Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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Background: Cancer patients frequently suffer from gastrointestinal complications. However, a comprehensive, practical and evidence-based guideline on this issue is not yet available.

Patients and methods: An expert group was put together by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) to develop a guideline on gastrointestinal complications in...
cancer patients. For each subtopic, a literature search was carried out in PubMed, Medline and Cochrane databases and the strength of recommendation and the quality of the published evidence for major therapeutic strategies were categorized using a modification of the ‘Infectious Diseases Society of America’ criteria. Consensus discussions were held on each of the topics.

**Results:** Recommendations were made with respect to non-infectious and infectious gastrointestinal complications. For all recommendations, the strength of the recommendation and the level of evidence are presented.

**Conclusion:** This guideline is an evidence-based approach to the diagnosis and management of gastrointestinal complications in cancer patients.

**Key words:** diarrhea, enterocolitis, fever, gastrointestinal, neutropenia

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**Introduction**

Abdominal complications are a frequent matter of concern in patients with hematological or oncological malignancies. Even though several existing guidelines cover selected abdominal pathologies, a comprehensive, practical and evidence-based guideline on gastrointestinal complications in cancer patients is not yet available. The present guideline intends to close this gap, covering the epidemiology, pathophysiology, diagnosis and treatment of most non-infectious and infectious complications as well as the corresponding hygiene measures. Whenever possible, pre-existent recommendations were incorporated into this overview.

**Methods**

Subtopics of this guideline were assigned to members of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) and a literature search was carried out in PubMed, Medline and Cochrane databases. The strength of recommendation and the quality of evidence for major therapeutic strategies were categorized using a modification of the ‘Infectious Diseases Society of America’ criteria (IDSA, Table 1) [1]. To increase transparency in the evaluation of the evidence, we added an index to the level II recommendations and to all transferred evidence, where appropriate.

Consensus discussions were held on each of the topics. After ratification of all topics by this expert group, recommendations were discussed and ratified by the AGIHO during the 2011 guideline meeting.

Treatment-associated anorexia, nausea and emesis were not included in the guideline. While they involve the gastrointestinal tract, a complete overview of their management would go beyond the scope of this guideline and has already been provided elsewhere.

**Guideline**

**Diarrhea**

Independent of its cause, diarrhea should always be treated with adequate oral or intravenous fluid and electrolyte replacement (AIII). Patients should be observed for signs of malnutrition and/or catabolic state. If indicated, enteral or parenteral electrolytes, carbohydrates, lipids, amino acids, protein and vitamins should be supplemented (AIII). Figure 1 provides important facts on the diagnostic workup of diarrhea in cancer patients. As a general rule, repeat testing for the same pathogen should not be carried out to avoid false-positive results.

**Non-infection-related diarrhea**

**Paraneoplastic diarrhea**. Paraneoplastic diarrhea is a rare phenomenon which may be triggered by a variety of pathophysiological mechanisms. Secretion of vasoactive intestinal polypeptides (VIPs), as typically observed in patients with non-β islet cell tumors of the pancreas, may cause watery diarrhea, hypokalemia and hypochlorhydria [2].Flush and diarrhea are the typical symptoms of serotonin-producing carcinoid tumors [3]. Other hormones that may cause paraneoplastic diarrhea include glucagon (glucagonoma), gastrin (gastrinoma or hepatocellular carcinoma), somatostatin (somatostatinoma or pheochromocytoma) and the prostaglandins (hepatocellular carcinoma) [4–8]. In association with small-cell lung carcinoma, antibodies directed against neuronal proteins

<table>
<thead>
<tr>
<th>Category, grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Strength of recommendation</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence to support a recommendation against use</td>
</tr>
<tr>
<td>E</td>
<td>Good evidence to support a recommendation against use</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from one or more properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from one or more well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time-series; from meta-analyses or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees</td>
</tr>
</tbody>
</table>

**Index**

<table>
<thead>
<tr>
<th>Index</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>Meta-analysis or systematic review of randomized, controlled trials</td>
</tr>
<tr>
<td>t</td>
<td>Transferred evidence, i.e. results from different patient cohorts, or similar immune-status situation</td>
</tr>
<tr>
<td>h</td>
<td>Comparator group is a historical control</td>
</tr>
<tr>
<td>u</td>
<td>Uncontrolled trial</td>
</tr>
<tr>
<td>a</td>
<td>Abstract published at an international meeting</td>
</tr>
</tbody>
</table>
may cause autonomic neuropathy and consequent diarrhea [9]. In patients with thymoma, diarrhea as part of a graft-versus-host-disease-like reaction has been described [10, 11].

In most cases of paraneoplastic diarrhea, diagnosis and treatment of the underlying disease are considered the only effective measure to reduce diarrhea. Carcinoid and some other neuroendocrine tumors might, however, respond to blockage of somatostatin receptors with octreotide or lanreotide (Table 2). Depot octreotide may be initiated at a dose of 20–30 mg im every 4 weeks. In case of severe initial or refractory symptoms, supplementation with short-acting octreotide at 150–250 µg tid sc is suggested. If clinical response is achieved, continuous therapy might be considered [12–14] (AII). Lanreotide may initially be administered at 60 mg qd im every 4 weeks [15] (AII).

**therapy-associated diarrhea.** In cancer patients, the factors related to toxic effects of chemotherapy are the most common cause of abdominal complications. 5-Fluorouracil, irinotecan, capecitabine, anthracyclines and a number of small molecules and monoclonal antibodies have been associated with an increased frequency of therapy-associated diarrhea [16–24]. Recent studies have reported incidence rates of diarrhea in 27%–76% of neutropenic patients. In only 5%–17% of these cases, an infectious agent was identified as the cause of diarrhea, suggesting primarily toxicity-related symptoms [16, 25–27]. Disruption of the gastrointestinal microflora after administration of antibiotics may result in osmotic diarrhea due to alterations in carbohydrate metabolism and impaired absorption of short-chain fatty acids in 5%–62% of patients [28–30]. In 7%–50% of these cases, overgrowth with *Clostridium difficile* may ensue, leading to *C. difficile*-associated diarrhea (see *Clostridium difficile* infection) [31, 32].

Chemotherapy-associated lactose intolerance presenting as diarrhea, bloating and malabsorption has also been discussed as a cause of non-infectious diarrhea in cancer patients. While up to 35% of patients have been shown to present with an abnormal lactose breath hydrogen test during chemotherapy, only up to 11% became symptomatic. Generally, test results returned to normal after completion of chemotherapy [33, 34].

Radiation therapy involving the gastrointestinal tract may cause severe mucosal bowel damage resulting in acute or chronic diarrhea. Symptoms usually peak about 7–14 days after initiation of radiation and may be intensified by combination treatment with chemotherapy. In some patients, surgical resection may result in impairment of physiological gastrointestinal function with diarrhea developing as a consequence of shortened gastric and intestinal transit times, bacterial overgrowth and altered secretion and absorption of bile acids.

Once an infectious cause of diarrhea has been discarded (see Figure 1), loperamide (2 mg po every 2 h and 4 mg po every 4 h at night) is recommended for first-line treatment of non-infectious diarrhea [35–38] (AIIa). In patients failing to respond to loperamide, octreotide at a dosage of 500 µg tid sc may be considered [39–41] (BII). In patients not responding to the initial dosage, dose increase until symptom control is recommended [39–43] (AIII). An alternative might be the administration of psyllium seeds, although this approach has not been evaluated in patients with chemotherapy-associated
Further options include diphenoxylate plus atropine and opiates such as paregoric, tincture of opium, codeine and morphine [35] (BIII).

While data on budesonide prophylaxis for late-onset diarrhea after treatment with irinotecan showed no significant advantage for preventive treatment [46] (CII), addition of budesonide [23] (BIIa) or acetorphan [24] (BII) to loperamide treatment was effective in two small clinical trials. In a small patient population, neomycin was assessed as secondary prophylaxis for irinotecan-induced diarrhea [47, 48] (BIII).

Patients with severe diarrhea persisting for >48 h despite administration of antimotility agents should be hospitalized [35] (AIII). Of note, in long-term neutropenic patients, overdosage of antimotility agents may lead to iatrogenic ileus with an increased risk of bacteremia.

Regarding chemotherapy-associated lactose intolerance, we do not recommend dietary restriction of milk products, unless clinical symptoms of lactose intolerance are observed after ingestion of milk products [33, 34] (BIIu).

A large number of trials assessing the protective effect of prophylactic probiotic treatment to avoid antibiotic-associated diarrhea have been conducted. Studies in immunocompetent patients suggest a protective effect for Saccharomyces boulardii, Lactobacillus rhamnosus and a combination of L. casei, L. bulgaricus and S. thermophiles [31, 49, 50]. However, the safety of probiotics in neutropenic patients has not been

### Table 2. Treatment of paraneoplastic and therapy-associated non-infection-related diarrhea

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic diarrhea in carcinoid tumors</td>
<td>Depot octreotide 20–30 mg im every 4 weeks</td>
<td>A</td>
<td>II</td>
<td>[12–14]</td>
<td>During first two weeks of treatment overlap with short acting octreotide at 150–250 µg tid sc</td>
</tr>
<tr>
<td></td>
<td>Depot lanreotide 60 mg im every 4 weeks</td>
<td>A</td>
<td>II</td>
<td>[15]</td>
<td>In case of refractory symptoms, supplement with short acting octreotide at 150–250 µg tid sc</td>
</tr>
<tr>
<td>Therapy-associated diarrhea</td>
<td>Loperamide 2 mg po every 2 h and 4 mg po every 4 h at night</td>
<td>A</td>
<td>IIu</td>
<td>[36–38]</td>
<td>Only in persisting and severe cases of diarrhea and after exclusion of infectious diarrhea</td>
</tr>
<tr>
<td></td>
<td>Psyllium seeds</td>
<td>B</td>
<td>IIu</td>
<td>[44,45]</td>
<td>Only in persisting and severe cases of diarrhea and after exclusion of infectious diarrhea</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis with budesonide 3 mg tid po or Neomycin 500 mg bid po</td>
<td>C</td>
<td>II</td>
<td>[46]</td>
<td>Neomycin was only assessed as secondary prophylaxis in patients with grade II-IV diarrhea during the first chemotherapy cycle.</td>
</tr>
<tr>
<td>Late-onset diarrhea after irinotecan therapy</td>
<td>Treatment with loperamide plus Budesonide 3 mg tid po until resolution of symptoms or Acetorphan 100 mg tid po for 48 h</td>
<td>B</td>
<td>IIu</td>
<td>[23]</td>
<td>Stop treatment, if no response after 72 h</td>
</tr>
<tr>
<td>Late-onset diarrhea after irinotecan therapy</td>
<td>Prophylaxis with loperamide plus Budesonide 3 mg tid po until resolution of symptoms or Acetorphan 100 mg tid po for 48 h</td>
<td>B</td>
<td>II</td>
<td>[24]</td>
<td>Stop treatment, if no response after 72 h</td>
</tr>
<tr>
<td>Chemotherapy-associated lactose intolerance</td>
<td>Dietary restriction of milk products</td>
<td>B</td>
<td>IIu</td>
<td>[33,34]</td>
<td>Only if clinical signs and symptoms present</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>Probiotic prophylaxis</td>
<td>C</td>
<td>III</td>
<td>[31,49,50]</td>
<td>No safety data in immunocompromised patients available</td>
</tr>
</tbody>
</table>

SoR, strength of recommendation; QoE, quality of evidence.
sufficiently assessed to recommend their prophylactic use in this population (CIII). In association with the yeast S. boulardii, bloodstream infections have been reported [51]. Recommendations on therapy-associated diarrhea have been summarized in Table 2.

infection-related diarrhea

The diagnosis of infection-related diarrhea should trigger adequate hygiene measures (BI) [52, 53]. The regular practice of appropriate hand hygiene is considered a cornerstone in the prevention of hospital-acquired infections [52, 53] and has been discussed in detail elsewhere [54]. Table 3 shows recommended hygiene procedures for most common infectious causes of gastroenteritis. Of note, hygiene measures can be subjected to local or national legislation which may differ from these recommendations.

clostridium difficile infection. Clostridium difficile is the most common cause of health-care associated infectious diarrhea and colitis, accounting for up to 50% of all cases of antibiotic-associated diarrhea [31, 32]. In adult patients with cancer, infections due to C. difficile (CDI) occur in 5%–9% of chemotherapy courses and 5%–20% of patients, respectively [26, 27, 55–60].

Binding of C. difficile toxins A and B to epithelial cells and subsequent internalization lead to diarrhea by induction of apoptosis [61]. An increase in the frequency of CDI has been reported and attributed to the emergence of a new and hypervirulent strain of C. difficile, named NAP1 (synonymous terms are BI, ribotype 027 and toxino-type III) [62–64]. In NAP1 strains, single-base deletion mutations at position 117 of the tcdC gene, a downregulator of toxin transcription, lead to disinhibition of toxins A and B production, thus contributing to increased intralocular toxin levels [65]. Major risk factors for CDI include age, chemotherapy, antibiotic agents, antimotility drugs, ventilation, proton pump inhibitors, H2 antagonists and hypalbuminemia [60, 64, 66–70].

Clinical signs and symptoms of CDI are diarrhea, fever, abdominal pain and distension. The severity of the disease ranges from mild diarrhea to fulminant pseudomembranous colitis with paralytic ileus, toxic megacolon or perforation [56, 59, 71]. The onset of diarrhea may occur at any time during and up to 2 weeks after the end of antibiotic treatment [71].

In accordance with ESCMID (European Society of Clinical Microbiology and Infectious Diseases) guidelines, CDI is defined as (i) >3 unformed stools within 24 h, (ii) ileus or toxic megacolon in combination with evidence of toxin-producing C. difficile in stools and absence of another cause of symptoms or (iii) pseudomembranous colitis diagnosed by endoscopy, colectomy or histopathological examination [72]. The proper laboratory specimen is an unformed stool promptly submitted to the laboratory [63, 73]. Processing a single specimen from a patient at onset of a symptomatic episode is sufficient and should not be repeated to avoid false-positive results through multiple testing [74].

Given the slow turnaround of highly sensitive (94%–100%) cytotoxin assays [63], stool samples should be tested for the presence of toxin-producing strains by enzyme immunoassays for cytotoxins A and B (sensitivity 50%–80%, specificity 98%–99%) [75] or for C. difficile common antigen (GDH; sensitivity 85%–95%, specificity 89%–99%) [76], or alternatively by real-time PCR assays for the gene-encoding toxin B (sensitivity 97%, specificity 93%) [77]. Samples with negative test results can be reported as negative, while samples with a positive first test result should be re-tested with a different method [73]. To avoid treatment delays in the setting of high-risk patients, we recommend early therapeutic intervention before confirmatory test results are available. In neutropenic patients, as well as in

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**Table 3.** Isolation procedures for the most common causes of infectious diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>SR</th>
<th>GG</th>
<th>M</th>
<th>Infectious Material</th>
<th>Stop</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>•</td>
<td>○</td>
<td></td>
<td>Feces</td>
<td>Normalization of clinical symptoms (diarrhea or colitis)</td>
<td>B</td>
<td>III</td>
<td>Use warm water and plain soap for hand hygiene after patient contact. No precautions for asymptomatically colonized patients. Do not re-test for <em>C. difficile</em> toxin to evaluate further necessity of isolation. Gloves and gown only if contact with infectious material or contaminated surfaces.</td>
</tr>
<tr>
<td><em>Salmonella, Shigella, Yersinia, Campylobacter</em> spp.</td>
<td>•</td>
<td>○</td>
<td></td>
<td>Feces, vomitus, possibly urine</td>
<td>Three negative stool samples</td>
<td>B</td>
<td>III</td>
<td>Gloves and gown only if contact with infectious material or contaminated surfaces.</td>
</tr>
<tr>
<td>Norovirus and other causes of viral gastroenteritis</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>Feces, vomitus</td>
<td>Three negative stool samples</td>
<td>B</td>
<td>III</td>
<td>Gloves and gown only if contact with infectious material or contaminated surfaces.</td>
</tr>
</tbody>
</table>

•, always required; ○, only required under certain circumstances specified in the comment box; SR, single room; GG, gloves and gown; M, mask; SoR, strength of recommendation; QoE, quality of evidence.
patients with severe colitis, diagnostic endoscopy is contraindicated because of the risk of colon perforation or hemorrhage [64].

Recently updated ESCMID and SHEA/IDSA guidelines differentiate between severe and non-severe cases of CDI [63, 72]. Leukocytosis, used as a crucial criterion for categorization in both the guidelines, is not a useful parameter in neutropenic patients. Neutropenic patients presenting with chemotherapy-associated bowel syndrome (CABS; T ≥ 37.8°C and abdominal pain and/or lack of bowel movement for ≥72 h) have been shown to be more likely to suffer complications and death and should be categorized as having severe disease [26].

Three large controlled, randomized trials including predominantly immunocompetent patients reported CDI cure rates between 76% and 97% and recurrence rates between 7% and 27% [78–80]. CDI-associated mortality is estimated at 2%–7% in immunocompetent and -compromised patients [27, 60, 81, 82].

To minimize the risk of developing CDI, antibiotics should cover a spectrum no broader than necessary, and should be adapted with respect to results of cultures and/or susceptibility test data (BIII). If possible, other antibiotics should be discontinued after diagnosis of CDI [83–85] (AII); however, in febrile neutropenia, this may not always be possible.

There is no evidence to support prophylactic antibiotic treatment to prevent CDI (CIII). While there may be a protective effect by probiotic prophylaxis [86, 87], the safety of probiotics in neutropenic patients has not been sufficiently assessed to recommend their use (CIII). The results from one small, monocentric observational study in a mixed patient population do not suffice to generally recommend empirical therapy of diarrhea with metronidazole [88] (CII). However, in severe or complicated clinical disease with suspected CDI, empirical metronidazole treatment may be considered (BIII). Antiperistaltic agents, including opiates, are discouraged [89] (DII).

For non-severe CDI, a randomized, controlled trial showed similar cure rates for oral metronidazole and oral vancomycin. For severe cases, however, superiority was shown for treatment with vancomycin [80]. In two large randomized, controlled trials, fidaxomicin, a new macrocyclic antibiotic, fulfilled non-inferiority criteria when compared with vancomycin for the treatment of CDI [78, 79]. While metronidazole, vancomycin and fidaxomicin might be used as first-line treatment of non-severe CDI [80] (AI), only fidaxomicin or oral vancomycin is recommended for the treatment of severe CDI [78–80] (AI).

There is no evidence to support combination therapy in patients with CDI (CIII). Intravenously administered metronidazole at a dosage of 1500 mg qd iv for 10 days is likely to result in effective concentrations in feces and colon [90, 91] and may be an option if oral antimicrobials cannot be administered (AIIIa). In severe cases of CDI, additional administration of vancomycin by a nasogastric tube and/or by a rectal catheter or retention enema at 500 mg may be discussed [90–92] (CIII). In case of complicated CDI, a surgical evaluation should be obtained at an early stage of disease, however, surgical intervention in the neutropenic and/or thrombocytopenic patient should be reserved to selected complicated cases (BIII). To reduce costs, the intravenous formulation of vancomycin may be used for oral administration without safety or efficacy hazards [63] (BIII). Recommendations on the prophylaxis and treatment of CDI, including recurrences are summarized in Table 4.

other bacterial infections causing diarrhea (nontyphoidal salmonella, shigella, yersinia or campylobacter spp.). In cancer patients, infection-related diarrhea due to nontyphoidal Salmonella, Shigella, Yersiniae or Campylobacter spp. (SSYC) is a rare event (0%–2.8%) [27, 93–97]. Clinical signs and symptoms include watery, mucoid or bloody diarrhea, abdominal tenderness, fever and nausia. Abdominal pain tends to be particularly severe in Campylobacter enteritis and may mimic appendicitis in Yersinia spp. and Campylobacter spp. infection. Gastrointestinal infections with SSYC may be followed by reactive arthritis. Campylobacter spp. infection has been associated with subsequent occurrence of Guillain–Barré syndrome, while hemolytic–uremic syndrome has been observed in association with Shigella spp. In rare cases, acute disease may be further complicated by rectal prolapse, bacteremia, ileus, toxic megacolon and perforation. Since SSYC are typically community-acquired, testing for these pathogens should be restricted to fecal samples taken within 72 h of hospital admission from symptomatic patients. In case of clinical deterioration, an abdominal ultrasound or X-ray may be carried out to detect an ileus or toxic megacolon. A thickened bowel wall may be detected by an abdominal ultrasound or a computer tomography (CT) scan. In this case, the differential diagnosis of NEC should be considered. Perforation rarely occurs in this setting and may be identified by plain abdominal X-ray.

Based on the low incidence of these entities, prophylactic treatment is not recommended [27, 93–97] (CII). While nonsevere cases of diarrhea caused by bacteria other than C. difficile may not always require antibiotic treatment, severely ill and/or immunocompromised individuals should receive systemic treatment (BIII). Given the lack of data in these populations, treatment recommendations for cancer patients were derived from studies carried out in immunocompetent individuals. For infections caused by Yersinia spp., treatment with a fluoroquinolone or trimethoprim–sulfamethoxazole (TMP–SMZ) or doxycycline is suggested [98, 99] (BIi). For patients with severe disease, the preferred regimen is a third generation cephalosporin combined with gentamicin [99] (BIi). For infections with Campylobacter spp., azithromycin has become the drug of choice due to an increase in fluoroquinolone resistance (19%) [100] (BIi). Two randomized, controlled trials on the treatment of shigellosis established ciprofloxacin or another fluoroquinolone as the treatment of choice with azithromycin being an effective alternative [167, 168] (BIii). Immunocompromised patients suffering from salmonellosis may benefit from therapy with ciprofloxacin. Alternatively, TMP–SMZ or amoxicillin may be administered depending on in vitro susceptibility test results [101] (BIi). In patients with Salmonella spp. bacteremia, treatment with a combination of ceftriaxone plus ciprofloxacin is recommended to avoid initial treatment failure before resistance test results are available and allow de-escalation to a monotherapy [101, 102] (BIi). Table 5 summarizes treatment recommendations for SSYC.
viral infections. The most common causes of viral gastroenteritis in cancer patients include norovirus (earlier known as Norwalk-like virus), rotavirus, adenovirus and cytomegalovirus (CMV). Self-limiting infections with norovirus and rotavirus may affect cancer patients of all risk groups. On the other hand, patients with impaired cellular immunity, e.g. due to a chronic lymphatic malignancy, immunosuppression after allo-SCT, treatment with alemtuzumab or other substances interfering with T-cell activity, are at an increased risk of developing clinically significant courses of viral gastroenteritis due to CMV or adenovirus, warranting treatment. These infections are unlikely to occur in patients undergoing conventional chemotherapy and those suffering from solid tumors. Impaired cellular immunity also predisposes to prolonged courses of diarrhea and viral shedding [103–107].

Norovirus is a frequent cause of acute gastroenteritis during the cold season. Transmission occurs by contact with excretions, even in the form of aerosols, and requires only 10–100 viral particles. The incubation period of 12–48 h is typically followed by vomiting, diarrhea, abdominal pain, myalgia and low fever. In the immunocompetent host, the course is self-limiting with symptoms lasting for 12–72 h and viral shedding continuing for up to 3 weeks [104]. Real-time PCR (sensitivity 94%, specificity 92%) is currently considered the mainstay of diagnosis with alternatives including norovirus antigen detection and electron microscopy [109, 110]. A considerable mortality rate of up to 25% has been attributed to norovirus gastroenteritis in allo-SCT patients [111]. No specific treatment options are currently available.

Rotavirus gastroenteritis may occur after ingestion of about 100 viral particles and an incubation period of 1–3 days. Symptoms include diarrhea, vomiting and fever for 4–7 days. Viral excretion continues for 8–14 days. Antigen tests show good sensitivity. Incidence rates of 2.5 and 1.3%, respectively,
have been reported from cohorts of neutropenic high-risk and allo-SCT patients presenting with diarrhea, respectively [26, 96]. Little is known on the associated morbidity and mortality in the immunocompromised patient [103, 112]. The only available vaccine is an attenuated live vaccine; however, fatal infections have been reported in children with severe combined immunodeficiency [113](EII).

A 3-day course of nitazoxanide significantly reduced the duration of rotavirus disease in immunocompetent hospitalized pediatric patients [114]. As this therapy has not been assessed in immunocompromised patients, further studies are required before a recommendation can be made (CI). In two patients, oral immunoglobulin has been successfully used to treat rotavirus gastroenteritis [115](CIII).

Adenovirus is typically associated with gastroenteritis in newborn and children as well as with keratoconjunctivitis epidemica and acute respiratory distress syndrome. In patients with impaired cellular immunity, life-threatening courses of disease have been reported [116, 117]. Regarding treatment recommendations, only limited data from case reports are available. Low-dose cidofovir (1 mg/kg thrice a week) was effective in one adult patient [116] and in a report from a pediatric hematology unit with an adenovirus outbreak, seven patients were successfully treated with cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week [118]. Treatment with cidofovir may therefore be discussed in severely ill patients with adenovirus-associated diarrhea (BII); however, its considerable nephrotoxicity should be taken into account.

CMV is found in blood and excretions of individuals with profound and long-lasting cellular immunosuppression and is a rare cause of gastrointestinal infections in other patient groups [119–122]. Patients may present with nausea, vomiting, bloody or non-bloody diarrhea, fever, abdominal pain and prolonged anorexia [123]. CMV infection is diagnosed by detection of antigen (pp65; antigenemia assay), DNA or mRNA. Quantification of viral load by PCR is also widely available [124]. However, for diagnosis of CMV enteritis, detection of CMV in peripheral blood is not appropriate and may be negative. Similarly, CMV detection in fecal samples does not suffice to establish a diagnosis. To this end, CMV detection in an endoscopically obtained biopsy specimen from suspicious areas in the esophagus, stomach, small bowel and large intestine is needed [125, 126]. The diagnosis is made by the association of CMV.

### Table 5. Treatment of nontyphoidal Salmonella, Shigella, Yersinia and Campylobacter spp. (SSYC)

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia or immunosuppression</td>
<td><em>Salmonella, Shigella, Yersinia or Campylobacter spp.</em> prophylaxis</td>
<td>C</td>
<td>IIu</td>
<td>[93,96,97]</td>
<td></td>
</tr>
<tr>
<td>Diarrhea caused by nontyphoidal <em>Salmonella</em> spp.</td>
<td>Ciprofloxacin 400 mg bid iv or 500 mg bid po; Alternatives: Levofloxacin 500 mg qd po or Amoxicillin 500 mg tid po or TMP–SMZ 160/180 mg bid po/iv</td>
<td>B</td>
<td>IIi</td>
<td>[101]</td>
<td>Alternative choice depending on <em>in vitro</em> susceptibility</td>
</tr>
<tr>
<td>Bacteremia caused by nontyphoidal <em>Salmonella</em> spp.</td>
<td>Ceftriaxone 2 g qd iv plus ciprofloxacin 500 mg bid iv</td>
<td>B</td>
<td>IIi</td>
<td>[101,102]</td>
<td>Start with combination therapy and de-escalate once resistance data becomes available</td>
</tr>
<tr>
<td>Diarrhea caused by <em>Shigella</em> spp.</td>
<td>Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv or 500 mg bid po, levofloxacin 500 mg qd po) or Azithromycin 500 mg qd iv/po</td>
<td>B</td>
<td>Ii</td>
<td>[167,168]</td>
<td></td>
</tr>
<tr>
<td>Diarrhea caused by <em>Campylobacter</em> spp.</td>
<td>Azithromycin 500 mg qd iv/po; Alternative: Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv or 500 mg bid po, levofloxacin 500 mg qd po)</td>
<td>B</td>
<td>IIi</td>
<td>[100]</td>
<td>High fluoroquinolone resistance rate of 19%</td>
</tr>
<tr>
<td>Diarrhea caused by <em>Yersinia</em> spp.</td>
<td>Fluoroquinolone (e.g. ciprofloxacin 400 mg bid iv or 500 mg bid po, levofloxacin 500 mg qd po) or Doxycycline 100 mb bid iv/po</td>
<td>B</td>
<td>IIi</td>
<td>[98,99]</td>
<td></td>
</tr>
<tr>
<td>Bacteremia caused by <em>Yersinia</em> spp.</td>
<td>Ceftriaxone 2 g qd iv plus gentamicin 5 mg/kg qd iv</td>
<td>B</td>
<td>IIi</td>
<td>[99]</td>
<td></td>
</tr>
</tbody>
</table>

SoR, strength of recommendation; QoE, quality of evidence; TMP–SMZ, trimethoprim–sulfamethoxazole.
disease with specific mucosa pathology and appropriate symptoms [127].

Recommendations on CMV prophylaxis and pre-emptive treatment are given in the updated ECIL recommendations on the management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpes virus (HHV-8) infections in patients with hematological malignancies and after SCT [128, 129].

We recommend treating gastrointestinal CMV disease with ganciclovir for 2 to 3 weeks with induction dosing of 5 mg/kg bid iv, followed by several weeks of maintenance therapy at a dose of 5 mg/kg qd iv on 5 to 6 days per week. The prolonged treatment interval is intended to cover the period of mucosal re-epithelialization [123] (BII). The addition of immunoglobulins to antiviral therapy may be considered; however, there are currently no data supporting this strategy [130–132] (CII). Regarding antiviral treatment alternatives, the administration of foscarnet [133] (BII), cidofovir [134–136] (BII), or the combination of foscarnet and ganciclovir may be considered [137, 138] (BII). Both substances, foscarnet and cidofovir, are associated with significant renal toxicity. Recommendations on the treatment of viral gastroenteritis have been summarized in Table 6.

parasitic infections. Given extensive travels, and growing populations of migrants, rising incidence rates of gastrointestinal infections with parasites are to be expected. Previous studies identified Cryptosporidium parvum in stools of 9.6%–14.4% of patients with hematological malignancies presenting with diarrhea. The majority of these patients had undergone allo-SCT [95, 139]. In cancer patients with chronic diarrhea, examination of stools for cysts may be warranted, if no other cause of diarrhea could be identified. In this case, other protozoans, e.g. Isospora belli, Sarcocystis hominis, S. suihominis and Cyclospora cayetanensis, should also be considered as potential causative pathogens. In rare cases, Entamoeba histolytica, Giardia lamblia and Strongyloides stercoralis may cause symptomatic disease in patients coming from endemic areas [140, 141].

There are currently no treatment options apart from supportive therapy for S. hominis and S. suihominis. However, symptomatic infections with I. belli and C. cayetanensis may be treated with TMP–SMZ 160 mg/800 mg bid po or ciprofloxacin 500 mg bid po for 7 days [142, 143] (AII). In a small case series of allo-SCT patients infected with C. parvum, therapy with nitazoxanide plus azithromycin yielded promising results. However, based on these data only, a reliable recommendation for antimicrobial treatment of C. parvum cannot be made (CIIu).

chemotherapy-associated bowel syndrome and neutropenic enterocolitis

Neutropenic enterocolitis (NEC) is a common chemotherapy-associated complication, particularly in patients with acute leukemia [16, 58, 144–146]. A pooled incidence rate of 5.3% was calculated for patients with hematological malignancies or those receiving high-dose chemotherapy for solid tumors or aplastic anemia. NEC has been associated with mortality rates between 30% and 82% [145, 147]. Administration of cytosine arabinosid and anthracyclines has been identified as major risk factors. However, many other cytostatic agents as well as radiotherapy have been identified as triggers of NEC [27, 148–157]. Mucosal barrier damage facilitates infiltration and penetration of the bowel wall by bacteria, viruses and fungi.

Table 6. Treatment of viral gastroenteritis

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus enteritis</td>
<td>Nitazoxanide 7.5 mg/kg bid po</td>
<td>C</td>
<td>I</td>
<td>[114]</td>
<td>Only assessed in immunocompetent pediatric patients</td>
</tr>
<tr>
<td>Adenovirus enteritis</td>
<td>Oral immunoglobulin</td>
<td>C</td>
<td>III</td>
<td>[115]</td>
<td>No sufficient evidence to recommend dosage</td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week</td>
<td>B</td>
<td>II u</td>
<td>[116,118]</td>
<td>To reduce cidofovir toxicity, add at least 2 l of iv prehydration and probenecid 2 g po 3 h prior and 1 g 2 and 8 h following cidofovir</td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Ganciclovir 5 mg/kg bid iv for 2–3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week</td>
<td>B</td>
<td>II</td>
<td>[123]</td>
<td></td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Foscarnet 90 mg/kg bid iv over 2 h followed by 60 mg/kg tid iv over 1 h or</td>
<td>B</td>
<td>I u</td>
<td>[133]</td>
<td>Used in a pre-emptive setting</td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every week or</td>
<td>B</td>
<td>II u</td>
<td>[134–136]</td>
<td>To reduce cidofovir toxicity, add at least 2 l of iv prehydration and probenecid 2 g po 3h prior and 1 g 2 and 8 h following cidofovir</td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Foscarnet 90 mg/kg bid iv over 2 h followed by 60 mg/kg tid iv over 1 h plus ganciclovir 5 mg/kg bid iv for 2 to 3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week</td>
<td>B</td>
<td>II</td>
<td>[137,138]</td>
<td></td>
</tr>
<tr>
<td>CMV enteritis</td>
<td>Addition of iv immunoglobulin</td>
<td>C</td>
<td>II u</td>
<td>[130–132]</td>
<td>No sufficient evidence to recommend dosage</td>
</tr>
</tbody>
</table>

SoR, strength of recommendation; QoE, quality of evidence.
From blood cultures drawn during episodes of NEC, gram-negative Enterobacteriaceae were the most frequently documented organisms [16, 26, 58]. A systematic review on fungal infections related to NEC found a pooled frequency of 6.2% [147].

Clinical signs and symptoms include abdominal pain, diarrhea, nausea and vomiting. In more severe cases rebound tenderness, decreased bowel sounds or guarding may develop. The proposed diagnostic criteria according to Gorschlüter et al. include the presence of fever, abdominal pain and a bowel wall thickening of >4 mm (transversal scan) or >30 mm (longitudinal scan) in any segment by ultrasonography (US) or CT [146].

Since this definition of NEC describes patients at a late pathophysiological stage of intestinal impairment, a clinical definition identifying neutropenic patients at risk of further clinical deterioration due to abdominal complications was recently developed. It could be shown that neutropenic patients with chemotherapy-associated bowel syndrome \((T \geq 37.8^\circ C)\) and abdominal pain and/or lack of bowel movement for \(\geq 72\) h were more likely to suffer complications and death [26].

Noninvasive imaging is generally recommended to confirm the diagnosis of NEC and to exclude bowel wall perforation. Blood cultures, stool cultures and a \(C.\) \textit{difficile} toxin test for exclusion of NEC-associated bacteremia and colitis due to \(C.\) \textit{difficile}, respectively, are recommended. Endoscopy to obtain biopsies is discouraged, due to the increased risk of bowel wall perforation.

Conservative therapy is preferred in most cases, consisting of a bland diet, hydration and an effective pain treatment (BIII). In accordance with IDSA guidelines for patients with complicated abdominal infections in non-neutropenic patients [158] and the guideline for antimicrobial therapy of unexplained fever in neutropenic patients of the AGIHO [159], we recommend administration of piperacillin/tazobactam or a carbapenem with anti-pseudomonal activity (imipenem/cilastatin, meropenem or doripenem) (BIII). There are no studies assessing the effect of additional metronidazole or vancomycin on patient outcome (CIII). Empirical antifungal therapy may be discussed if it has not yet been administered for the indication of persistent febrile neutropenia [147, 160, 161] (BIII). The use of hematopoietic growth factors should be considered, even though corresponding evidence is not available (BIII). Therapy should be administered until resolution of clinical signs and neutropaenia. While a surgical consultation should be obtained at an early stage of disease evolution, surgical interventions in the neutropenic and/or thrombocytopenic patient is reserved to severe cases, e.g. patients with bowel wall perforation (BIII).

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**references**

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