

# Guidance on the management of diarrhoea during chemotherapy

*Jelena Dimitrijević*

*Institute for Oncology and Radiology of Serbia*

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- ↑stool losses ↔ individual bowel elimination pattern(baseline)
- Common in cancer patients
- 50-80%
- Chemotherapy
- Targeted therapies
- Radiation (pelvic)

# Clinical factors predictive for CID

- Increasing age (> 65)
- Gender (female)
- BMI
- Performans status
- GI tumors
- Biliary obstruction
- Other bowel diseases (IBD)
- Previous or concomitant radiation
- Genetic polymorphisms

	<b>Regimen</b>	<b>Proportion with grade 3-4 diarrhoea (%)</b>
Saltz et al,2001	Irinotecan	6%
	Irinotecan with infused fluorouracil or folinic acid	15 %
O'Saughnessy et al, 2002	Docetaxel	5%
	Docetaxel with capecitabine	14%
Chau et al, 2005	Bolus fluorouracil with folinic acid	16%
	Infused fluorouracil	5%
Falcone et al, 2007	FOLFOXIRI	20%
	FOLFIRI	12%
Fuchs et al, 2007	FOLFIRI	14%
	mIFL	19%
	capeIRI	47%
Van Cutsern et al, 2011	FOLFIRI	11%
	FOLFIRI with cetuximab	16%
Tweit et al, 2012	FLOX	10%
	FLOX with cetuximab	17%
FOLFOXIRI-oxaliplatin, irinotecan, fluorouracil and folinic acid (leucovorin). FOLFIRI-irinotecan, fluorouracil and folinic acid (leucovorin). mIFL-irinotecan wuth bolus fluorouracil. capeIRI- capecitabine and irinotecan. FLOX-folinic acid (leucovorin), oxaliptain and bolus fluorouracil		

**Randomised trial data of the frequency of grade 3-4 diarrhoea with different chemotherapy regimens**

# 5-FU induced diarrhoea

- Mitotic arrest in epithelial crypt cells
- Dose dependent
- Bolus regimens
- Leucovorin ↑ risk
- DPYD (homozygous mutations)
- Thymidilate synthase, methylen tetrahydrofolate reductase
- Capecitabine (prodrug)
- Cytidine deaminase

# Irinotecan induced diarrhoea

## ❖ Acute onset:

- up to 24 h
- inhibition of acetylcholine esterase
- ↑ cholinergic effect

## ❖ Delayed onset:

- deconjugation of SN38-G by GI bacteria
- mucosal damage
- Gilbert Sy (↓ glucuronidation)

# Targeted therapies

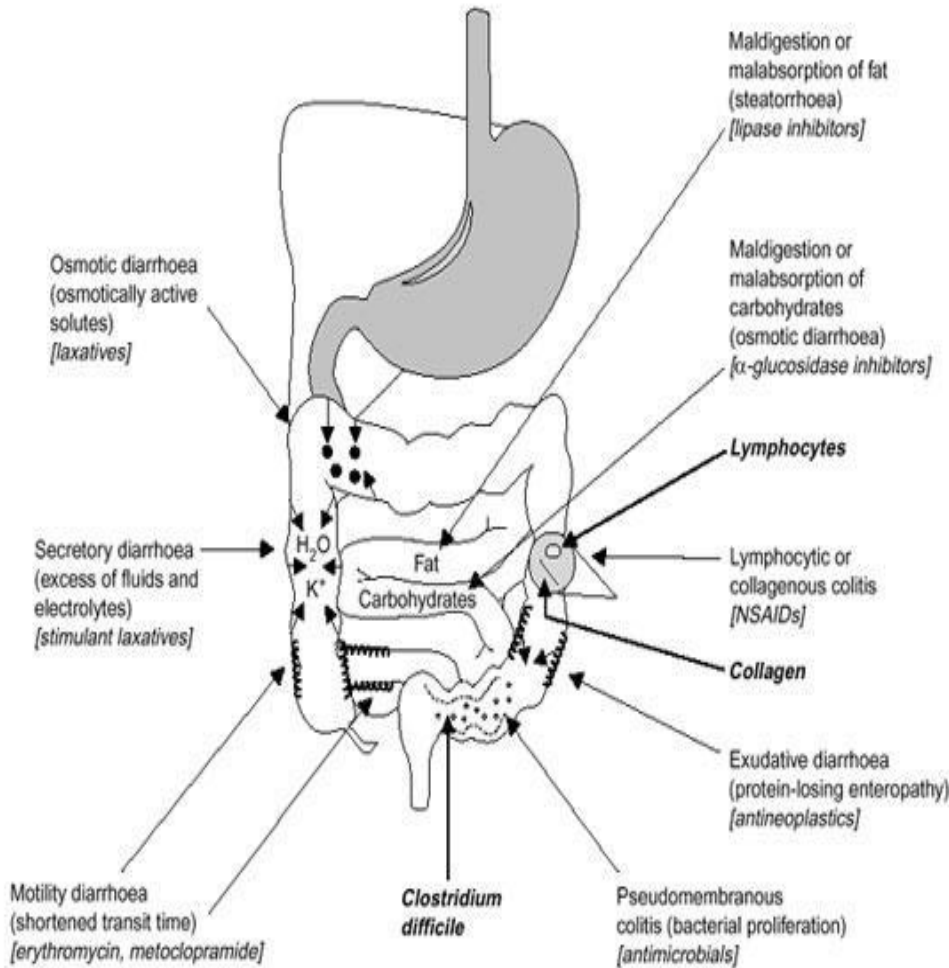
## ❖ Thyrosine-kinase inhibitors

- most common AE (50%)
- dose dependant
- ↑ chloride secretion

## ❖ Small molecule antibodies

- ipilimumab
- T-cell immune response → anti CTLA 4 Ab

# Mechanisms of underlying diarrhoea



	Chemotherapy	Radiotherapy*
Lactose intolerance	10-50%	50%
Malabsorption of non-lactose disaccharides	?	?
Bile acid malabsorption	?	50%
Small bowel bacterial overgrowth	?	25%
Reduced transit time	?	100%
Viral infection (eg. <i>Clostridium difficile</i> )	?	?
Parasitic or oportunistic infection	?	?
Pancreatic insufficiency	?	?
Drug related (non-chemotherapy)	?	?
Other(eg.hormone secretion, changes in neural pathway signalig stess)	?	?

\* Pelvic radiotherapy

Acute physiological changes in normal gastrointestinal function that cause diarrhoea

Andreyev J. et al. 2014. *Lancet Oncol*;15:e447-60



# Severity of diarrhoea-CTCAE

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of $\geq 7$ stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					

# Diarrhoea



## 1. UNCOMPLICATED

- ❖ Grade 1-2 without worrying clinical features
- ❖ Outpatient management

## 2. COMPLICATED

- ❖ Grade 1-2 with worrying clinical features
- ❖ Grade 3-4
- ❖ Immediate admission

# Clinical assessment

- Normal bowel function
- Previous irradiation
- Other chronic bowel diseases
- Previous GI surgery
- Time of diarrhoea onset
- Number and stool consistency

# Clinical assessment

- Fever
- Abdominal pain/colics
- Nausea and vomiting
- Increasing fatigue and weakness
- Dizziness
- Dehydration
- Inability to eat

# Physical assessment

- Temperature, pulse, blood pressure, respiratory rate, oxygen saturation
- Full physical examination

# Investigations

- CBC +LF
- Blood chemistry
- C-reactive protein
- Stool culture
- *C.difficile*
- Oxygen saturation
- Acid base balance
- Lactate concentrations
- Abdominal radiography
- CT

# Treatment of diarrhoea

- Pharmacologic
- Non pharmacologic

# Pharmacologic treatment

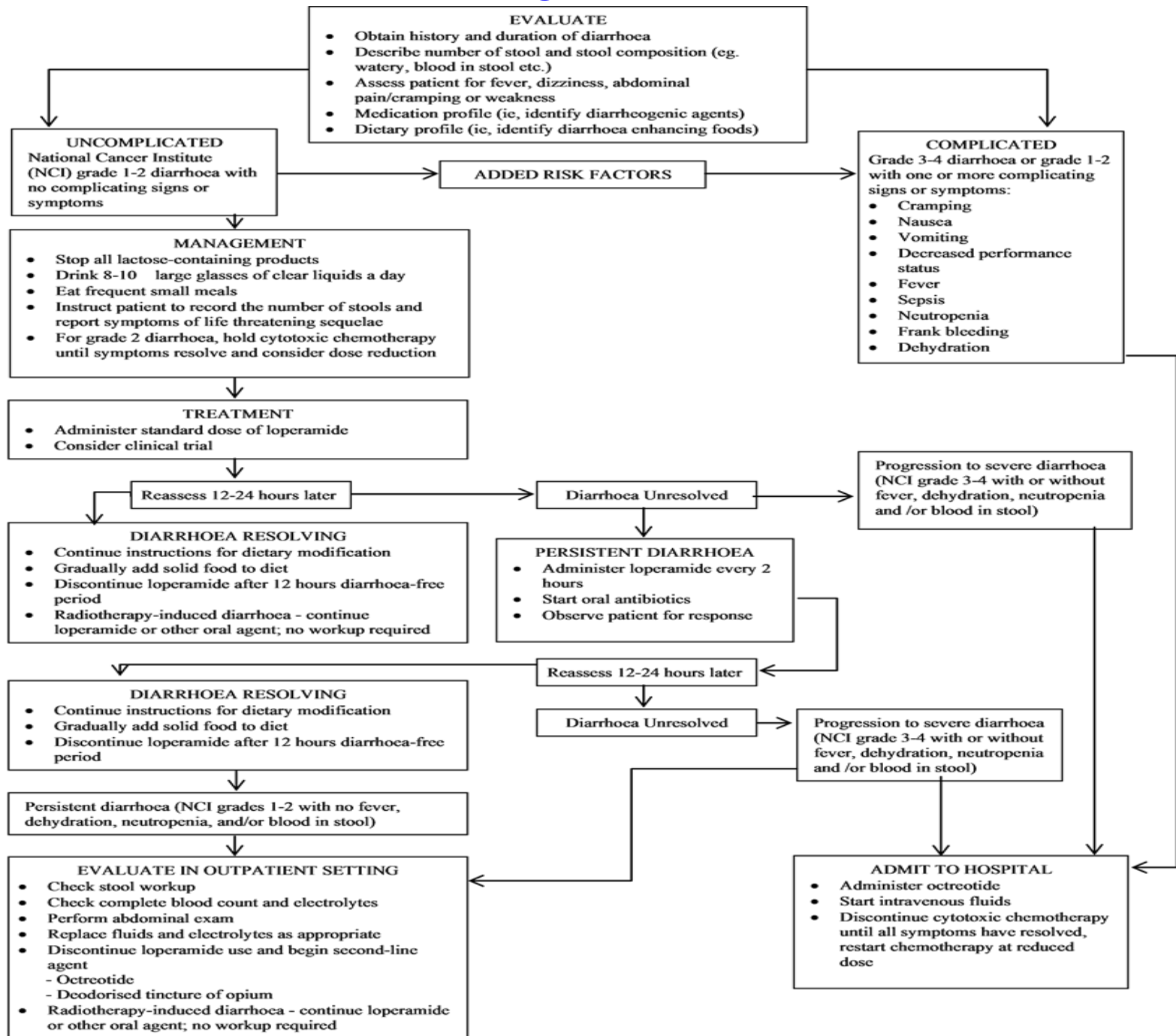
	Indication	Mode of action	Dosing
<b>Loperamide</b>	First-line treatment of diarrhoea	A synthetic opiate with direct effects on smooth muscle, which decreases motility and increases anal sphincter tone; minimum absorption and no central activity	Initial 4 mg dose followed by 2 mg every 2-4 h (higher frequency for persistent diarrhoea (max 16 mg per day)
<b>Codeine</b>	Alternative to loperamide, no evidence for its use in chemotherapy induced diarrhoea	Opioid that works through possibly a central and a local mechanism to delay transit through the small and large bowel	15-60 mg maximum four times per day
<b>Octreotide</b>	Grade 1-2 high risk Persistent diarrhoea despite loperamide First line in grade 3-4 diarrhoea	Decreases hormone secretion (eg vasoactive intestinal peptide), reduces motility and pancreatic secretions and promotes absorption	100 µg three times daily; increase if no improvement after 24 h (maximum 500 µg per day) for intractable diarrhoea. In severely ill patients start at 500 µg three times daily
<b>Budesonide</b>	Second line therapy for persistent grade 1-2 uncomplicated diarrhoea refractory to loperamide	Topically active corticosteroid that might restore mucosal function and fluid absorption	9 mg, once daily for 3-5 days
<b>Atropine</b>	Acute diarrhoea starting < 24 h after irinotecan administration caused by inhibition of acetylcholinesterase	Competitive inhibition of acetylcholine at the muscarinic receptors	0.25 mg for prophylaxis or treatment of cholinergic effects of irinotecan
<b>Antibiotics</b>	Grade 3-4 diarrhoea associated with neutropenia in outpatients	Broad spectrum antibiotics that targets small intestinal bacterial overgrowth of aerobic and anaerobic organisms	Prophylactically, eg. Oral ciprofloxacin 250-500 mg twice daily; as treatment eg. 400 mg norfloxacin twice daily; 100-200 mg doxycycline daily or 400 mg metronidazole three times daily for 7-14 days
<b>Bile acid sequestrants</b>	Diarrhoea or steatorrhea caused by bile acid malabsorption	Prevent water secretion into the colon induced by non-sequestered bile acids	Colestyramine initially 2-4 mg per day taken with food (max dose 24 mg per day) or colesevelam up to 6x625 mg three times daily with food plus low fat diet



# Non pharmacologic treatment

- Fluid and electrolyte replacement
- Sodium, potassium, magnesium
- Oral rehydration (grade 1-2)
- I.v. rehydration (grade 3-4)
  - 0.9% saline
  - Ringer lactate
- Diet
- Probiotics

# Algorithm



# Conclusions

- Frequency of CID
- Prompt and effective assessment and management
- Patients+their families
- Possible underlying infections
- Octreotide
- Multidisciplinary team