading of recommendations, assessment, development, and Evaluation (GRADE) methodology. *Journal of Trauma and Acute Care Surgery*. 2012;73(5 SUPPL.4). doi:10.1097/TA.0b013e31827013e9

19. SFDA Drug List J. SFDA Drug List . Published 2023. Accessed June 20, 2023. https://www.sfda.gov.sa/en/drugs-list

20. Vowst (fecal microbiota spores, live-brpk). Accessed July 25, 2023. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4856-vowst-fecal-microbiota-spores-live-brpk

21. Rebyota (fecal microbiota, live - jslm) suspension. Accessed July 25, 2023. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4824-rebyota-fecal-microbiota-live-jslm-suspension

22. Zinplava (bezlotoxumab). Accessed July 25, 2023. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4511-zinplava-bezlotoxumab

23. Mytesi (crofelemer). Accessed July 25, 2023. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/3861-mytesi-crofelemer

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Non-Infectious Symptomatic Treatment of Diarrhea Scope

Comparison of the 2020 and the 2023 Report

2020	Changes Performed	2023	Rationale
Section 1.0 Non-Infectious Symptomatic Treatment of Diarrhea Clinical Guidelines			
American College of Gastroenterology Guidelines for Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults (2016)	**N/A**		
European Society for Pediatric Gastroenterology, Hepatology, and	**N/A**		

Nutrition/European society for pediatric infectious diseases guidelines Evidence based Guidelines for the management of acute Gastro-enteritis in children in Europe (2014)			
World Gastroenterology Organization Global Guidelines (2013)	**N/A**		
NICE Guidelines for Eluxadoline for Irritable bowel syndrome with diarrhea (2017)		**GUIDELINE WITHDRAWN**	This guideline has been withdrawn since Eluxadoline is no longer marketed for commercial reasons and its marketing authorization has been withdrawn.
World Gastroenterology Organization Guidelines on IBS-Induced diarrhea (2012)	**Updated**	**World Gastroenterology Organization Guidelines on Irritable Bowel Syndrome:** **a Global Perspective (2015)**[14]	• Too outdated to include
American College of Gastroenterology IBS Guidelines (2018)	**Updated**	**ACG Clinical Guideline: Management of Irritable Bowel Syndrome**	• Bile acid sequestrants are not recommended to treat global IBS-D symptoms. (Conditional recommendation; very low quality of evidence)

		(2020)[3]	• Rifaximin is strongly recommended for treating overall symptoms of IBS-D (Strong recommendation, moderate quality of evidence) • Alosetron is conditionally recommended for relieving overall symptoms of IBS-D in women with severe symptoms who have not responded to conventional therapy. (Conditional recommendation; low quality of evidence). • Mixed opioid agonists/antagonists are suggested for treating overall symptoms of IBS-D (Conditional recommendation; moderate quality of evidence). **New Drugs (SFDA-registered):** • Rifaximin **New Drugs (Non-SFDA registered):** • Alosetron
American Gastroenterology Association Guidelines on pharmacological management of IBS: 2014	**Updated**	**AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome with Diarrhea (2022)**[15]	• Eluxadoline is suggested for use in patients with IBS-D. However, caution should be exercised in patients without a gallbladder or those who consume more than 3 alcoholic beverages per day. (Conditional recommendation, moderate certainty in evidence)

			• Rifaximin is suggested for use in patients with IBS-D (Conditional recommendation, moderate certainty in evidence) • For patients with IBS-D who initially respond to rifaximin but experience recurrent symptoms, retreatment with rifaximin is suggested (Conditional recommendation, moderate certainty in evidence) • Alosetron is suggested for use in patients with IBS-D (Conditional recommendation, moderate certainty in evidence) • Loperamide is suggested for use in patients with IBS-D (Conditional recommendation, very low certainty in evidence) • Tricyclic antidepressants (TCAs) are suggested for use in patients with IBS (Conditional recommendation, low certainty in evidence) • Selective serotonin reuptake inhibitors (SSRIs) are not recommended for use in patients with IBS (Conditional recommendation, low certainty in evidence) • Antispasmodics are suggested for use in

			patients with IBS (Conditional recommendation, low certainty in evidence) **<u>New Drugs (SFDA-registered):</u>** • Rifaximin **<u>New Drugs (Non-SFDA registered):</u>** • Alosetron
	Missing	**British Society of Gastroenterology guidelines on the management of irritable bowel syndrome (2021)**[5]	• Loperamide can be effective for treating diarrhea in IBS, but common side effects like abdominal pain, bloating, nausea, and constipation may limit its tolerability. Careful dose adjustment can help manage these side effects (recommendation: strong; quality of evidence: very low). • Eluxadoline, a mixed opioid receptor drug, is considered an effective second-line treatment for IBS with diarrhea in specialized healthcare settings. However, there are contraindications to its use, such as prior sphincter of Oddi problems or cholecystectomy, alcohol dependence, pancreatitis, or severe liver impairment. Limited availability may also restrict its use. (Recommendation: weak,

			quality of evidence: moderate). • 5-Hydroxytryptamine 3 (5-HT3) receptor antagonists are effective second-line drugs for IBS with diarrhea in specialized healthcare settings. Medications like alosetron and ramosetron may not be available in many countries, so titrating ondansetron can be a reasonable alternative. Constipation is a common side effect of this drug class. Overall, 5-HT3 receptor antagonists are likely the most effective treatment option for IBS with diarrhea. (Recommendation: weak, quality of evidence: moderate to high). • Rifaximin, a non-absorbable antibiotic, is a recommended second-line treatment for IBS with diarrhea in specialized healthcare settings. It has been found to be effective, although its impact on abdominal pain is somewhat limited. While rifaximin is approved for this use in the United States, its availability for this specific indication may be limited in other countries. (Recommendation: weak, quality of evidence:

			moderate)
	Missing	**Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines (2018)**[6]	Insert figure 2 Management of ChT-related diarrhea **Approach to uncomplicated diarrhea**: • Manage conservatively using oral hydration and loperamide [V, A]. • For mild to moderate diarrhea, start with dietary changes (remove lactose-containing products and high-osmolar dietary supplements). Keep track of stool frequency and watch for serious symptoms (fever, dizziness upon standing). • Begin loperamide at 4 mg, then take 2 mg every 4 hours or after each loose stool (maximum 16 mg/day) [V, A]. **Approach to complicated diarrhea** (moderate-severe cramping, nausea, vomiting, diminished performance status, fever, sepsis, neutropaenia, bleeding or dehydration) • Severe diarrhea is considered 'complicated,' requiring hospitalization and

			intensive evaluation and treatment [V, A]. • In complicated cases, hospital admission is usually necessary. Treatment involves intravenous (i.v.) fluids, starting octreotide at 100–150 mcg s.c. three times a day (tid) or i.v. (25–50 mcg/h) for severely dehydrated patients. Octreotide dose can be increased up to 500 mcg s.c. tid until diarrhea is controlled, along with administering antibiotics (e.g., fluoroquinolone) [V, A]. • Patients should undergo evaluation with a complete blood count, electrolyte profile, and stool analysis to check for blood, Clostridium difficile, Salmonella, Escherichia coli, Campylobacter, and infectious colitis [V, A]. **Special case—Management of neutropenic enterocolitis:** • Neutropenic enterocolitis is initially treated medically, involving broad-spectrum antibiotics, granulocyte colony-stimulating factors (G-

			CSFs), nasogastric decompression, intravenous (i.v.) fluids, bowel rest, and regular abdominal examinations [V, A]. • The antibiotics administered should cover enteric gram-negative organisms, gram-positive organisms, and anaerobes [V, A]. • Initial antibiotic choices may include piperacillin-tazobactam or imipenem-cilastatin monotherapy, or combination therapy with cefepime or ceftazidime along with metronidazole [V, A]. If bacterial treatment fails, amphotericin should be considered due to the common occurrence of fungemia [V, A]. • Blood transfusions may be necessary as the diarrhea often contains blood [V, A]. • Avoid the use of anticholinergic, antidiarrheal, and opioid agents as they can worsen ileus [V, A]. • The indications and timing for surgical intervention are debated. The mortality rate is high for patients

			who do not respond to medical treatment, and not all patients may be salvageable. However, surgery may be beneficial in select cases to prevent progressive bowel necrosis, perforation, and sepsis. Common indications for surgery include: (i) ongoing gastrointestinal bleeding despite correction of thrombocytopenia and coagulopathy, (ii) evidence of intraperitoneal perforation, (iii) abscess formation, (iv) clinical deterioration despite aggressive measures, (v) radiological exams to rule out other intra-abdominal issues such as bowel obstruction or acute appendicitis [V, A]. • If exploratory surgery is performed, resection of visibly affected bowel is necessary. Complete removal of necrotic tissue, typically through a right hemicolectomy, ileostomy, and mucous fistula, is crucial. Failure to remove the necrotic area in these severely immunocompromised patients often leads to

			fatality [V, A]. • Primary anastomosis is generally not recommended in severely immunocompromised patients due to the increased risk of anastomotic leakage [V, A]. **Treatment approaches for diarrhea** *Fluids and electrolytes* • Oral rehydration therapy (ORT) is suitable for mild diarrhea [I, A]. • For mild cases, diluted fruit juices, flavored soft drinks, saltine crackers, broths, or soups may provide adequate fluid and salt. In more severe cases, standard World Health Organization (WHO) ORSs or commercial ORSs are more appropriate [II, A]. • Rapid fluid resuscitation is not necessary for patients with mild to moderate hypovolemia [I, A]. The fluid administration rate should exceed the rate of fluid losses, which includes urine output, estimated insensible losses (usually 30-50 mL/h), and gastrointestinal losses,

			to prevent worsening of the volume deficit [I, A]. *IV rehydration* • Most patients receive isotonic saline or balanced salt solution, but the choice may vary based on serum sodium, potassium levels, or metabolic acidosis [I, A]. • If a patient has tachycardia and potential sepsis, an initial fluid bolus of 20 mL/kg is recommended [I, A]. • Concurrent potassium replacement is necessary for those with potassium depletion. Fluid replacement continues rapidly until signs of hypovolemia improve (e.g., low blood pressure, low urine output, impaired mental status) [I, A]. • Consider monitoring with a central venous pressure line and urinary catheter to measure urinary output but be cautious of infection and bleeding risks [V, B]. • Aim for adequate central venous pressure and urine output > 0.5 mL/kg/h for fluid balance [I, A].

			• Patients with oliguric acute kidney injury (< 0.5 mL/kg/h) despite adequate volume resuscitation, as indicated by central venous pressure, are at risk of pulmonary edema. Immediate consultation with intensive-care experts or nephrologists is essential [V, B]. Opioids (loperamide): • Loperamide can be initiated at 4 mg, followed by 2 mg every 2-4 hours or after each unformed stool [II, B]. The maximum daily dose is 16 mg. • Other opioids like tincture of opium, morphine, or codeine can be used as antidiarrheal agents [V, C]. • Deodorized tincture of opium is commonly used and recommended as an alternative to loperamide. It contains the equivalent of 10 mg/mL morphine, and the suggested dose is 10-15 drops in water every 3-4 hours [V, C]. • Be cautious not to confuse it with paregoric, a

			camphorated (alcohol-based) tincture. Paregoric is less concentrated and contains the equivalent of 0.4 mg/mL morphine. The recommended dose is 5 mL in water every 3-4 hours [V, C]. Somatostatin analogues (octreotide) • For severe or persistent diarrhea, consider using the somatostatin analogue octreotide along with continuing loperamide for the first 48 hours, starting at a usual dose of 100-150 mg s.c./i.v. tid [IV, B] and titrating up to 500 mg s.c./i.v. tid or 25-50 mg/h by continual i.v. infusion due to its multiple antidiarrheal actions [V, B]. Uridine triacetate (for 5-FU/capecitabine-induced diarrhea) • In cases of severe diarrhea occurring within 96 hours after completing treatment with 5-FU or capecitabine, consider administering uridine triacetate, an orally administered prodrug of uridine, which serves as a specific

			pharmacological antidote to fluoropyrimidines and is a potentially life-saving treatment for overdoses of these agents. The recommended dose for adults is 10 g orally every 6 hours for 20 doses [II, A]. Steroids • Budesonide, an orally administered, topically active steroid with high activity in inflammatory bowel disease (IBD), is commonly used to manage diarrhea in patients with low- to medium-grade IBD, and it has shown efficacy in managing chemotherapy-induced diarrhea that did not respond to loperamide [IV, C]. • Prophylactic budesonide is not recommended [II, B]. Antibiotics • Antibiotics should only be used in patients with specific indications, including fever, hypotension, peritoneal signs, neutropenia, small intestinal bacterial overgrowth, perianal sepsis, or bloody diarrhea, which may

			suggest conditions like neutropenic enterocolitis, Clostridium difficile infection, or other infectious causes (refer to relevant sections). Bile acid sequestrants • Bile acid sequestrants use is limited because they can cause gastrointestinal side effects such as bloating, flatulence, abdominal discomfort, and constipation [III, B]. **Treatment of immunotherapy-induced diarrhea and colitis** • Grade 1 diarrhea is managed with symptomatic treatment, including oral rehydration and antidiarrheal medications like racecadotril or loperamide [III, A]. • Grade 2 Diarrhea: Stop immunotherapy treatment. Add budesonide 9 mg once daily if no bloody diarrhea [V, C]. Use oral corticosteroids (0.5–1 mg/kg/day prednisone equivalent) for diffuse ulceration, bleeding under endoscopic evaluation, or persistent

			symptoms after 3 days with symptomatic treatment and budesonide [III, A]. • Grade 3 and 4 Diarrhea and Colitis: Administer 1–2 mg/kg/day prednisone equivalent via i.v. injections [III, A]. Avoid loperamide and opioids. Consider non-steroidal immunosuppressive medication (e.g., infliximab) if symptoms persist for > 3–5 days or recur after improvement [III, A]. Vedolizumab may be an alternative to infliximab; further studies needed for confirmation [V, C]. Empirical antibiotics for patients with fever or leukocytosis. • Pneumocystosis Antibiotic Prophylaxis: Add oral trimethoprim/ sulfamethoxazole (400 mg once a day) for prolonged immune suppression. • Rare cases may lead to bowel perforation, necessitating colectomy. • Subtotal colectomy is preferred due to extensive colonic lesions and potential postoperative flare-ups.

			• Immunotherapy can be resumed when symptoms disappear, or diarrhea recovers to grade 1.
			• Immunotherapy should be definitively discontinued for grade 4 or recurrent grade 3 diarrhea, or grade 2 that does not resolve after 3 months despite appropriate treatment.
			
			Prevention and treatment of acute RT-induced diarrhea
			
			• Technical RT measures:
			  ○ Utilizing RT techniques like IMRT (intensity-modulated radiotherapy) [IV, B].
			  ○ Implementing physical measures such as the belly board device, bladder distension, and surgical approaches to displace small bowel volume [IV, C].
			• Nutritional status and prophylactic measures:
			  ○ Providing dietary counseling, which includes reducing fatty foods, adopting a lactose-free diet

			for lactose intolerance, and avoiding caffeine, alcohol, and tobacco [III, B]. o Incorporating a high-fiber diet [II, B]. o Administering oral supplements like colesevelam for patients with bile salt malabsorption [IV, B]. o Considering probiotics (Lactobacillus, Bifidobacterium, and cocci) with caution and emphasizing the need for further safety analysis in immunocompromised patients [II, B]. • Treatment approaches: o Managing caloric and fluid intakes [IV, B]. o Using loperamide with an initial dose of 4 mg, followed by 2 mg every 4 hours or after each unformed stool, while ensuring the total daily dose does not

			exceed 16 mg [I, A]. ○ Administering octreotide (100 mcg three times daily) for patients who do not respond to loperamide and have severe toxicity [II, B]. ○ Employing anticholinergic antispasmodic agents to alleviate bowel cramping [IV, B] **Treatment of chronic RT-induced diarrhea** • After completing a 7-day dietary diary, referral to an expert dietician is recommended [IV, C]. • Lifestyle advice, such as smoking cessation, is also important [IV, C]. • Considering referral for psychological support can be beneficial [IV, C]. • Highly caloric nutritional supplements containing essential nutrients like iron, folic acid, vitamin B12, vitamin D, magnesium, calcium, trace elements, and fat-soluble vitamins are recommended [IV, B]. • Colesevelam is

			preferred over colestyramine for the treatment of bile salt malabsorption due to better tolerance [IV, B]. • Broad-spectrum antimicrobial therapy (often empirical) may be required, with some cases necessitating prolonged and cyclical courses [V, C]. • The use of antidiarrheal agents (e.g., loperamide) is beneficial [IV, B]. • Pelvic floor and toileting exercises are suggested if evidence of radiation proctopathy and increased defecation frequency is present [IV, C]. **Diarrhoea in advanced care patients not receiving oncological treatments: practical management:** • Patients must be rehydrated either orally or, when suitable, through parenteral infusion. • Special attention should be provided to patients who are incontinent of stool, as they are at risk of pressure ulcer formation. The use of skin barriers is essential to prevent skin irritation caused by fecal

			material.
			• Cause and Management:
			  ○ Drugs: laxatives, antibiotics, antacids, PPIs, NSAIDs, iron, antidiabetics: adjust medication.
			  ○ Overflow diarrhea (incomplete obstruction or constipation and impacted stools); Enema
			  ○ Resections, fistulae, or manifestations of tumor which reduce absorptive surfaces: Symptomatic therapy with loperamide.
			  ○ Exocrine pancreatic insufficiency; Enzyme therapy
			  ○ Immune: Late effects of immunotherapy GvHD: Immunosuppression
			Role of diet in managing diarrhea:
			• Avoid spices, coffee, and alcohol, as well as consider reducing

			intake of insoluble fiber, as they may exacerbate symptoms [V, C]. • For patients experiencing diarrhea during chemotherapy (ChT), it is recommended to avoid milk and most dairy products, except for yogurt and firm cheeses, to potentially alleviate the intensity and duration of symptoms [V, C]. **New Drugs (SFDA-registered):** • Morphine • Octreotide • Colestyramine • Racecadotril • Prednisone • Infliximab • Vedolizumab **New Drugs (Non-SFDA registered):** • Tincture of opium • Codeine • Paregoric • Uridine triacetate • Budenoside • Colesevelam
	Missing	**ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile**	Prevention • Probiotics are not recommended for the prevention of Clostridium difficile infection (CDI) in

		Infections (2021)[7]	patients being treated with antibiotics (primary prevention) (Conditional recommendation, moderate quality of evidence). • Probiotics are not recommended for the prevention of CDI recurrence (secondary prevention) (Strong recommendation, very low quality of evidence). Diagnosis • CDI testing algorithms should include both a highly sensitive and a highly specific testing modality to help distinguish colonization from active infection (Conditional recommendation, low quality of evidence). Treatment • Initial treatment of non-severe CDI: o Oral vancomycin 125 mg 4 times daily for 10 days is recommended (Strong recommendation, low quality of evidence). o Oral fidaxomicin 200 mg twice daily for 10 days is recommended (Strong

			recommendation, moderate quality of evidence). o Oral metronidazole 500 mg 3 times daily for 10 days may be considered in low-risk patients (Strong recommendation, moderate quality of evidence). • Initial therapy for severe CDI: o Vancomycin 125 mg 4 times a day for 10 days is recommended (Strong recommendation, low quality of evidence). o Fidaxomicin 200 mg twice daily for 10 days can be considered (Conditional recommendation, very low quality of evidence). • Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin

			every 6 hours daily for the first 48-72 hours. Combination therapy with parenteral metronidazole 500 mg every 8 hours can be considered (Conditional recommendation, very low quality of evidence). • For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial (Conditional recommendation, very low quality of evidence). • Fecal microbiota transplantation (FMT) should be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, especially when they are poor surgical candidates (Strong recommendation, low quality of evidence). • Tapering/pulsed-dose vancomycin is suggested for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (Strong recommendation, very low quality of evidence). • Fidaxomicin is

			recommended for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (Strong recommendation, moderate quality of evidence). Prevention of Recurrence • FMT is recommended for patients experiencing their second or further recurrence of CDI to prevent further recurrences (Strong recommendation, moderate quality of evidence). • FMT should be delivered through colonoscopy (Strong recommendation, moderate quality of evidence) or capsules (Strong recommendation, moderate quality of evidence) for the treatment of recurrent CDI. Enema delivery can be considered if other methods are unavailable (Conditional recommendation, low quality of evidence). • Repeat FMT is suggested for patients experiencing a recurrence of CDI within

			8 weeks of an initial FMT (Conditional recommendation, very low quality of evidence). • For patients with recurrent CDI (rCDI) who are not candidates for FMT, relapsed after FMT, or require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences (Conditional recommendation, very low quality of evidence). • Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (Conditional recommendation, low quality of evidence). • Bezlotoxumab (BEZ) may be considered for the prevention of CDI recurrence in patients who are at high risk of recurrence (Conditional recommendation, moderate quality of evidence). • Antisecretory therapy should not be

			discontinued in patients with CDI, provided there is an appropriate indication for their use (Strong recommendation, very low quality of evidence). Special Populations • C. difficile testing is recommended in patients with inflammatory bowel disease (IBD) presenting with an acute flare associated with diarrhea (Strong recommendation, low quality of evidence). • Vancomycin 125 mg p.o. 4 times a day for a minimum of 14 days is suggested for CDI treatment in patients with IBD (Strong recommendation, very low quality of evidence). • FMT should be considered for recurrent CDI in patients with IBD (Strong recommendation, very low quality of evidence). **New Drugs (SFDA-registered):** • Vancomycin (+ enema) • Fidaxomicin
	Missing	**Canadian Association of Gastroenterolog**	Diagnosis of BAD: • Use risk factors (history of terminal ileal

		y Clinical Practice Guideline on the Management of Bile Acid Diarrhea (2020)[8]	resection, cholecystectomy, or radiotherapy) to identify possible BAD in patients with chronic nonbloody diarrhea. (Strong recommendation, very low-certainty evidence). • Do not rely on symptom presentation as the initial assessment to identify possible BAD in patients with chronic nonbloody diarrhea. (Conditional recommendation, very-low-certainty evidence). • Consider SeHCAT testing to identify BAD in patients with chronic diarrhea, including irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea. (Conditional recommendation, very-low-certainty evidence). • Consider SeHCAT testing in patients with small intestinal Crohn's disease without objective evidence of inflammation who have persistent diarrhea. (Conditional recommendation, very-low-certainty evidence). • Consider using a C4 assay to identify possible BAD in patients with chronic diarrhea,

			including IBS-D and functional diarrhea. (Conditional recommendation, very-low-certainty evidence). • Avoid initiating empiric bile acid sequestrants (BAST) without performing SeHCAT testing to diagnose BAD. (Conditional recommendation, very-low-certainty evidence). Induction Therapy for BAD (BAST): • For patients with type 1 or type 3 BAD, use treatments for remediable causes (e.g., Crohn's disease, microscopic colitis, SIBO) in addition to treatment for BAD to induce a clinical response. (Conditional recommendation, very-low-certainty evidence). • Use cholestyramine over no treatment to induce a clinical response in patients with BAD. (Conditional recommendation, very-low-certainty evidence). • Consider cholestyramine as the initial therapy over other BASTs to induce a clinical response in patients with BAD. (Conditional

			recommendation, very-low-certainty evidence). • Use an alternative BAST if patients with BAD are unable to tolerate cholestyramine for induction of clinical response. (Conditional recommendation, low-certainty evidence). • Employ gradual daily dose titration of BAST in patients with BAD to minimize side effects. (Good practice statement). • Avoid using BAST in patients with Crohn's disease with extensive ileal involvement or resection. (Conditional recommendation, very-low-certainty evidence). Maintenance Therapy for BAD (BAST): • Consider intermittent, on-demand dosing of BAST in patients with BAD who respond to treatment. (Conditional recommendation, very-low-certainty evidence). • In patients unable to tolerate BAST for long-term symptomatic therapy, consider using alternative antidiarrheal agents over no treatment. (Conditional recommendation, very-low-certainty evidence).

			• Use the lowest effective dose of BAST in patients with BAD for maintenance therapy to minimize symptoms. (Good practice statement). • Conduct diagnostic re-evaluation in patients with BAD and recurrent or worsening symptoms despite stable BAST. (Good practice statement). • Review concurrent medications in patients being considered for BAST to minimize potential drug interactions. (Good practice statement). Statements with No Recommendations: • No recommendation A. The use of FGF19 assay to identify possible BAD in patients with chronic diarrhea, including IBS-D and functional diarrhea. (Very-low-certainty evidence). • No recommendation B. The measurement of fat-soluble vitamin levels at baseline and annually in patients receiving long-term maintenance therapy with BAST. (Very-low-certainty evidence).

			<u>New Drugs (SFDA-registered):</u> • Colestyramine
	Missing	**Management of Digestive Disorders and Procedures Associated With COVID-19 (2020)**[9]	Management of Diarrhea • COVID-19-associated diarrhea is usually mild or moderate and resolves on its own. • Antiviral drug-induced diarrhea typically resolves spontaneously without treatment. • Adjust the dosage of antiviral agents for patients experiencing frequent diarrhea (≥4 times/day) or drug intolerance. • There is no specific therapy for diarrhea caused by SARS-CoV-2. • Dioctahedral montmorillonite and probiotics may provide benefits for COVID-19-associated diarrhea. • Certain Lactobacillus probiotics have been effective in relieving animal coronavirus-associated diarrhea. • The effectiveness of these probiotics on human coronavirus-associated diarrhea is still uncertain. • Probiotic preparations containing Lactobacillus can be considered for clinical trials in patients

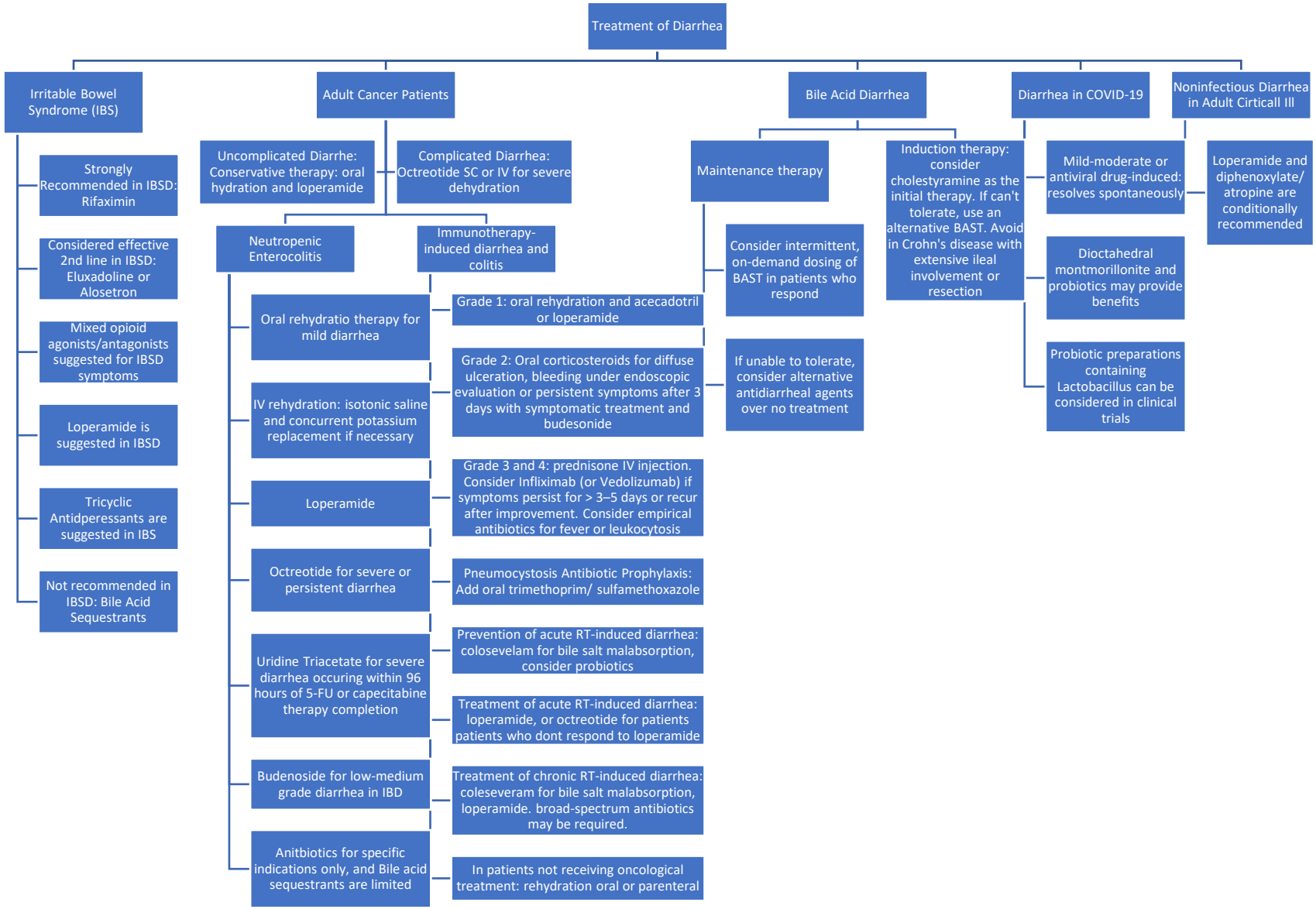
			with COVID-19 diarrhea. • Clinicians should be vigilant for antibiotic-associated diarrhea or Clostridium difficile infection (CDI) in critical COVID-19 patients. • CDI tests should be performed, and probiotics should be given to prevent or control the occurrence of CDI in severe COVID-19 patients
	Missing	**Antimotility agents for the treatment of acute noninfectious diarrhea in critically ill patients: A practice management guideline from the Eastern Association for the Surgery of Trauma (2019)**[10]	• Conditionally recommend administering loperamide to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults. • Conditionally recommend administering diphenoxylate/atropine to improve clinical diarrhea, fecal frequency, and time to diarrhea resolution in critically ill adults. • No specific recommendations can be made regarding the use of an elemental diet to treat diarrhea in critically ill adult patients due to the lack of relevant studies.

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for Diarrhea guideline search:

Query	Filters	Search Details	Results
(Diarrhea[MeSH Terms]) OR (diarrheas[Title/Abstract])	Guideline, in the last 5 years, English	("diarrhea"[MeSH Terms] OR "diarrheas"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]) AND (english[Filter]))	15

Appendix D. Treatment Algorithm 1



Appendix E. Treatment Algorithm 2