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SYSTEMATIC REVIEWS

Gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy in the years 2000

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Abstract

AIM: To review gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy. To look at gut microflora features in oncology children.

METHODS: We selected studies published after year 2000, excluding trials on transplanted pediatric patients. We searched English language publications in MEDLINE using the keywords: "gastrointestinal infection AND antineoplastic chemotherapy AND children", "gastrointestinal infection AND oncology AND children", "liver infection AND antineoplastic chemotherapy AND children", "liver abscess AND chemotherapy AND child", "neutropenic enterocolitis AND chemotherapy AND children", "thyphlitis AND chemotherapy AND children", "infectious diarrhea AND children AND oncology", "abdominal pain AND infection AND children AND oncology", "perianal sepsis AND children AND oncology", "colonic pseudo-obstruction AND oncology AND child AND chemotherapy", "microflora AND children AND malignancy", "microbiota AND children AND malignancy", "fungal flora AND children AND malignancy". We also analysed evidence from several articles and book references.

RESULTS: Gastrointestinal and liver infections represent a major cause of morbidity and mortality in children undergoing antineoplastic chemotherapy. Antineoplastic drugs cause immunosuppression in addition to direct toxicity, predisposing to infections, although the specific risk is variable according to disease and host features. Common pathogens potentially induce severe diseases whereas opportunistic microorganisms may attack vulnerable hosts. Clinical manifestations can be subtle and not specific. In addition, several conditions are rare and diagnostic process and treatments are not standardized. Diagnosis may be challenging, however early diagnosis is needed for quick and appropriate interventions. Interestingly, the source of infection

in those children can be exogenous or endogenous. Indeed, mucosal damage may allow the penetrance of endogenous microbes towards the bowel wall and their translocation into the bloodstream. However, only limited knowledge of intestinal dysbiosis in oncology children is available.

CONCLUSION: The diagnostic work-up requires a multimodal approach and should be implemented (also by further studies on new biomarkers) for a prompt and individualized therapy.

Key words: Gastrointestinal tract; Liver; Microflora; Infection; Oncology; Chemotherapy; Children

Core tip: The presence of an infectious complication should be always suspected in children with cancer who experience abdominal symptoms. Gastrointestinal and liver infections may be severe complications of chemotherapy that require early diagnosis and appropriate treatment. In these patients there are no absolute predictive markers of gastrointestinal infections, with the possible exception of viral hepatitis. Therefore diagnosis requires a comprehensive approach based on medical history, clinical examination, microbiological tests, imaging and sometimes also invasive procedures.

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INTRODUCTION

Children with cancer often have gastrointestinal and liver symptoms and/or dysfunction. Risk factors include neoplastic infiltration, mechanical obstruction by tumor mass, abdominal tumor rupture, abdominal surgery, radiation therapy and, primarily, antineoplastic chemotherapy, with different effects according to drugs, dosing, schedule and associated treatments[1-6]. Antineoplastic chemotherapy may cause direct damage such as bowel motility disturbance and cytotoxic injury to gastrointestinal and liver tissue, in addition to immunosuppression and nutritional impairment[7-9]. Cancer children are prone to develop gastrointestinal and liver infections that may have a significant impact on morbidity and mortality[10-20].

Aim of the present paper was to describe the digestive and liver infections in children undergoing antineoplastic chemotherapy.

MATERIALS AND METHODS

Search of English language publications in MEDLINE from January 1st 2000 to December 31st 2015 was performed using the following keywords: "gastrointestinal infection AND antineoplastic chemotherapy AND children", "gastrointestinal infection AND oncology AND children", "liver infection AND antineoplastic chemotherapy AND children", "liver abscess AND chemotherapy AND child", "neutropenic enterocolitis AND chemotherapy AND children", "thyphlitis AND chemotherapy AND children", "infectious diarrhea AND children AND oncology", "abdominal pain AND infection AND children AND oncology", "perianal sepsis AND children AND oncology", "colonic pseudo-obstruction AND oncology AND child AND chemotherapy","microflora AND children AND malignancy", "microbiota AND children AND malignancy", "fungal flora AND children AND malignancy". Data from patients undergoing allogenic hemopoietic stem cell transplant were excluded due to the peculiarities of this patients' population. Studies providing information unrelated to our search objective were excluded. In adjunct, we also considered references from several articles and several books. Major papers were critically reviewed to produce a summary of best available evidence.

RESULTS

Gastrointestinal infections

Gastrointestinal infections may present with heterogenous and non-specific signs and symptoms in children undergoing antineoplastic chemotherapy. These include hemorrhage, abdominal pain, with or without fever. On the other hand, gastrointestinal symptoms are described both in infectious and non-infectious diseases of abdominal and extra-abdominal sites.

Gastrointestinal hemorrhage: Gastrointestinal hemorrhage is not a frequent clinical condition in pediatric oncology, but it may be life threatening in cancer children because of thrombocytopenia, sometime associated with coagulopathy. Fever is generally absent and neutropenia (absolute granulocyte count < 500/cmm, or < 1000/cmm but rapidly declining) can be frequently but not consistently detected. Infections are a rare cause of isolated hemorrhage. Neutropenic enterocolitis has been associated with gastrointestinal bleeding[21-26] induced by a number of pathogens. *Helicobacter pylori (H. pylori)* has been detected in gastrointestinal bleeding, mainly in leukemic adolescents receiving steroids[27,28]. Cytomegalovirus is an established enteric pathogen in transplanted patients, whereas it is rarely reported in non-transplanted patients with malignancy, mostly in adults[29,30]. Fungal infections can also cause

gastrointestinal hemorrhage. *Candida*-associated vasculitis (CAV) is a rare but challenging complication of *Candida* infection. This probably represents a broad spectrum of disease, whose severity ranges from a self-limiting condition to a diffuse life-threatening evolutive process requiring prolonged antifungal treatment, surgery, and quite paradoxically, high dose steroids for its treatment[31-33].Its pathogenesis is unclear, but immunomediated injury seems more plausible than direct fungal toxicity, since no agent is found near vessel walls and vasculitic damage is similar to that found in polyarteritis nodosa[31,32]. Hematemesis and melena are described when *Aspergillus* localizes in the gastrointestinal tract[33]. Mucorales infect the gut more frequently in children than in adults[34] and children with leukemia seem to be at higher risk of *Zygomycetes* infection than other oncology patients[35]. Mucorales species localize preferentially in the gastric rather than the intestinal tract. The fungus is angiotropic and invasive, and may cause massive and life-threatening hemorrhage[36].

Endoscopy is useful in case of gastrointestinal bleeding in cancer children both for its potential diagnostic value and for possible therapeutic interventions. This procedure was safe and of great diagnostic usefulness in a large series of cancer children with gastrointestinal bleeding despite the presence of neutropenia and thrombocytopenia[37]. Finally, search for *H. pylori* antigen in the stools should be done in symptomatic subjects in order to early identify this pathogen[27,28] before the occurrence of severe bleeding.

Abdominal pain: Abdominal pain is a frequent condition in cancer children and may have different infectious and non-infectious causes. The presence or absence of neutropenia deeply affects the etiology and clinical management.

Neutropenic enterocolitis (NE) is a peculiar condition associated with abdominal pain and may be life-threatening. It encompasses a broad pathological and clinical spectrum of diseases with a multifactorial etiopathogenesis, but all characterised by mucosal injury and transmural microbial invasion in the absence of granulocyte infiltration (due to the presence of neutropenia). Typical features are abdominal pain usually generalized or localized to the right lower quadrant, fever (so mimicking an acute appendicitis), and bowel wall thickening documented by ultrasound or CT scan, in a neutropenic patient. Major symptoms may be nausea, vomiting, abdominal distension, constipation and diarrhea (also hemorrhagic),with abdominal pain and fever[22-26,38-44]. Although NE is sometimes termed "typhlitis" or "ileocecal syndrome", any intestinal segments can be affected, despite its predilection for ileocecal wall[21,38,41-43,45-48]. The true incidence of NE is unknown, with reports ranging from 0.2% to 46%[7,21-23,26,38-42,47,49-51]. Such a wide range likely depends on intrinsic variability of the disease and on heterogeneous study design. Definitions also play a role since nosographic definitions are based on autopsy findings rather than clinical features and diagnostic criteria are not uniform (Table 1). In addition, populations are different among studies, mainly for patients' age (sometimes both adults and children) and underlying malignancy. However, the recently observed incidence increase could be at least partially explained by improved diagnostics[38,42] and intensification of antineoplastic regimens[25,52,53]. Anyway, NE is more frequently described in hematologic malignancies[7,22,23,38,40,42,50], in children on specific drugs or drug combinations (*e.g.,* granulocyte-colony-stimulating factor and topotecan, topotecan and idarubicin, cyclophosphamide and hydrocortisone, cyclophosphamide and methotrexate, cyclophosphamide and carboplatin, carboplatin and methotrexate; anthracyclines, cytosine arabinoside, steroids)[42,51,53] administered in the 2-3 wk preceeding the onset of symptoms[38,54], and in the presence of mucositis[54]. Different factors are associated with severe clinical presentation[22,26,38,42,55-57], as summarized in Table 2. Before year 2000 50%-100% mortality was reported, but in the last years this proportion has been reduced from 50% to 30%,or even lesser[7,22,25,26,38,41,47], probably as a consequence of earlier diagnosis and improved treatment strategies. In most patients, a conservative multifaceted approach with the administration of broad-spectrum anti-infectious drugs (including agents against anaerobes and *Candida*), bowel rest, intravenous fluids, and drugs to limit cytopenia may be successful. Surgery may be considered in refractory or complicated cases. Differential diagnosis should include appendicitis[7,23,24,38,40-41,51,56,58-61], infectious colitis[7,23], *Clostridium difficile* (*C. difficile*) - induced diarrhea[38,41] and veno-occlusive disease[7,23].

Appendicitis has been described as a rare complication in neutropenic children with a frequency of about 1.5% in patients with severe abdominal pain[24,51,62].

Patients with hematologic malignancy may experience abdominal pain due to intestinal zygomycosis[63,64]. Intestinal aspergillosis is rare and available data mainly come from adult patients on intensive chemotherapy for hematologic malignancies and solid tumors[65-72]. This condition may be severe and even fatal, sometimes within a disseminated disease. Life-threatening complications include bowel infarction, toxic megacolon and bowel perforation.

Pancreatitis is another possible origin of abdominal pain in oncologic children, but is generally due to non-infectious etiologies, although it can be the cause of bloodstream infections especially in the presence of neutropenia[7,24,73]. Similarly, gallbladder disease is mainly related to therapy and not to infections[73].

Intestinal mechanical obstruction may occur due to tumor itself. Intussusception should be taken into account in patients with abdominal tumors[24,74,75]. Bowel adenocarcinoma is rare in pediatric oncology,

Table 1 Different definitions of neutropenic enterocolitisamong studies

Neutropenic enterocolitis definition	Neutropenia (Neutrophil count/mm^3)	Abnormal bowel wall thickness thresholds (imaging technique)	Ref.
Neutropenia in addition to fever and abdominal pain (generalized or localized to right lower quadrant) without any other obvious cause of abdominal discomfort	< 500	Not specified	Jain *et al*[26], 2000
Al least 1 suggestive clinical sign (fever, abdominal tenderness, diarrhea, nausea, emesis, abdominal pain, and/or constipation) associated with bowel wall thickness ⩾ 0.3 cm	< 500	⩾ 0.3 cm (either CT or US; CT and US findings were significantly different)	McCarville *et al*[42], 2005
Abdominal pain, fever, and neutropenia associated with radiological abnormalities in the terminal ileum and/or ascending colon (comprising increased wall thickness, pericecal edema, pneumatosis intestinalis)	< 1000	Not specified (CT)	Hobson *et al*[51], 2005
Recent abdominal pain (global or right lower quadrant), fever and severe neutropenia in absence of prior abdominal discomfort	< 500	> 5 mm (US and CT)	Alioglu *et al*[24], 2007
One or more of clinical signs (fever, abdominal pain, diarrhea, abdominal tenderness, nausea, emesis, and/or evidence of peritonitis) and one or more imaging findings on US, CT, x-ray (bowel wall thickening, bowel edema, relative paucity of bowel gas, bowel mass, thumb printing of the mucosa or air in the bowel wall)	< 500	Not specified (x-ray or US or CT)	Moran *et al*[54], 2009
Clinical triad (abdominal pain, fever and neutropenia) or 2 clinical features with thickened bowel wall in imaging	< 1.65	Not specified (US or CT)	Mullassery *et al*[23], 2009
1 or more signs and/or symptoms related to the effects of treatment (abdominal pain, abdominal distention, vomiting, diarrhea, fever defined as TC ⩾ 38 ℃, gastrointestinal bleeding, or obstipation) associated with increased intestinal wall thickness in US	⩽ 500	⩾ 3 mm (US)	Rizzatti *et al*[22], 2010
Clinical triad (abdominal pain, high fever and neutropenia) associated with the evidence of image signs (thickened bowel wall) by abdominal US or CT scan	< 500	> 4 mm (US or CT)	Li *et al*[40], 2011
Fever (TC > 38.5 ℃), abdominal pain, neutropenia associated with radiologically confirmed thickening of the bowel wall	< 500	> 3 mm (CT and US concordant)	Sundell *et al*[38], 2012
Clinical triad (abdominal pain, fever and neutropenia) or 2 clinical features with thickened bowel wall in imaging	< 500	> 5 mm (US/CT)	Altinel *et al*[39], 2012
Proposed diagnostic criteria: Major criteria Compatible histology At least borderline neutropenia Gastrointestinal symptoms Immunosuppression Recent chemotherapy Exclusion of other treatable etiologies Minor criteria Fever of > 38 ℃ Bowel wall thickening of > 4 mm over > 30 mm Positive microbiologic studies "Definitive" NE satisfies the major criteria			Sachak *et al*[175], 2015

US: Ultrasonography; CT: Computed tomography.

however it should be suspected in children with familiar cancer predisposition[76]. A marked colon dilation without mechanical obstruction characterizes acute colonic pseudo-obstruction, otherwise named Ogilvie's syndrome[77-79]. This gastrointestinal motility disorder is probably due to an imbalanced autonomic innervation of the bowel. Predisposing conditions include sepsis, dyselectrolytemia, drugs influencing gastrointestinal motility such as vincristine or major antidolorific drugs like morphine. Ogilvie's syndrome is rare and awareness of this condition is minimal. The clinical presentation is characterized by abdominal pain, abdominal distention, nausea, vomiting and constipation, and it may progress to ischaemia and bowel perforation[77,78]. Sudden onset abdominal pain, abdominal distension and peritonism (sometimes also called "abdominal crisis") may also indicate tumor rupture[80]. Gerota capsule distension, hemorrhage within the capsule, spontaneous rupture may cause abdominal pain in Wilms tumor[81]. Acute abdomen may be due to vascular complications such as aneurysm rupture[82]. Ovarian torsion is reported in children and adolescents with neoplasms, although it is not usually associated with malignancy[83,84].

Perianal infections: Perianal infections may be catastrophic in immunocompromised children. High-risk hematologic malignancies treated with aggressive protocols, use of diapers and neutropenia are associated with severe local infections[85]. Anal

Table 2 Clinical, laboratory and imaging factors associated with severe neutropenic enterocolitis

Factor	Outcome	Ref.
Previous therapy with cytarabine	Higher death rate	Rizzatti *et al*[22], 2010
Age > 16 yr	Worse response to medical therapy	McCarville *et al*[42], 2005
Presence of abdominal distention	Higher risk of death	Rizzatti *et al*[22], 2010
Presence of abdominal tenderness	Prolonged duration	McCarville *et al*[42], 2005
Presence of fever	Prolonged duration	McCarville *et al*[42], 2005
4 or more symptoms of enterocolitis	Higher risk of death	Rizzatti *et al*[22], 2010
Severe (absolute neutrophil count < 10^8/L) or prolonged (> 7 d) neutropenia	Disease progression	Jain *et al*[26], 2000
Duration of neutropenia	Prolonged duration	McCarville *et al*[42], 2005
Increased serum Interleukin-8 levels on the first day of clinical illness	Higher risk of admission in Intensive Care Unit	van de Wetering *et al*[55], 2008
Bowel wall tickness	Prolonged duration	Sundell *et al*[38], 2012
	Higher mortality rate	Cartoni *et al*[57], 2001
	Higher death rate	Rizzatti *et al*[22], 2010
	Prolonged duration	McCarville *et al*[42], 2005
Appendiceal thickening	Higher risk of serious complications	McCarville *et al*[56], 2004

fissuration is often the presenting manifestation, then local infection may progress towards deeper strata and cause bacteremia, severe disease and even death. Prevention is probably the most effective measure[7]. In case of perianal sepsis, conservative management is usually applied, although not always effective. Recently, early diverting colostomy has proved successful in a small group of children with acute leukemia[85].

Diarrhea: Diarrhea can be due to infections, although non-infectious causes, such as tumor itself[86-88] or drug toxicity, should be considered. Clinicians should consider three infectious disease scenarios, not mutually excluding: (1) common pathogens, which may be more aggressive in cancer patients; (2) nosocomial infections; and (3) opportunistic pathogens.

Rotavirus is a cause of diarrhea in cancer children. Prolonged shedding is observed among immunocompromised subjects and hygiene measures are essential for infection control[89]. Other viral agents responsible for diarrhea include adenovirus and calicivirus. Norovirus is the most common calicivirus detected in gastroenteritis and its shedding in immunocompromised patients is prolonged[90,91]. Sapovirus is an unfrequent cause of gastroenteritis, whose symptoms are usually milder than in Norovirus infection[90]. Bacteria and protozoa can be significant causes of diarrhea in oncology children, at least in specific regions. In a single-center Egyptian survey an infectious cause was found in 74/104 episodes (71.1%), with a not negligible mortality in presence of mixed etiology[13]. Lothstein *et al*[92] performed a 11-year retrospective study and found zoonotic diseases in 88/10197 acute leukemia children (0.86%). Intestinal pathogens (*Campylobacter*, *Cryptosporidium*, *Giardia* and *Salmonella*) were responsible for the vast majority (86.4%) of cases, and, despite rare, their individual incidence rates appeared to be higher than in the general population. Cryptosporidiosis may be a cause of severe and/or prolonged diarrhea in children with acute leukemia and may be complicated by cholangitis[93]. Ehrlichiosis should be suspected in presence of fever and gastrointestinal symptoms associated with epidemiological criteria (living in an endemic area)[94].

Children with malignancy are at higher risk of developing *C. difficile* infection (CDI), the rate being 15 fold than in all other pediatric patients' populations[10,95]. Recent exposure to antibiotics, especially anti-pseudomonal B-lactams was associated with increased risk, also with a significant effect of total exposure time within the 30 d preceeding the symptoms[10,95]. Indeed, CDI in hospitalised children is associated with prolonged hospital stay, increased risk of death and costs[96,97]. Prolonged colonization (intermittent or persistent) has been found in more than 50% of oncology children after treatment[98]. In a recent study, malignancy was significantly associated with CDI recurrence (OR = 3.39, 95%CI: 1.52-7.85), but recent surgery and the number of antibiotic courses by class also were significant predictors of recurrence[99]. Crews and coworkers studied the epidemiology of CDI in children in Texas (both in the community and in hospital setting), excluding those under 1 year of age, due to the high rate of colonisation at this young age. Children with hematologic malignancies or undergoing solid organ transplantation had more frequently hospital-acquired CDI than community acquired-CDI. Authors also evaluated the risk factors for severe CDI, according to the following criteria: (1) presence of at least 2 clinical manifestations (fever, bloody stools, leukocytosis, hypoalbuminemia, elevated creatinine); and (2) CDI-related complications (pneumatosis intestinalis, pseudomembranous colitis, toxic megacolon, gastrointestinal perforation, surgical intervention, admission to intensive care unit, death). Fever was observed in 38% of cases, abdominal manifestations

included diarrhea, bloody stools in 25%, abdominal pain in 46% and vomiting in 28%. Severe disease was observed in 21% of cases and gastrostomy tube and recent hospitalisation were identified as significant risk factors[96]. CDI is associated to higher mortality rate than other etiologies in cancer children with symptomatic gastroenteritis[13]. Neutrophils may have a role in the development of *C. difficile*-associated pseudomembranous colitis[100]. Fulminant colitis has been reported in 3% of cases of CDI, typically in patients suffering from high fever, abdominal pain, diarrhea orileus[16]. Furthermore, CDI is of concern also due to possible clusters of cases[100,101].

Strongyloides, despite rare, may be a cause of diarrhea (and disseminated infection) especially in high endemic areas and high-risk populations. In an American (Texas) 30-years survey, the frequency of *Strongyloides stercoralis* infection was 0.8 per 10000 new cancer cases (adults and children) but its frequency was 2.0 per 10000 new cases of leukemia. Interestingly, Authors observed that subjects with hematologic malignancy were at risk for persistent intestinal infestation, and infestation cannot be excluded in the absence of increased eosinophil counts[102].

Therefore, in specific settings, differential diagnosis of diarrhea in oncology children should include a broad pattern of classical and opportunistic agents. This may also be important for hospital infection control purposes due to the high diffusion of selected (especially viral and *C. difficile*) agents in pediatric hemato-oncology wards.

Liver infections: Liver disease in cancer children may be due to viral, bacterial or fungal pathogens, with clinical features varying from mild to fulminant disease.

A viral infection can be present before diagnosis and treatment of a neoplastic disease, with reactivation during immunosuppression[19,103] especially with drugs like rituximab[104], or may be acquired during treatment, generally through contaminated and poorly controlled blood transfusions[105,106]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most typical agents associated with hepatitis in cancer patients, but their infection pattern has changed over time. Before year 2000 HCV infection ranged from 3% to 9% of survivors of childhood malignancies[107,108], with higher frequencies in acute leukemias[105], with patients experiencing coinfections with HBV or HIV[107,109]. Immunisation programs have significantly influenced HBV epidemiology, while HCV (and HIV) infection incidence almost disappeared after the introduction of blood testing[110]. At present, even if there is no doubt that the risk is minimal, it is not null and it is important to consider viral hepatitis in the differential diagnosis of liver dysfunction in cancer children. In several settings, nosocomial outbreaks have been recently reported[111]. Serology can provide false negative results in immunocompromised patients and molecular techniques should be used for the diagnosis[112,113].

Other viral agents may be responsible for severe hepatic complications in oncology children. Adenovirus-induced fulminant hepatitis and life-threatening illness have been rarely described in standard chemotherapy regimens[20,114], while Varicella Zoster Virus may be the cause of severe liver dysfunction in immunocompromised hosts[115-117].

Other etiologies, like *Mycobacterium fortuitum*[118], *Aspergillus*[34,119] and Mucorales[35] have been found from children with disseminated diseases. A few cases of isolated liver mucormycosis have also been reported[120]. Among disseminated infections hepatic candidiasis (frequently associated with spleen and/or kidney localization, producing the clinical picture of hepatosplenic, also defined as chronic disseminated candidiasis) plays a major role[121-126], particularly in children with acute leukemias. The clinical picture is characterized by long lasting fever and abdominal pain, mainly at the upper-right quadrant, in presence of prolonged neutropenia. Typical (owl's eye) liver and spleen lesions become evident at imaging only after granulocyte recovery[122,124]. Steroids, quite paradoxically, may be effective in adjunct to antifungal as treatment of chronic disseminated candidiasis in the presence of persistent fever and abdominal pain since these symptoms are at least partially related to an immuno reconstitution syndrome[127,128]. Liver abscesses in children can be due to bacteria, fungi and parasites and sometimes present with abdominal and extra-abdominal complications[129-133]. Amebic and pyogenic abscesses are solitary and right-sided in the vast majority of cases[130,133]. Epidemiology, microbiological tests, imaging and response to treatment may support the diagnosis[129,130].

Differential diagnosis of liver infections may include underlying disease localizations, drug toxicity (methotrexate, thioguanine, dactinomycin, mercaptopurine and busulphan)[1,110], or other life-threatening conditions, like veno-occlusive disease. Imaging (ultrasound, computed tomography), antibody and viral genome detection are pivotal tools for the diagnosis of these complications.

Microbes in the gastrointestinal tract: Friends or foe?

Dysbiosis in oncology children: Intestinal microbiota is a dynamic organ composed by micro-organisms that live in the host with a symbiotic relationship, composing the microbiome. Microflora exerts local and systemic effects and significantly contribute to homeostasis. Dysbiosis, that defines any perturbation in healthy commensal communities, has been described in intestinal and extraintestinal diseases and represents an area of growing interest[134-137]. Quantitative and qualitative alterations of the normal microflorain cancer subjects depends on many factors, such as underlying disease, mucosal disruption, bowel motility disturbance,

enteral/parenteral nutrition, broad-spectrum antibiotic administration. Antineoplastic drugs may also play an important role, that is different for different moieties as demonstrated by in vitro studies showing specific effects on bacterial growth depending on drug type and concentrations[138].

Microbiological analysis of fecal samples of children treated for acute myeloid leukemia demonstrated that the total number of bacteria was 100 fold lower in patients during chemotherapy compared to healthy controls. The microbiota composition was different and, in particular, a 10000-fold decrease in anaerobic bacteria was observed, in concomitance with a 100-fold increase of potentially pathogenic enterococci[138]. Huang *et al*[139] also found a decreased amount of microbial flora (and in particular of *Bifidobacteria*, *Lactobacillus* and *E. coli*) in acute lymphoblastic leukemia children treated with high dose methotrexate compared to healthy controls. Moreover, a study of fungal flora in stool samples from children receiving chemotherapy or stem cell transplant showed that the incidence of *Candida* non-*albicans* species was significantly higher in patients than in controls, with *C.glabrata* and *C.kruzei* being the most common non-*albicans* species. An increase in *Candida* non-*albicans* species was observed in prolonged hospital stay, suggesting a nosocomial origin. Interestingly, fungal colonisation was not associated with the type of underlying disease[140]. In another study, *Candida* colonisation rate resulted not significantly different between children with cancer and healthy subjects, and no difference was found between children with haematological cancer and solid tumours[141]. Also oral microbiota shows distinctive features in oncology patients compared to healthy subjects. Reduced richness, reduced diversity and higher abundance of *Firmicutes/Bacilli/Lactobacillales/Carnobacteriaceae/Granullicatella and Firmicutes/Bacilli/Lactobacillales/Aerococcaceae/Abiotrophia* were found in children with acute lymphoblastic leukemia compared with healthy controls[142]. Oral ecology changes have been reported both during radiation therapy[143] and chemotherapy[144-146], underlying again the dynamic nature of endogenous microflora. Unfortunately, at present, knowledge about dysbiosis in malignancy is limited, studied populations are heterogeneous and, in addition, study methodology is not uniform. Moreover, only few studies focused on microbiological and clinical outcomes and effects of microflora modifications in cancer children[147-149].

Gastrointestinal tract as a source of pathogens: Pathogens may originate from the gastrointestinal tract and invade the bloodstream through disrupted intestinal barriers. Therefore, intestinal microbial translocation may lead to systemic disease[34,35,140,150-164] with or without localization in other organs. For these reasons gut colonization with resistant phenotypes pose great concern. Carbapenem-resistant Enterobacteriaceae (CPE) colonization and infection represent an emerging treat in oncology children[165-167]. Also Vancomycin-Resistant *Enterococcus* (VRE) colonization have been reported as a possible cause of severe disease in pediatric cancer patients[164,168]. The presence of gastrostomy or nasogastric tube and inadequate hygiene measures were associated with VRE acquisition. Reduced VRE positive screens were found after the implementation of infection control measures[168]. Similar considerations can be made for *Candida* species that may cause invasive disease in immunocompromised subjects and spread to one or more organs, frequently affecting the gastrointestinal tract, liver, lung and spleen[121,140,169-171].

DISCUSSION

In summary, Children undergoing antineoplastic treatment are at risk of gastrointestinal or liver complications, including infections that may have a negative impact on quality of life and may preclude, delay or modify antineoplastic treatment. Moreover, they may be clinically severe in susceptible hosts and even be life threatening and sometimes, it may be difficult to distinguish between infectious and not infectious etiology. Furthermore, as the catalogue of antineoplastic agents increases, the infection profile in cancer children might change[103,172-174].

Prompt diagnostic workup must be implemented, even including invasive procedures, to set up appropriate interventions. Unfortunately, infectious etiologies of gastrointestinal diseases in cancer children are not frequently documented and therefore literature data are lacking and optimal management is unclear. In addition, studies are not uniform because of different definitions or non-comparable settings (different age of enrolled patients, cancer type, antineoplastic treatment, comorbidities), and therefore no generalisation is allowed for most infectious complications. The availability of new diagnostic criteria will improve knowledge and management strategies, at least for specific conditions[175]. Biomarkers may be used to support differential diagnosis. Miedema *et al*[176] analyzed several inflammatory markers (CRP, PCT, sTREM-1, IL8) in febrile neutropenic children with malignancy, founding that IL-8 (especially associated with clinical features or PCT) is the best marker for the early detection of bacterial infections, whereas, during mucositis, PCT might be more useful. However, based on available evidence, no ideal biomarker has been found, and undoubtedly diagnosis is multimodal. Medical history and physical examinations remain the best tools for the clinicians. Laboratory tests (including local and blood cultures), imaging and invasive procedures may be helpful and sometimes also conclusive in the diagnostic process. New prediction models with items on medical history, clinical features and laboratory tests should be defined and applied to predict infectious risk in oncology children. Moreover,

empirical therapy response could significantly help diagnosis and decision making in clinical practice.

However, children with malignancy are not all the same and the infectious risk might be influenced by exogenous and endogenous factors. Interestingly, in recent years, there is growing interest on genetic susceptibility to specific infections, and future studies may reveal the impact of genetic background on the infectious risk and severity, possibly leading a personalised approach. Similarly, more data on the gastrointestinal microecology modifications in children with malignancy might provide useful insights into gastrointestinal and liver complications. Further studies should characterize intestinal microflora in this setting with the aim of clarifying the cause-effect relationship between specific agents and mucositis, intestinal inflammation, colonisation and infection. Moreover, it could be interesting to look for microbial "signatures" (distinctive microbial patterns for specific conditions) as diagnostic tool and potential therapeutic target[136]. New approach such as the opportunity to restructure intestinal microbiota with the use of specific probiotics in combination with other approaches could open new opportunities for prevention of microbial infections.

COMMENTS

Background

Gastrointestinal and liver infections have a significant impact on morbidity and mortality in children undergoing antineoplastic chemotherapy. Infections may delay antineoplastic treatment, impair the quality of life and also jeopardise patients' life. Unfortunately, diagnosis is often difficult, although a quick and appropriate intervention is needed. The first aim of this review was to critically analyze evidence on gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy published in the years 2000. The authors also added some recent evidences on the role of dysbiosis as a possible risk factor for in cancer children.

Research frontiers

The management of infections needs implementation based on a multifaceted approach. Several nosological entities should be clearly and uniformly defined. Further studies should focus on the definition of the infectious risk and should assess the use of combined diagnostic markers towards precision medicine. Response to empirical treatment should be further investigated as indirect and practical diagnostic tool for differential diagnosis.

Innovations and breakthroughs

Infections are a major threat to children with cancer, despite scientific advance. Furthermore, as a natural consequence of scientific progress, cancer survival will increase and new short- and long-term complications from antineoplastic therapies will emerge, including infections. Unfortunately, clinical presentation may be subtle and nonspecific, available evidence is heterogeneous, and data are lacking especially for rare diseases. Moreover, definite diagnosis of several diseases requires invasive procedures that are not easily appliable in vulnerable subjects. Advances from basic and applied science may provide key insight in the management of gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy.

Applications

This review should be considered for practical and research purposes. It analyses the wide differential diagnosis for gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy based on available evidence obtained in the last 15 years and suggests potential preventive and diagnostic tools to improve patients' management.

Terminology

Neutropenia (or granulocytopenia) is a condition of bone marrow suppression induced by antineoplastic chemotherapy. It is defined by an absolute granulocyte count < 500/cmm, or < 1000/cmm but in rapid decrease. Neutropenic enterocolitis is a spectrum of diseases characterised by mucosal injury and transmural microbial invasion in the absence of granulocyte infiltration. Hepatosplenic (chronic) candidiasis is a deep organ localization of a disseminated *Candida* infection, that is acquired during neutropenia but that can be diagnosed by imaging only after granulocyte recovery. Dysbiosis can be defined as any imbalance in healthy commensal microbial communities.

Peer-review

This review paper has summarized data from abdominal symptoms, diagnostic methods and data from gut microbiota in oncology children with digestive infections. This is a very well done paper. And in this study, authors have edited the review on the evidences, diagnostic criteria and results of gastrointestinal and liver infections in children suffering from oncologic diseases. This study has achieved to present the factors contributing to infections and the procedures improving quality of life with exact diagnosis and prevention.

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