Chapter 5

Risk analysis, diagnosis and management of gastrointestinal mucositis in pediatric cancer patients

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ABSTRACT

Mucositis is a complex inflammatory reaction of the mucous membranes of the alimentary tract upon chemotherapy and radiotherapy treatment in oncology patients. Mucositis can be subdivided in oral and gastrointestinal mucositis (GI mucositis). The damage to the gastrointestinal tract compromises the intestinal function and thereby the nutritional status and the quality of life, and eventually affects survival. The literature on GI mucositis focuses mainly on adults. This review focuses on data available on GI mucositis in pediatric cancer patients. An evaluation of the clinical presentation and consequences of GI mucositis in children is outlined. The review summarizes key issues for clinicians with respect to risk analysis for developing mucositis and the diagnosis of this condition in children. Information on these issues is obtained from clinical trials in children and adults, and from animal models. Diagnostic tools and assessment of severity of GI mucositis in children is elaborated on. Furthermore, the clinical management of the symptoms and consequences of GI mucositis in children, with specific focus on nutritional support, are discussed.
INTRODUCTION

The survival of children with cancer has increased extensively over the last decades due to improved radiotherapy and surgery, and more intensive chemotherapeutic protocols [1,2]. The disadvantage of these more intensive treatment protocols is a higher frequency of side effects, one of which is mucositis. Mucositis, which is a complex inflammatory reaction of the mucous membranes of the alimentary tract, can be subdivided in oral and gastrointestinal mucositis (GI mucositis). To date, there is no treatment for GI mucositis, thus giving a primary role to supportive care during GI mucositis. Over the years, research in this field has mainly focused on oral mucositis or on GI mucositis in adults. Knowledge in children is scarce, therefore the main focus of this review is GI mucositis in pediatric cancer patients.

Incidence

GI mucositis is a clinical problem with an estimated incidence of 40-100% of patients with chemotherapy [3]. However, in adults and children the incidence of GI mucositis has been examined in detail in only four studies (Table 1) [4-7]. Since there is no gold standard for the diagnosis there has been no consistency in the methods to establish the frequency of GI mucositis. In children the incidence of GI mucositis has been determined in two studies (Table 1). In nine children with acute myeloid leukemia, GI mucositis was experienced in 55% of the chemotherapy cycles, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE criteria) [6]. In a heterogeneous group of fifteen children with cancer, the children experienced GI mucositis during 28% of the chemotherapy cycles. However, in this study GI mucositis was determined using the World Health Organization (WHO) scale for oral mucositis in combination with abdominal symptoms [7]. This is remarkable, since it is possible to experience GI mucositis without oral complaints and vice versa. Both studies have been performed in a relatively small number of patients.

Pathophysiology

The current understanding of GI mucositis is largely based on the five phase pathophysiological model of oral mucositis [8,9]. The first phase is the initiation phase, followed by phase two with a primary damage response. In phase three there is a positive feedback system, with signal amplification of the primary damage initiated by chemotherapy. The most symptomatic is the fourth phase, the ulceration phase, in which mucositis becomes clinically relevant [8,10,11]. The last phase of mucositis is self-resolution when the chemotherapy is stopped [8]. This five phase model has been adapted for GI mucositis, although it has been suggested to be more complex due to columnar epithelium, tight junctions, more varied microbiota and different functions in different parts of the small intestine [12,13]. It has been suggested by several authors that there is
<table>
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<th>Study</th>
<th>Study design</th>
<th>Included patients (number)</th>
<th>Age range (years)</th>
<th>Type of cancer</th>
<th>Scoring system</th>
<th>Patients with GI mucositis (percentage)</th>
<th>Number of chemotherapy courses</th>
<th>Chemotherapy courses with GI mucositis (percentage)</th>
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<td>Adults</td>
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<td>Elting et al 2003[4]</td>
<td>Retrospective</td>
<td>599</td>
<td>16-?</td>
<td>Solid tumors, lymphomas</td>
<td>NCI-CTCAE version 3.0</td>
<td>51% (oral and/or GI mucositis)</td>
<td>1236</td>
<td>15%</td>
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<tr>
<td>Krishna et al 2011[5]</td>
<td>Prospective</td>
<td>303</td>
<td>32-75</td>
<td>Multiple myeloma</td>
<td>NCI-CTCAE version 3.0(^a)</td>
<td>15.5%</td>
<td>1529</td>
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<td>Children</td>
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<td>Tooley et al 2006[7]</td>
<td>Prospective</td>
<td>15</td>
<td>5-17</td>
<td>ALL, AML, neuroblastoma, NHL, Ewing's sarcoma</td>
<td>WHO criteria for oral mucositis + abdominal symptoms</td>
<td>-</td>
<td>25</td>
<td>28%</td>
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\(^a\) Krishna et al. defined mucositis as colitis and/or enteritis (grades II-IV) that occurred during chemotherapy-induced neutropenia and in the absence of C. Difficile infection. Abbreviations: NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse events, scoring system versions 3.0 based on clinical symptoms like vomiting, diarrhea and pain. WHO, World Health Organization. AML, acute myeloid leukemia. ALL, acute lymphoid leukemia. NHL, non Hodgkin lymphoma.
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an interaction between the microbiota and the development of mucositis, but there is no scientific evidence for this assertion [14-18].

Clinical consequences

The clinical presentation is probably similar for adults and children experiencing GI mucositis. The adult patients suffer from nausea, vomiting, abdominal pain and diarrhea [8,19,20]. It has been suggested that diarrhea induced by chemotherapy is multifactorial and a combination of osmotic, secretory and exudative diarrhea [21]. Although the mechanisms remain unclear, several factors are likely to be involved: an altered gut motility with consequently decreased transit time and reduced water absorption, altered fluid transport, changes in the microbiota, and fermentation [21,22].

GI mucositis can significantly affect the nutritional status. First, nutritional intake during GI mucositis is severely reduced. Second, there is an increased loss due to vomiting and diarrhea [23,24]. Finally, the nutritional absorption and digestion are altered, which will be discussed later on in this review. This combination leads to weight loss and malnutrition. Thus, nutritional support is of importance during GI mucositis. In pediatric oncology patients adequate nutrient intake is even more important than in adults, since it is needed to continue growth and development during chemotherapy treatment. Moreover, malnutrition in children with cancer has been associated with a reduction of the chemotherapy dose or delay of chemotherapy cycle [25,26].

Another consequence of GI mucositis is the increased risk of developing an infection. The patients are already at risk to develop an infection, due to the alterations in the immune response caused by the high doses of chemotherapeutic agents. Because of GI mucositis the patients have an even greater risk of developing bacteraemia or sepsis, due to breaks in the mucosa which are an entry for several microorganisms [8,27]. In adult patients with solid tumors or lymphomas there are significantly more episodes of infection during a chemotherapy cycle with GI mucositis (73%) than during cycles without GI mucositis (36%) [4].

Due to the above mentioned consequences, patients with GI mucositis are admitted to the hospital for longer periods, which has major economic consequences [4]. In one study, for example, the duration of hospitalization in adults was 12 days with GI mucositis compared to 4 days without GI mucositis [4].

Finally, the reduced nutritional intake, the pain and the increased duration of hospitalization all influence the quality of life. Moreover, the symptoms and consequences of GI mucositis eventually cause a delay of the next chemotherapy cycle, a reduction of the doses or even discontinuation of the regimen, which eventually affects survival [3]. In one study, for instance, reduction of the next chemotherapy course in adults happened in 23% after a course with GI mucositis compared to 11% after a course without GI mucositis [4].
Although the clinical consequences in adults are enormous, as shown above, there are no data on the clinical consequences specifically in children suffering from GI mucositis. Moreover, the age differences in children, from infant to teenager, possibly also influences the consequences of GI mucositis. It seems reasonable to think that at different ages some consequences are more pronounced than others. However, there are no data on the clinical consequences of mucositis in children in general, not to mention the impact of age differences in children. Therefore we can only speculate that at a younger age the consequences might be more pronounced and causes more problems, partly due to the challenging recognition and measurement of the severity of GI mucositis. Therefore timely supportive care in the younger child is challenging.

It is important to diagnose GI mucositis in children as early as possible and give the required supportive care. But how do we recognize GI mucositis in children objectively and what supportive care should be given? To answer these questions we reviewed the literature and first summarize key issues for clinicians with respect to risk analysis for developing GI mucositis. Second, we discuss the diagnosis of this condition in children, and finally we discuss the supportive care to manage the symptoms and consequences of GI mucositis, with specific focus on nutritional support.

**LITERATURE SEARCH**

We performed a search for possible risk factors, diagnostic tools and supportive care in Pubmed, including only English papers from 1982 up to and including 31 December 2013. The following search terms were used:

- **Mucositis**: mucositis or mucosal barrier injury or mucosal injury
- **Gastrointestinal**: intestine or small intestine or intestinal or gastrointestinal or alimentary tract
- **Children**: child or children or pediatric or pediatrics or pediatric patients
- **Cancer treatment**: cancer or cancer treatment or chemotherapy or antineoplastic therapy or cytotoxic agent or chemotherapeutic agent
- **Risk factors**: predictive factors or risk analysis or risk factors or genetic factors or genetics or polymorphisms
- **Diagnosis and assessment**: assessment scale or assessment score or marker or biomarker or biological marker or diagnosis or diagnostic tool
- **Pain management**: pain or pain management or pain treatment
- **Diarrhea management**: diarrhea or diarrhea management or diarrhea treatment
- **Nutritional support**: nutrition or nutritional support or tube feeding or enteral feeding or enteral nutrition or parenteral feeding or parenteral nutrition
- **Nutrient digestion and absorption**: nutrient or absorption or digestion or permeability
Variable combinations of these search terms were used to find studies which included GI mucositis specifically in children. Studies about nutritional support during GI mucositis in either adult or pediatric cancer patients are lacking. Therefore, we performed a search for the nutrient digestion and absorption in the intestine during GI mucositis in children, adults and animal models, in order to give possible suggestions about the effectiveness of enteral nutrition. Furthermore, we searched for studies with the use, and comparison, of enteral and parenteral nutrition in pediatric cancer patients in general for possible suggestions for nutritional support. We excluded the studies concerning only oral mucositis. There were few studies concerning only children with GI mucositis. Therefore we included adult studies for suggestions in children. Additional relevant studies were found by the references of the initially included studies.

**RISK ANALYSIS**

In order to predict which patient will develop GI mucositis after chemotherapy, it is useful to do a risk analysis, based on treatment, patient-associated characteristics and genetic factors.

**Treatment-related factors**

The probability of developing GI mucositis varies among patients, both in adults and children. The chemotherapeutic agents affect the rapidly dividing cells, which makes the gastrointestinal tract especially vulnerable [3]. Every chemotherapeutic agent affects different levels of the crypt cell hierarchy [3,28,29]. In general, the type of cancer together with treatment-related factors like the type of chemotherapeutic agent, the schedule and the dosage of chemotherapy all influence the risk of developing GI mucositis [30]. Elting et al., performed a meta-analysis of the risk for developing GI mucositis in adult patients receiving targeted agents and concluded that targeted agents seem to increase the risk of diarrhea in adults [31]. In a review by Sonis et al., the risk of oral and GI mucositis is mentioned in relation to the different antineoplastic therapies in both adults and children [3]. In this study, adult patients receiving hematopoietic stem cell transplantation experienced particularly high rates of mucositis [3]. The risk of GI mucositis in relation to the different antineoplastic therapies specifically in children was higher in pediatric bone marrow transplant with total body irradiation [3]. However, more than half of the studies in children with other antineoplastic therapies included in the review of Sonis et al., considered only oral mucositis and had no report on the risk of GI mucositis [3]. Thus, there is no good evidence concerning treatment related factors indicating the risk to develop GI mucositis in children.
Patient-associated factors

In several reviews, possible patient-associated risk factors in adults are mentioned like age, body mass and sex [3,19,30,32,33]. In a clinical trial with 303 adult patients with myeloma, increased risk of GI mucositis was associated with lower body surface area (BSA), decreased renal function and lower albumin levels [5]. In this trial the calculated dose of all chemotherapeutic agents was based on the BSA [5]. Three adult studies concluded that women had a higher risk of developing 5-fluourouracil-induced GI mucositis compared to men [34-36]. In an adult study of McCollum et al., African-Americans suffered significantly less from GI mucositis than Caucasian patients [37]. Moreover, the pathogenetic pathways of GI mucositis might be influenced by comorbid conditions. In adults, patients with psoriasis had 77% less risk and patients with Addison’s disease had 20% more risk of developing GI mucositis [30]. Nevertheless, little is known about the influence of other comorbid conditions in the development of GI mucositis. In children, there are no data on patient-associated risk factors related to the development of GI mucositis.

Genetic factors

Genetic factors are very likely to influence the risk of developing mucositis. Different polymorphisms have been studied as possible influencing factors on chemotherapy-induced toxicities. In children, polymorphisms in folate-related genes are in particular studied in association with side effects of methotrexate (MTX), an antifolate chemotherapeutic agent. There are conflicting results concerning the influence of methylenetetrahydrofolate reductase (MTHFR) polymorphisms. In the MTHFR gene two polymorphisms have been described, MTHFR C677T and MTHFR A1298C. Three studies found a significant association between MTHFR C677T and MTX-induced toxicities including gastrointestinal toxicities in children [38-40]. In contrast, Huang et al. and Shimasaki et al., found no correlation between MTX-induced toxicities and MTHFR C677T in children [41,42]. Recently, these studies were included in a meta-analysis which assessed the possible associations between MTHFR polymorphisms and MTX-induced toxicities in patients with ALL. MTHFR C677T polymorphism was significantly associated with gastrointestinal toxicity in children with an odds ratio of 12.15 (95% CI 3.71-39.80) [43]. Furthermore, one report in children suggested that DNA repair gene XRCC1 polymorphisms influence toxicities, although in this study mucositis was defined in general and not specified as oral or GI mucositis [44]. XRCC1 Arg 399 Gln polymorphism has been suggested as a risk factor for severe mucositis. This is in contrast to XRCC1 194Trp, which has a protective effect against mucositis in children with leukemia and lymphoma [44].

Thus, during treatment for leukemia and lymphoma in children, XRCC1 Arg 399 Gln polymorphism might be a risk factor. Furthermore, polymorphisms in children as risk factors for developing GI mucositis have been studied during MTX treatment, and only MTHFR C677T seems to be a risk factor for GI mucositis. However, these studies are about genes associated with
drug metabolism of chemotherapy treatment. Unfortunately, there have been no studies concerning genes associated with the complex pathophysiology of mucositis. We speculate that SNP’s in these genes might be more relevant than those in drug metabolism genes, since they are more likely to be impactful on risk.

**DIAGNOSIS AND ASSESSMENT OF SEVERITY**

The diagnosis and assessment of the severity of GI mucositis in a child are important in order to give the needed supportive care. Nevertheless, the objective recognition of the condition and the severity are challenging, due to the lack of a gold standard diagnostic tool. Possible diagnostic tools in children can be divided into assessment scales and biomarkers.

**Assessment scales**

There are different clinical GI mucositis assessment scales. The most commonly used symptomatic scale for adverse events is the NCI-CTCAE criteria scale version 4.0. This scale ranges from 1 – 5, based on pain; medical interventions, like tube feeding and parenteral nutritional support; and activities of daily living (ADL) [6,45]. Another clinical assessment scale is the daily gut score, ranging from 0 – 20. It is a sum score based on the frequency of vomiting and diarrhea, and the occurrence of nausea, abdominal complaints, fecal incontinency and volume of diarrhea [46]. The assessment scales are subjective and based on symptoms, interventions and ADL. Symptoms like vomiting, diarrhea and pain, can have several different causes and may not have been necessarily caused by GI mucositis [47]. In addition, pain relief medication influences symptoms like pain and diarrhea, without altering the severity of GI mucositis. Moreover, the existing assessment scales for scoring and measuring the severity of GI mucositis have never been validated for young children [48]. In young children symptoms like fecal incontinence and pain have limited use, due to the non-pathological age-related incontinence and a lower ability of the young child to express the level of pain. The NCI-CTCAE scale is based on interventions like tube feeding, parenteral nutritional support and hospitalization, but these interventions are often indicated also in children treated for cancer without GI mucositis. Furthermore, limited self-care in ADL in the NCI-CTCAE criteria has been assessed as grade three GI mucositis, although self-care in ADL is limited in young children due to their developmental stage. Thus, assessment scales are probably not the most accurate method to diagnose GI mucositis in children.

**Biomarkers**

Biomarkers would be very useful in the objective assessment and measurement of chemotherapy-induced GI mucositis in children. However, to date there is no gold standard biomarker for GI
mucositis. As a possible biomarker, the 13C-sucrose breath test has been shown to non-invasively assess the status of the small intestine in children [7,49,50]. But the major disadvantages of this test are the time-frame and the highly specialized equipment necessary for analysis. Breath samples are required every 15 min for 2 hours, multiple times during admission [7,49-51]. In addition, this test is really invasive for children who are severely ill and difficult for very young children.

Another optional biomarker is plasma citrulline. Plasma citrulline is an amino acid synthesized almost exclusively by the enterocytes of the small intestine, therefore a reliable marker of the enterocyte mass [52]. Plasma citrulline has been correlated significantly with villus length in preclinical studies in an MTX-induced GI mucositis rat model [53-56]. In addition, in a preclinical study a decrease in citrulline has been correlated with mucosal atrophy independent of nutritional intake [57]. Furthermore, in several clinical studies in adults a decrease of plasma citrulline has been correlated with the severity of GI mucositis and low citrulline concentration was associated with bacteraemia [51,58-61]. Moreover, citrulline has been shown to be a marker for chemotherapy-induced GI mucositis in pediatric cancer patients [6]. In this study, citrulline was compared to the NCI-CTCAE GI mucositis assessment scale, the daily gut score, plasma interleukin-8, fecal interleukin-8, fecal calprotectin and the sugar absorption test, in pediatric cancer patients with GI mucositis [6]. Of all these parameters plasma citrulline was shown to have the strongest correlation with the NCI-CTCAE criteria and the daily gut score, and it possibly detected even subclinical GI mucositis [6]. Furthermore, one report has concluded that a citrulline-based assessment scale should be considered for measuring and monitoring GI mucositis in adults [62]. Thus, plasma citrulline is a possible diagnostic tool for GI mucositis.

**CLINICAL MANAGEMENT**

To date there is no prevention or treatment for GI mucositis, neither in adults nor children. Several agents have been tested to either prevent or treat GI mucositis. In a recent review of the MASCC/ISOO, all agents for the management of GI mucositis have been systematically reviewed. The authors concluded that for most investigated interventions there was not enough data, but that there was evidence for a new recommendation not to use misoprostol suppositories for the prevention of proctitis induced by radiotherapy [63]. Therefore, to date, the clinical management has mainly been focused on the supportive care of the symptoms and clinical consequences. We divided the clinical management into pain management, management of diarrhea and nutritional support.
Pain management

One of the major symptoms of GI mucositis is abdominal pain. There is no specific guideline for the management of pain due to GI mucositis. The WHO provides guidelines for the use of analgesia in children with pain due to medical illnesses, in which a two-step strategy has been recommended instead of the previously used three-step strategy. In step one for mild pain, paracetamol or ibuprofen is recommended. However, since nonsteroidal anti-inflammatory drugs (NSAID’s) potentially cause thrombopathy in this population, already at high risk of thrombocytopenia, the use of ibuprofen and other NSAID’s might not be preferred in this population. In the second step, for moderate to severe pain, a strong opioid such as morphine is recommended [64]. Nevertheless, even morphine does not cause complete relieve of pain in some children suffering GI mucositis. In a retrospective review of consecutive episodes of mucositis in children, morphine managed pain insufficiently in 26%, and children needed additive ketamine therapy [65]. The combination of ketamine and morphine treatment improved the pain management in children with mucositis [66]. In addition, in a double-blind comparison in children with mucositis pain, morphine was not superior to pethidine and caused more constipation [67]. Thus, the management of pain due to GI mucositis in children is still challenging.

Management of diarrhea

Two therapeutic agents are currently being used for diarrhea induced by chemotherapy, with or without GI mucositis. In general in adults, loperamide has been the therapeutic agent of first choice, although the overall efficacy of loperamide is relatively minimal and even high dose treatment with loperamide is in many cases ineffective [21,68]. Octreotide is also a potential drug to reduce diarrhea and has been recommended in adults if loperamide fails to control the diarrhea [19,21,22,63,68]. Octreotide has been shown to be effective rapidly, even if given as second line treatment in adults [21,69,70]. In children with chemotherapy-induced diarrhea, not specifically during GI mucositis, octreotide caused in 92% a complete response with only few side effects, although in the long-term, the odds for complete response was lower [71]. Unfortunately, there have been no studies concerning the management of diarrhea especially focused on children suffering from GI mucositis.

Nutritional support

Different methods of nutritional support have been used in the care of children with cancer. Nutritional support given as enteral nutrition (EN) and parenteral nutrition (PN) both have advantages and disadvantages. In a systematic review of nutrition during chemotherapy in children with cancer, not specifically during mucositis, there was limited evidence that PN is more effective than oral nutrition. However, no studies compared PN with EN [72].
Unfortunately, there has been no consistency in clinical practice concerning nutritional support in children with cancer [73]. In adults during non-surgical oncolgy treatment, both American and European nutrition societies recommend EN as first step in nutritional support in a functioning gastrointestinal tract [74-76]. In addition, in children with an unaffected and functioning gut, EN is the preferred way of administering nutrition [77]. PN is indicated in case oral nutrition or EN is inadequate [77,78]. Unfortunately, children with GI mucositis do not have an unaffected gastrointestinal tract. Due to the damage in the intestine of children with GI mucositis, it is questionable if nutritional support via the enteral route is effective.

For EN the function of the intestine during GI mucositis is determinative for the ability to reach the goals of nutritional support. In children it has been shown that chemotherapy reduces lactose absorption [79]. However, it does not influence the uptake of the amino acid leucine in the intestine during GI mucositis [80]. There have been no other clinical studies concerning nutrient digestion and absorption during GI mucositis. Meanwhile, in the last few years in our lab, research has been performed on the uptake of several macronutrients in an MTX-induced GI mucositis rat model [53-56]. In this rat model it has been established that during GI mucositis glucose and amino acids are still absorbed when administered continuously, in comparison with lactose and fatty acids which are not digested and absorbed [53-56]. In general, EN offers advantages like the stimulation of the intestinal growth, the enterocyte function and the maintenance of the barrier function. This has been shown in preclinical and clinical studies of intestinal diseases, like short bowel disease, prematurity and after surgery [81-85]. However, the effects of EN on the intestine specifically during GI mucositis are unknown.

If the enteral route is problematic, the parenteral route can be an option for administering nutritional support. In general, the downside is that patients receiving PN are at greater risk of developing infectious complications [86,87]. The effects of PN during GI mucositis are unknown, and there have been few studies about the use of PN in pediatric cancer patients in general. PN in children with cancer has been suggested to improve the caloric intake as a possible additive to EN in case of gastrointestinal complications [88]. In addition, PN in children undergoing haematopoietic stem cell transplantation has improved the nutritional status and has contributed to reconstitution of hematopoiesis [89,90].

EN and PN have been compared in pediatric cancer patients in only one study. Azarnoush et al. concluded that EN is the first option for nutritional support in children undergoing allogeneic haematopoietic stem cell transplantation, while PN should be the second option [91]. However, the tolerance of EN was limited in this study: 23% of the patients still required PN despite EN, and this study did not determine the effect of nutritional support on the nutritional status.

Thus, there have been no studies about either the use or comparison of EN and PN as nutritional support in children or adults suffering from GI mucositis.
DISCUSSION

GI mucositis is a dose-limiting side effect of the chemotherapeutic treatment in children of all ages, from infant to teenager, with cancer. In general, in research little attention is given to children suffering from GI mucositis. Since different methods have been used to establish the frequency of GI mucositis in children, the exact incidence remains unknown. To date the focus of GI mucositis in clinical practice is the supportive care of symptoms and consequences. This review focused on data available on the supportive care of children suffering from GI mucositis by clarifying the risk factors, the methods for diagnosis and the possible supportive care. We suggest that three steps are important in order to be able to give the required supportive care in children suffering from GI mucositis. The first step is to know in advance which patient is at risk for developing GI mucositis, which makes it possible to give timely supportive care. Regarding the different risk factors, unfortunately studies on treatment-related and patient-associated factors have only been carried out in adults. Although the cancer types and treatment protocols in children are different from adults, the effects of mucositis might be comparable. Although from adult studies we cannot draw any certain conclusion for the pediatric population, these adult studies are the only available data and therefore the most useful information at this moment. These data might help to design future studies to develop a risk analysis in children. There are a few studies which examined genetic polymorphisms in children, specifically during MTX treatment [38-44]. However, these studies focused on genes associated with drug metabolism of specific chemotherapy treatment. These genes are relatively rare and therefore it seems reasonable that other genes associated with the complex pathophysiology of mucositis are also involved. However, no data is available about genes other than the studies concerning genes associated with drug metabolism. Since it is likely that more than one gene is impactful on risk, like a network of genes functioning together, it would be interesting to analyze the combination of several polymorphisms, which might give inside in the at-risk population. One possible option to study the genetic risk is by using a SNP-based analysis. This seems to be helpful in the risk analysis of oral mucositis [92]. We speculate that this would be of interest for future studies concerning genetic risk factors of GI mucositis in children. In conclusion, to date the risk factors related to treatment, the patient and genetics have not been clarified in children and research is needed.

The second step is the objective recognition of the symptoms and severity of GI mucositis, in order to optimize the supportive care and to be used as endpoint in future clinical studies. Existing studies all used different methods to diagnose and establish the severity of GI mucositis, including assessment scales and biomarkers. The clinical assessment scales are subjective and are based on clinical symptoms. In children, these scales might underestimate the actual severity of GI mucositis, due to several influencing factors, like pain relief medication, and factors related to the developmental stage of the child. We suggest that the subjective assessment scales are not the
most accurate method to diagnose and determine the severity of GI mucositis, especially not in the younger children. In our eyes a biomarker is needed as a diagnostic tool for objective recognition. In addition, with this standard diagnostic tool both the incidence and risk factors could be determined. We speculate that the sucrose breath test is difficult and not practical for young children with mucositis and therefore not preferable. However, in several reports studies have been described about the use of plasma citrulline as a biomarker. Plasma citrulline has been shown to correlate with the severity of GI mucositis in animal models, adult studies and pediatric cancer patients [52-56,58-62]. Thus, plasma citrulline might serve as a diagnostic tool in children suffering GI mucositis and we strongly suggest plasma citrulline to be used as objective measurement in all future studies concerning GI mucositis. We speculate that the use of plasma citrulline in clinical practice will improve the management, partly because it might be possible to detect mucositis before it becomes clinically overt. According to the pathophysiology there are three stages of mucositis before it becomes clinically overt. If we can detect a decrease of plasma citrulline in this non-clinical phase of mucositis, we can start timely supportive care and interventions. Moreover, an intervention will not be studied in the complete population, but will indeed be studied only in the patients who will actually develop mucositis. This will improve the quality and efficiency of future clinical trials, and moreover this will prevent unnecessary treatment of patients who will not develop mucositis. Therefore, we speculate that plasma citrulline will contribute to the development of an intervention to decrease the severity of GI mucositis, increase quality of life and improve clinical practice.

Finally, the most important step when GI mucositis is objectively determined is to give the required supportive care to the children. The management of the symptoms of GI mucositis remains challenging. Pain and diarrhea are severe symptoms for children. Although the WHO provides guidelines for the management of pain in children, the guidelines are not specifically focused on pain caused by GI mucositis. Based on current research it is still unclear what the best clinical management is with regard to pain and diarrhea, and the management remains challenging. We suggest to give paracetamol as first step, with an easy accessible second step, the administration of morphine. Nutritional support in children suffering from GI mucositis has clinical priority and should be monitored by a dietician and other professionals. Nutritional care aims to reduce weight loss, prevent nutrient deficiency, preserve the nutritional status and moreover to continue growth and development of the child. Unfortunately, not one study has been performed considering the nutritional support in children or adults during GI mucositis. In order to give possible suggestions we performed a search for the nutrient digestion and absorption in the intestine during GI mucositis in animal models. Results from animal studies suggest that a large part of the enterally provided food will probably not be digested and absorbed in children with GI mucositis. However, continuous administrated elementary nutrients will probably be better absorbed [53-56]. Moreover, there is no consistency in the clinical practice in adults and children with GI mucositis. In the Netherlands most of the adult patients suffering from GI
mucositis receive PN, in contrast to children who receive EN as the first choice for nutritional support (unpublished observation). However, since no studies have compared different feeding strategies during GI mucositis in children, and both EN and PN have advantages and disadvantages, we do not know what the best method is to administer nutritional support to the child suffering from GI mucositis. We suggest to give EN as first choice for nutritional support, with an elementary diet administered as continuous tube feeding. Furthermore, we suggest that if the patient suffers from severe pain, severe diarrhea or vomiting, there should be an easy access to administer PN as nutritional support. Currently, in our department a study is being performed to compare different feeding strategies in children suffering from GI mucositis.

In conclusion, risk analysis and diagnosis of GI mucositis are dependent on the use of a standard diagnostic tool, for which we propose to use plasma citrulline in future studies. The management of GI mucositis in pediatric cancer patients remains challenging, and no conclusions can be drawn concerning the management of diarrhea, pain or nutritional support.
REFERENCES


