Drug induced diarrhea

102.6.9

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>700 drugs have been implicated as causing diarrhea, accounting for approximately 7% of all adverse drug effects

- Adverse effects
  - Pharmacologic effect
  - Allergic reaction
Adverse effects
## Adverse effects

<table>
<thead>
<tr>
<th>症状</th>
<th>通報数</th>
<th>百分比</th>
<th>症状</th>
<th>通報数</th>
<th>百分比</th>
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<tbody>
<tr>
<td>Rash</td>
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<td>Pyrexia</td>
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<td>Pruritus</td>
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<td>7.40</td>
<td>Stevens-Johnson syndrome</td>
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<td>Rash pruritic</td>
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<td>5.78</td>
<td>Urticaria</td>
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<td>Dizziness</td>
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<td>4.36</td>
<td>Vaginal haemorrhage</td>
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<td>Vomiting</td>
<td>428</td>
<td>4.30</td>
<td>Myalgia</td>
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<td>Nausea</td>
<td>333</td>
<td>3.35</td>
<td>Extrapyramidal disorder</td>
<td>131</td>
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<td>Eye swelling</td>
<td>317</td>
<td>3.19</td>
<td>Palpitations</td>
<td>118</td>
<td>1.19</td>
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<td>Dyspnoea</td>
<td>282</td>
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<td>Cough</td>
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<td>Headache</td>
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<td>Oedema peripheral</td>
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<td>Diarrhoea</td>
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<td>2.39</td>
<td>Anaphylactic shock</td>
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Definition

* Individuals
  * Bowel habits
  * Stool characteristics
  * Daily stool output
  * Comorbid conditions

* Frequency > 3 /day
* Consistency
* Stool weight >200 g/day
* Acute
  * Onset <72 hr
  * Duration < 2 week
Diagnosis

Medication history
- Prescription, Non prescription
- Herbal
- Nutritional supplements
- Drug interactions (Additive or Synergistic)
- Eating habits
- Alcohol
- Caffeine

Environmental

Diseases processes

Comorbid complications
8 L of fluids reach the upper small bowel

- 2 L from ingested fluids
- 6 L from salivary, gastric, biliary, pancreatic secretions

Reabsorbed

- Distal small bowel remaining 7 L
- Colon remaining < 200 ml is excreted in the stool
Mechanisms

* Decrease absorption
* Increase secretory
Clinical Classification

* Watery diarrhea
  * Osmotic
  * Secretory
  * Increased motility
* Inflammatory diarrhea
* Fatty diarrhea
Osmotic diarrhea

* Poorly absorbed solute traps fluid in the lumen for osmotic activity of stool water
  * Magnesium containing salts (Antacids, Laxatives)
  * Phosphates (Fleet)
  * Long-chain polyethylene glycols (PEG)
  * Sugar (Lactulose)
  * Alcohols (Mannitol, Sorbitol, Xylitol)
  * Alpha-glucosidase inhibitors (Acarbose, Miglitol)
  * Enteral nutrition
Inhibition of Na\(^+\) absorption

Stimulation of Cl\(^-\)/HCO\(_3\)^- secretion

- Antiarrhythmics (Quinidine, Digoxin)
- Antibiotics
- Chemotherapeutic agents
- Phosphodiesterase inhibitors (Theophylline, Caffeine)
- Biguanides (Metformin)
- Calcitonin
- Colchicine
- NSAIDs
- Misoprostol
- Bile acid
- Ricinoleic acid (Castor oil)
- Stimulant laxatives (Anthraquinones, Diphenylmethane)
- Ticlopidine
Prokinetic agents reduce intestinal contact time between luminal fluid and the epithelium

- Cholinergic drugs (Bethanecol)
- Acetylcholinesterase inhibitors
  - Donepezil, Galantamine, Rivastigmine, Neostigmine, Irinotecan
- SSRIs (Paroxetine, Sertraline)
- Levothyroxine
- Macrolides (Erythromycin)
- Antiemetics (Metoclopramide, Domeperidone, Mosapride)
- Stimulant laxatives
  - Anthraquinones, Diphenylmethane, Ricinoleic acid (Castor oil)
Inflammatory diarrhea

- Damage of mucosa which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids
  - Antibiotics
  - NSAIDs
  - Immunosuppressive agents
  - Chemotherapeutic agents
Fatty diarrhea

* Presence of excess fat in feces
  * Highly active antiretroviral therapy (HAART)
  * Lipase inhibitor (Orlistat)
  * Artificial fats (Olestra)
  * Cholestyramine (24–30 g per day)
  * Ezetimibe
  * Octreotide
Diet in general is not generally thought of as drugs; however, it is clear that they can have a profound effect on intestinal function and therefore should be considered in the evaluation of any diarrhea:

- Caffeine, Theophylline
- Olestra
- Lactose, Fructose
- Sorbitol, Mannitol
- Prebiotics: Oligosaccharides
Sucrose joined at esters to 6 ~ 8 fatty acids
* Fat-reducing drug in 1975
* Used in foods as an artificial fat
* Lipid that possesses properties of conventional fats and oils, but is neither digested nor absorbed
* Modest stool softening
* Inhibits absorption of fat-soluble vitamins (A, D, E, K) and other fat-soluble nutrients
Orlistat (Xenical®)

- Gastrointestinal lipase inhibitor
- Treat Obesity
- If taken with a diet high in fat (>30% total daily calories from fat), gastrointestinal adverse events may increase
- Inhibits absorption of fat-soluble vitamins (A, D, E, K) and other fat-soluble nutrients
- Severe liver injury (rarely)
* Major substrate for bacterial growth, selectively stimulating the growth
* Oligosaccharides
  * Fructo-oligosaccharides (FOS), Inulin
* Gut microorganisms ferment prebiotics to produce short-chain fatty acids
* > 30 g/day
  * Caused gastrointestinal discomfort (flatulence, cramping, diarrhea) through fermentation in the colon and production of an osmotic effect in the intestinal lumen
Laxatives

- Magnesium-containing salts
- Sodium phosphates
- Long-chain polyethylene glycols
- Lactulose
- Stimulant laxatives
  - Anthraquinones (Sennoside)
  - Diphenylmethane derivatives (Bisacodyl)
  - Ricinoleic acid (Castor oil)
  - Sodium dioctyl sulfosuccinate (Docusate)
Lactulose

- Non-absorbable disaccharide that causes an osmotic diarrhea
- Dose-dependent diarrhea
- Metabolized by bacterial flora to short chain fatty acids
  - Lactic acid, Acetic acid
- Hepatic encephalopathy
  - Reduce blood ammonia

Galactose linked by β-1,4-linkage to Fructose
**Cholinergic drugs**

- **Muscarinic acetylcholine receptor**
  - Smooth muscle (M2 and M3)
  - Gastrointestinal and pancreatic secretion (M3)
- **Cholinergic (Bethanecol)**
- **Acetylcholinesterase inhibitors**
  - Neostigmine, Physostigmine
  - Nicotine
  - Irinotecan
  - Alzheimer’s dementia (donepezil, galantamine, and rivastigmine) the odds ratio comparison to placebo 1.91 (95% CI [1.59–2.30])

**GI medications**

* Mesalamine compounds  
  * Stimulation of bicarbonate and NaCl secretion in the ileum
* Prostaglandin analogues  
  * Misoprostol stimulates epithelial Cl\(^{-}\) secretion
* Prokinetic agents  
  * Reduce intestinal contact time  
  * 5-HT\(_4\)-receptor agonists
* Cholestyramine
* Bile acid  
  * Chenodeoxycholic acid
* Octreotide  
  * Inhibition of biliary and pancreatic function through decreased bicarbonate and lipase secretion
**Diabetes medications**

* **Biguanide**
  * Reducing disaccharidase activity and leading to malabsorptive diarrhea
  * Metformin are 3.4 times more likely to develop diarrhea compared to placebo ($p = 0.002$)

* **Alpha-glucosidase inhibitors**
  * Acarbose, Miglitol
  * Acarbose, tolbutamide + acarbose to placebo, 27% of patients taking acarbose and 35% taking acarbose + tolbutamide diarrhea in comparison to 6% of patients taking placebo or tolbutamide ($p < 0.05$)
Calcitonin
- Increase in jejunal secretion of water, sodium, chloride, and potassium, and reduced absorption of bicarbonate, which was reversed immediately with discontinuation of the infusion

Levothyroxine
- Accelerate small and large intestinal transit, causing diarrhea, may be a secondary effect of increased motility
Antibiotics

- Antibiotic associated diarrhea (AAD)
  - 25% of drug-induced diarrhea
- Drug factors
  - With large spectrum
  - Duration
  - Combination
  - High biliary excretion
- Imbalance normal colonic flora
- Stimulation of motilin receptor
- Impaired fermentation of carbohydrates
- Decrease production of short chain fatty acids
- Decrease digestion of bile salts
Two types of AAD

* Osmotic diarrhea
  - Antibiotics alter colonic microflora
  - Carbohydrate digestion in colon reduced
  - Increased osmotic load in colon lumen
  - Osmotic diarrhea

* Clostridium difficile
  - Antibiotics alter colonic microflora
  - Colonization by *C. difficile*
  - Release of toxins
  - Colitis and diarrhea
* Anaerobic, G (+), spore-forming bacillus
* Any and all antibiotics
  * Clindamycin, amoxicillin, ampicillin, cephalosporins
  * Fluoroquinolones – highest risk for NAP1 strain
* Toxin producing – A & B
  * Bind to colonic brush border, causing mucosal PMN infiltration, colonic secretion and shedding and necrosis, resulting in colitis and diarrhea
* Pseudomembranous colitis
* Fecal-oral route of transmission
*Clostridium difficile*

- Spores
- Vegetative cells

Most vegetative cells are killed in the stomach, but spores can survive the acid environment.

*C. difficile* multiplies in the colon.

*C. difficile* spores germinate in the small bowel upon exposure to bile acids.

Flagellae facilitate *C. difficile* movement; a polysaccharide capsule discourages phagocytosis.

Gut mucosa facilitates adherence to the colonic epithelium.

http://www.humenhealth.com/clostridium-difficile-infection
C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2), opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhea.
<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
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<tbody>
<tr>
<td>Mild or moderate</td>
<td>WBC ≤ 15,000 cells/mcL</td>
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<tr>
<td></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>Scr ≤ 1.5 x above baseline</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC ≥ 15,000 cells/mcL</td>
</tr>
<tr>
<td></td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td></td>
<td>Scr &gt; 1.5 x above baseline</td>
</tr>
<tr>
<td>Complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
</tr>
</tbody>
</table>

Cohen SH et al. IDSA Guidelines 2010
Pseudomembranous colitis

* Cessation of the inciting antibiotic as soon as possible
  * Alternative: Aminoglycosides, Sulfonamides, Macrolides, Vancomycin, Tetracycline
* Hand hygiene with soap and water
* Antimotility agents
  * Loperamide
* Supportive care
  * Correction of fluid losses
  * Electrolyte imbalance
* Antibiotic for 10~14 days
  * Metronidazole: po or IV 250 mg Q6H/ 500 mg Q8H
  * Vancomycin: 125 mg Q6H po/ 500 mg Q6H enema
  * Fldaxomicin: 200 mg Q12H po
* Probiotics: Inconclusive
<table>
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<th>Cure rates</th>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>98%</td>
<td>90%</td>
<td>ns</td>
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<tr>
<td>Severe</td>
<td>97%</td>
<td>76%</td>
<td>0.02</td>
</tr>
<tr>
<td>Recurrent</td>
<td>7%</td>
<td>14%</td>
<td>ns</td>
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### Infectious Diseases Society of America (IDSA) Guidelines

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Recommended Treatment</th>
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<tr>
<td>Mild or moderate</td>
<td>Metronidazole 500 mg PO Q8h x 10-14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Vancomycin 125 mg PO Q6h x 10-14 days</td>
</tr>
<tr>
<td>Complicated</td>
<td>Vancomycin 500 mg PO Q6h PLUS Metronidazole 500 mg IV Q8h +/- Vancomycin 500 mg enema for ileus</td>
</tr>
<tr>
<td>First recurrence</td>
<td>Same as for initial episode</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Vancomycin taper or pulsed regimen</td>
</tr>
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</table>

Cohen SH et al. IDSA guidelines 2010
Fidaxomicin

- Macrolide antibiotic
  - FDA approved for CDAD in May 2011
  - Kills *C. difficile* (bactericidal)
  - Post-antibiotic effect
- Dose: 200 mg PO BID x 10 days
- Pharmacokinetics: poor absorption in gut
- Non-inferior to oral vancomycin
  - Lower rate of recurrence of non-NAP1 strain
  - Less effect on normal colonic flora
- Adverse effects: Nausea, vomiting
- Minimal drug interactions

Louie TJ et al. NEJM 2011
Probiotics

* World Health Organization
  * Live microorganisms which when administered in adequate amounts confer a health benefit on the host
  * Survive stomach acid and bile
  * Establish residence in the intestines
  * Impart health benefits
Probiotics

- **Lactobacillus sp.**
  - *reuteri*
  - *casei*
  - *ramnosus*
  - *acidophilus*
- **Streptococcus sp.**
- **Bifidobacterium sp.**
  - *Infantis (breastmilk)*
  - *lactis*
  - *longum*
  - *breve*
  - *bifidum*
- **Sacharomyces boulardii**
- **Enterococcus sp.**
Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea
A Systematic Review and Meta-analysis

Susanne Hempel, PhD
Sydne J. Newberry, PhD
Alicia R. Maher, MD
Zhen Wang, PhD
Jeremy N. V. Miles, PhD
Roberta Shanman, MS
Breanne Johnsen, BS
Paul G. Shekelle, MD, PhD

The use of antibiotics that disturb the gastrointestinal flora is associated with clinical symptoms such as diarrhea, which occurs in as many as 30% of patients. Symptoms range from mild and self-limiting to severe, particularly in Clostridium difficile infections, and antibiotic-associated diarrhea (AAD) is an important reason for nonadherence with antibiotic treatment.

Probiotics are microorganisms intended to have a health benefit when consumed. Synbiotics refer to preparations in which probiotic organisms and prebiotics (nondigestible food ingredients that may benefit the host by selectively stimulating bacteria in the colon) are combined.

Potentially, probiotics maintain or re-

Context Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

Objective To evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea (AAD).

Data Sources Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA) and references of included studies and reviews were screened from database inception to February 2012, without language restriction.

Study Selection Two independent reviewers identified parallel randomized controlled trials (RCTs) of probiotics (Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and/or Baci-

Data Extraction Two independent reviewers extracted the data and assessed trial quality.

Results A total of 82 RCTs met inclusion criteria. The majority used Lactobacillus-based interventions alone or in combination with other genera; strains were poorly documented. The pooled relative risk in a DerSimonian-Laird random-effects meta-

Conclusions The pooled evidence suggests that probiotics are associated with a reduction in AAD. More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics.

Chemotherapy

- Cytotoxic effects leading to intestinal mucosa
- Fluoropyrimidines (5-FU, Capecitabine, Tegafur)
- Irinotecan
  - Early: cholinergic effect
  - Late: SN-38
- Bortezomib
- Tyrosine kinase inhibitors
  - EGFR
  - VEGFR
## Grade Description

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<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>1</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>3</td>
<td>Increase of &gt;=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
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</table>
**EVALUATE**
- Obtain history of onset and duration of diarrhea
- Describe number of stools and stool composition (e.g., watery, blood in stool, nocturnal)
- Assess patient for fever, dizziness, abdominal pain/cramping, or weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Medications profile (i.e., to identify diarrheogenic agents)
- Dietary profile (i.e., to identify diarrhea-enhancing foods)

**UNCOMPPLICATED**
CTC grade 1-2 diarrhea with no complicating signs or symptoms

**COMPLICATED**
CTC grade 3 or 4 diarrhea or grade 1 or 2 with one or more of the following signs or symptoms
- Cramping
- Nausea/vomiting (= grade 2)
- Fever
- Sepsis
- Neutropenia
- Frank bleeding
- Dehydration

**ADDED RISK FACTORS**

**MANAGEMENT**
- Stop all lactose-containing products, alcohol, and high-osmolar supplements
- Drink 8 - 10 large glasses of clear liquids a day (e.g., Gatorade or broth)
- Eat frequent small meals (e.g., bananas, rice, applesauce, toast, plain pasta)
- Instruct patient to record the number of stools and report symptoms of life-threatening sequelae (e.g., fever or dizziness upon standing)
- For grade 2 diarrhea, hold cytotoxic chemotherapy until symptoms resolve and consider dose reduction

**TREATMENT**
- Administer standard dose of loperamide: initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool
- Consider clinical trial

**Diarrhea resolving**
- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hour diarrhea-free interval
- RT-induced: Continue loperamide

**Diarrhea unresolved**
- Persistent diarrhea (NCI grades 1 - 2)
  - Administer loperamide 2 mg every 2 hours
  - Start oral antibiotics
  - Observe patient for response
  - RT-induced: Oral antibiotics not generally recommended

**Diarrhea resolved**
- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hour diarrhea-free interval
- RT-induced: Continue loperamide

**Persistent diarrhea (NCI grades 1 - 2)**
- Check blood workup (blood, fecal leukocytes, Clostridium difficile, Salmonella, Escherichia coli, Campylobacter, infectious colitis)
- Check CBC and electrolytes
- Perform abdominal exam
- Replace fluids and electrolytes as appropriate
- Discontinue loperamide and begin second-line agent
  - Octreotide (100 to 150 µg SC TID with dose escalation up to 500 µg TID)
  - Other second-line agent (e.g., tincture of opium)
- RT-induced: Continue loperamide or other oral agent; no workup required

**Progression to severe diarrhea**
(NCI grades 3 - 4 with or without fever, dehydration, neutropenia, and/or blood in stool)

**ADMIT TO HOSPITAL**
- Administer octreotide (100 to 150 µg SC TID or IV 25-50 µg/hr)
- Start intravenous fluids and antibiotics as needed (e.g., fluoroquinolone)
- Stool work-up, CBC, and electrolyte profile
- Discontinue cytotoxic chemotherapy until all symptoms resolve; restart chemotherapy at reduced dose
50% of AIDS patients have diarrhea during the course of illness

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-NRTI
- Protease inhibitors
- Steatorrhea
- **Digoxin**
  - Inhibition of intestinal or colonic Na\(^+\) pumps, most frequently at supertherapeutic drug levels, especially in elderly patients

- **Quinidine and propafenone**
  - Impede transepithelial Na\(^+\) and water absorption
Colchicine

- Inhibition of Na\(^+\), K\(^+\)-ATPase activity
- Microtubule inhibitor
- Inhibits neutrophil motility and activity, leading to a net anti-inflammatory effect
- Induce diarrhea by interfering with the migration of epithelial cells from the crypt to the villus causing villous atrophy
Prevention

* Adjust dosage
  * Age, weight, renal/hepatic function
* Avoid foods with artificial sweeteners
  * Sorbitol, Mannitol, Fructose
* Identify liquid medications with high sorbitol content
* Rational antibiotics
* Drug intolerance or allergy history
* Probiotic therapy
* Low residual diet, low fat meal(with orlistat)
* Eat frequent, small meals
* Alternative medications with a low risk of diarrhea
Management

* Identification of the offending agents
  * Medication history
  * DC or change
* Preventive measures
* Rehydration (Electrolyte)
  * Mild 50 ml/kg
  * Moderate 75 ml/kg
  * Severe 100 ml/kg
* Antidiarrheal drugs
  * Antimotility (Loperamide)
  * Absorbents (Pectin, Al(OH)₃)
  * Adsorbents (Koalin)
Opioids
- Meperidine derivative
- μ opioid receptor agonist
- Intestinal: motility, absorption
- CNS
- 40-50 times more potent than morphine
- T½ 11 hours
- Not recommended in children <2 years
- Overdose: CNS depression, paralytic ileus, toxic megacolon
**Conclusion**

- A detailed history is important to identify the offending agent in drug induced diarrhea.

- Drug induced diarrhea can be self-limited despite continuous usage, can resolve with removal of the offending medication, or can be controlled with antidiarrheal therapies.

- Increased monitoring, better infection control (gloves, isolation, hand-washing) and more antibiotic restraint.