**Name of Journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 25870**

**Manuscript Type: SYSTEMATIC Review**

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

Castagnola E *et al*. Gut and liver infections in oncology

Elio Castagnola, Eliana Ruberto, Alfredo Guarino

**Elio Castagnola**, Infectious Diseases Unit, Istituto Giannina Gaslini, 16147 Genoa, Italy

**Eliana Ruberto, Alfredo Guarino,** Department of Translational Medical Science, Section of Pediatrics, University of Naples Federico II, 80131 Naples, Italy

**Author contributions:** All authors contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and approval of the final version.

**Conflict-of-interest statement:** All the authors declare that they have no competing interests.

**Data sharing statement:** no additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondence to: Elio Castagnola, MD, PhD,** Infectious Diseases Unit, Istituto Giannina Gaslini, Largo G. Gaslini 5, 16147 Genoa, Italy.eliocastagnola@gaslini.org

**Telephone:** +39-10-56362428

**Fax:** +39-10-384323

**Received:** March 24, 2016

**Peer-review started:** March 25, 2016

**First decision:** May 12, 2016

**Revised:** May 27, 2016

**Accepted:** June 15, 2016

**Article in press:**

**Published online:**

**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 microrganisms 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

**©The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Castagnola E, Ruberto E, Guarino A. Gastrointestinal and liver infections in children undergoing antineoplastic chemotherapy in the years 2000. *World J Gastroenterol* 2016; In press

**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 belief 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 a 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 en compasses 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. Majorsymptoms 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 week 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 inrefractory 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 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, 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 disorders 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 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 andcalicivirus. 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 K and coworkers 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 the general population[92]. 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 etiologies, 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, and indicated as hepatosplenic candidiasis) plays a major role[121-126], particularly in children with acute leukemias. The clinical pictures 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 in 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].

**CONCLUSION**

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 and coworkers 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[176]. 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 jeopardisepatients’ 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.

**REFERENCES**

1 **Altaf S**, Enders F, Lyden E, Donaldson SS, Rodeberg D, Arndt C. Age-related toxicity in patients with rhabdomyosarcoma: a report from the children's oncology group. *J Pediatr Hematol Oncol* 2014; **36**: 599-604 [PMID: 24936741 DOI: 10.1097/MPH.0000000000000192]

2 **Dubowy R**, Graham M, Hakami N, Kletzel M, Mahoney D, Newman E, Ravindranath Y, Camitta B. Sequential oral hydroxyurea and intravenous cytosine arabinoside in refractory childhood acute leukemia: a pediatric oncology group phase 1 study. *J Pediatr Hematol Oncol* 2008; **30**: 353-357 [PMID: 18458568 DOI: 10.1097/MPH.0b013e318166247e]

3 **Hijiya N**, Stewart CF, Zhou Y, Campana D, Coustan-Smith E, Rivera GK, Relling MV, Pui CH, Gajjar A. Phase II study of topotecan in combination with dexamethasone, asparaginase, and vincristine in pediatric patients with acute lymphoblastic leukemia in first relapse. *Cancer* 2008; **112**: 1983-1991 [PMID: 18318429 DOI: 10.1002/cncr.23395]

4 **Horton TM**, Ames MM, Reid JM, Krailo MD, Pendergrass T, Mosher R, Reaman GH, Seibel NL; Children's Oncology Group. A Phase 1 and pharmacokinetic clinical trial of paclitaxel for the treatment of refractory leukemia in children: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; **50**: 788-792 [PMID: 17668866]

5 **Rodriguez-Galindo C**, Crews KR, Stewart CF, Furman W, Panetta JC, Daw NC, Cain A, Tan M, Houghton PH, Santana VM. Phase I study of the combination of topotecan and irinotecan in children with refractory solid tumors. *Cancer Chemother Pharmacol* 2006; **57**: 15-24 [PMID: 16001174]

6 **Daw NC**, Santana VM, Iacono LC, Furman WL, Hawkins DR, Houghton PJ, Panetta JC, Gajjar AJ, Stewart CF. Phase I and pharmacokinetic study of topotecan administered orally once daily for 5 days for 2 consecutive weeks to pediatric patients with refractory solid tumors. *J Clin Oncol* 2004; **22**: 829-837 [PMID: 14990638]

7 **Chui CH**. Surgical management of complications of multimodal therapy. *Pediatr Blood Cancer* 2012; **59**: 405-409 [PMID: 22434785 DOI: 10.1002/pbc.24147]

8 **Parbhoo DM**, Tiedemann K, Catto-Smith AG. Clinical outcome after percutaneous endoscopic gastrostomy in children with malignancies. *Pediatr Blood Cancer* 2011; **56**: 1146-1148 [PMID: 21488164 DOI: 10.1002/pbc.22873]

9 **Sacks N**, Hwang WT, Lange BJ, Tan KS, Sandler ES, Rogers PC, Womer RB, Pietsch JB, Rheingold SR. Proactive enteral tube feeding in pediatric patients undergoing chemotherapy. *Pediatr Blood Cancer* 2014; **61**: 281-285 [PMID: 24019241 DOI: 10.1002/pbc.24759]

10 **Fisher BT**, Sammons JS, Li Y, de Blank P, Seif AE, Huang YS, Kavcic M, Klieger S, Harris T, Torp K, Rheam D, Shah A, Aplenc R. Variation in Risk of Hospital-Onset Clostridium difficile Infection Across β-Lactam Antibiotics in Children With New-Onset Acute Lymphoblastic Leukemia. *J Pediatric Infect Dis Soc* 2014; **3**: 329-335 [PMID: 26625453 DOI: 10.1093/jpids/piu008]

11 **Cortés JA**, Cuervo S, Gómez CA, Bermúdez D, Martínez T, Arroyo P. Febrile neutropenia in the tropics: a description of clinical and microbiological findings and their impact on inappropriate therapy currently used at an oncological reference center in Colombia. *Biomedica* 2013; **33**: 70-77 [PMID: 23715309 DOI: 10.1590/S0120-41572013000100009]

12 **Wang A**, Fan S, Yang Y, Shen X. Nosocomial infections among pediatric hematology patients: results of a retrospective incidence study at a pediatric hospital in China. *J Pediatr Hematol Oncol* 2008; **30**: 674-678 [PMID: 18776759 DOI: 10.1097/MPH.0b013e3181758110]

13 **El-Mahallawy HA**, El-Din NH, Salah F, El-Arousy M, El-Naga SA. Epidemiologic profile of symptomatic gastroenteritis in pediatric oncology patients receiving chemotherapy. *Pediatr Blood Cancer* 2004; **42**: 338-342 [PMID: 14966830]

14 **Aksoylar S**, Cetingül N, Kantar M, Karapinar D, Kavakli K, Kansoy S. Meropenem plus amikacin versus piperacillin-tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. *Pediatr Hematol Oncol* 2004; **21**: 115-123 [PMID: 15160510]

15 **Petrilli AS**, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A. Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. *Med Pediatr Oncol* 2000; **34**: 87-91 [PMID: 10657866]

16 **Vaiphei K**, Trehan A, Sachdeva MU, Malhotra P. A young leukemic patient with unusual catastrophic intestinal complication. *Indian J Pathol Microbiol* 2015; **58**: 48-54 [PMID: 25673592 DOI: 10.4103/0377-4929.151187]

17 **Asim M**, Zaidi A, Ghafoor T, Qureshi Y. Death analysis of childhood acute lymphoblastic leukaemia; experience at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan. *J Pak Med Assoc* 2011; **61**: 666-670 [PMID: 22204242]

18 **Gray TL**, Ooi CY, Tran D, Traubici J, Gerstle JT, Sung L. Gastrointestinal complications in children with acute myeloid leukemia. *Leuk Lymphoma* 2010; **51**: 768-777 [PMID: 20350277 DOI: 10.3109/10428191003695652]

19 **Elkady A**, Aboulfotuh S, Ali EM, Sayed D, Abdel-Aziz NM, Ali AM, Murakami S, Iijima S, Tanaka Y. Incidence and characteristics of HBV reactivation in hematological malignant patients in south Egypt. *World J Gastroenterol* 2013; **19**: 6214-6220 [PMID: 24115819 DOI: 10.3748/wjg.v19.i37.6214]

20 **Steiner I**, Aebi C, Ridolfi Lüthy A, Wagner B, Leibundgut K. Fatal adenovirus hepatitis during maintenance therapy for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2008; **50**: 647-649 [PMID: 17278117]

21 **de Lijster MS**, Smets AM, van den Berg H, Reekers JA. Embolisation for caecal bleeding in a child with typhlitis. *Pediatr Radiol* 2015; **45**: 283-285 [PMID: 24917127 DOI: 10.1007/s00247-014-3059-0]

22 **Rizzatti M**, Brandalise SR, de Azevedo AC, Pinheiro VR, Aguiar Sdos S. Neutropenic enterocolitis in children and young adults with cancer: prognostic value of clinical and image findings. *Pediatr Hematol Oncol* 2010; **27**: 462-470 [PMID: 20578807 DOI: 10.3109/08880018.2010.489934]

23 **Mullassery D**, Bader A, Battersby AJ, Mohammad Z, Jones EL, Parmar C, Scott R, Pizer BL, Baillie CT. Diagnosis, incidence, and outcomes of suspected typhlitis in oncology patients--experience in a tertiary pediatric surgical center in the United Kingdom. *J Pediatr Surg* 2009; **44**: 381-385 [PMID: 19231539 DOI: 10.1016/j.jpedsurg.2008.10.094]

24 **Alioglu B**, Avci Z, Ozcay F, Arda S, Ozbek N. Neutropenic enterocolitis in children with acute leukemia or aplastic anemia. *Int J Hematol* 2007; **86**: 364-368 [PMID: 18055346]

25 **Larsen TK**, Qvist N, Bak M. Delayed neutropenic enterocolitis in a 12-year-old girl treated with total colectomy and J-pouch reservoir. *J Pediatr Surg* 2001; **36**: 1066-1067 [PMID: 11431780]

26 **Jain Y**, Arya LS, Kataria R. Neutropenic enterocolitis in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2000; **17**: 99-103 [PMID: 10689720]

27 **Castagnola E**, Calvillo M, Gigliotti AR, Fioredda F, Hanau G, Caviglia I, Lanino E, Dufour C. Helicobacter pylori as cause of gastrointestinal disease in children with hemato-oncologic diseases. *Pediatr Blood Cancer* 2006; **47**: 89-91 [PMID: 16007605]

28 **Fioredda F**, Haupt R, Castagnola E, Barabino A, Micalizzi C, Dini G, Dufour C. Helicobacter pylori-associated large gastric ulcer during treatment for childhood leukemia. *J Pediatr Hematol Oncol* 2002; **24**: 759-762 [PMID: 12468920]

29 **Papadopoulos IN**, Konstantiadou I, Papantoni E. Enterocolitis with multiple ulcers of ileum and right colon in a patient with leukaemia attributed to cytomegalovirus. *BMJ Case Rep* 2012; **2012**: [PMID: 22669855 DOI: 10.1136/bcr.01.2012.5651]

30 **Torres HA**, Kontoyiannis DP, Bodey GP, Adachi JA, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF. Gastrointestinal cytomegalovirus disease in patients with cancer: a two decade experience in a tertiary care cancer center. *Eur J Cancer* 2005; **41**: 2268-2279 [PMID: 16143517]

31 **Kwon S**, Ho JW, Drugas G, Avansino JR. Presentation and management of Candida-associated vasculitis with gastrointestinal involvement in a pediatric patient. *J Pediatr Gastroenterol Nutr* 2013; **56**: e46-e48 [PMID: 22659888 DOI: 10.1097/MPG.0b013e318261030e]

32 **Sargent J**, O'Marcaigh A, Smith O, Butler K, Gavin P, O'Sullivan M. Candida albicans-associated necrotizing vasculitis producing life-threatening gastrointestinal hemorrhage. *Hum Pathol* 2010; **41**: 602-604 [PMID: 20153510 DOI: 10.1016/j.humpath.2009.09.015]

33 **Mantadakis E**, Danilatou V, Stiakaki E, Kalmanti M. Infectious toxicity of dexamethasone during all remission-induction chemotherapy: report of two cases and literature review. *Pediatr Hematol Oncol* 2004; **21**: 27-35 [PMID: 14660304]

34 Castagnola E, Viscoli C.Invasive aspergillosis in malignancy and stem cell transplant recipients. In: Latgé JP, Steinbach WJ. Aspergillus fumigatus and Aspergillosis.Washington: ASM press, 2009: 519-530

35 **Petrikkos G**, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis* 2012; **54** Suppl 1: S23-S34 [PMID: 22247442 DOI: 10.1093/cid/cir866]

36 **Dehority W**, Willert J, Pong A. Zygomycetes infections in pediatric hematology oncology patients: a case series and review of the literature. *J Pediatr Hematol Oncol* 2009; **31**: 911-919 [PMID: 19855304 DOI: 10.1097/MPH.0b013e3181bbc516]

37 **Buderus S**, Sonderkötter H, Fleischhack G, Lentze MJ. Diagnostic and therapeutic endoscopy in children and adolescents with cancer. *Pediatr Hematol Oncol* 2012; **29**: 450-460 [PMID: 22612259 DOI: 10.3109/08880018.2012.678568]

38 **Sundell N**, Boström H, Edenholm M, Abrahamsson J. Management of neutropenic enterocolitis in children with cancer. *Acta Paediatr* 2012; **101**: 308-312 [PMID: 21910749 DOI: 10.1111/j.1651-2227.2011.02465.x]

39 **Altınel E**, Yarali N, Isık P, Bay A, Kara A, Tunc B. Typhlitis in acute childhood leukemia. *Med Princ Pract* 2012; **21**: 36-39 [PMID: 22024548 DOI: 10.1159/000331587]

40 **Li K**, Zheng S, Dong K, Gao Y, Wang H, Liu G, Gao J, Xiao X. Diagnosis and outcome of neutropenic enterocolitis: experience in a single tertiary pediatric surgical center in China. *Pediatr Surg Int* 2011; **27**: 1191-1195 [PMID: 21667116 DOI: 10.1007/s00383-011-2938-9]

41 **Ullery BW**, Pieracci FM, Rodney JR, Barie PS. Neutropenic enterocolitis. *Surg Infect (Larchmt)* 2009; **10**: 307-314 [PMID: 19566419 DOI: 10.1089/sur.2008.061]

42 **McCarville MB**, Adelman CS, Li C, Xiong X, Furman WL, Razzouk BI, Pui CH, Sandlund JT. Typhlitis in childhood cancer. *Cancer* 2005; **104**: 380-387 [PMID: 15952190]

43 **Wilson DB**, Rao A, Hulbert M, Mychaliska KP, Luchtman-Jones L, Hill DA, Foglia RP. Neutropenic enterocolitis as a presenting complication of acute lymphoblastic leukemia: an unusual case marked by delayed perforation of the descending colon. *J Pediatr Surg* 2004; **39**: e18-e20 [PMID: 15213940]

44 **Schlatter M**, Snyder K, Freyer D. Successful nonoperative management of typhlitis in pediatric oncology patients. *J Pediatr Surg* 2002; **37**: 1151-1155 [PMID: 12149691]

45 **Ozgen U**, Uzüm I, Mizrak B, Saraç K. "Typhlitis" in rectum. *Pediatr Int* 2010; **52**: e32-e33 [PMID: 20158643 DOI: 10.1111/j.1442-200X.2009.02989.x]

46 **Gupta S**, Kapoor S, Ravi RN, Prakash A, Aggarwal SK. Rectal involvement in neutropenic enterocolitis. *Indian J Pediatr* 2012; **79**: 535-537 [PMID: 21706240 DOI: 10.1007/s12098-011-0506-x]

47 **Ozçay F**, Kayiran SM, Ozbek N. Successful medical management of neutropenic enterocolitis (typhlitis) in a child with acute lymphoblastic leukemia. *Turk J Pediatr* 2003; **45**: 248-250 [PMID: 14696805]

48 **Gayer G**, Apter S, Zissin R. Typhlitis as a rare cause of a psoas abscess. *Abdom Imaging* 2002; **27**: 600-602 [PMID: 12173006]

49 **El-Matary W**, Soleimani M, Spady D, Belletrutti M. Typhlitis in children with malignancy: a single center experience. *J Pediatr Hematol Oncol* 2011; **33**: e98-100 [PMID: 21127432 DOI: 10.1097/MPH.0b013e3181eda606]

50 **Fike FB**, Mortellaro V, Juang D, St Peter SD, Andrews WS, Snyder CL. Neutropenic colitis in children. *J Surg Res* 2011; **170**: 73-76 [PMID: 21435655 DOI: 10.1016/j.jss.2011.01.041]

51 **Hobson MJ**, Carney DE, Molik KA, Vik T, Scherer LR, Rouse TM, West KW, Grosfeld JL, Billmire DF. Appendicitis in childhood hematologic malignancies: analysis and comparison with typhilitis. *J Pediatr Surg* 2005; **40**: 214-29; discussion 214-29; [PMID: 15871157]

52 **Yaniv I**, Fischer S, Mor C, Stark B, Goshen Y, Stein J, Cohen IJ, Zaizov R. Improved outcome in childhood B-cell lymphoma with the intensified French LMB protocol. *Med Pediatr Oncol* 2000; **35**: 8-12 [PMID: 10881001]

53 **Kelly KM**, Hutchinson RJ, Sposto R, Weiner MA, Lones MA, Perkins SL, Massey V; Children's Oncology Group. Feasibility of upfront dose-intensive chemotherapy in children with advanced-stage Hodgkin's lymphoma: preliminary results from the Children's Cancer Group Study CCG-59704. *Ann Oncol* 2002; **13** Suppl 1: 107-111 [PMID: 12078889]

54 **Moran H**, Yaniv I, Ashkenazi S, Schwartz M, Fisher S, Levy I. Risk factors for typhlitis in pediatric patients with cancer. *J Pediatr Hematol Oncol* 2009; **31**: 630-634 [PMID: 19644402 DOI: 10.1097/MPH.0b013e3181b1ee28]

55 **van de Wetering MD**, Caron HN, Biezeveld M, Taminiau JA, ten Kate FJ, Spanjaard L, Kuijpers TW. Severity of enterocolitis is predicted by IL-8 in paediatric oncology patients. *Eur J Cancer* 2004; **40**: 571-578 [PMID: 14962725]

56 **McCarville MB**, Thompson J, Li C, Adelman CS, Lee MO, Alsammarae D, May MV, Jones SC, Rao BN, Sandlund JT. Significance of appendiceal thickening in association with typhlitis in pediatric oncology patients. *Pediatr Radiol* 2004; **34**: 245-249 [PMID: 14722695]

57 **Cartoni C**, Dragoni F, Micozzi A, Pescarmona E, Mecarocci S, Chirletti P, Petti MC, Meloni G, Mandelli F. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol* 2001; **19**: 756-761 [PMID: 11157028]

58 **McAteer JP**, Sanchez SE, Rutledge JC, Waldhausen JH. Isolated appendiceal typhlitis masquerading as perforated appendicitis in the setting of acute lymphoblastic leukemia. *Pediatr Surg Int* 2014; **30**: 561-564 [PMID: 24448913 DOI: 10.1007/s00383-014-3473-2]

59 **Wiegering VA**, Kellenberger CJ, Bodmer N, Bergstraesser E, Niggli F, Grotzer M, Nadal D, Bourquin JP. Conservative management of acute appendicitis in children with hematologic malignancies during chemotherapy-induced neutropenia. *J Pediatr Hematol Oncol* 2008; **30**: 464-467 [PMID: 18525466 DOI: 10.1097/MPH.0b013e318168e7cb]

60 **Chui CH**, Chan MY, Tan AM, Low Y, Yap TL, Jacobsen AS. Appendicitis in immunosuppressed children: Still a diagnostic and therapeutic dilemma? *Pediatr Blood Cancer* 2008; **50**: 1282-1283 [PMID: 18306278 DOI: 10.1002/pbc.21554]

61 **Ozyurek E**, Arda S, Ozkiraz S, Alioglu B, Arikan U, Ozbek N. Febrile neutropenia as the presenting sign of appendicitis in an adolescent with acute myelogenous leukemia. *Pediatr Hematol Oncol* 2006; **23**: 269-273 [PMID: 16517543]

62 **Velez MC**, Athale UH, Loe W, Warrier RP. Acute perforative appendicitis during preoperative chemotherapy for Wilms tumor. *Pediatr Hematol Oncol* 2003; **20**: 147-150 [PMID: 12554525]

63 **Radhakrishnan N**, Yadav SP, Oberoi J, Kulshreshta R, Bhalla S, Sachdeva A. Intestinal mucormycosis: a rare entity in pediatric oncology. *Pediatr Hematol Oncol* 2013; **30**: 178-183 [PMID: 23410194 DOI: 10.3109/08880018.2013.769286]

64 **Cheng VC**, Chan JF, Ngan AH, To KK, Leung SY, Tsoi HW, Yam WC, Tai JW, Wong SS, Tse H, Li IW, Lau SK, Woo PC, Leung AY, Lie AK, Liang RH, Que TL, Ho PL, Yuen KY. Outbreak of intestinal infection due to Rhizopus microsporus. *J Clin Microbiol* 2009; **47**: 2834-2843 [PMID: 19641069 DOI: 10.1128/JCM.00908-09]

65 **Enjoji M**, Ohtsukasa S, Nagano H, Matsuki M, Kawachi Y, Kurisu A, Maruyama H, Kusakabe M, Nagata K, Hamaguchi H, Taki K. Localized small-bowel infarction caused by Aspergillus during chemotherapy for acute myeloid leukemia: report of a case. *Surg Today* 2008; **38**: 449-452 [PMID: 18560970 DOI: 10.1007/s00595-007-3639-9]

66 **Mohite U**, Kell J, Haj MA, O'Brien C, Kundu S, Rees J, Burnett AK. Invasive aspergillosis localised to the colon presenting as toxic megacolon. *Eur J Haematol* 2007; **78**: 270-273 [PMID: 17328784]

67 **Saitoh T**, Matsushima T, Matsuo A, Yokohama A, Irisawa H, Handa H, Tsukamoto N, Karasawa M, Nojima Y, Murakami H. Small-bowel perforation accompanied by Aspergillus endocarditis in a patient with angioimmunoblastic T-cell lymphoma. *Ann Hematol* 2007; **86**: 71-73 [PMID: 17043778]

68 **Eggimann P**, Chevrolet JC, Starobinski M, Majno P, Totsch M, Chapuis B, Pittet D. Primary invasive aspergillosis of the digestive tract: report of two cases and review of the literature. *Infection* 2006; **34**: 333-338 [PMID: 17180588]

69 **Chaudhary A**, Jain V, Dwivedi RS, Misra S. Invasive aspergillosis causing small bowel infarction in a patient of carcinoma breast undergoing chemotherapy. *J Carcinog* 2006; **5**: 18 [PMID: 16753069]

70 **Ouaïssi M**, Moutardier V, Emungania O, Lelong B, Forel JM, Guiramand J, Turrini O, Delpero JR. Fatal bowel infarction due to aspergillosis after chemotherapy. *Eur J Surg Oncol* 2003; **29**: 628 [PMID: 12943632]

71 **Sousa AB**, Ferreira G, Veiga J, Carvalho A. Clinical picture: Bowel infarction due to aspergillosis. *Lancet* 2002; **359**: 210 [PMID: 11812556]

72 **Chambon-Pautas C**, Costa JM, Chaumette MT, Cordonnier C, Bretagne S. Galactomannan and polymerase chain reaction for the diagnosis of primary digestive aspergillosis in a patient with acute myeloid leukaemia. *J Infect* 2001; **43**: 213-214 [PMID: 11798263]

73 **Khoury NJ**, Kanj V, Abboud M, Muwakkit S, Birjawi GA, Haddad MC. Abdominal complications of chemotherapy in pediatric malignancies: imaging findings. *Clin Imaging* 2009; **33**: 253-260 [PMID: 19559346 DOI: 10.1016/j.clinimag.2008.10.029]

74 **Ramdial PK**, Sing Y, Hadley GP, Chotey NA, Mahlakwane MS, Singh B. Paediatric intussusception caused by acquired immunodeficiency syndrome-associated Kaposi sarcoma. *Pediatr Surg Int* 2010; **26**: 783-787 [PMID: 20535484 DOI: 10.1007/s00383-010-2625-2]

75 **Wang SM**, Huang FC, Wu CH, Ko SF, Lee SY, Hsiao CC. Ileocecal Burkitt's lymphoma presenting as ileocolic intussusception with appendiceal invagination and acute appendicitis. *J Formos Med Assoc* 2010; **109**: 476-479 [PMID: 20610150 DOI: 10.1016/S0929-6646(10)60080-0]

76 **Hryhorczuk AL**, Lee EY. Imaging evaluation of bowel obstruction in children: updates in imaging techniques and review of imaging findings. *Semin Roentgenol* 2012; **47**: 159-170 [PMID: 22370194 DOI: 10.1053/j.ro.2011.11.007]

77 **Lee GE**, Lim GY, Lee JW, Cho B. Acute colonic pseudo-obstruction complicating chemotherapy in paediatric oncohaematological patients: clinical and imaging features. *Br J Radiol* 2012; **85**: 377-381 [PMID: 21828148 DOI: 10.1259/bjr/13281402]

78 **Jessop M**, Choo K, Little M. Acute colonic pseudo-obstruction in paediatric oncology patients. *J Paediatr Child Health* 2010; **46**: 698-699 [PMID: 21077980 DOI: 10.1111/j.1440-1754.2010.01906.x]

79 **Kim TS**, Lee JW, Kim MJ, Park YS, Lee DH, Chung NG, Cho B, Lee S, Kim HK. Acute colonic pseudo-obstruction in postchemotherapy complication of brain tumor treated with neostigmine. *J Pediatr Hematol Oncol* 2007; **29**: 420-422 [PMID: 17551407]

80 **Davies JQ**, de la Hall PM, Kaschula RO, Sinclair-Smith CC, Hartley P, Rode H, Millar AJ. Hepatoblastoma--evolution of management and outcome and significance of histology of the resected tumor. A 31-year experience with 40 cases. *J Pediatr Surg* 2004; **39**: 1321-1327 [PMID: 15359384]

81 **Li A**, Asch M, Lasky J, Sieger L, Lee SL. The surgical management of a stage III Wilms tumor presenting with perforated appendicitis. *J Pediatr Hematol Oncol* 2012; **34**: e193-e194 [PMID: 22395216 DOI: 10.1097/MPH.0b013e3182425b72]

82 **Guler N**, Ozkara C, Kaya Y, Saglam E. Ruptured abdominal aortic aneurysm after resection of an infected cardiac myxoma. *Tex Heart Inst J* 2007; **34**: 233-235 [PMID: 17622377]

83 **Tsai TC**, Wong LY, Wu HP. Ovarian torsion caused by teratoma masquerading as perforated appendicitis in a 5-year-old girl. *Pediatr Neonatol* 2011; **52**: 51-54 [PMID: 21385659 DOI: 10.1016/j.pedneo.2010.12.002]

84 **Correa-Rivas MS**, Colón-González G, Lugo-Vicente H. Cavernous hemangioma presenting as a right adnexal mass in a child. *P R Health Sci J* 2003; **22**: 311-313 [PMID: 14619460]

85 **Pini Prato A**, Castagnola E, Micalizzi C, Dufour C, Avanzini S, Pio L, Guida E, Mattioli G, Jasonni V, Disma N, Mameli L, Montobbio G, Buffa P. Early diverting colostomy for perianal sepsis in children with acute leukemia. *J Pediatr Surg* 2012; **47**: e23-e27 [PMID: 23084226 DOI: 10.1016/j.jpedsurg.2012.05.034]

86 **Nazir Z**. Long-term follow-up of a child with primary lymph node gastrinoma and Zollinger-Ellison syndrome. *J Pediatr Surg* 2011; **46**: 969-972 [PMID: 21616263 DOI: 10.1016/j.jpedsurg.2011.02.002]

87 **Al-Saleem T**, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. *Blood* 2005; **105**: 2274-2280 [PMID: 15542584]

88 **Young G**, Toretsky JA, Campbell AB, Eskenazi AE. Recognition of common childhood malignancies. *Am Fam Physician* 2000; **61**: 2144-2154 [PMID: 10779255]

89 **Rogers M**, Weinstock DM, Eagan J, Kiehn T, Armstrong D, Sepkowitz KA. Rotavirus outbreak on a pediatric oncology floor: possible association with toys. *Am J Infect Control* 2000; **28**: 378-380 [PMID: 11029139]

90 **Moser O**, Lück S, Dilloo D, Eis-Hübinger AM, Simon A. Sapovirus as a gastrointestinal pathogen in febrile pediatric patients with cancer. *J Med Virol* 2011; **83**: 2233-2236 [PMID: 22012734 DOI: 10.1002/jmv.22219]

91 **Ludwig A**, Adams O, Laws HJ, Schroten H, Tenenbaum T. Quantitative detection of norovirus excretion in pediatric patients with cancer and prolonged gastroenteritis and shedding of norovirus. *J Med Virol* 2008; **80**: 1461-1467 [PMID: 18551595 DOI: 10.1002/jmv.21217]

92 **Lothstein K**, Fisher B, Li Y, Seif A, Harris T, Torp K, Kavcic M, Huang YS, Rheingold SR, Aplenc R. Zoonotic infections in pediatric patients with acute leukemia. *Pediatr Blood Cancer* 2013; **60**: E160-E162 [PMID: 23956002 DOI: 10.1002/pbc.24596]

93 **Domenech C**, Rabodonirina M, Bleyzac N, Pagès MP, Bertrand Y. Cryptosporidiosis in children with acute lymphoblastic leukemia on maintenance chemotherapy. *J Pediatr Hematol Oncol* 2011; **33**: 570-572 [PMID: 21941152 DOI: 10.1097/MPH.0b013e31820e2d3a]

94 **Esbenshade A**, Esbenshade J, Domm J, Williams J, Frangoul H. Severe ehrlichia infection in pediatric oncology and stem cell transplant patients. *Pediatr Blood Cancer* 2010; **54**: 776-778 [PMID: 20052776 DOI: 10.1002/pbc.22392]

95 **Chaudhry R**, Joshy L, Kumar L, Dhawan B. Changing pattern of Clostridium difficile associated diarrhoea in a tertiary care hospital: a 5 year retrospective study. *Indian J Med Res* 2008; **127**: 377-382 [PMID: 18577793]

96 **Crews JD**, Koo HL, Jiang ZD, Starke JR, DuPont HL. A hospital-based study of the clinical characteristics of Clostridium difficile infection in children. *Pediatr Infect Dis J* 2014; **33**: 924-928 [PMID: 25361022 DOI: 10.1097/INF.0000000000000338]

97 **Asensio A**, Di Bella S, Lo Vecchio A, Grau S, Hart WM, Isidoro B, Scotto R, Petrosillo N, Watt M, Nazir J. The impact of Clostridium difficile infection on resource use and costs in hospitals in Spain and Italy: a matched cohort study. *Int J Infect Dis* 2015; **36**: 31-38 [PMID: 26003403 DOI: 10.1016/j.ijid.2015.05.013]

98 **Dominguez SR**, Dolan SA, West K, Dantes RB, Epson E, Friedman D, Littlehorn CA, Arms LE, Walton K, Servetar E, Frank DN, Kotter CV, Dowell E, Gould CV, Hilden JM, Todd JK. High colonization rate and prolonged shedding of Clostridium difficile in pediatric oncology patients. *Clin Infect Dis* 2014; **59**: 401-403 [PMID: 24785235 DOI: 10.1093/cid/ciu302]

99 **Nicholson MR**, Thomsen IP, Slaughter JC, Creech CB, Edwards KM. Novel risk factors for recurrent Clostridium difficile infection in children. *J Pediatr Gastroenterol Nutr* 2015; **60**: 18-22 [PMID: 25199038 DOI: 10.1097/MPG.0000000000000553]

100 **Castagnola E**, Battaglia T, Bandettini R, Caviglia I, Baldelli I, Nantron M, Moroni C, Garaventa A. Clostridium difficile-associated disease in children with solid tumors. *Support Care Cancer* 2009; **17**: 321-324 [PMID: 18802726 DOI: 10.1007/s00520-008-0507-0]

101 **Warrack S**, Duster M, Van Hoof S, Schmitz M, Safdar N. Clostridium difficile in a children's hospital: assessment of environmental contamination. *Am J Infect Control* 2014; **42**: 802-804 [PMID: 24751141 DOI: 10.1016/j.ajic.2014.03.008]

102 **Safdar A**, Malathum K, Rodriguez SJ, Husni R, Rolston KV. Strongyloidiasis in patients at a comprehensive cancer center in the United States. *Cancer* 2004; **100**: 1531-1536 [PMID: 15042689]

103 **Rapti IN**, Hadziyannis SJ. Treatment of special populations with chronic hepatitis B infection. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 323-339 [PMID: 21651351 DOI: 10.1586/egh.11.7]

104 **Oh MJ**, Lee HJ. A study of hepatitis B virus reactivation associated with rituximab therapy in real-world clinical practice: a single-center experience. *Clin Mol Hepatol* 2013; **19**: 51-59 [PMID: 23593610 DOI: 10.3350/cmh.2013.19.1.51]

105 **Sevinir B**, Meral A, Günay U, Ozkan T, Ozuysal S, Sinirtas M. Increased risk of chronic hepatitis in children with cancer. *Med Pediatr Oncol* 2003; **40**: 104-110 [PMID: 12461794]

106 **Fioredda F**, Gigliotti AR, Haupt R, Calevo MG, Giudice CL, Bocciardo L, Giacchino R. HCV infection in very-long-term survivors after cancer chemotherapy and bone marrow transplantation: a single-center experience. *J Pediatr Hematol Oncol* 2005; **27**: 481-485 [PMID: 16189441]

107 **Karim B**, Alex G, Smith AL, Hardikar W. Hepatitis C infection in children: a Melbourne perspective. *J Paediatr Child Health* 2000; **36**: 385-388 [PMID: 10940177]

108 **Matsuzaki A**, Ishii E, Nagatoshi Y, Eguchi H, Koga H, Yanai F, Inada H, Nibu K, Tamai Y, Akiyoshi K, Nakayama H, Hara T, Take H, Miyazaki S, Okamura J. Long-term outcome of treatment with protocols AL841, AL851, and ALHR88 in children with acute lymphoblastic leukemia: results obtained by the Kyushu-Yamaguchi Children's Cancer Study Group. *Int J Hematol* 2001; **73**: 369-377 [PMID: 11345205]

109 **Kołtan S**, Wysocki M, Kołtan A, Swiatkiewicz V, Styczyński J, Debski R, Balcar-Boroń A. Course of viral hepatitis B and combined B and C hepatitis in children treated for neoplastic diseases. *Med Sci Monit* 2002; **8**: CR274-CR279 [PMID: 11951070]

110 **Mulder RL**, Kremer LC, Koot BG, Benninga MA, Knijnenburg SL, van der Pal HJ, Koning CC, Oldenburger F, Wilde JC, Taminiau JA, Caron HN, van Dalen EC. Surveillance of hepatic late adverse effects in a large cohort of long-term survivors of childhood cancer: prevalence and risk factors. *Eur J Cancer* 2013; **49**: 185-193 [PMID: 22901831 DOI: 10.1016/j.ejca.2012.07.009]

111 **Büchner A**, Du Plessis NM, Reynders DT, Omar FE, Mayaphi SH, Haeri Mazanderani AF, Avenant T. Nosocomial outbreak of hepatitis B virus infection in a pediatric hematology and oncology unit in South Africa: Epidemiological investigation and measures to prevent further transmission. *Pediatr Blood Cancer* 2015; **62**: 1914-1919 [PMID: 26047015 DOI: 10.1002/pbc.25605]

112 **Durmaz O**. Hepatitis C infection in childhood. *Clin Res Hepatol Gastroenterol* 2012; **36**: 294-296 [PMID: 22521559 DOI: 10.1016/j.clinre.2012.03.024]

113 **Swilley S**, Strickland DK, Davila R, Levstik M, Ribeiro R, Hudson MM. Hepatitis C infection during treatment for childhood cancer: pitfalls in diagnosis and management. *Med Pediatr Oncol* 2002; **39**: 58-59 [PMID: 12116084]

114 **Hough R**, Chetwood A, Sinfield R, Welch J, Vora A. Fatal adenovirus hepatitis during standard chemotherapy for childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2005; **27**: 67-72 [PMID: 15701979]

115 **Matsuzaki A**, Suminoe A, Koga Y, Kusuhara K, Hara T, Ogata R, Sata T, Hara T. Fatal visceral varicella-zoster virus infection without skin involvement in a child with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2008; **25**: 237-242 [PMID: 18432508 DOI: 10.1080/08880010801938215]

116 **Mantadakis E**, Anagnostatou N, Danilatou V, Markaki EA, Spanaki AM, Briassoulis G, Kalmanti M. Fulminant hepatitis due to varicella zoster virus in a girl with acute lymphoblastic leukemia in remission: report of a case and review. *J Pediatr Hematol Oncol* 2005; **27**: 551-553 [PMID: 16217259]

117 **Müller I**, Aepinus C, Beck R, Bültmann B, Niethammer D, Klingebiel T. Noncutaneous varicella-zoster virus (VZV) infection with fatal liver failure in a child with acute lymphoblastic leukemia (ALL). *Med Pediatr Oncol* 2001; **37**: 145-147 [PMID: 11496356]

118 **Zainal Muttakin AR**, Tan AM. Mycobacterium fortuitum catheter-related sepsis in acute leukaemia. *Singapore Med J* 2006; **47**: 543-545 [PMID: 16752025]

119 **Hwang YK**, Joo NH, Tee GY, Tan P, Tan L, Girija R. Clinical activity of the new triazole drug voriconazole (UK 109, 496) against disseminated hepatosplenic aspergillosis in a patient with relapsed leukemia. *Haematologia (Budap)* 2001; **31**: 73-80 [PMID: 11345409]

120 **Tuysuz G**, Ozdemir N, Senyuz OF, Emre S, Kantarcioglu S, Adaletli I, Kepil N, Tutuncu C, Celkan T. Successful management of hepatic mucormycosis in an acute lymphoblastic leukaemia patient: a case report and review of the literature. *Mycoses* 2014; **57**: 513-518 [PMID: 24635874 DOI: 10.1111/myc.12184]

121 **Lewis RE**, Cahyame-Zuniga L, Leventakos K, Chamilos G, Ben-Ami R, Tamboli P, Tarrand J, Bodey GP, Luna M, Kontoyiannis DP. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. *Mycoses* 2013; **56**: 638-645 [PMID: 23551865 DOI: 10.1111/myc.12081]

122 **Yen TY**, Huang LM, Lee PI, Lu CY, Shao PL, Chang LY. Clinical characteristics of hepatosplenic fungal infection in pediatric patients. *J Microbiol Immunol Infect* 2011; **44**: 296-302 [PMID: 21524963 DOI: 10.1016/j.jmii.2010.08.005]

123 **Ridola V**, Chachaty E, Raimondo G, Corradini N, Brugieres L, Valteau-Couanet D, Hartmann O. Candida infections in children treated with conventional chemotherapy for solid tumors (transplant recipients excluded): The Institut Gustave Roussy Pediatrics Department experience. *Pediatr Blood Cancer* 2004; **42**: 332-337 [PMID: 14966829]

124 **Edwards JE.** Candida Species. In: Mandell GL, Bennett JE, Dolin R, Mandell, Douglas, and Bennett’s Principle and practice of infectious diseases,7th ed.Philadelphia: Churchill Livingstone Elsevier, 2009: 3225-3240

125 **Avci Z**, Alioglu B, Anuk D, Ozbek OY, Azap OK, Ozbek N. Double invasive fungal infection and typhlitis in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 2008; **25**: 99-106 [PMID: 18363175 DOI: 10.1080/08880010701885235]

126 **Lin PC**, Chang TT, Jang RC, Chiou SS. Hepatosplenic microabscesses in pediatric leukemia: a report of five cases. *Kaohsiung J Med Sci* 2003; **19**: 368-374 [PMID: 12926524]

127 **Legrand F**, Lecuit M, Dupont B, Bellaton E, Huerre M, Rohrlich PS, Lortholary O. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. *Clin Infect Dis* 2008; **46**: 696-702 [PMID: 18230039 DOI: 10.1086/527390]

128 **Saint-Faust M**, Boyer C, Gari-Toussaint M, Deville A, Poiree M, Weintraub M, Sirvent N. Adjuvant corticosteroid therapy in 2 children with hepatosplenic candidiasis-related IRIS. *J Pediatr Hematol Oncol* 2009; **31**: 794-796 [PMID: 19770685 DOI: 10.1097/MPH.0b013e3181b795ec]

129 **Srivastava A**, Yachha SK, Arora V, Poddar U, Lal R, Baijal SS. Identification of high-risk group and therapeutic options in children with liver abscess. *Eur J Pediatr* 2012; **171**: 33-41 [PMID: 21537924 DOI: 10.1007/s00431-011-1481-y]

130 **Mishra K**, Basu S, Roychoudhury S, Kumar P. Liver abscess in children: an overview. *World J Pediatr* 2010; **6**: 210-216 [PMID: 20706820 DOI: 10.1007/s12519-010-0220-1]

131 **Rao S**, Solaymani-Mohammadi S, Petri WA, Parker SK. Hepatic amebiasis: a reminder of the complications. *Curr Opin Pediatr* 2009; **21**: 145-149 [PMID: 19242252 DOI: 10.1097/MOP.0b013e32831ef249]

132 **Muorah M**, Hinds R, Verma A, Yu D, Samyn M, Mieli-Vergani G, Hadzić N. Liver abscesses in children: a single center experience in the developed world. *J Pediatr Gastroenterol Nutr* 2006; **42**: 201-206 [PMID: 16456416]

133 **Sifri CD**, Madoff LC.Infections of the liver and biliary system In: Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett’s Principle and practice of infectious diseases, 7th ed.Philadelphia: Churchill Livingstone Elsevier, 2009: 1035-1039

134 **Wong M**. What has happened in the last 50 years in immunology. *J Paediatr Child Health* 2015; **51**: 135-139 [PMID: 25677480 DOI: 10.1111/jpc.12834]

135 **Chan YK**, Estaki M, Gibson DL. Clinical consequences of diet-induced dysbiosis. *Ann Nutr Metab* 2013; **63** Suppl 2: 28-40 [PMID: 24217034 DOI: 10.1159/000354902]

136 **Buccigrossi V**, Nicastro E, Guarino A. Functions of intestinal microflora in children. *Curr Opin Gastroenterol* 2013; **29**: 31-38 [PMID: 23196853 DOI: 10.1097/MOG.0b013e32835a3500]

137 **Döerffel Y**, Pavel M, Loening-Baucke V, Swidsinski A. Common biostructure of the fecal flora in celiac disease, Crohn's disease, and carcinoid tumors. *Inflamm Bowel Dis* 2008; **14**: 1613-1614 [PMID: 18521905 DOI: 10.1002/ibd.20507]

138 **van Vliet MJ**, Tissing WJ, Dun CA, Meessen NE, Kamps WA, de Bont ES, Harmsen HJ. Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. *Clin Infect Dis* 2009; **49**: 262-270 [PMID: 19514856 DOI: 10.1086/599346]

139 **Huang Y**, Yang W, Liu H, Duan J, Zhang Y, Liu M, Li H, Hou Z, Wu KK. Effect of high-dose methotrexate chemotherapy on intestinal Bifidobacteria, Lactobacillus and Escherichia coli in children with acute lymphoblastic leukemia. *Exp Biol Med (Maywood)* 2012; **237**: 305-311 [PMID: 22362190 DOI: 10.1258/ebm.2011.011297]

140 **Agirbasli H**, Ozcan SA, Gedikoğlu G. Fecal fungal flora of pediatric healthy volunteers and immunosuppressed patients. *Mycopathologia* 2005; **159**: 515-520 [PMID: 15983737]

141 **Gammelsrud KW**, Sandven P, Høiby EA, Sandvik L, Brandtzaeg P, Gaustad P. Colonization by Candida in children with cancer, children with cystic fibrosis, and healthy controls. *Clin Microbiol Infect* 2011; **17**: 1875-1881 [PMID: 21745258 DOI: 10.1111/j.1469-0691.2011.03528.x]

142 **Wang Y**, Xue J, Zhou X, You M, Du Q, Yang X, He J, Zou J, Cheng L, Li M, Li Y, Zhu Y, Li J, Shi W, Xu X. Oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. *PLoS One* 2014; **9**: e102116 [PMID: 25025462 DOI: 10.1371/journal.pone.0102116]

143 **Srithavaj T**, Thaweboon S. Determination of oral microflora in irradiated ocular deformed children. *Southeast Asian J Trop Med Public Health* 2006; **37**: 991-995 [PMID: 17333745]

144 **Ye Y**, Carlsson G, Agholme MB, Wilson JA, Roos A, Henriques-Normark B, Engstrand L, Modéer T, Pütsep K. Oral bacterial community dynamics in paediatric patients with malignancies in relation to chemotherapy-related oral mucositis: a prospective study. *Clin Microbiol Infect* 2013; **19**: E559-E567 [PMID: 23829394 DOI: 10.1111/1469-0691.12287]

145 **de Mendonça RM**, de Araújo M, Levy CE, Morari J, Silva RA, Yunes JA, Brandalise SR. Prospective evaluation of HSV, Candida spp., and oral bacteria on the severity of oral mucositis in pediatric acute lymphoblastic leukemia. *Support Care Cancer* 2012; **20**: 1101-1107 [PMID: 21597938 DOI: 10.1007/s00520-011-1190-0]

146 **Sixou JL**, Aubry-Leuliette A, De Medeiros-Battista O, Lejeune S, Jolivet-Gougeon A, Solhi-Pinsard H, Gandemer V, Barbosa-Rogier M, Bonnaure-Mallet M. Capnocytophaga in the dental plaque of immunocompromised children with cancer. *Int J Paediatr Dent* 2006; **16**: 75-80 [PMID: 16430520]

147 **Wada M**, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, Asahara T, Nomoto K. Effects of the enteral administration of Bifidobacterium breve on patients undergoing chemotherapy for pediatric malignancies. *Support Care Cancer* 2010; **18**: 751-759 [PMID: 19685085 DOI: 10.1007/s00520-009-0711-6]

148 **Avcin SL**, Pokorn M, Kitanovski L, Premru MM, Jazbec J. Bifidobacterium breve Sepsis in Child with High-Risk Acute Lymphoblastic Leukemia. *Emerg Infect Dis* 2015; **21**: 1674-1675 [PMID: 26291071 DOI: 10.3201/eid2109.150097]

149 **Cesaro S**, Chinello P, Rossi L, Zanesco L. Saccharomyces cerevisiae fungemia in a neutropenic patient treated with Saccharomyces boulardii. *Support Care Cancer* 2000; **8**: 504-505 [PMID: 11094997]

150 **Kara A**, Devrim İ, Bayram N, Katipoğlu N, Kıran E, Oruç Y, Demiray N, Apa H, Gülfidan G. Risk of vancomycin-resistant enterococci bloodstream infection among patients colonized with vancomycin-resistant enterococci. *Braz J Infect Dis* 2015; **19**: 58-61 [PMID: 25529366 DOI: 10.1016/j.bjid.2014.09.010]

151 **van der Velden WJ**, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. *Br J Haematol* 2014; **167**: 441-452 [PMID: 25196917 DOI: 10.1111/bjh.13113]

152 **Olczak-Kowalczyk D**, Daszkiewicz M, Krasuska-Sławińska B, Gozdowski D, Daszkiewicz P, Fronc B, Semczuk K. Bacteria and Candida yeasts in inflammations of the oral mucosa in children with secondary immunodeficiency. *J Oral Pathol Med* 2012; **41**: 568-576 [PMID: 23019688]

153 **Brook I**. The role of anaerobic bacteria in bacteremia. *Anaerobe* 2010; **16**: 183-189 [PMID: 20025984 DOI: 10.1016/j.anaerobe.2009.12.001]

154 **Sakaguchi S**, Saito M, Tsuji H, Asahara T, Takata O, Fujimura J, Nagata S, Nomoto K, Shimizu T. Bacterial rRNA-targeted reverse transcription-PCR used to identify pathogens responsible for fever with neutropenia. *J Clin Microbiol* 2010; **48**: 1624-1628 [PMID: 20351213 DOI: 10.1128/JCM.01724-09]

155 **Huang WT**, Chang LY, Hsueh PR, Lu CY, Shao PL, Huang FY, Lee PI, Chen CM, Lee CY, Huang LM. Clinical features and complications of viridans streptococci bloodstream infection in pediatric hemato-oncology patients. *J Microbiol Immunol Infect* 2007; **40**: 349-354 [PMID: 17712470]

156 **Alazmi W**, Bustamante M, O'Loughlin C, Gonzalez J, Raskin JB. The association of Streptococcus bovis bacteremia and gastrointestinal diseases: a retrospective analysis. *Dig Dis Sci* 2006; **51**: 732-736 [PMID: 16614996]

157 **Pasqualotto AC**, Rosa DD, Medeiros LR, Severo LC. Candidaemia and cancer: patients are not all the same. *BMC Infect Dis* 2006; **6**: 50 [PMID: 16542444]

158 **Butler KM**. Enterococcal infection in children. *Semin Pediatr Infect Dis* 2006; **17**: 128-139 [PMID: 16934707]

159 **André N**, Coze C, Gentet JC, Perez R, Bernard JL. Geotrichum candidum septicemia in a child with hepatoblastoma. *Pediatr Infect Dis J* 2004; **23**: 86 [PMID: 14743060]

160 **Posteraro B**, Bruno S, Boccia S, Ruggiero A, Sanguinetti M, Romano Spica V, Ricciardi G, Fadda G. Candida parapsilosis bloodstream infection in pediatric oncology patients: results of an epidemiologic investigation. *Infect Control Hosp Epidemiol* 2004; **25**: 641-645 [PMID: 15357154]

161 **Safdar A**, Armstrong D. Listeriosis in patients at a comprehensive cancer center, 1955-1997. *Clin Infect Dis* 2003; **37**: 359-364 [PMID: 12884160]

162 **Tunkel AR**, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis* 2002; **34**: 1524-1529 [PMID: 12015700]

163 **Moore DL**. Essentials of paediatric infection control. *Paediatr Child Health* 2001; **6**: 571-579 [PMID: 20084127]

164 **Gray JW**, George RH. Experience of vancomycin-resistant enterococci in a children's hospital. *J Hosp Infect* 2000; **45**: 11-18 [PMID: 10833339]

165 **Caselli D**, Cesaro S, Fagioli F, Carraro F, Ziino O, Zanazzo G, Meazza C, Colombini A, Castagnola E; Infectious Diseases Study Group of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Incidence of colonization and bloodstream infection with carbapenem-resistant Enterobacteriaceae in children receiving antineoplastic chemotherapy in Italy. *Infect Dis (Lond)* 2016; **48**: 152-155 [PMID: 26393496 DOI: 10.3109/23744235.2015.1087647]

166 **Haeusler GM**, Mechinaud F, Daley AJ, Starr M, Shann F, Connell TG, Bryant PA, Donath S, Curtis N. Antibiotic-resistant Gram-negative bacteremia in pediatric oncology patients--risk factors and outcomes. *Pediatr Infect Dis J* 2013; **32**: 723-726 [PMID: 23838774 DOI: 10.1097/INF.0b013e31828aebc8]

167 **Logan LK**. Carbapenem-resistant enterobacteriaceae: an emerging problem in children. *Clin Infect Dis* 2012; **55**: 852-859 [PMID: 22700827 DOI: 10.1093/cid/cis543]

168 **Nolan SM**, Gerber JS, Zaoutis T, Prasad P, Rettig S, Gross K, McGowan KL, Reilly AF, Coffin SE. Outbreak of vancomycin-resistant enterococcus colonization among pediatric oncology patients. *Infect Control Hosp Epidemiol* 2009; **30**: 338-345 [PMID: 19239375 DOI: 10.1086/596202]

169 **Kurucu N**, Kul S, Tosun I, Erduran E, Köksal I. Fungemia and renal fungus ball formation with Candida norvegensis in a child with acute lymphoblastic leukemia. *Turk J Pediatr* 2011; **53**: 448-451 [PMID: 21980850]

170 **Lehrnbecher T**, Frank C, Engels K, Kriener S, Groll AH, Schwabe D. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 2010; **61**: 259-265 [PMID: 20624423 DOI: 10.1016/j.jinf.2010.06.018]

171 **Schwesinger G**, Junghans D, Schröder G, Bernhardt H, Knoke M. Candidosis and aspergillosis as autopsy findings from 1994 to 2003. *Mycoses* 2005; **48**: 176-180 [PMID: 15842333]

172 **Roberts ME**, Bishop JL, Fan X, Beer JL, Kum WW, Krebs DL, Huang M, Gill N, Priatel JJ, Finlay BB, Harder KW. Lyn deficiency leads to increased microbiota-dependent intestinal inflammation and susceptibility to enteric pathogens. *J Immunol* 2014; **193**: 5249-5263 [PMID: 25339668 DOI: 10.4049/jimmunol.1302832]

173 **Kobos R**, Shukla N, Renaud T, Prockop SE, Boulad F, Steinherz PG. High-dose cyclophosphamide for the treatment of refractory T-cell acute lymphoblastic leukemia in children. *J Pediatr Hematol Oncol* 2014; **36**: e265-e270 [PMID: 24327129 DOI: 10.1097/MPH.0000000000000080]

174 **Trelinska J**, Dachowska I, Kotulska K, Fendler W, Jozwiak S, Mlynarski W. Complications of mammalian target of rapamycin inhibitor anticancer treatment among patients with tuberous sclerosis complex are common and occasionally life-threatening. *Anticancer Drugs* 2015; **26**: 437-442 [PMID: 25719621 DOI: 10.1097/CAD.0000000000000207]

175 **Sachak T**, Arnold MA, Naini BV, Graham RP, Shah SS, Cruise M, Park JY, Clark L, Lamps L, Frankel WL, Theodoropoulos N, Arnold CA. Neutropenic Enterocolitis: New Insights Into a Deadly Entity. *Am J Surg Pathol* 2015; **39**: 1635-1642 [PMID: 26414225 DOI: 10.1097/PAS.0000000000000517]

176 **Miedema KG**, de Bont ES, Elferink RF, van Vliet MJ, Nijhuis CS, Kamps WA, Tissing WJ. The diagnostic value of CRP, IL-8, PCT, and sTREM-1 in the detection of bacterial infections in pediatric oncology patients with febrile neutropenia. *Support Care Cancer* 2011; **19**: 1593-1600 [PMID: 20803037 DOI: 10.1007/s00520-010-0987-6]

**P-Reviewer:** Plaza MA, Yucel O **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Different definitions of neutropenic enterocolitisamong studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Neutropenic enterocolitis definition** | **Neutropenia (Neutrophil count/mm3)** | **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 °C, 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°C), 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 °C
* 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.

**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 < 108/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 durationHigher mortality rateHigher death rateProlonged duration | Sundell *et al*[38], 2012Cartoni *et al*[57], 2001Rizzatti *et al*[22], 2010McCarville *et al*[42], 2005 |
| * Appendiceal thickening
 | Higher risk of serious complications | McCarville *et al*[56], 2004 |