Drug induced diarrhea

102.6.9

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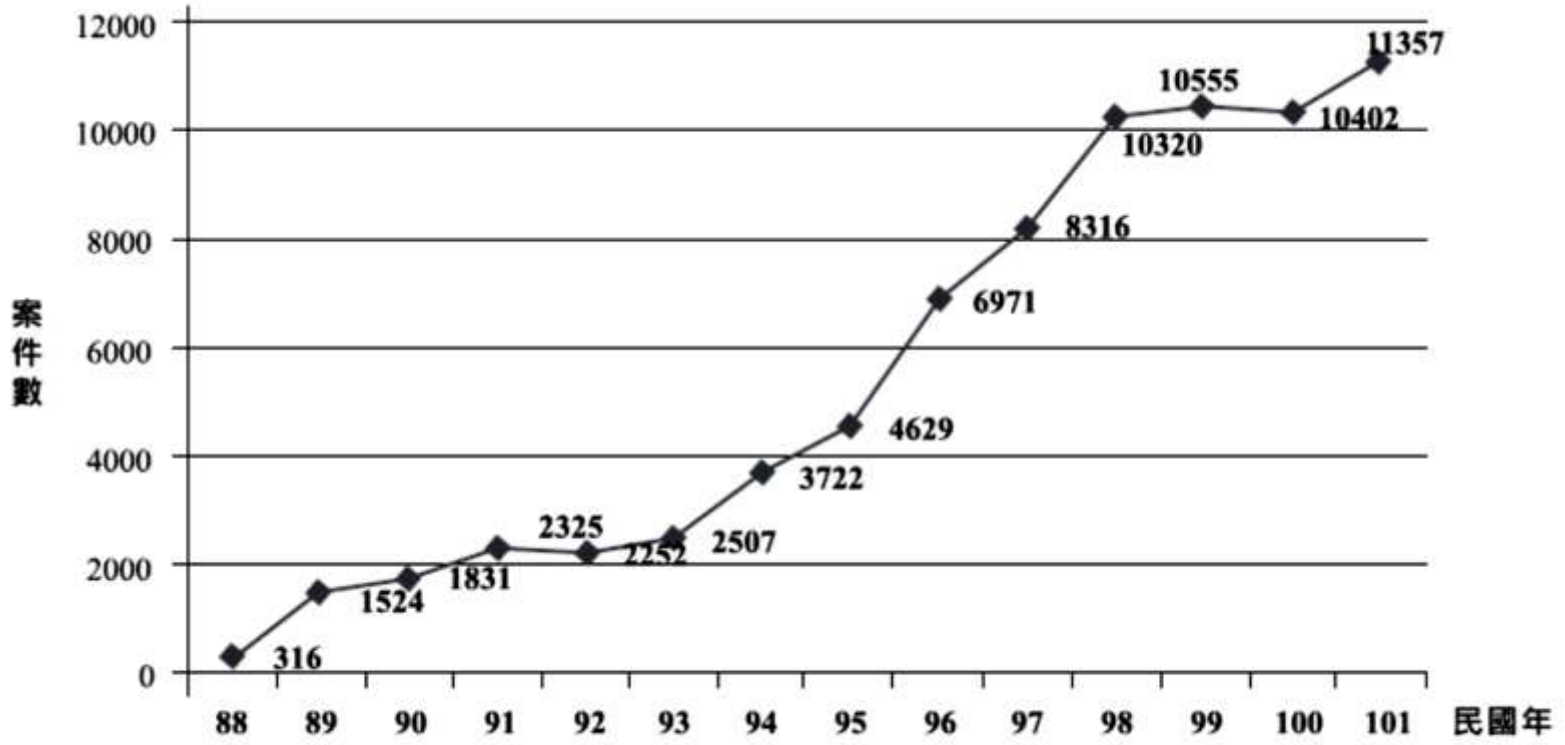
Introduction

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

* Adverse effects
  * Pharmacologic effect
  * Allergic reaction

Drug Saf 2000;22:53–72.

Adverse effects



圖一　歷年藥品不良反應通報案件數

Drug Safety Newsletter 2013 March vol. 41

Adverse effects

通報症狀	通報數	百分比	通報症狀	通報數	百分比
Rash	2127	21.38	Pyrexia	210	2.11
Pruritus	736	7.40	Stevens-Johnson syndrome	209	2.10
Rash pruritic	575	5.78	Urticaria	176	1.77
Dizziness	434	4.36	Vaginal haemorrhage	141	1.42
Vomiting	428	4.30	Myalgia	134	1.35
Nausea	333	3.35	Extrapyramidal disorder	131	1.32
Eye swelling	317	3.19	Palpitations	118	1.19
Dyspnoea	282	2.84	Cough	117	1.18
Headache	254	2.55	Oedema peripheral	110	1.11
Diarrhoea	238	2.39	Anaphylactic shock	105	1.06
			小計	7175	72.13
			總計	9947	100.00

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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

Normal Physiology

* 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

Secretory Diarrhea

* 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

Disordered or deregulation motility

* 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)

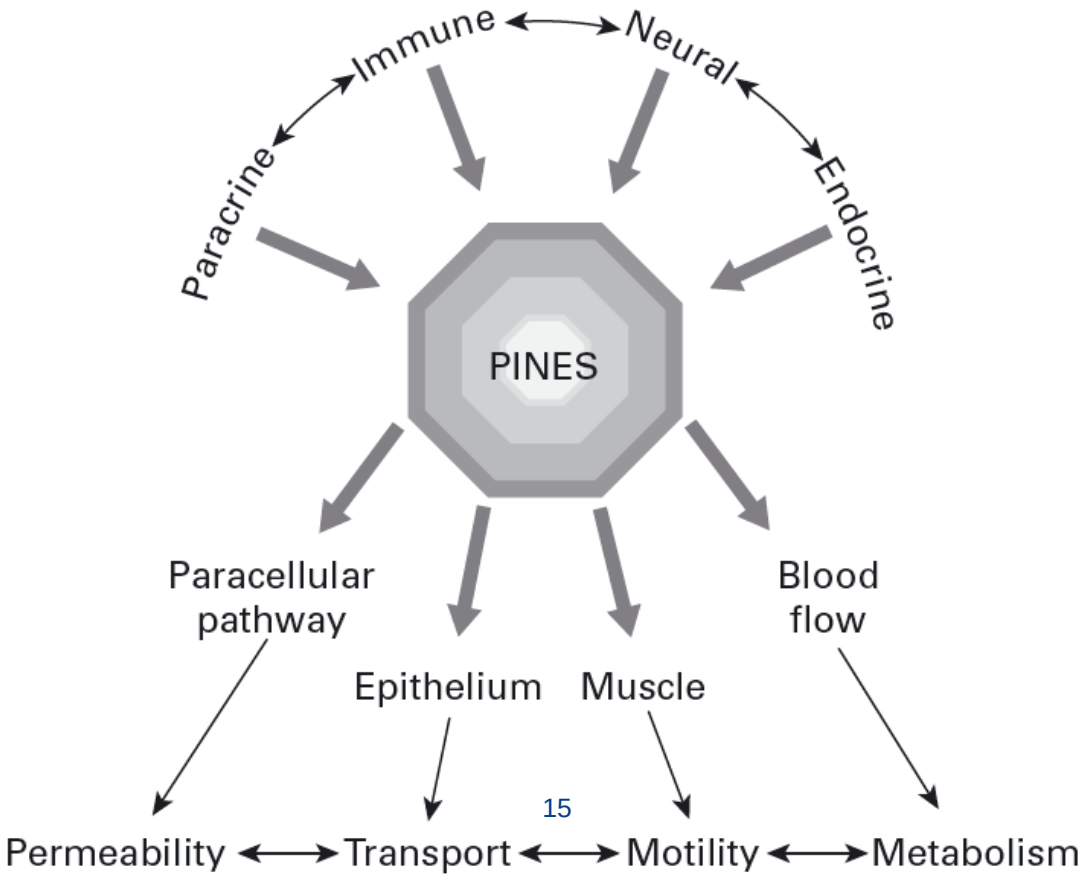
Inflammatory diarrhea

* 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

Complex diarrheas

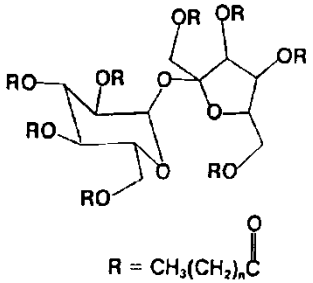


Diet

* 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

Olestra (Olean)

* 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)

Prebiotics

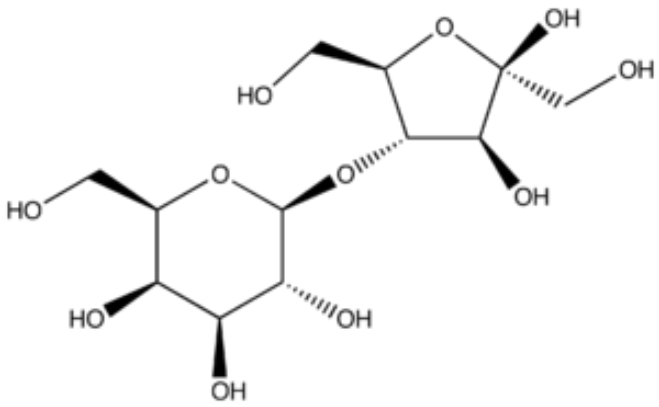
- Major substrate for bacterial growth, selectively stimulating the growth
- Oligosaccharides
  - Fructo-oligosaccharides (FOS), Inulin
- Gut microorganisms ferment prebiotics to produce short-chain fatty acids
- > 30 g/day
  - Caused gastrointestinal discomfort (flatulence, cramping, diarrhea) through 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 ß-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])

Cochrane Database Syst Rev. 2006; Issue 1. Art. No.: CD005593.

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 ($p < 0.05$)

Cochrane Database Syst Rev 2005; 3. Art. No.: CD002966.
Am J Med 1995;98:443–451.

Endocrine medicines

* 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*

↓

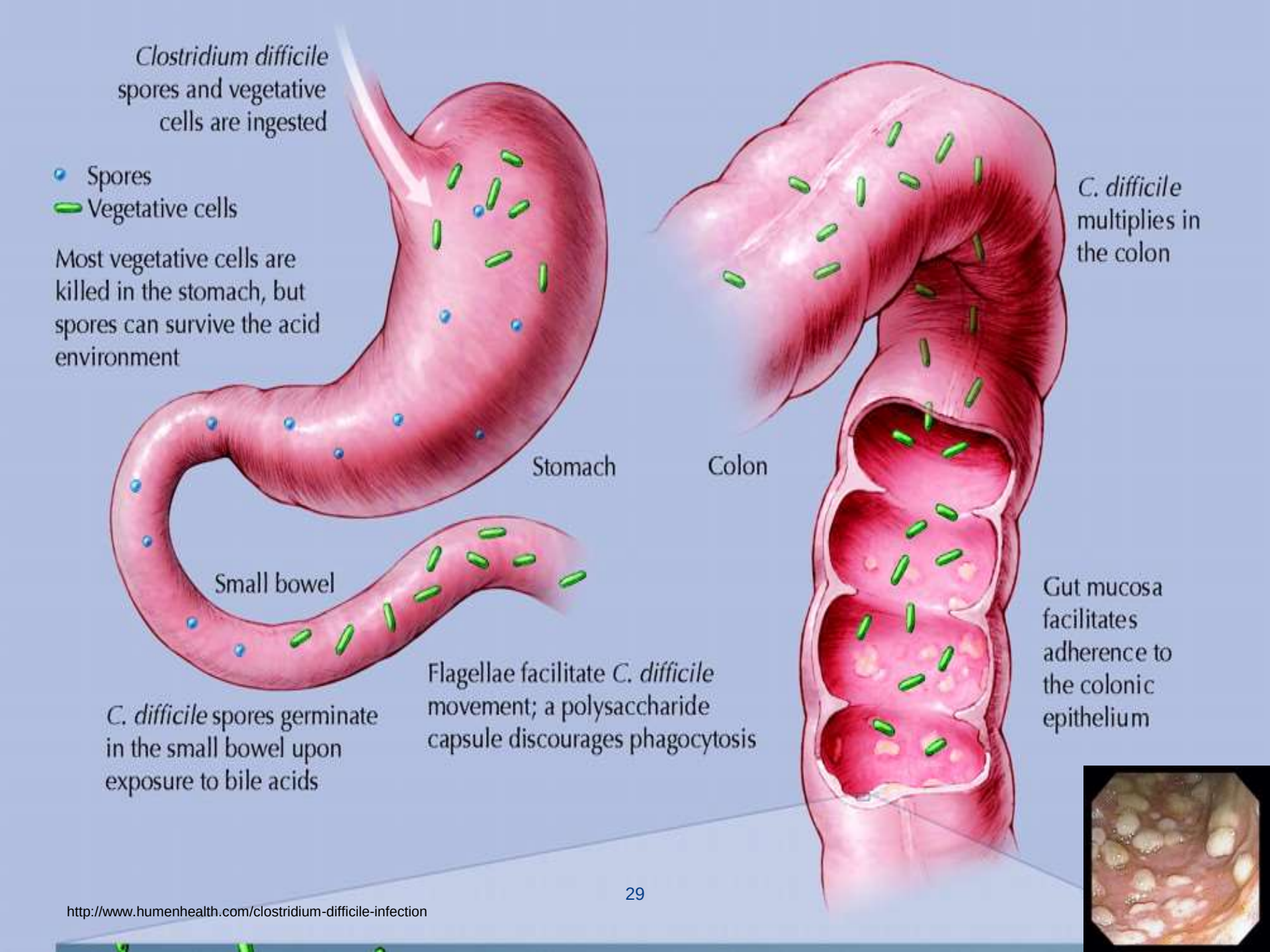
Release of toxins

↓

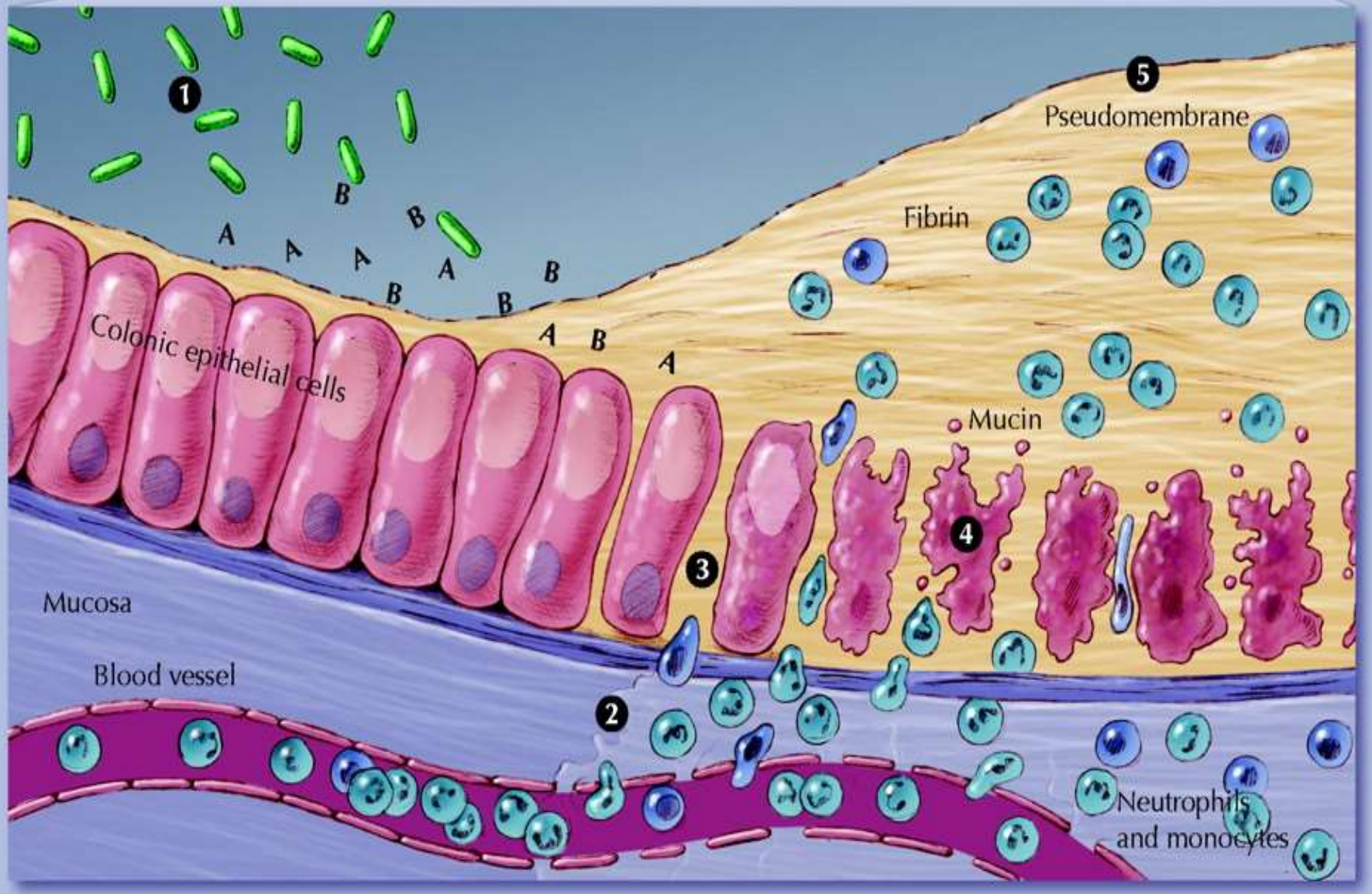
Colitis and diarrhea

Clostridium difficile

* 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



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.

Disease Severity

Clinical Definition	Supportive Clinical Data
Mild or moderate	WBC ≤ 15,000 cells/mcL OR Scr ≤ 1.5 x above baseline
Severe	WBC ≥ 15,000 cells/mcL OR Scr > 1.5 x above baseline
Complicated	Hypotension or shock, ileus, megacolon

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

Vancomycin >> Metronidazole?

* Flagyl 250 QID vs Vanco 125 QID x 10d

Cure rates	Vancomycin	Metronidazole	
Mild :	98%	90%	ns
Severe :	97%	76%	0.02
Recurrent :	7%	14%	ns

Zar FA et al. Clin Infect Dis 2007;45:302

Infectious Diseases Society of America (IDSA) Guidelines

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

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

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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 *Bacillus*) for the prevention or treatment of AAD.

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-analysis of 63 RCTs, which included 11 811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68; $P<.001$; I^2, 54%; [risk difference, −0.07; 95% CI, −0.10 to −0.05], [number needed to treat, 13; 95% CI, 10.3 to 19.1]) in trials reporting on the number of patients with AAD. This result was relatively insensitive to numerous subgroup analyses. However, there exists significant heterogeneity in pooled results and the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

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.

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.[1,2] 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.[3]

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-

JAMA. 2012;307(18):1959-1969

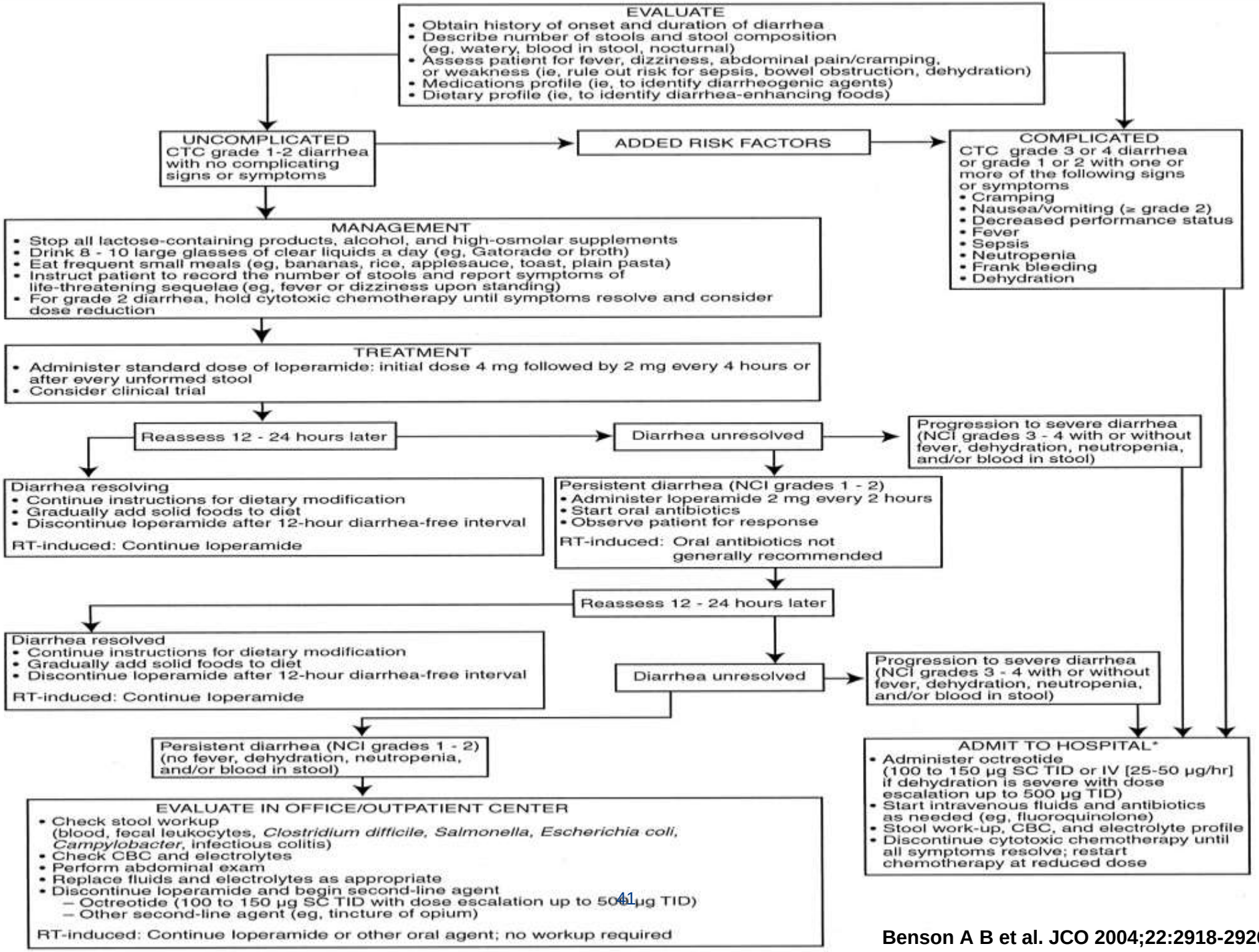
Chemotherapy

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

National cancer institute criteria

Grade	Description
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death

Common Terminology Criteria for Adverse Events (CTCAE) v4.03: June 14, 2010



Benson A B et al. JCO 2004;22:2918-2926

HIV medications

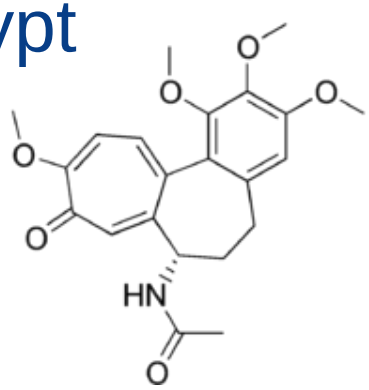
* 50 % of AIDS patients have diarrhea during the course of illness
* Nucleoside reverse transcriptase inhibitors (NRTI)
* Non-NRTI
* Protease inhibitors
* Steatorrhea

Cardiac medications

* 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

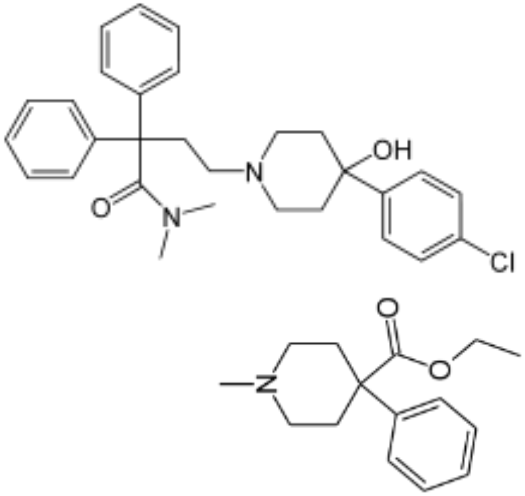
* Adjust dosage
  * Age, weight, renal/hepatic function
* Avoid foods with artificial sweeteners
  * Sorbitol, Mannitol, Fructose
* Identify liquid medications with high sorbitol content
* Rational antibiotics
* Drug intolerance or allergy history
* Probiotic therapy
* Low residual diet, low fat meal(with 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)

Loperamide

* Opioids
  * Meperidine derivative
* μ opioid receptor agonist
  * Intestinal: motility, absorption
  * CNS
* 40-50 times more potent than morphine
* T ½ 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