management of gastrointestinal symptoms in pediatric palliative care

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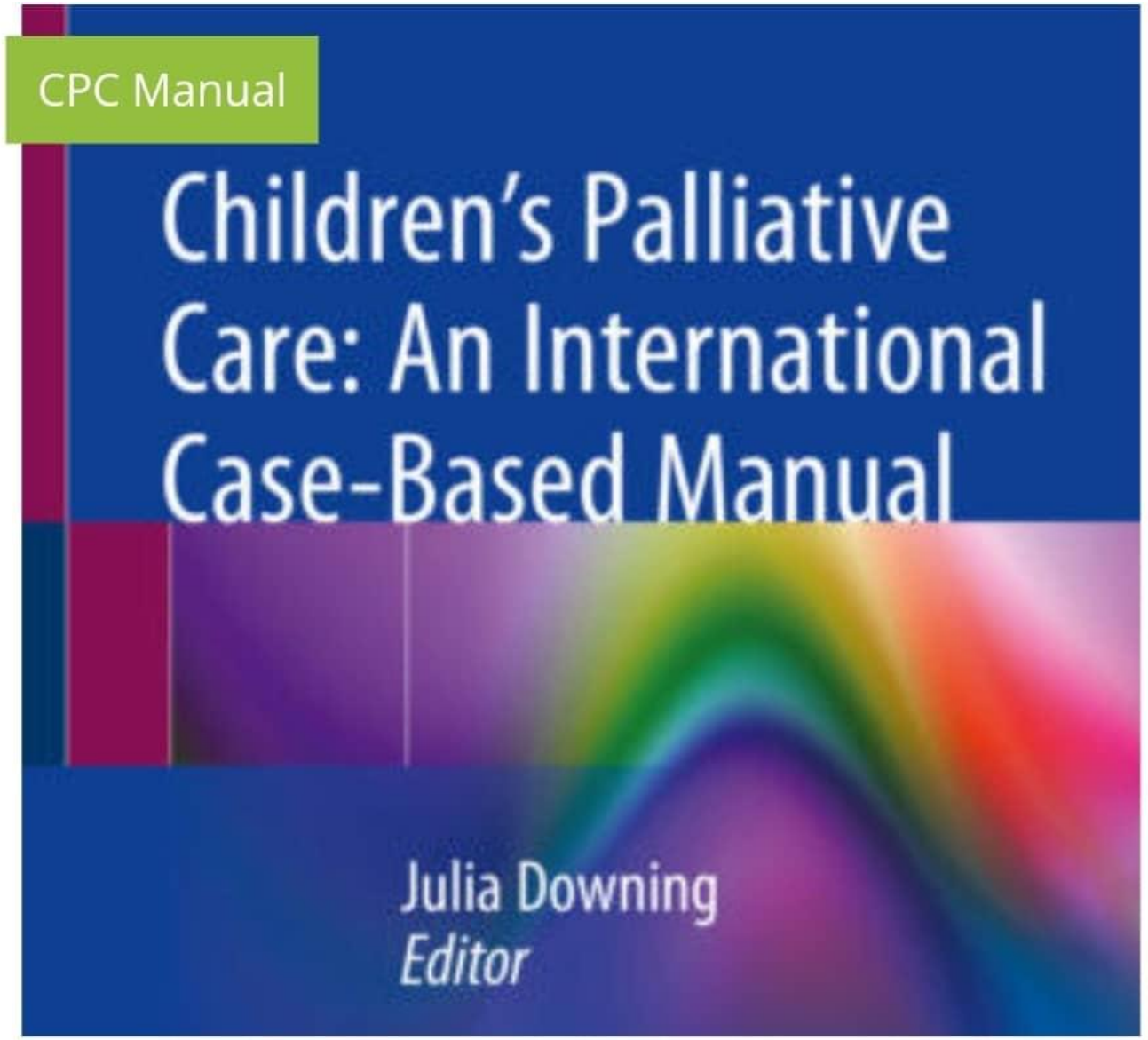
icpcn

international children's palliative care network

The **ICPCN**'s mission is to achieve the **best quality of life** and care for **children and young people** with life-limiting conditions, their families and carers worldwide, by **raising awareness** of children's palliative care, lobbying for the **global development** of children's palliative care services, and **sharing expertise, skills and knowledge**



ICPCN's new Case-Based Manual on Children's Palliative Care aimed at a Global audience

Key Learning Points

- 1. Gastrointestinal symptoms are a common source of suffering in children receiving palliative care (PC).
- 2. There are a variety of gastrointestinal symptoms experienced in children receiving PC including, but not limited to: nausea and vomiting, diarrhea constipation and mucositis.
- 3. Using a structured approach including comprehensive evaluation, treating the underlying cause (if possible), the use of non-pharmacological as well as pharmacological therapies will help in the management of gastrointestinal symptoms.
- 4. Non-pharmacological therapies should be used alongside pharmacological therapies, and have an important role to play.
- 5. There is a need for close clinical monitoring of symptoms and the side effects of medication to enable good symptom control.

Case Study

- Martin was a healthy 10-year-old boy who loved playing football until the beginning of his illness. Martin is currently in grade 5 and loves school. He lives with his mother and his sister. In January 2019, after a football match Martin presented with pain and swelling of the left lower leg. A diagnosis of non-metastatic proximal tibia osteosarcoma was made. A weekly regimen of chemotherapy was commenced (cisplatin and doxorubicin). During the chemotherapy he developed nausea and frequent vomiting

Question 1. What Is the Most Likely Cause of Martin's Nausea and Vomiting?

- Even though, in children, there are many causes of nausea and vomiting the most likely cause, in this case, is **the side effect of the chemotherapy.**

Question 2. How Can We Manage Martin's Nausea and Vomiting?

- **1. Comprehensive Evaluation**

Nausea and vomiting may be triggered by different stimuli acting in different areas (brain's vomiting center, vagal afferent gut receptors, etc.), thus a complete history and physical examination is needed.

It is important to consider that anxiety, fear and pain may also cause or increase nausea and vomiting.

The **complete history should include**: Timing, frequency, consistency and volume of the vomiting. Is there associated constipation or diarrhoea? Does anything make it worse or better? Does the child have any contributing disorder: swallowing problems, gastro-oesophageal reflux or poor gut motility, Is the child in pain? Is the child anxious? Is nausea and vomiting related to positioning or movement?

2. Treat the Underlying Cause (if Possible)

Ideally nausea and vomiting caused by antineoplastic drugs should be prevented (Dupuis et al. 2013). Although, sometimes it may be necessary to transiently interrupt or even withdraw chemotherapy to allow recovery.

3. Non-pharmacological (Integrative) Therapies

As nausea and vomiting can cause and result in anxiety, a good explanation to the child and family about the source and management is very important.

The child should be offered small meals frequently, avoiding strong smells or foods that may worsen the nausea and vomiting: those that are very fatty, spicy or sweetened.

Ensure adequate hydration by giving small amounts of fluids.

Feed the child in an upright position if reflux is concern.

Encourage the child to gently rinse out the mouth and brush teeth after vomiting.

If vomiting is associated with a certain medication, split the dosages where possible.

Address psychological issues such as anxiety or fear.

Massage (Mazlum et al. 2013), acupressure (Garcia et al. 2013) or hypnosis (Richardson et al. 2007) can be used to reduce nausea.

4. Pharmacological Therapies

A combination of medications, according to the presumed aetiological mechanism involved, may be required to achieve the best symptom control(Dupuis et al. 2013) (Table 8.1).

Table 8.1 Medication useful for nausea and vomiting

Condition	First-line medication
Drug-induced (e.g. morphine)	Ondansetron, haloperidol
Delayed gastric emptying	Domperidone
Chemotherapy or radiotherapy	Ondansetron/granisetron Dexamethasone, aprepitant
Bowel obstruction	Cyclizine, hyoscine butylbromide, dexamethasone
Raised intracranial pressure	Cyclizine, dexamethasone
Metabolic causes	Haloperidol

Case Study…

- Martin was given dexamethasone and ondansetron which helped, and his nausea and vomiting improved.
- At the end of the 4th cycle of chemotherapy, he developed diarrhoea, diffuse abdominal pain, refusal to eat due to oral pain and fever.
- On assessment he was alert, well hydrated with pale mucous membranes, slimmed down with globally diminished muscular mass. He was also found to have tooth cavities and oral ulceration. His abdomen was soft without organomegaly.

Question3. What Are the Possible Causes of Martin's Diarrhoea?

- While diarrhoea is a known side effect of the chemotherapy he is receiving, the most likely diagnosis of Martin's diarrhoea is gastrointestinal mucositis or neutropenic enterocolitis (typhlitis). Gastrointestinal mucositis causes diarrhoea as a consequence of enteral inflammatory mucosal damage and malabsorption. Typhlitis is a life-threatening necrotising enterocolitis occurring in immunosuppressed patients causing diarrhoea, pain and fever.
- Other possible causes of diarrhoea include: Infections: bacteria, viruses and parasites. Food intolerance: a pre-existing food intolerance or temporary intolerance caused by chemotherapy. Drug side effects: antibiotics.

Question 4. How Should We Manage Martin's Diarrhoea?

- **1. Comprehensive Evaluation:**

Are there signs of acute infection? (mucous/blood in the stool, fever, abdominal pain) What is the hydration status of the child? What is the nutrition status of the child? How long has the diarrhoea persisted? Is the diarrhoea made worse by specific drugs or foods?

2. Treat the Underlying Cause (If Possible)

Given that diarrhoea is frequently a consequence of chemotherapy, in some cases treatment needs to be transiently withdrawn. In addition, when infection is suspected, intravenous antibiotics must be given.

3. Non-pharmacological (Integrative) Therapies

- The child and family should be counselled about the condition, risks of cross-infection and correct handwashing.
- Feeding should be continued during acute diarrhoea. If the child has neutropenic enterocolitis, his gut should be rested using total parenteral nutrition if available (Rodrigues et al. 2017).
- Food and medicines that might be aggravating diarrhoea should be stopped when feasible.
- Ensure regular nappy changes (where wearing nappies) and barrier creams to protect the skin.

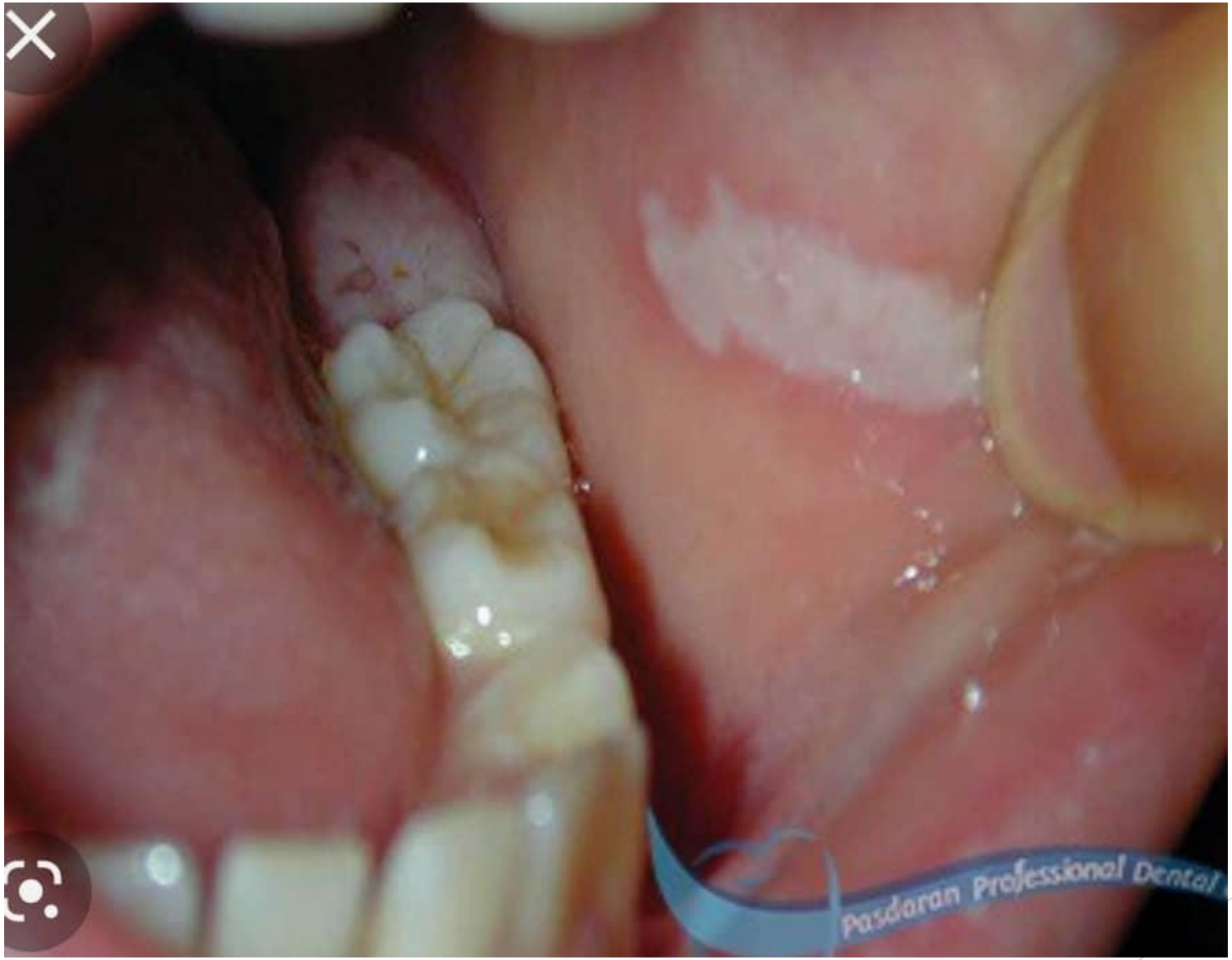
4. Pharmacological Therapie

- Hydration is the mainstay of acute diarrhoea treatment.
- Zinc supplementation for 14 days is advised (WHO 1979).
- Acute diarrhoea does not usually require anti-diarrhoeal drugs.
- When dysentery is suspected (blood/mucous in the stool), an antibiotic should be used.
- If the child has stomach cramps, hyoscine butylbromide may help.
- For chronic persistent diarrhoea, loperamide, bismuth subsalicylate, colestyramine and octreotide could be used with caution, in special circumstances (Friedrichsdorf et al. 2011). The constipating side effect of morphine can be beneficial in this group.

Question 5. What Are the Possible Causes of Martin's Oral Pain?

- **Oral mucositis**, is one of the most common symptomatic complications of antineoplastic therapy. It is a hugely painful condition, associated with a significant increase in morbidity, pain, functional limitation and deterioration in quality of life (Molina and Estupiñán 2010).
- Chemotherapy causes inflammation and ulceration through tissue damage along the entire digestive tract, frequently resulting, as in Martin's case, in oral mucositis and diarrhoea.
- Most common oral lesions include: mucositis, xerostomia, tooth decay, , trismus, mucosal ulcerations, sores, gingival bleeding, periodontitis, viral, bacterial or fungal infections and necrosis (Molina and Estupiñán 2010; Carreón et al. 2018; Fekrazad and Chiniforush 2014).

- The earliest signs and symptoms of oral mucositis appear in the oral mucosa after the 5th to 10th day of chemotherapy or radiotherapy.
- Includes: erythema, oedema and swelling of the gums, burning sensations and an increase in sensitivity to hot or spicy food.
- The erythematous areas progress to white scaly raised patches and subsequently to painful ulcers, which can be secondarily infected (Fekrazad and Chiniforush 2014)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Question 6. How Severe Is Martin's Mucositis?

- The most commonly used scale to measure mucositis is the World Health Organization (WHO) scale, which classifies the severity of lesions into 4 grades (WHO 1979; Sonis et al. 2004) (Table 8.2).

Table 8.2 WHO grades of oral mucositis

Grade	Description
0	None
1	Oral soreness, erythema
2	Oral erythema, ulcers, solid diet tolerated
3	Oral ulcers, liquid diet only
4	Oral alimentation impossible

Case Study

- Martín had grade 4 lesions with very intense pain and discomfort preventing him from swallowing solids and liquids. It had affected his quality of life and ultimately leads to malnutrition.

Question 7. How Can We Manage Martin's Oral Pain?

1. Comprehensive Evaluation

Assessment and identify: difficulty in swallowing, food refusing or mouth pain and a complete physical examination that includes the entire mouth to identify possible factors that require specific treatment: oral candidiasis and tooth caries (Fekrazad and Chiniforush 2014).

2. Treat Underlying Causes (If Possible)

Martin has previously had tooth cavities. It is important to identify and treat this, and other oral co-morbidities, such as oral candidiasis, xerostomia and bleeding gums, because mucositis may get worse or develop due to poor oral health.

3. Non-pharmacological (Integrative) Therapies

Prevention

Pain control

Nutritional support (Molina and Estupiñán 2010).

Good oral hygiene: it is recommended to brush gently with a soft toothbrush, dental floss and non-medicinal mouth rinses with saline solution or bicarbonate water.

Mouthwashes that contain alcohol should be avoided (Molina and Estupiñán 2010).

- Good hydration
- Soft foods that are easy to swallow and drink through a straw.
- Use lip balm to keep the child's lips from peeling or cracking.
- Avoid food with extreme temperatures, both hot and cold.
- Cryotherapy: may be offered to cooperative children receiving chemotherapy or regimens associated with a high rate of mucositis as prevention. Regimens appropriate for cryotherapy are restricted to agents with a short infusion time and short half-life. It is an attractive intervention because of its low cost and universal access. Oral cryotherapy involves placing ice cubes or ice chips in the mouth and continually replenishing fresh ice during the period of cytotoxic treatment (typically 30–60 min). Flavoured ice popsicles, ice slushy drinks or "freezies" are likely to be more acceptable to children than plain ice. Be careful if ice chips are to be used, as they may be a choking hazard in very young children (Fekrazad and Chiniforush 2014; Sung et al. 2017).

- Low level laser therapy (LLLT) is a new modality for managing mucositis via photo biomodulation (PBM). It requires expertise and specialised equipment (Sung et al. 2017).
- LLLT is administered intraorally and is performed by diode lasers including red and infra-red wavelengths.
- Shorter wavelengths are the most effective. The main effects are anti-inflammatory , analgesic and it is favourable for wound healing. LLLT effects are: reduction of the severity of mucositis, reduction of the incidence, severity and duration of pain. There is no consensus regarding intensity of wavelength, energy density, time of exposure and ideal time of starting laser therapy (Fekrazad and Chiniforush 2014; Sung et al. 2017; Anschau et al. 2019). Unfortunately, LLLT is not available in many countries

4. Pharmacological Therapies

- Pain management is an important part of severe oral mucositis:
- local anaesthetics (lidocaine) combined with oral or parenteral analgesics according to severity of pain should be prescribed (Costa et al. 2018).
- Several“magic”solutions with compounds like: lidocaine, diphenhydramine, aluminium hydroxide, saline, nystatin, dexamethasone, morphine, sucralfate, glutamine and B complex are used in different countries. Although, many of this strategies and products have been studied, so far there is no consistent evidence about their usefulness (Molina and Estupiñán 2010; Sung et al. 2017; Costa et al. 2018).
- Palifermin is a keratinocyte growth factor (KGF), available in some countries, for children receiving regimens associated with a high rate of severe mucositis. It significantly reduces severe oral mucositis. KGF should be administered at a dose of 60– 90 mg/kg/day for 3 days prior to conditioning and 3 days following stem cell infusion. KGF should be used carefully in individual patients after weighing risks and benefits (Molina and Estupiñán 2010; Sung et al. 2017).

Case Study

- Martin was admitted with strict isolation measures, and intravenous cefepime, fluconazole were started. Analgesia with NSAID and regular intravenous morphine every 4 h plus rescue doses were given. He received red blood cell transfusion, and mucositis treatment was initiated with bicarbonate water rinse and laser therapy. In the hospital his diarrhoea stopped and all stool cultures were negative.
- Over the next few days his oral mucosal lesions worsened, with bleeding and uncontrolled pain that hindered oral feeding and speaking. Analgesia was titrated and parenteral feeding started. He remained admitted for 15 days with partial pain control. After 10 days of parenteral feeding and treatment, the mucosal lesions improved and he started eating again. On day 14, he complained of moderate abdominal pain without stools for 5 days. At examination, on abdominal palpation, a large faecal mass in the colon and rectum was found.

Question 8. What Could Be the Cause of Martin's Abdominal Pain and Reduced Stools?

- In a child with cancer, any pain and appearance of a new tumor must alert you to the presence of metastasis. Nevertheless, in this case, the lack of stools for 5 days, the presence of a large fecal mass in the colon and rectum, in a child receiving opioids, indicate a diagnosis of constipation with fecal impaction. Children receiving PC commonly experience constipation as a result of: use of medicines (e.g. morphine), disease, dietary and mobility factors (Rabia and Turgay 2016)
- Rome III consensus for healthy children with functional constipation defines it when a child at age 4 years or older presents with at least two of the following criteria for 2 months or more: two or fewer defecations per week, at least one episode of incontinence per week, history of excessive stool retention, painful or hard bowel movements, presence of large faecal mass in the rectum, large-diameter stools that may obstruct the toilet (Tabbers et al. 2014).

- Similar definition for children living with LT and life-limiting conditions (LLCs) do not exist. So, even though Rome III definitions may be used as a baseline guide in children receiving PC, a systematic assessment should always be done in order to promptly identify children at risk of constipation (Table 8.3)

Table 8.3 Risk factors for constipation in children with LTC and LLC

• Chronic neurological conditions
• Intra-abdominal cancer
• Inactivity
• Low liquid and/or food intake
• Medication: opioids, antiemetics, tricyclic antidepressants, phenothiazines, diuretics, antihistamines, anticholinergics, vincristine

Question 9. How Could We Manage Martin's Constipation?

- **1. Comprehensive Evaluation Complete clinical history:**
- **Identification of the risk factors:**
- previous intestinal patterns, food preferences and habits, defecation routines, privacy and environmental conditions.
- **Physical examination:** particularly an abdominal exam to identify stool mass in colon or rectum, inspection of the perianal region, looking for skin tags, fissures or dermatitis.
- The digital anorectal examination may give important information (presence and characteristics of stools). Nevertheless, it was not done in Martin because in a child with neutropenia or thrombocytopenia, invasive examination is contraindicated because it can cause bleeding and/or infection.

Question 9. How Could We Manage Martin's Constipation?

- **2. Treat the Underlying Cause (If Possible)**

- Review the indication and doses of medications contributing to the constipation.
- Give special attention to privacy and environmental factors, particularly in admitted adolescents.

3. Non-pharmacological (Integrative) Therapies

- Educate the parent and child about the cause of constipation and discuss the treatment options.
- A common myth is that laxative use leads to dependence or addiction, which may result in parental under-dosing or “only as needed” administration.
- Whenever possible, encourage regular bowel routine: scheduled toilet time for 5–10 min after meals.
- Increase activity or passive movements
- Increase intake of fluids and carbohydrates, especially sorbitol(found in juices) and increase the fruit, vegetables in the diet.
- Clockwise abdominal massage may help.

4. Pharmacological Therapies

There is no evidence-based pharmacological protocol for the management of constipation in children with LTC and LLC. Most protocols are based on expert opinions for functional constipation and on adult research. The last Cochrane systematic review ("Laxatives for the management of constipation in people (adults) receiving palliative care") did not show any difference in effectiveness of three laxatives: senna and lactulose. None of the studies evaluated the effectiveness of polyethylene glycol which is strongly recommended in children (Candy et al. 2015)

- The pharmacological treatment of constipation in children includes disimpaction, maintenance and specific treatment of anal fissures when present (Madani et al. 2016) (Table 8.4). Particular treatment for opioid-induced constipation is described.

Table 8.4 Medication dosages for treatment of constipation in children (Friedrichsdorf et al. 2011)

Lactulose	Infants: 0.8–3.5 ml (not per kg) Children: 10–30 ml (not per kg)	bd–td/PO bd–td/PO
Polyethylene glycol 3350	8.5–17 g in 120–240 ml fluid	qd/PO
Senna	Sennoside: • 6 mo–2 yrs: 3.75 mg (not per kg) • 3–10 yrs: 7.5–15 mg (not per kg) • >10 yrs: 15–30 mg (not per kg)	*qhs*/PO
Bisacodyl	6–11 yrs: 5 mg >12 yrs: 5–15 mg 1 suppository daily	qd/PO qd/PO qd/PR
Surfactant laxatives	Docusate sodium oral:	1–4 dos/day/PO

5. Disimpaction

The presence of a palpable fecal mass on abdominal examination or hard stool in a dilated rectum on a digital rectal exam justifies disimpaction.

This can be done via oral or rectal therapy or a combination of both. Although rectal disimpaction has been shown to be faster, children prefer and tolerate better the oral route, because it is not invasive and it gives them a sense of control. The method of choice should be determined with a discussion among the physician, parent and child.

- **Stoolsoftener laxatives:**

They are the first line therapy for oral fecal disimpaction. Polyethylene glycol 3350, lactulose or sorbitol can be used according to availability, cost or child preference and tolerance. All of them are best given in water/juice/milk in the morning when the child is most likely to finish it at once.

- **Stimulant laxatives:**

The most frequently used are oral senna and bisacodyl. They should be given intermittently or for a short period if the child has a full rectum with soft faeces or when stoolsoftener laxatives are ineffective.

- **Rectal disimpaction:** In cases of severe impaction, a child may need a rectal suppository or enema for resolution. In communicative children and adolescents, it always should be explained and discussed with them. In children with cancer, when neutropenia or thrombocytopenia is present, the risks (infection/bleeding) should be balanced with the potential benefits.

6. Maintenance Therapy

- When faecal disimpaction has been accomplished, the goal is to prevent recurrences with maintenance therapy. It consists of: Continued application of non-pharmacological measures. Laxatives: Polyethylene glycol 3350 or lactulose on a scheduled regimen.

7. Anal Fissure Treatment

- An anal fissure is a tear in the skin of the anal canal, usually as a result of trauma caused by the expulsion of hard stool.
- It is a very painful injury that causes suffering and/or bleeding at the time of defaecation, thus children hold the stool in, increasing constipation.
- With appropriate treatment, most heal in the short term, but can sometimes transform into chronic lesions requiring specific treatments:
- Softening stools.
- Delicate hygiene of the area without rubbing.
- Application of anesthetic and corticosteroid creams.

8. Opioid-Induced Constipation

- Methylnaltrexone is an antagonist of peripheral receptors without central nervous system action. Its efficacy for opioid-induced constipation has been largely demonstrated in adults, and some evidence of its benefit in children is appearing.
- When enteral or rectal measures have been unsuccessful, or when clinical deterioration prevents enteral medication administration (Flerlage and Baker 2015).

Case Study

- Martin’s constipation responded very well to PEG 3350. Throughout his antineoplastic therapy he continued to have gastrointestinal problems that were well managed by his team.

Conclusion

- Gastrointestinal symptoms are a common source of suffering in children receiving PC. Using a structured approach which includes: comprehensive evaluation, treating the underlying source, offering non-pharmacological-integrative measures and pharmacological treatment, contributes to managing them. Close clinical monitoring of symptom control and medication's side effects should be taken in order to provide optimum symptom control.

Thank you