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CLINICAL PRACTICE GUIDELINES

Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines†

P. Bossi[1], A. Antonuzzo[2], N. I. Cherny[3], O. Rosengarten[3], S. Pernot[4], F. Trippa[5], U. Schuler[6], A. Snegovoy[7], K. Jordan[8] & C. I. Ripamonti[9], on behalf of the ESMO Guidelines Committee*

[1]Head and Neck Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; [2]U.O. Oncologia Medica 1, Polo Oncologico Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; [3]Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel; [4]Department of Hepato-Gastroenterology and Digestive Oncology, Georges Pompidou European Hospital, APHP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [5]Radiation Oncology Centre, "S. Maria" Hospital, Terni, Italy; [6]Department of Internal Medicine I, Palliative Care Centre, University Hospital Carl Gustav Carus, Dresden, Germany; [7]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [8]Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany; [9]Oncology-Supportive Care in Cancer Unit, Department Onco-Haematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

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Definition

Diarrhoea is defined as the frequent passage of loose stools with urgency (or more frequent passage than is normal for the individual). Objectively defined, it is the passage of more than three unformed stools in 24 hours [1]. Often the patient's definition of diarrhoea varies and needs to be clarified by medical staff, through an adequate assessment.

Epidemiological data

Diarrhoea is often seen in patients with cancer, with several potential causes. Prominent in this context is the association with:

- Certain chemotherapies (ChTs), where incidences of grade 4 toxicities up to 20% or more are seen;
- A variety of signal transduction inhibitors;
- Immunotherapeutic approaches;
- Radiotherapy (RT);
- Surgery.

However, other causes should also be considered. Diarrhoea is reported as an issue even in long-term cancer survivors, being one of the symptoms with the highest impact on health-related quality of life (QoL) [2].

Assessment (Figure 1)

Medical history and warning signs

History includes the development of the diarrhoea over the previous days and, particularly, the frequency of bowel movements during the past 24 hours. Stool consistency and admixture of blood, mucus or pus should be noted. It is also important to distinguish diarrhoea from steatorrhoea, according to stool characteristics. Questions should cover possible causes other than cancer and oncological therapies [food and fluid intake in the last few days, recent travel, recent use of antibiotics, use of proton pump inhibitors (PPIs), contact with possibly infected persons, use of laxatives and other over-the-counter medications] and previous admission for diarrhoea. Earlier history of gastrointestinal diseases [e.g. inflammatory bowel disease (IBD)] should also be assessed before the initiation of antineoplastic therapy.

Patients should be asked about incontinence as a factor included in the grading, as they may be reluctant to volunteer the information. Fever should be assessed, and temperature measured. Other symptoms include abdominal cramps and pain, nausea and vomiting, dizziness and thirst. The combination of multiple symptoms (such as vomiting or fever and diarrhoea) in cancer patients is frequently linked to the toxicity of treatments; some of them may indicate a more complicated clinical condition (Table 1). The presence of these worrying symptoms, the unresponsiveness to treatment and/or the frailty status of the patient (due to advanced age, immunocompromised conditions and multiple comorbidities) should prompt a multidisciplinary management, with the expertise of gastroenterologists, infectious disease specialists, nutritionists and intensive care specialists. Oncogastroenterology has been advocated as a new discipline in the care of cancer patients suffering from gastrointestinal toxicities [3]. It focuses on the approach to pre-existing diseases which may impact on antineoplastic therapies, the early recognition and treatment of gastrointestinal complications due to oncological treatments and the identification and care of late toxicities.

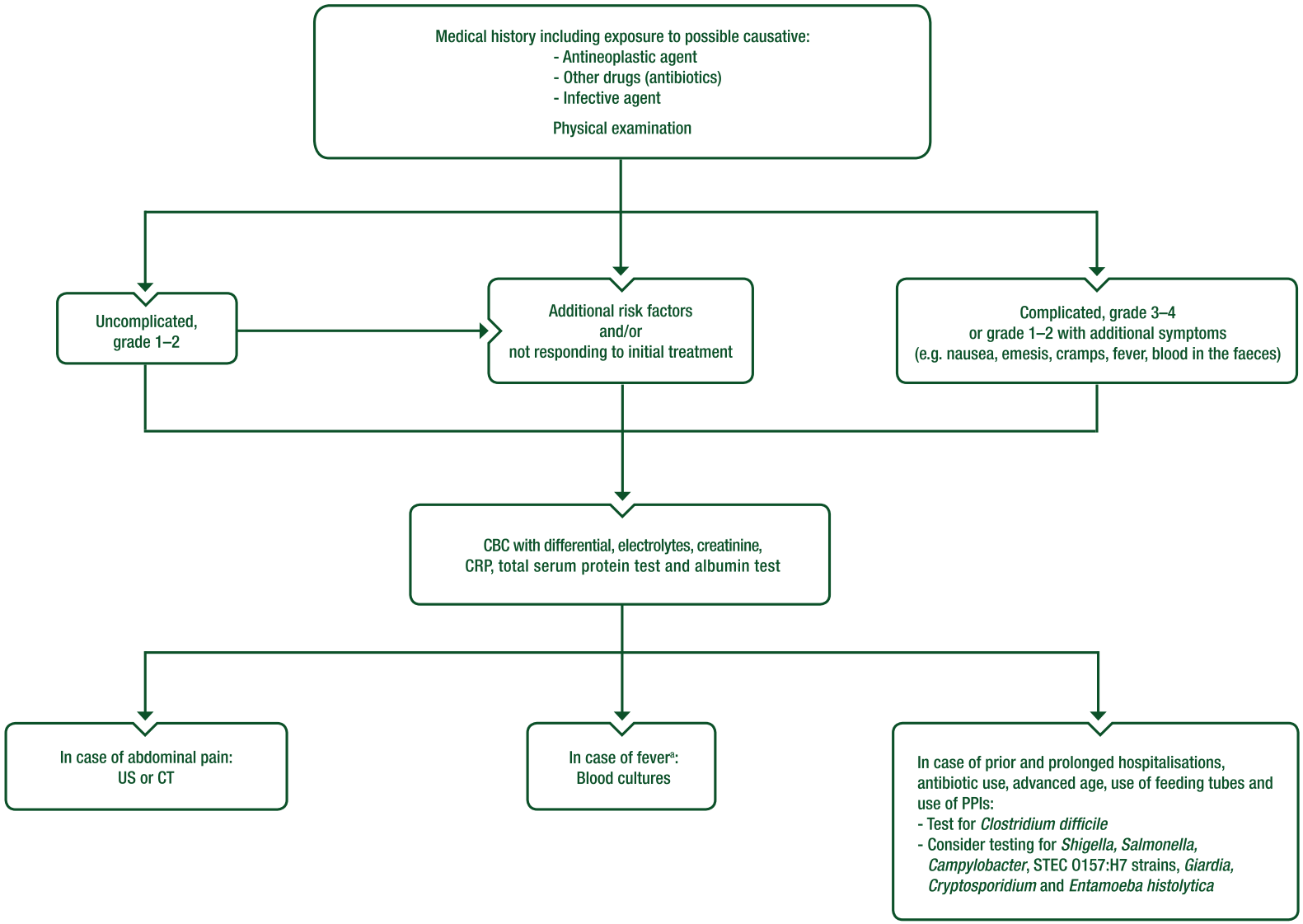

Figure 1. Algorithm for diagnostic exams of ChT-related diarrhoea.
[a]In case of neutropaenic fever, management according to ESMO guidelines on management of febrile neutropaenia [11].
CBC, complete blood count; ChT, chemotherapy; CRP, C-reactive protein; CT, computed tomography; ESMO, European Society for Medical Oncology; PPI, proton pump inhibitor; STEC, Shiga toxin-producing *Escherichia coli*; US, ultrasound.

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Table 1. Clinical warning signs for potentially complicated courses

Warning signs
Massive dehydration
Fever
Peritonitis
Blood loss
Delirium
Renal impairment
Febrile neutropaenia, neutropaenic sepsis
Sepsis
Shock
Electrolyte disturbances
Abdominal cramps not relieved by loperamide
Inability to eat
Persistent nausea, vomiting and dehydration accompanied by urine reduced output
Previous admission for diarrhoea

Grading

The most frequently used system for the grading of diarrhoea is the Common Terminology Criteria for Adverse Events (CTCAE) (Supplementary Table 1 in Supplementary Material, available at *Annals of Oncology* online).

Although important, this grading system has limitations as it does not include either volume and duration or subjective complaints such as abdominal cramps, and does not take into account the patient's perception about the severity of this symptom.

As it is well known that there is low agreement between patients and physicians in reporting toxicities, with physicians underestimating the presence and severity of adverse events (AEs) [4, 5], it is important to collect measures of diarrhoea directly from the patients, as they provide information that can otherwise be missed [6]. In this regard, the implementation of the patient-reported outcomes (PROs) CTCAE system will allow a clearer pattern of symptoms to be collected; there is a rapid need to complement the current way of measuring diarrhoea, both in everyday practice and in clinical trials.

It should be recognised that diarrhoea, caused by the disease itself and as a consequence of oncological treatments, impacts greatly on the QoL of cancer patients.

Examinations and investigations (Figure 1)

Physical examination

Lying and standing blood pressure, heart rate, oxygen saturation, skin turgor and dry mucous membranes may help to assess the degree of dehydration. The general nutritional status [body mass index (BMI)] and overall appearance (severely ill or still compensated) may predict the patient's resistance to this complication. Evaluation for fever is indicated. Abdominal auscultation should determine hyperactive, normal or absent bowel sounds. Palpation for tenderness (localised or generalised) and rebound tenderness may lead to the diagnosis of peritonitis or peritoneal involvement. Abdominal or rectal masses may lead to the diagnosis of overflow diarrhoea, i.e. liquid stool passing around the obstruction, that should be investigated with radiological imaging. Rectal examination should be performed to exclude perianal abscess formation. Stool rectal examination may help to detect blood or mucus, especially when the patient is unsure about the characteristics.

Investigations

It is almost impossible to devise an algorithm applicable in all cancer settings for the indication of laboratory tests, radiology and endoscopy which avoids over-diagnosis with additional costs and burden to the patient and the risks of under-diagnosis at the same time. However, specific algorithms have been developed for patients with gastrointestinal symptoms after pelvic or abdominal radiation; they are useful in the assessment and the treatment of diarrhoea [7–9].

In general, the choice of the investigations to be carried out should be guided by the patient's clinical status (with a lower threshold for laboratory and radiological exams in more compromised patients), the duration of the symptoms and the presence of a prominent cause.

In patients with good performance status and with a highly suggestive aetiology [e.g. ChT based on 5-fluorouracil (5-FU) and/or irinotecan administration in the previous few days], microbiological examinations may not be necessary, or may be deferred if the situation does not improve after initial therapeutic measures.

Further examinations into the differential diagnosis are indicated if the diarrhoea takes a severe or persistent course, notably in the presence of fever, but also neutropaenia, haematochezia, steatorrhoea and other signs or symptoms not easily explained by the tumour or therapy. A broader diagnostic approach is recommended for patients with a history of earlier complications from diarrhoea.

Laboratory and microbiological tests. A list of suggested clinical chemistry and blood count laboratory tests is provided in Table 2.

In patients with diarrhoea without cancer, stool cultures usually have a diagnostic yield of $< 5\%$. In a situation of drug-induced diarrhoea, the yield might be even lower. On the other hand, in patients with cancer, direct or indirect contacts with other infected patients and the inherent immunosuppression might lead to a higher rate.

In patients on antibiotics, a stool sample to test for *Clostridium difficile* may be the most important measurement. Stool samples may include *Shigella*, *Salmonella*, *Campylobacter*, Shiga toxin-producing *Escherichia coli* (STEC) O157: H7 strains, *Giardia lamblia*, *Cryptosporidium* and *Entamoeba histolytica*. Tests for *Clostridium difficile* include enzyme immunoassays (EIAs) detecting glutamate dehydrogenase, EIAs detecting toxins A and B and nucleic acid amplification tests. Most guidelines recommend a two-step approach. For a detailed discussion, microbiological guidelines should be consulted [10].

In patients with fever (especially in the case of manifest or developing neutropaenia), it is very important to take a minimum of two sets of blood cultures including cultures from indwelling intravenous (i.v.) catheters and to follow the ESMO guidelines for febrile neutropaenia [11].

Table 2. Suggested clinical chemistry and blood count laboratory tests

Laboratory test	Assessment	Consequences
WBC count and differential	Neutropaenia after ChT Leukocytosis	Risk-stratification in the case of fever (low/high risk of complications) Possible infection as cause
Hb	Blood-loss, bone marrow function Haemoconcentration	Transfusion Infusion
Potassium, sodium, calcium, magnesium	Electrolyte disturbances	Composition of infusion fluids
Creatinine, urea	(secondary) Renal impairment	Replacement therapy prognostication
Coagulation tests	Bleeding risk (inflammation)	Further studies for clarification
CRP, PCT	Infection, inflammation	Need for antibiotic therapy
Blood gases and lactate	Acidosis	Need for intensive care
TSH	Hyperthyroidism	Rare cause of diarrhoea
ACTH	Hypoadrenalism	Rare cause of diarrhoea

ACTH, adrenocorticotropic hormone; ChT, chemotherapy; CRP, C-reactive protein; Hb, haemoglobin; PCT, procalcitonin; TSH, thyroid-stimulating hormone; WBC, white blood cell.

In patients with diarrhoea after administration of checkpoint inhibitors, a microbial cause (bacterial enteropathogens and *Clostridium difficile* toxin) should be ruled out in every patient with significant diarrhoea (please consult the corresponding ESMO Clinical Practice Guidelines on management of toxicities from immunotherapy) [12].

A quantitative culture of jejunal aspirates may help in the diagnosis of small intestinal bacteria overgrowth syndrome (SIBO), possibly due to chronic radiation enteropathy, long-term use of PPIs or as a post-surgical consequence of colectomy with the loss of ileo-caecal valve or altered gut motility [13].

Patients with diarrhoea after allogeneic stem cell transplantations may have intestinal graft-versus-host disease (GvHD); however, this is beyond the scope of these guidelines.

Imaging studies and radiology. Ultrasound may be helpful to evaluate peristalsis, intestinal wall thickening and intra-abdominal tumour manifestations. In the presence of clinical signs of peritoneal involvement (local tenderness or rebound tenderness) computed tomography (CT) is the preferred method to diagnose further complications as early as possible (perforation, malignant intestinal obstruction, enterocolitis).

Indications for endoscopy. There is usually no primary indication for endoscopy, except for refractory cases or for patients with chronic diarrhoea, who should be referred to a gastroenterologist. Investigations such as duodenal biopsy [for diagnosis of cytomegalovirus (CMV), other viral infections and diagnosis of *Giardia lamblia*] are usually only done in the situation of persistent or increasing symptoms. On sigmoidoscopy or colonoscopy, infection with *Clostridium difficile* may show a typical morphology. However, in neutropaenic enterocolitis, colonoscopy is not recommended, as the risk of perforation might be increased; moreover, in neutropaenic patients, the typical pseudomembranes cannot develop, as their formation seems to require neutrophils.

Table 3. Cancers associated with diarrhoea as a symptom

Type of cancer
Carcinoid syndrome from neuroendocrine tumours (NETs)
Colon cancer
Lymphoma
Medullary carcinoma of the thyroid
Pancreatic tumours, particularly islet cell tumours (Zollinger-Ellison syndrome)
Pheochromocytoma

Diarrhoea as a cancer-related symptom

Diarrhoea is a common symptom of presentation of several types of malignant tumours (Table 3). Gastroenteropancreatic and lung neuroendocrine tumours (NETs) and colorectal cancer are the most frequent diarrhoea-associated tumours (∼20% of the cases).

NETs-related diarrhoea is mainly related to released bioactive amines (mainly serotonin) that cause carcinoid syndrome. In colorectal cancer, this symptom often presents at the same time as constipation and is linked to the primary site of presentation. Bile salt malabsorption may occur in patients with pancreatic disease and cause diarrhoea. Other less frequent cancer-related diarrhoea is seen with intestinal lymphoma and thyroid medullary carcinoma (5%–16% and 16%, respectively).

Chemotherapy-induced diarrhoea

Diarrhoea is a common side effect of many ChT agents. Most of the drugs induce diarrhoea that is not severe but, in some cases, it may be dose limiting and even life threatening (Table 4) [14].

Table 4. Frequency and severity of diarrhoea with frequently used combinations of ChT agents

ChT	Incidence of grade 3 and 4 diarrhoea (%)
CapeIRI	47
FOLFOXIRI	20
mIFL	19
Bolus fluorouracil with folinic acid	16
Irinotecan with fluorouracil and folinic acid	15
Docetaxel with capecitabine	14
FOLFIRI	14
FLOX	10

CapeIRI, capecitabine/irinotecan; ChT, chemotherapy; FLOX, bolus fluorouracil/leucovorin/oxaliplatin; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mIFL, irinotecan/bolus fluorouracil.

Cytotoxic drugs most frequently associated with diarrhoea

5-FU. The diarrhoea associated with 5-FU therapy may be watery or bloody. Disruption of the integrity of the gut lining may permit access of enteric organisms into the blood stream, with the potential for overwhelming sepsis, particularly if the granulocyte nadir coincides with diarrhoea. Severity is variable, but it may be severe and at times life-threatening [15].

Risk factors: Diarrhoea is most commonly observed when 5-FU is co-administered with leucovorin (LV). It is slightly more common with bolus rather than continuous administration of 5-FU/LV, particularly with high-dose LV ($\geq$ 500 mg/m^2), but it occurs with all administration schedules. In the initial reports of weekly 5-FU/LV, diarrhoea was seen in up to 50% of patients, with one-half of these requiring hospitalisations for i.v. fluids and, in one study, a 5% mortality rate. Other risk factors have been identified including unresected primary tumour, previous episodes of ChT-induced diarrhoea and female gender.

Administration of 5-FU to patients with metabolising enzyme dihydropyrimidine dehydrogenase (DPD) deficiency can lead to life-threatening complications, including severe diarrhoea, mucositis and pancytopaenia (see 'Personalised medicine' section).

Irinotecan. Irinotecan may often cause acute diarrhoea (immediately after drug administration) or delayed-onset diarrhoea. Immediate-onset diarrhoea is caused by acute cholinergic properties and it is often accompanied by other symptoms of cholinergic excess, including abdominal cramping, rhinitis, lacrimation and salivation. The mean duration of symptoms is 30 minutes and it usually responds rapidly to atropine [0.25–1 mg subcutaneously (s.c.) or i.v.] and premedication with 0.5 mg atropine s.c. may prevent acute diarrhoea [16]. The delayed-onset diarrhoea usually occurs at least 24 hours after drug administration and can be potentially life-threatening, especially in combination with ChT regimens with bolus of i.v. 5-FU and LV. Late diarrhoea associated with irinotecan is unpredictable, noncumulative and occurs at all dose levels. It is more common with 3-weekly dose schedules than with lower weekly dosing. The median time to onset is 6–14 days.

Risk factors: Polymorphisms that alter uridine 5′-diphosphoglucuronosyltransferase (UGT) activities have been identified; the homozygous presence of the *UGT1A1*28* polymorphism, leading to less efficient glucuronidation of SN-38, has been identified as a potential risk factor for the occurrence of delayed-onset diarrhoea and grade 3–4 neutropaenia. In one study, heterozygote had a twofold increase of risk of severe diarrhoea.

Capecitabine. Capecitabine, an oral precursor of 5-FU, when administered at usual doses (2000 mg/m^2 per day for 14 of every 21 days) entails a risk of diarrhoea in 30%–40% of the patients (severe in 10%–20%) [17].

Other cytotoxic drugs associated with diarrhoea

Taxanes.

Cabazitaxel: In studies for prostate cancer, the prevalence of diarrhoea of all grades was 47%, of which 6% were $\geq$ grade 3. Up to 10% of patients required hospitalisation for treatment of diarrhoea.

Docetaxel: In patients receiving neo-adjuvant treatment of breast cancer, the reported rate of diarrhoea was up to 47%, with low rates of grade 3 and 4. However, in a study using docetaxel in gynaecological malignancies, all-grade diarrhoea ranged from 19% to 47%; $\geq$ grade 3 ranged from 0% to 27%, with more pronounced effects in patients $>$ 65 years of age.

Paclitaxel: Different schedules of paclitaxel are associated with different prevalence of diarrhoea. Early studies of doses of 175–225 mg/m^2 administered over 24 hours resulted in prevalence of all-grade diarrhoea of 39%, with 3% grade 3 and 4, and weekly schedules may result in 3%–7% $\geq$ grade 3 diarrhoea. Cases of severe enteritis and colitis have been reported.

Nab-paclitaxel (albumin-bound paclitaxel): Its gastrointestinal toxicity resembles that of paclitaxel with any grade diarrhoea, prevalence being as much as 44% but no $\geq$ grade 3 events.

Anthracyclines. Diarrhoea with the regular form of anthracyclines is not common, with all-grade occurring in 15% of patients. In contrast, for PEGylated liposomal doxorubicin the prevalence of diarrhoea may be up to 45%, grade 3 and 4 in 3% of cases, mostly in the elderly.

Platinum salts.

Cisplatin and carboplatin: Whereas the prevalence of diarrhoea is low with i.v. administration, it is somewhat higher when cisplatin is administered intraperitoneally. Hyperthermic intraperitoneal chemotherapy (HIPEC) is associated with more severe and prolonged diarrhoea. Oxaliplatin is seldom used as a single agent and most studies reporting gastrointestinal toxicity of oxaliplatin refer to combinations with drugs that potentially contribute to diarrhoea, such as fluoropyrimidines or irinotecan [18].

Targeted therapy-induced diarrhoea

Diarrhoea is associated with the use of several targeted therapies, mainly tyrosine kinase inhibitors (TKIs), but also monoclonal antibodies and other targeted agents [19]. Diarrhoea is observed in patients treated with vascular endothelial growth factor receptor (VEGFR) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, (multi-targeted) TKIs, mammalian target of rapamycin (mTOR) inhibitors, cyclin-dependent kinase (CDK) 4/6 and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors (Table 5).

Many targeted agents studied were associated with significantly higher risks (up to eightfold) of developing diarrhoea than the conventional regimens. Patients treated with several TKIs, such as erlotinib, gefitinib, lapatinib, sorafenib and sunitinib, have a significantly higher risk of having both all-grade and high-grade diarrhoea than those receiving conventional regimens. A very high risk can be observed in patients treated with lapatinib for breast cancer. Diarrhoea is a common side effect of targeted therapy and these targeted drugs can cause severe diarrhoea when combined with ChT. Moreover, there is a strong association between anti-EGFR TKIs and diarrhoea.

As far as mTOR inhibitors are concerned, diarrhoea has been related to several alterations, such as microflora disequilibrium and malabsorption.

However, little is known about the possible underlying mechanisms of new targeted therapies, such as CDK4/6 and PARP inhibitors, and this causes difficulties in addressing the problem properly. In fact, there is little consensus regarding the proper management and treatment of diarrhoea from new targeted therapies.

Table 5. Incidence of diarrhoea from targeted therapies

Class of drug	Drug	Incidence of diarrhoea (%)	Incidence of grade 3 and 4 diarrhoea (%)
Anti-EGFR	Gefinitib	26–52	1–5
	Erlotinib	18–57	3–6
	Afatinib	87–95	14–22
	Cetuximab	13–28	4–28
	Panitumumab	21	8–20
Anti-HER2	Lapatinib	47–75	3–14
	Trastuzumab	2–63	2–6
	Pertuzumab	67	5–8
Anti-BRAF	Vemurafenib	5–6	0
	Dabrafenib	1	0
Anti-MEK	Cobimetinib	45–50	4
	Trametinib	45–50	4
Anti-EML4/ALK	Crizotinib	50–60	0
Anti-VEGF	Bevacizumab	20	2–7
	Aflibercept	58–69	13–19
Multi-targeted TKI	Imatinib	20–26	1
	Pazopanib	52	4
	Sunitinib	44–55	5–8
	Axitinib	55	11
	Sorafenib	43–55	2–8
	Vandetanib	74	10
	Regorafenib	34–40	5–8
	Cabozantinib	64	12
	Levantinib	59	8
Anti-mTOR	Everolimus	30	1–3
	Temsirolimus	27	1
Anti-CDK4/6	Palbociclib	21–26	1–4
	Ribociclib	35	1.2
	Abemaciclib	86–90	13–20
Anti-PARP	Olaparib	11–18	0
	Rucaparib	13–20	0

Toxicities are considered with single drug arm or in combination with other drugs.

CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; EML4/ALK, echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase; HER2, human epidermal growth factor receptor 2; MEK, MAPK ERK kinase; mTOR, mammalian target of rapamycin; PARP, poly(adenosine diphosphate-ribose) polymerase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Immunotherapy-induced diarrhoea

Immune checkpoint inhibitors lead to specific immune AEs, close to auto-immune disorders, which require a specific management. Diarrhoea is one of the most frequent immune AEs, particularly with anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) therapy, and shares characteristics with IBD. Colitis may occur, even if it is not a pathognomonic characteristic of this toxicity, as a significant proportion of patients have diarrhoea with no evidence of colitis on biopsy. For further details please consult the corresponding guidelines from ESMO on management of toxicities from immunotherapy [12].

Diarrhoea associated with hormonal therapy

Hormonal agents are the cornerstone of the treatment of several tumours, such as breast, prostate and endometrial cancer. Older hormonal agents, such as gonadotropin-releasing hormone agonists, antiandrogens and antioestrogens, are correlated to a low and variable incidence of diarrhoea, often without clinical relevance. Aromatase inhibitors are not usually associated with gastrointestinal issues and diarrhoea is an infrequent event (i.e. for anastrozole, around 4%–6%). New hormonal agents, used in breast and prostate cancer, are often associated with mild intensity diarrhoea (see Table 6). It should be recognised that patients treated with systemic drugs may also have diarrhoea because of other causes, such as bile salt malabsorption or pancreatic insufficiency. So, an accurate assessment and treatment of all possible causes may lead to improvement in symptoms.

Table 6. Incidence of diarrhoea from new hormonal agents

Class of drug	Drug	Incidence of diarrhoea (%)	Incidence of grade 3 and 4 diarrhoea (%)
Androgen synthesis inhibitors	Abiraterone	18	1
Antiandrogens	Enzalutamide	21	1
	Apalutamide	8–11	0
Antioestrogens	Fulvestrant	6	0

RT-induced diarrhoea

The widespread use of RT in pelvic cancer treatment (e.g. gynaecological and gastrointestinal cancers) is related to the increasing incidence of radiation-induced side effects. The RT-induced damage can be the direct result of the energy absorption from incident radiation or the effect of the free radicals realised by the interaction of radiation with cellular water. Moreover, damage of stem cells within intestinal crypts during replication or differentiation causes a reduction or a loss of mucosal integrity and the flattening of intestinal villi. Also, a modification of the intestinal microflora and a deterioration of enzymatic activities are related to RT damage. Accordingly, a decrease of absorptive intestinal surface area and a reduction of intestinal transit time are present.

Diarrhoea is reported in these cases, but it represents just one of the many symptoms (e.g. urinary, sexual, cutaneous) after pelvic or abdominal irradiation. To better identify and treat these patients, a new term, 'pelvic radiation disease', is used and defined as 'transient or longer-term problem, ranging from mild to very severe, arising in non-cancerous tissues, resulting from RT treatment to a tumour located in the pelvis' [20]. In clinical practice, diarrhoea is defined as *acute* when occurring during RT or within 3 months, while it is considered as *chronic* when lasting for, or developing in, a longer period [21].

Acute diarrhoea

Generally, ∼60% of patients have an experience of temporary mild diarrhoea during pelvic RT treatment.

There are several risk factors that play a role in developing radiation-induced intestinal injury, which can be divided into patient- and treatment-related risk factors.

Patient-related risk factors include: low BMI, comorbid diseases (e.g. diabetes, hypertension, collagen vascular and IBD) and smoking history. Moreover, previous intestinal surgery may predispose to acute diarrhoea for anatomical changes leading to an increase in small bowel exposure to RT field, which explains the higher incidence after postoperative rather than preoperative chemoradiotherapy (CRT). Treatment risk factors include: volume of small bowel in RT field, RT dose, fractionation, technique and concomitant ChT administration. Although the probability of tumour control increases with the radiation dose, so does the damage to normal tissues. Acute side effects to the intestine occur at ∼10 Gy. Because curative doses for many abdominal or pelvic tumours range between 50 Gy and 75 Gy, enteritis is likely to occur.

In clinical practice, a rate of $< 10\%$ of grade 3 toxicity is registered when a volume of < 120 cc of individual small bowel loops receives a dose of < 15 Gy.

The kind of ChT concomitant to RT may influence the severity of intestinal toxicity. Generally, fluoropyrimidine alone or associated with new agents (i.e. oxaliplatin and irinotecan) is related to an increase of acute toxicity.

Intestinal transit may be a major factor in the pathophysiology of RT-induced diarrhoea, whereas lactose malabsorption may contribute to the severity of the diarrhoea. There is further evidence that lactose malabsorption develops as a side effect of pelvic RT, and that the severity of this malabsorption can be related to the small bowel area exposed to RT. Furthermore, cholerheic enteropathy can be one of the causes of RT-induced diarrhoea, as a result of ileal dysfunction, with impaired bile salt absorption and secretion of water and electrolytes in the colon [22].

Acute RT-induced diarrhoea may be associated with nausea, vomiting, abdominal cramping or rectal tenesmus. Patients must be evaluated regarding related symptoms that may indicate a concomitant haemodynamic injury. Digestive and absorptive functions of the gastrointestinal tract are altered or damaged, resulting in malabsorption of fat, lactose, bile salts and vitamin B_{12}. Finally, intestinal bacterial overgrowth is present in about a quarter of patients during RT treatment and may worsen the acute diarrhoea [23].

Chronic diarrhoea

The exact prevalence of chronic RT-induced diarrhoea toxicity is difficult to determine, as data mainly derive from retrospective studies. About 90% of patients who received pelvic RT may develop a permanent change in their bowel habit after treatment, 50% of whom may have their QoL affected by gastrointestinal symptoms (moderate or severe effect in 20%–40% of cases) [20].

Chronic diarrhoea is only a symptom of pelvic radiation disease, an expression of changes in the normal physiology of the gastroenteric tract. In fact, the inflammation that appears during and immediately after RT is replaced almost completely by progressive ischaemia and fibrosis, which largely occurs not in the mucosa but in the submucosa. Subsequently, the intestinal tract shows mucosal atrophy, vascular sclerosis and progressive wall fibrosis. So, the term 'radiation enteropathy' must be used to describe chronic radiation damage, rather than 'radiation enteritis' (acute damage).

Normal tissue responses are also influenced by the dose accumulation and other factors related to the RT schedule. Serious chronic diarrhoea is strongly related to the RT characteristics (i.e. total RT dose administered and intestinal volume irradiated). The dose at which 50% of patients would develop late intestinal toxicity at 5 years is 60 Gy and 55 Gy for one-third of the volume and the whole volume of the small bowel, respectively. The tolerance for the large intestine is slightly higher: 65 Gy for one-third of the volume and 60 Gy for the whole volume of the colon irradiated.

Unconventional (e.g. hypofractionation) or more aggressive RT regimes are usually associated with aggravation of acute reactions, particularly in those organ systems in which there is a

barrier against mechanical and/or chemical stress. Delayed radiation injury may develop in the wake of severe acute injury, this phenomenon was termed 'consequential late effects'. The concept of consequential late effects eradicated the old dogma of independence between early and delayed radiation effects. As a result, in tissues with a consequential component of the late effect (e.g. intestinal tract), an amelioration of the acute RT toxicity can be a useful approach to reduce late sequelae.

About 5% of patients show a persistent lactose malabsorption causing chronic diarrhoea. Conversely, bile salt malabsorption is common but it causes few symptoms in most patients (e.g. onset of a mild diarrhoea after a high-fat meal). The role of bile salts and carbohydrate malabsorption in chronic diarrhoea is unclear.

Another clinical situation possibly occurring as a late effect of RT is steatorrhea, which is usually caused by bacterial overgrowth or bile salt malabsorption or, more rarely, by the little-recognised disorder of free fatty acid or late pancreatic insufficiency after abdominal RT.

Finally, other causes to be considered in chronic diarrhoea are small bowel strictures, new intestinal neoplasia and new onset or recrudescence of primary inflammatory disease.

The symptoms associated with chronic RT-induced diarrhoea are progressive and characterised by malabsorption of nutrients and abnormal propulsion of intestinal contents. Recurrent intestinal bleeding, abdominal pain and, in limited cases, intestinal stenosis with tenesmus, ulcers and fistula formation can be present. In some patients, a latency period of 20–30 years after pelvic RT is not uncommon.

Other causes of diarrhoea in cancer patients

Clostridium difficile

Clostridium difficile diarrhoea occurs when the normal intestinal flora is altered, allowing *Clostridium difficile* to flourish in the intestinal tract and produce a toxin that causes a watery diarrhoea. It can be triggered by repeated enemas, prolonged nasogastric tube insertion, gastrointestinal tract surgery and the use of antibiotics, especially penicillin (ampicillin), clindamycin and cephalosporins. Occasionally, however, it is reported after ChT in the absence of antibiotic therapy. The most common confirmatory study is an EIA for *Clostridium difficile* toxins A and B which yields results in 2–4 hours. Specificity of the assay is high (93%–100%), but sensitivity ranges from 63% to 99% and this limited sensitivity may require two to three repeat stool samples to document disease. A polymerase chain reaction test 'Xpert® *Clostridium difficile* assay' has been approved by the United States Food and Drug Administration (FDA). Limited data indicate that this test may have greater sensitivity [24].

Enteral feeding

Tube feeding, either by nasogastric tube, gastrostomy or jejunostomy may be associated with the development of diarrhoea [25]. This is a common problem occurring in 10%–60% of patients. Many potential factors may contribute to the problem; indeed, it is often multifactorial. Both formula osmolality and rate of delivery may be associated with diarrhoea.

Partially hydrolysed guar gum is a soluble fibre added to enteral formulas and has the largest body of evidence supporting its use in diarrhoea prevention, when compared with fibre-free formulas. There are data from randomised, controlled trials indicating that partially hydrolysed guar gum may be preferable to insoluble fibre in this setting [II, B] [26].

There is conflicting evidence of efficacy of probiotics in preventing diarrhoea in patients receiving enteral nutrition, and there is no consensus regarding the use of this approach prophylactically [27]; moreover, attention should be paid to immunocompromised patients as, rarely, probiotics may cause sepsis [28].

Contamination of the enteral formula may be a contributing or causative factor. Recommendations to reduce the risk of contamination include:

- proper handwashing before handling the feeding administration set;
- use of clean gloves before working with the feeding tube and administration set;
- use of aseptic techniques in setting up and connecting the feeding administration set and related equipment;
- adherence to 'hanging time' guidelines of individual formulations and refrigerated storage of prepared bags for no longer than 96 hours until use [V, B].

Coeliac plexus block

Coeliac plexus block is commonly associated with self-limiting acute diarrhoea. Occasionally, diarrhoea may be persistent. This diarrhoea may be amenable to treatment with loperamide, drugs with anticholinergic properties (e.g. hyoscine butylbromide) or with octreotide [V, B].

Diarrhoea due to surgical procedures

Diarrhoea may result from resection of part of the digestive tract; the pathogenesis and the severity of the toxicity depend on the extent and site of surgery itself.

For oesophageal and gastric resection, the incidence of diarrhoea is about 15%.

In case of intestinal resection, it is important to know the remaining length of small intestine, as this can affect the risk and severity of diarrhoea [29].

In case of right hemicolectomy, chronic diarrhoea occurs in about 20% of patients because of bile salt malabsorption or small bowel bacterial overgrowth. Malabsorption occurs due to the dysfunction of the terminal ileum, causing an increased passage of bile in the colon. The loss of the ileocecal valve barrier may cause an increase of bacteria growth in the small bowel [30].

Patients with rectal cancer undergoing sphincter-preserving rectal resection may suffer from low anterior resection syndrome (LARS) which is quite different to diarrhoea, but possibly comprising incontinence, stool high frequency, urgency and evacuatory dysfunctions [31].

It has also been reported that patients with pancreatic cancer treated with neoadjuvant CRT followed by pancreatectomy with nerve plexus resection have higher rates of intractable diarrhoea. However, the causal role of radiation in such cases should also be considered.

Specific clinical manifestations

Neutropaenic enterocolitis

Neutropaenic enterocolitis (also called necrotising enterocolitis or typhlitis) is an acute life-threatening complication of ChT, most commonly observed with high-dose treatments in the setting of myeloablative therapies. However, it is also observed with non-myeloablative therapies, particularly with taxanes.

Neutropaenic enterocolitis may occur when the absolute neutrophil count (ANC) falls below 500 cells/μL. Patients present with fever, abdominal pain, nausea, vomiting, diarrhoea and, not uncommonly, sepsis. Abdominal pain may be diffuse or localised to the right lower quadrant. Sometimes pain is absent, particularly if the patient has received steroid therapy.

Established standardised diagnostic criteria include the presence of neutropaenia (ANC $<$ 500 cells/μL), bowel wall thickening $>$ 4 mm on radiographic imaging and the exclusion of other diagnoses such as *Clostridium difficile*-associated colitis, GvHD or other abdominal syndromes [V, A].

CT scanning is the preferred imaging modality [V, A]. CT scanning techniques can evaluate the entire abdomen for pathology, especially in patients with distended loops of bowel and ileus for whom ultrasound would not be possible. Scans commonly demonstrate concentric thickening of the bowel wall, a fluid filled caecum, pericolic fluid collections or abscesses, pneumatosis intestinalis and free air if an underlying perforation exists. Bowel wall thickening $>$ 3–5 mm is considered abnormal and is consistent with, but not sufficient for, the diagnosis of necrotising enterocolitis. Indeed, *Clostridium difficile*-related colitis in neutropaenic patients may be associated with wall thickening. *Pneumatosis intestinalis* along with caecal and colonic wall thickening is very suggestive of neutropaenic enterocolitis.

Abdominal ultrasonography can identify thickening of the bowel wall. A study showed that the neutropaenic enterocolitis-related mortality rate was higher in patients with pathological wall thickening (29.5% versus 0%); moreover, a thickness $>$10 mm had a significantly higher mortality rate (60%) than those with bowel wall thickness $\leq$ 10 mm (4.2%) [32]. Ultrasound is useful as a follow-up tool to assess the gradual decrease in bowel wall thickening [V, A]. Additionally, signs of pericolic fluid and intramural or abdominal free air often indicate perforation.

Ischaemic colitis (non-neutropaenic enterocolitis)

Rarely, ischaemic colitis, in the absence of neutropaenia, has been reported with docetaxel-containing regimens. Patients present 4–10 days following administration with rapid onset of pain and tenderness over the affected bowel, followed by the development of rectal bleeding or bloody diarrhoea within 24 hours of the onset of pain.

Diarrhoea in elderly cancer patients

With active oncological treatment (ChT, targeted agents)

There are no specific data about the incidence of diarrhoea in elderly cancer patients. In a self-reported cohort study involving people $>$ 65 years of age during ChT, in a 5.6 month follow-up period, 74% of patients reported diarrhoea [33].

In this frailer population, diarrhoea could more frequently lead to dehydration, electrolyte imbalance, renal function decline, malnutrition or pressure ulcer formation.

The most common causes of diarrhoea are ChT and targeted agents, as already reported. Older patients seem to have a moderately increased risk for 5-FU-associated diarrhoea and may be at higher risk with irinotecan; dose reductions for patients $\geq$ 70 years of age are recommended in some countries. About 30%–50% of elderly patients treated with capecitabine need dose reduction to improve tolerability.

With regard to targeted agents, no greater incidence of diarrhoea in elderly patients has been reported with EGFR TKIs, multitargeted TKIs (such as sunitinib or sorafenib) or with the Bcr-Abl TKI imatinib.

In the palliative setting

There are no specific data about the incidence of diarrhoea in elderly cancer patients with advanced disease; however, this is a less common symptom than constipation. Less than 10% of those with cancer admitted to hospital or palliative care units have diarrhoea.

Faecal impaction or partial bowel obstruction can manifest as alternating constipation and diarrhoea.

In the elderly, abuse of laxatives, malabsorption or previous surgery can be responsible for altered fluid absorption in the bowel and consequent diarrhoea.

Management

General principles of management of ChT-related diarrhoea (Figure 2)

Approach to uncomplicated diarrhoea. Patients with grade 1 or 2 diarrhoea with no other complicating signs or symptoms may be classified as 'uncomplicated' and managed conservatively with oral hydration and loperamide [V, A] [34, 35]. Initial management of mild to moderate diarrhoea should include dietary modifications (e.g. eliminating all lactose-containing products and high-osmolar dietary supplements) and the patient should be instructed to record the number of stools and report symptoms of life-threatening sequelae (e.g. fever or dizziness on standing). Special attention should be given to patients who are incontinent of stool due to the risk of pressure ulcer formation. Skin barriers should be used to prevent skin irritation caused by faecal material.

Loperamide should be started at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/day) [V, A] [36].

Sometimes, it may be difficult to define the threshold between complicated and uncomplicated diarrhoea. In this regard, the role of dedicated supportive care services may limit hospitalisation and allow a better control of the symptoms [37, 38].

Approach to complicated diarrhoea. Patients with mild to moderate diarrhoea, complicated by moderate to severe cramping, nausea and vomiting, diminished performance status, fever,

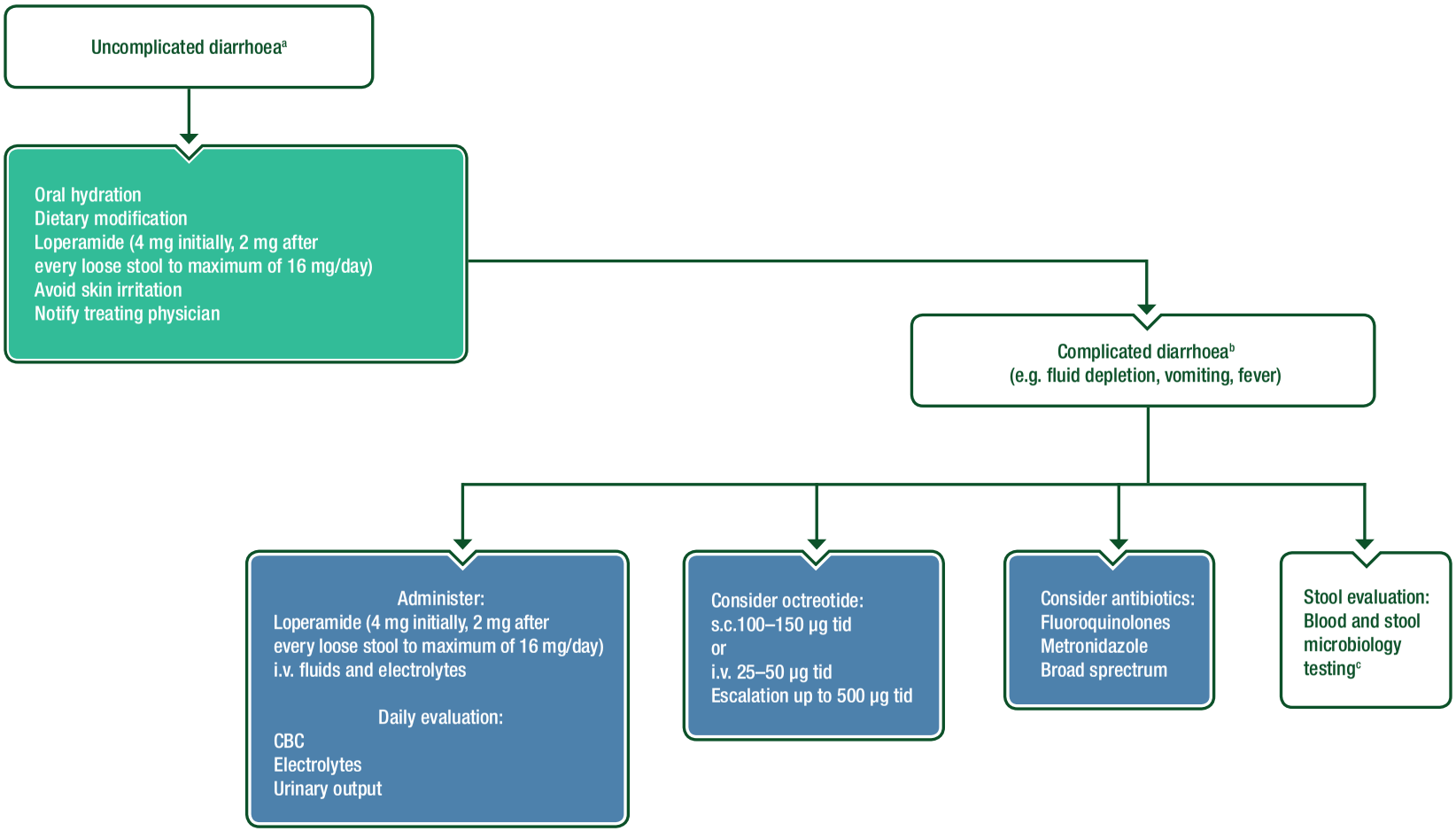

Figure 2. Algorithm for therapeutic approach.
[a]Treatment setting: ambulatory and/or outpatient supportive care outpatient unit.
[b]In-hospital treatment.
[c]Consider *Clostridium difficile*, *Salmonella*, *Campylobacter* and other causes of infectious colitis.
CBC, complete blood count; i.v., intravenous; s.c., subcutaneous; tid, three times a day.

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sepsis, neutropaenia, bleeding or dehydration, and patients with severe diarrhoea are classified as 'complicated' and should be hospitalised and evaluated further, monitored closely and treated aggressively [V, A] [34, 35].

Intensive management of complicated cases usually necessitates hospital admission and involves i.v. fluids; octreotide at a starting dose of 100–150 μg s.c. three times a day (tid) or i.v. (25–50 μg/h) if the patient is severely dehydrated, with dose escalation up to 500 μg s.c. tid until diarrhoea is controlled and administration of antibiotics (e.g. fluoroquinolone) [V, A]. These patients should be evaluated with complete blood count, electrolyte profile and a stool work-up evaluating for blood, *Clostridium difficile*, *Salmonella*, *Escherichia coli*, *Campylobacter* and infectious colitis [V, A].

In cases of neutropaenia, the possibility of neutropaenic enterocolitis should be considered.

Special case—Management of neutropaenic enterocolitis: Management of neutropaenic enterocolitis is challenging and the risk of mortality is high. There are roles for both medical and surgical interventions [39].

The initial treatment of neutropaenic enterocolitis is medical, with the administration of broad-spectrum antibiotics, granulocyte colony-stimulating factors (G-CSFs), nasogastric decompression, i.v. fluids, bowel rest and serial abdominal examinations [V, A]. In most patients, these measures are sufficient and symptoms resolve after correction of the neutropaenia.

The administered antibiotics should cover enteric gram-negative organisms, gram-positive organisms and anaerobes [V, A]. Causative microorganisms include *Pseudomonas*, *Staphylococcus aureus*, *Escherichia coli* and *group A Streptococcus* (GAS). Reasonable initial choices include monotherapy with piperacillin-tazobactam or imipenem-cilastatin or combination therapy with cefepime or ceftazidime along with metronidazole [V, A]. In cases which do not respond to antibacterial agents, amphotericin should be considered, because fungaemia is common [V, A]. Blood transfusions may be necessary because the diarrhoea is often bloody [V, A].

Anticholinergic, antidiarrhoeal and opioid agents should be avoided since they may aggravate ileus [V, A].

The indications for and timing of surgical intervention are controversial. The mortality rate of patients who fail to respond to medical interventions is high and many patients may not be salvageable. Nonetheless, in selected patients, surgery may be helpful to avoid progressive bowel necrosis, perforation and to help control sepsis. Commonly cited indications for surgery include: (i) persistent gastrointestinal bleeding after correction of thrombocytopaenia and coagulopathy; (ii) evidence of free intraperitoneal perforation; (iii) abscess formation; (iv) clinical deterioration despite aggressive supportive measures; (v) to rule out other intra-abdominal processes such as bowel obstruction or acute appendicitis through radiological examinations [V, A].

If exploratory surgery is carried out, resection of grossly involved bowel is necessary. All necrotic material must be removed, usually by a right hemicolectomy, ileostomy and mucous fistula. Failure to remove the necrotic focus in these severely immunocompromised patients is often fatal [V, A]. Primary anastomosis is not generally recommended in such severely immunocompromised patients because of the increased incidence of anastomotic leak [V, A].

Treatment approaches for diarrhoea (Figure 2)

Fluids and electrolytes. The most critical therapy in diarrhoeal illness is rehydration, with solutions that contain water, salt and sugar.

Oral rehydration: Oral rehydration therapy (ORT) is generally appropriate for mild diarrhoea [I, A]. Diluted fruit juices and flavoured soft drinks along with saltine crackers and broths or soups may meet the fluid and salt needs in patients with mild illness. Oral rehydration solutions (ORSs), including standard World Health Organization (WHO) ORSs or commercial ORSs may be more appropriate in patients with more severe diarrhoeal disease [II, A]. In elderly patients, who represent the group with the highest risk of severe complications and death from diarrhoea, and in all patients with grade 2 diarrhoea, an ORS is indicated. A well-balanced ORS should contain 65–70 mEq/L sodium and 75–90 mmol/L glucose [40]. ORSs can be combined with other types of fluids or with i.v. fluids when the patient's compliance is suboptimal. The total amount of fluids that should be prescribed varies between 2200 and 4000 mL/day.

ORSs can be used both to replete a volume-depleted patient and to maintain adequate volume status once replete. Caution should be paid to overhydration in elderly patients, especially when diagnoses of chronic heart or kidney failures are present. During the administration of fluids and/or ORSs, patients must be frequently re-assessed to ensure that signs of dehydration are not worsening.

Rapid fluid resuscitation is not necessary in patients with mild to moderate hypovolaemia [I, A]. To avoid worsening of the volume deficit, the rate of fluid administration must be greater than the rate of continued fluid losses, which is equal to the urine output plus estimated insensible losses (usually 30–50 mL/h) plus gastrointestinal losses [I, A].

Intravenous rehydration: In grade 3 or 4 diarrhoea, or in all grades when signs of severe dehydration are present, the i.v. route for fluid replacement is preferred.

Most patients are treated with isotonic saline or a balanced salt solution, but the choice of therapy is influenced by concurrent abnormalities in serum sodium or potassium or the presence of metabolic acidosis. If the patient has tachycardia and is potentially septic, an initial fluid bolus of 20 mL/kg should be given [I, A]. Concurrent potassium replacement is indicated in patients who have developed potassium depletion. Fluid replacement is continued at a rapid rate until the clinical signs of hypovolaemia improve (e.g. low blood pressure, low urine output and/or impaired mental status) [I, A].

Monitoring with a central venous pressure line and urinary catheter to measure urinary output should be considered but must be balanced against risks of infection and bleeding [V, B]. Fluid balance should aim for an adequate central venous pressure and urine output > 0.5 mL/kg/h [I, A]. Patients who develop oliguric acute kidney injury (< 0.5 mL/kg/h) despite adequate volume resuscitation, as judged by central venous pressure, are at risk of developing pulmonary oedema and the advice of

intensive-care experts or nephrologists must be urgently sought [V, B].

Opioids (loperamide). Loperamide is generally the opioid of choice because it has local activity in the gut and is absorbed only minimally (this accounts for the lack of systemic effects). It reduces stool weight, frequency of bowel movements, urgency and faecal incontinence in acute and chronic diarrhoea. Loperamide can be started at an initial dose of 4 mg followed by 2 mg every 2–4 hours or after every unformed stool [II, B]. The maximum daily dose of loperamide is 16 mg. One should pay attention to the risk of causing paralytic ileus and, even if rare, these patients need to be monitored while using high-dose loperamide. Other opioids, such as tincture of opium, morphine or codeine can be used [V, C].

Tincture of opium is a widely used antidiarrhoeal agent. It is often recommended as an alternative to loperamide. Deodorised tincture of opium contains the equivalent of 10 mg/mL morphine and the recommended dose is 10–15 drops in water every 3–4 hours [V, C]. It is important not to confuse this with paregoric which is a camphorated (alcohol based) tincture. The latter is a less-concentrated preparation that contains the equivalent of 0.4 mg/mL morphine. The recommended dose is 5 mL in water every 3–4 hours [V, C].

After 48 hours, in case of absence of efficacy of opioids, administration of other drugs should be considered.

Somatostatin analogues (octreotide). In cases of severe or persistent diarrhoea, the somatostatin analogue octreotide should be considered, continuing loperamide in the first 48 hours. Octreotide has multiple antidiarrhoeal actions including: suppression of release of insulin, glucagon, vasoactive intestinal peptide and gastric acid secretion; reduction in motility and pancreatic exocrine function; and alteration of increased absorption of water, electrolytes and nutrients from the gastrointestinal tract. The usual starting dose for octreotide is 100–150 μg s.c./i.v. tid [IV, B]. Since there is a dose response relationship for its antidiarrhoeal effect, the dose can be titrated up to 500 μg s.c./i.v. tid or 25–50 μg/h by continual i.v. infusion [V, B].

Uridine triacetate (for 5-FU/capecitabine-induced diarrhoea). In cases of severe diarrhoea within 96 hours of completion of treatment with 5-FU or capecitabine, uridine triacetate can be administered. Uridine triacetate is an orally administered prodrug of uridine which is a specific pharmacological antidote to fluoropyrimidines and it is a potentially life-saving treatment of overdoses of these agents. It is licenced for the management of early-onset, severe or life-threatening toxicity including diarrhoea and/or neutropaenia within 96 hours following the end of 5-FU or capecitabine administration [II, B] [41].

The recommended dose and schedule for uridine triacetate in adults is 10 g orally every 6 hours for 20 doses [II, A].

Steroids. Budesonide is an orally administered, topically active steroid with high activity in IBD, a 90% first-pass effect in the liver and therefore low systemic availability. It is commonly used in the management of diarrhoea in patients with low- to medium-grade IBD. A small study demonstrated efficacy of oral budesonide in the management of ChT-induced diarrhoea that was refractory to loperamide [IV, C] [42]. Prophylactic budesonide is not recommended [II, B] [43].

Antibiotics. Antibiotics are only indicated for patients with fever, hypotension, peritoneal signs, neutropaenia small intestinal bacterial overgrowth, perianal sepsis or bloody diarrhoea suggestive of either neutropaenic enterocolitis, *Clostridium difficile* infection or other infective cause (see specific sections).

Bile acid sequestrants. Unabsorbed bile salts cause diarrhoea by stimulating colonic secretion and motility. A multidisciplinary approach is often needed and helps in managing symptoms.

A low-fat diet and the use of bile acid sequestrants (e.g. cholestyramine, colestipol, colesevelam) may be an effective integrated therapy [44]. The use of bile acid sequestrants is limited because it is associated with gastrointestinal side effects, including bloating, flatulence, abdominal discomfort and constipation [III, B] [45]. Among them, colesevelam appears to be better tolerated.

Treatment of immunotherapy-induced diarrhoea and colitis

A specific management algorithm has been depicted in the recently published ESMO Clinical Practice Guidelines for management of toxicities from immunotherapy [12]. The main topics are reported hereafter.

Management for anti-CTLA-4 and anti-programmed cell death protein 1 (PD-1)-related diarrhoea/colitis is the same. Faster treatment, within 5 days after start of symptoms, leads to more rapid resolution or downgrading of symptoms.

Treatment of grade 1 diarrhoea is based on symptomatic treatment with oral rehydration and antidiarrhoeal treatment, racecadotril or loperamide [III, A].

In the case of grade 2 diarrhoea, immunotherapy treatment should be stopped. Budesonide 9 mg once a day can be added to the symptomatic treatment, if no bloody diarrhoea [V, C]. Oral corticosteroids (0.5–1 mg/kg/day prednisone equivalent) are recommended in the case of diffuse ulceration or bleeding under endoscopic evaluation, or persistent symptoms after 3 days with symptomatic treatments ± budesonide [III, A]. If symptoms worsen or persist for > 3–5 days with oral steroids, behaviour is the same as for grade 3–4 toxicity.

Treatment of grade 3 and 4 diarrhoea and colitis is based on administration of 1–2 mg/kg/day prednisone equivalent, with i.v. injections first [III, A]. At this stage, loperamide and opioids should be avoided. If symptoms persist for > 3–5 days, or recur after improvement, non-steroidal immunosuppressive medication such as infliximab, an antitumour necrosis factor antibody, 5 mg/kg once every 2 weeks until resolution is recommended [III, A]. A recent case series suggests that vedolizumab, a gut-specific immunosuppressive agent, could be an efficient and safe alternative to infliximab. Further studies would be needed to confirm these preliminary results [V, C]. Empirical antibiotics should be considered for patients who present with fever or leukocytosis.

Pneumocystosis antibiotic prophylaxis with oral trimethoprim/sulfamethoxazole (400 mg once a day) should be added when immune suppression is prolonged.

Rare cases resulting in bowel perforation may require colectomy. In this case, a subtotal colectomy is preferred as colonic lesions are generally extensive, with a potential flare-up in the postoperative phase.

Resumption of immunotherapy is possible at disappearance of symptoms or when diarrhoea recovers to grade 1. Definitive discontinuation of immunotherapy is required in the case of grade 4 or recurrent grade 3 diarrhoea, or grade 2 not resolving after 3 months despite appropriate treatment.

Prevention and treatment of acute RT-induced diarrhoea

A rigorous assessment of signs and symptoms, including duration and severity, is necessary for the management of acute RT-induced diarrhoea. Diarrhoea stops only upon completion of the RT, so prompt therapy is necessary to ensure that patients complete the RT cycle. Dietary counselling is suggested in this treatment setting.

Table 7 shows the prevention measures and treatment approaches; for additional details please refer to Supplementary Material, available at *Annals of Oncology* online.

Treatment of chronic RT-induced diarrhoea

Despite the relatively high prevalence of chronic diarrhoea in patients submitted to pelvic RT, there is low level of evidence for available treatments [21, 46]. In particular, there is limited evidence about the beneficial effects of sucralfate, amifostine, corticosteroid enemas, bile acid sequestrants, famotidine and selenium. On the contrary, the use of aminosalicylates (mesalazine, olsalazine), misoprostol suppositories, oral magnesium oxide and octreotide injections may worsen gastrointestinal symptoms, such as diarrhoea or rectal bleeding.

Dietary counselling may reduce diarrhoeal symptoms in the long term with a beneficial effect on gastrointestinal symptoms and QoL. Table 8 lists the currently available approaches (for more details, refer to Supplementary Material, available at *Annals of Oncology* online).

Table 7. Prevention and treatment of acute RT-induced diarrhoea

Technical RT measures:
- RT techniques (e.g. IMRT) [IV, B]
- Physical measures (belly board device, bladder distension and surgical approach to displace small bowel volume) [IV, C]

Nutritional status and prophylactic agent
- Dietary counselling (e.g. reduction of fatty food, lactose-free diet in case of lactose intolerance, avoidance of drinks with caffeine or alcohol and of tobacco) [III, B]
- High-fibre diet [II, B]
- Oral supplements (e.g. administration of colesevelam for patients with bile salt malabsorption) [IV, B]
- Probiotics (*Lactobacillus*, *Bifidobacterium* and cocci) [II, B]. Need of further safety analysis in immunocompromised patients

Treatment
- Caloric and fluid intakes [IV, B]
- Loperamide (4 mg as initial dose, followed by 2 mg every 4 h, or after each unformed stool; daily total dose should not exceed 16 mg) [I, A]
- Octreotide in patients not responsive to loperamide and with severe toxicity (100 μg three times daily) [II, B]
- Anticholinergic antispasmodic agent to alleviate bowel cramping [IV, B]

IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

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

The prevalence of diarrhoea in palliative care has been reported to be ∼20%, at least in older patient populations [47]. Causes and possible management are reported in Table 9.

As for patients on active treatment, patients with advanced care experiencing diarrhoea must be rehydrated either orally or, when appropriate, by parenteral infusion. In cases of large volume diarrhoea, there is the potential for very rapid dehydration with risk of prerenal impairment or even, in extreme cases, shock. Patients may suffer electrolyte imbalance (mainly hypokalaemia).

Special attention should be given to patients who are incontinent of stool, due to the risk of pressure ulcer formation. Skin barriers should be used to prevent skin irritation caused by faecal material.

Diarrhoea may pose a major management issue for cancer and palliative care clinicians.

Role of diet: nutritional strategies during acute and chronic diarrhoea

Nutritional care

Modification of the diet is not recommended for prophylactic purposes but can be useful when the patient is developing diarrhoea.

Table 8. Treatment of chronic RT-induced diarrhoea

Referral to expert dietician after the completion of a 7-day dietary diary [IV, C]
Lifestyle advice (e.g. smoking cessation) [IV, C]
Consider referral for psychological support [IV, C]
Highly caloric nutritional supplements containing iron, folic acid, vitamin B12, vitamin D, magnesium, calcium, trace elements and fat-soluble vitamins [IV, B]
Colesevelam is better tolerated than colestyramine for bile salt malabsorption treatment [IV, B]
Broad-spectrum antimicrobial therapy (often empirical) requiring in some cases prolonged and cyclical courses [V, C]
Antidiarrhoeal agents (e.g. loperamide) [IV, B]
Pelvic floor and toileting exercises if evidence of radiation proctopathy and increased frequency of defaecation [IV, C]

RT, radiotherapy.

Table 9. Diarrhoea in advanced care patients not receiving oncological therapies

Cause	Example	Management
Drugs	Laxatives, antibiotics, antacids, PPIs, NSAIDs, iron, antidiabetics	Adjust medication
Local	Overflow diarrhoea (incomplete obstruction or constipation and impacted stools)	Enema
	Resections, fistulae or manifestations of tumour which reduce absorptive surfaces	Symptomatic therapy with loperamide
	Exocrine pancreatic insufficiency	Enzyme therapy
	Late effects of RT	See Table 8
Immune	Late effects of immunotherapy GvHD	Immunosuppression

GvHD, graft-versus-host disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RT, radiotherapy.

Most of the studies on the effects of food on gastrointestinal symptoms in patients with diarrhoea have been carried out in irritable bowel syndrome patients, so the following indications can only be used as general recommendations and must be further investigated in oncological patients. Spices like chili and beverages like coffee and alcohol have a known effect on gastrointestinal motility and can worsen gastrointestinal symptoms in patients with diarrhoea. Therefore, their consumption should be avoided during acute illness or, at least, limited. Reduction of insoluble fibre intake may also be useful [V, C].

Lactose

Bowel mucosal injury associated with ChT may lead to secondary lactose intolerance whose common manifestations are abdominal pain, flatulence, diarrhoea and, in some cases, poor nutritional status. Significant increase in the frequency of hypolactasia—revealed through an oral lactose absorption test—may be present during adjuvant 5-FU-based ChT, but it is fully reversible after therapy discontinuation. There are no studies testing the effects of a lactose-free diet in adults with diarrhoea during ChT.

In patients presenting with diarrhoea during ChT, avoidance of milk and dairy products (apart from yogurt and firm cheeses) may be a reasonable strategy to reduce the intensity and duration of symptoms [V, C].

There is insufficient evidence to suggest a lactose-free diet in patients with RT-induced diarrhoea and in the palliative setting, except for those cases in which a clear diagnosis of lactose intolerance has been made.

Lactose as an excipient. Lactose is also a common excipient in many pharmaceutical compounds. The majority of people who have lactose malabsorption can tolerate lactose amounts < 12 g, so medications are rarely able to induce symptoms in these subjects. In clinical practice, it is not rare to encounter patients complaining of gastrointestinal symptoms after the ingestion of a minimal amount of sugar (like the quantity of lactose in drugs), so lactose in drugs can be mistakenly responsible for those symptoms. It should be noted that research on lactose-containing drugs has been conducted in non-oncological patients, therefore further studies are needed to confirm these findings in oncological populations.

Even considering the possibility of different symptom thresholds among patients after lactose ingestion, we recommend caution in de-prescribing or avoiding lactose-containing drugs in cancer patients with diarrhoea in the active setting as in the palliative setting.

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols

A relatively new area of research, which is in rapid expansion, is that concerning the effect of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) on gastrointestinal symptoms in patients with IBD and irritable bowel disease. There is not sufficient evidence in oncological patients to consider a low FODMAP diet in the prevention or in the treatment of cancer-related diarrhoea and research in this direction is needed.

Pharmaconutrients and probiotics

Despite the positive effect with the use of glutamine and omega fatty acids, their use in ChT-induced diarrhoea is not recommended, as evidence of their effectiveness requires more studies. Specifically, glutamine was shown to reduce duration of diarrhoea but not its severity [II, C] [48]. The use of probiotics for the prevention of diarrhoea is also a controversial issue: if on one hand, they may create a protective barrier reducing diarrhoea and abdominal discomfort, on the other, they could put the immunocompromised patient at higher risk of severe infections.

Personalised medicine: research and potential biomarkers

A large panel of sera markers, polymorphisms or variation of microbiome are under investigation for prediction of diarrhoea under targeted therapies, ChT or immunotherapy. Homozygous *UGT1A1*28* phenotype increases the risk of irinotecan-induced toxicity including, but not restricted to, diarrhoea and the dose should be reduced for the first administration of a high-dose regimen (250 mg/m^2). Partial or complete DPD deficiency caused by non-functional *DPYD* variants can lead to increased risk of toxicity including diarrhoea with the use of 5-FU, and a dose reduction of at least 50% of the starting dose is recommended in the case of partial deficiency. However, DPD or UGT (*UGT1A1*) testing are not yet widely used before starting therapy. Additional research concerning predictors of diarrhoea caused by antitumour

Table 10. Summary of recommendations

General principles of management

- Patients with grade 1 or 2 diarrhoea with no other complicating signs or symptoms may be managed conservatively with oral hydration and loperamide [V, A]
- Patients with mild to moderate diarrhoea complicated by moderate to severe cramping, nausea and vomiting, diminished performance status, fever, sepsis, neutropaenia, bleeding or dehydration, and patients with severe diarrhoea should be hospitalised and evaluated further, monitored closely and intensively treated [V, A]. These patients should be evaluated by a multidisciplinary team including the expertise of gastroenterologists

Management of neutropaenic enterocolitis

- The initial treatment of neutropaenic enterocolitis is medical, with the administration of broad-spectrum antibiotics, G-CSFs, nasogastric decompression, i.v. fluids, bowel rest and serial abdominal examinations [V, A]
- The administered antibiotics should cover enteric gram-negative organisms, gram-positive organisms and anaerobes [V, A]
- Reasonable initial choices include monotherapy with piperacillin-tazobactam or imipenem-cilastatin or combination therapy with cefepime or ceftazidime along with metronidazole [V, A]. In cases which do not respond to antibacterial agents, amphotericin should be considered, because fungaemia is common [V, A]
- Blood transfusions may be necessary because the diarrhoea is often bloody [V, A]
- Anticholinergic, antidiarrhoeal and opioid agents should be avoided since they may aggravate ileus [V, A]
- Indications for surgery include: (i) persistent gastrointestinal bleeding after correction of thrombocytopaenia and coagulopathy; (ii) evidence of free intraperitoneal perforation; (iii) abscess formation; (iv) clinical deterioration despite aggressive supportive measures; (v) to rule out other intra-abdominal processes such as bowel obstruction or acute appendicitis through radiological examinations [V, A]
- Failure to remove the necrotic focus in these severely immunocompromised patients is often fatal [V, A]. Primary anastomosis is not generally recommended in such severely immunocompromised patients because of the increased incidence of anastomotic leak [V, A]

Treatment approaches[a]

- ORT is generally appropriate for mild diarrhoea [I, A]. ORSs, including standard WHO ORSs or commercial ORSs may be more appropriate in patients with more severe diarrhoeal disease [II, A]
- Rapid fluid resuscitation is not necessary in patients with mild to moderate hypovolaemia [I, A]. The rate of fluid administration must be greater than the rate of continued fluid losses, which is equal to the urine output plus estimated insensible losses (usually 30–50 mL/h) plus gastrointestinal losses [I, A]
- If the patient has tachycardia and is potentially septic, an initial fluid bolus of 20 mL/kg should be given [I, A]
- Fluid replacement is continued at a rapid rate until the clinical signs of hypovolaemia improve [I, A]
- Fluid balance should aim for an adequate central venous pressure and urine output $>$ 0.5 mL/kg/h [I, A]. Patients who develop oliguric acute kidney injury ($<$ 0.5 mL/kg/h) despite adequate volume resuscitation, as judged by central venous pressure, are at risk of developing pulmonary oedema and the advice of intensive-care experts or nephrologists must be urgently sought [V, B]
- Loperamide can be started at an initial dose of 4 mg followed by 2 mg every 2–4 h or after every unformed stool [II, B]. The maximum daily dose of loperamide is 16 mg
- Other opioids, such as tincture of opium, morphine or codeine can be used [V, C]
- The usual starting dose for octreotide is 100–150 μg s.c./i.v. tid [IV, B]. The dose can be titrated up to 500 μg s.c./i.v. tid or 25–50 μg/h by continual i.v. infusion [V, B]
- Uridine triacetate (dose of 10 g orally every 6 h for 20 doses) is indicated for the management of early-onset, severe or life-threatening toxicity including diarrhoea within 96 h following the end of 5-FU or capecitabine administration [II, B]
- Oral budesonide may be suggested for treatment of ChT-induced diarrhoea that was refractory to loperamide [IV, C]. Prophylactic use of budesonide is not recommended [II, B]
- In the case of bile salt malabsorption, bile acid sequestrants (e.g. cholestyramine, colestipol, colesevelam) may be an active adjuvant therapy [III, B]
- Immunotherapy-induced diarrhoea:
  - Grade 1: symptomatic treatment with oral rehydration and antidiarrhoeal treatment, racecadotril or loperamide [III, A]
  - Grade 2: budesonide 9 mg once a day can be added to the symptomatic treatment, if no bloody diarrhoea [V, C]; oral corticosteroids (0.5–1 mg/kg/day prednisone equivalent) are recommended in the case of diffuse ulceration or bleeding, or persistent symptoms after 3 days with symptomatic treatments ± budesonide [III, A]
  - Grade 3 and 4: 1–2 mg/kg/day prednisone equivalent, with i.v. injections first [III, A]. Loperamide and opioids should be avoided. If symptoms persist for $>$ 3–5 days, infliximab 5 mg/kg once every 2 weeks until resolution is recommended [III, A]. Vedolizumab could be an efficient and safe alternative to infliximab [V, C].

Role of diet

- Spices and beverages such as coffee and alcohol should be avoided and reduction of insoluble fibre intake may also be useful [V, C].
- In patients presenting with diarrhoea during ChT, avoidance of milk and dairy products (apart from yogurt and firm cheeses) may be a reasonable strategy to reduce the intensity and duration of symptoms [V, C].

[a]For treatment of acute and chronic RT-induced diarrhoea, see Tables 7 and 8.

5-FU, 5-fluorouracil; ChT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; i.v., intravenous; ORS, oral rehydration solution; ORT, oral rehydration therapy; RT, radiotherapy; s.c., subcutaneous; tid, three times a day; WHO, World Health Organization.

Table 11. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

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].

treatment will probably allow the clinician to individualise the therapeutic approach for each patient.

DPD deficiency is relatively common among Caucasians (3%–5%). Although the diagnosis can be made by radioimmunometric assay for the DPD enzyme, this test is not readily available. More recently, a simple breath test has been developed and this may provide an effective screening tool.

Limitations

Some other aspects of the association of diarrhoea-neoplastic disease and/or treatment are not covered in this guideline, especially the evaluation in the context of GvHD and/or infection after allogeneic stem cell transplantation, where specific literature overviews already exist [49].

Conclusions

Diarrhoea in cancer patients is a symptom with high impact on QoL and social functioning. The clinical approach should follow the correct identification of pathogenesis of this symptom, to tailor the therapies according to the underlying causes. Prevention of associated complications is one of the pillars of the therapeutic strategy. In the future, identification of patients at higher risk of developing diarrhoea following specific treatments will allow for selection of personalised programmes to reduce the severity and duration of this symptom.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 10. Levels of evidence and grades of recommendation have been applied using the system shown in Table 11. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

PB has reported honoraria from Roche, Merck, Mundipharma, Kyowa Kirin Pharmaceutical Development and AstraZeneca; KJ has reported advisory boards and/or honoraria for presentations for Merck, Merck Sharp & Dohme, Helsinn, Tesaro, Amgen, Hexal and Pfizer; AA, NC, OR, SP, FT, US, AS and CIR have reported no conflicts of interest.

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