GAME CHANGERS

Evidence-based guideline development in pediatric oncology

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UNIVERSITY OF GRONINGEN

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Supportive care: evidence-based guideline development in pediatric oncology

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Voor alle Brams
en alle Ella's

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PREFACE

Game changers [plural noun]; an event, idea, or procedure that effects a significant shift in the current way of doing or thinking about something.

It feels like stating the obvious, but for those who don't know me, I am a big fan of playing games. Actually, games, puzzles, quizzes or anything related. While I was considering a catchy title for my thesis, – as 'supportive care: evidence-based guideline development in pediatric oncology' isn't quite attractive – this was an easy decision for me. Not only because I like to play games (and quite good in them as well), but for a couple of other reasons as well.

For me, this whole PhD project has been a game changer. During my medical training, my focus was never on research but only on clinical practice. Because of this specific project in the Princess Máxima Center, I decided to apply, but remained hesitant about 4 years of doing research. The truth is, I wanted to cancel the interview beforehand, because "doing research wasn't for me". My boyfriend stimulated me to go anyways, and so I did. This PhD project has been a game changer for me in so many ways. I got to know so many great people, have developed and learned in so many ways and importantly, had fun – most of the time. I wouldn't have missed it for the world.

Then, during my PhD project, and mainly during COVID-19, I was self-promoted to 'game-master'. To keep everyone involved and to get to know each other better while not being able to see each other, I threw myself on developing quizzes. One can say, that single handedly, I contributed to the general knowledge on many of my colleagues. We did picture quizzes, in which you had to hand in baby photos and we had to guess who it was, or partner and/or family photos, pictures of corners in your (house), and then you had to guess whose house it was, and even a seasonal Christmas tree photo round. Also, we had 'get-to-know' quizzes in which you had to guess which fact matched which person. When we knew each other through and through, we switched to general knowledge quizzes about when Michael Jackson died, which bird can fly backwards, logo quizzes, what country starts with the letter Q, how many players are in a basketball team, who was president of the USA during WWII, what does this traffic sign mean and what is the yellow teletubby called (as this is basic knowledge). Also, bingo with the group and also with the whole department

was organized multiple times (including prizes) and online 30 seconds tournaments were held. Those who didn't like games, had a tough time with me.

But, most importantly, our guidelines are game changers – if I may say so. Discussing meaningful topics for parents and children such as swimming and going to school, emphasized the importance of these guidelines. For example, with our new recommendations, children with a tunneled central venous line (Hickmann) are allowed to swim, while they were not allowed to before. A true game changer.

Thanks to everyone who made this 'game' worth playing.

PS. Throughout this thesis, you will find a game adapted to 'find Wally'. You will go on a literary quest to find multiple bath ducks (you know – the representative of my thesis) with a little crown (reference to the Princess Máxima Center). It is hidden in different spots throughout the book. Enjoy!

1

GENERAL INTRODUCTION

1. CHILDHOOD CANCER

Every year more than 600 children are diagnosed with cancer in the Netherlands [1, 2]. Childhood cancer etiology can be divided into subgroups; hematological tumors (approximately 45% of diagnoses), solid tumors (30-35%), and neuro-oncological tumors (20-25%) [1, 2]. Most common types of diagnoses are leukemia (30%), brain tumors (20-25%) and lymphomas (11%) [1, 2]. Of all children diagnosed with cancer, one-third is under the age of 5 [1, 2].

Treatment protocols differ per diagnosis, but can consist of chemotherapy, surgery, radiotherapy and/or immunotherapy. Each of these treatment strategies has its own adverse effects and its own duration (varies from short – e.g. a surgical procedure, to long– three years of anti-leukemia treatment).

A lot of research is being done to improve treatment modalities for children with cancer (for example CAR-T cell therapy) to improve survival. This obviously is very important, but should go hand in hand with research and better supportive care aimed at improving quality of life, as will be elaborated on further.

Childhood cancer survival & treatment-related mortality and morbidity
Over the past decades, survival for children with cancer has increased substantially. In the early 1950s-60s, childhood cancer was not curable, and focus was on prolonging life and relieving symptoms. Over the years, survival drastically improved due to improved treatment regimens and improved supportive care. For acute lymphoblastic leukemia, this resulted in a survival of approximately 10% in the 1970s to more than 90% in 2000-2005 [3].

Recent numbers show a general 5-year survival rate of 73% in the 1990s, versus 83% in 2020 [1, 4]. Highest survival rates are described in children with for example Hodgkin lymphoma, with a 5-year survival rate of 95%. Due to these improved survival rates, morbidity and adverse effects of anti-cancer treatment have become increasingly important in care for children with cancer. Nowadays, focus is shifting towards *how* children survive cancer (regarding quality of life, late effects) rather than *if* they survive.

To gain more insight and knowledge, Loeffen et al [5] reported on treatment-related mortality (TRM) in children with cancer. Remarkably, this study showed that in

children with a hematological malignancy, more children died due to TRM than due to progression of their disease. The most important cause of TRM was infection, during the whole treatment period and specifically during the first 3 months of treatment. Other causes of treatment related mortality were hemorrhage, CNS-related and cardiac or respiratory system failure [5]. These results emphasize the importance of recognizing the treatment-related side effects of anti-cancer treatment, such as bone marrow suppression from chemotherapy resulting in infections and hemorrhages, and gaining more knowledge on how to improve care for these morbidities in children with cancer, i.e. supportive care, to decrease mortality.

During treatment, side effects of anti-cancer therapy decrease the quality of life. All different treatment regimens have their own known side effects. Chemotherapy, overall, causes nausea and vomiting, alopecia, mucositis, neurotoxicity, and bone marrow suppression [2]. This bone marrow suppression makes a child prone to infections due to low white blood cells and prone to bleeding due to a low platelet count. Prophylactic antibiotics are often necessary, as well as prophylactic platelet transfusions to prevent bleeding.

Other known and very common side effects are fatigue and concentration problems. Other bothersome symptoms for children, reported by their parents, are mood swings, feeling worried about treatment and its outcome, and disappointment for missing activities with friends or peers [6].

In addition, *after* treatment late effects can occur, e.g. psychosocial problems, infertility, osteonecrosis, endocrine and metabolic disorders, second malignancies, cardiotoxicity, kidney- or other- organ problems and more [2]. 3 out of 4 childhood cancer survivors report on having any late effect of their anti-cancer treatment; 40% reports a severe, life-threatening or disabling adverse event [7].

2. SUPPORTIVE CARE

I would define supportive care as the care for children with cancer *besides* their anti-cancer treatment. According to the Multinational Association of Supportive Care in Cancer (MASCC), Supportive Care is defined as "*the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical*

and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through anticancer treatment to post-treatment care [8]."

Important topics in the field of supportive care are prevention and treatment of infections (bacterial, viral and fungal), red blood cell and platelet transfusions, nutrition, psychosocial care, nausea and vomiting and pain management [2, 9]. Over the past years, a lot of research has been performed and improvements have been made in supportive care for children with cancer. For example, more precise and better prophylaxis for chemotherapy-induced nausea and vomiting [10], the effect of malnourishment during treatment on infections on mortality and survival [11], how to reduce pain and distress related to needle procedures in children with cancer [12], azole therapy for fungal infection [13], the impact of changes of taste and smell [14] and much more.

Research priorities within supportive care

A study performed by Loeffen et al [9] investigated the different fields of interest within supportive care and which research topics should be prioritized, according to clinicians. The most important topic was infection, the importance of which was already emphasized in treatment-related mortality. In their top 10 of research priorities, also "restrictions in daily life and activities" was mentioned by many clinicians. This is a topic regarding restrictions in the daily life of children with cancer, for example in order to prevent infections, such as not being allowed to swim or being restricted in going to school or to crowded places. This topic is also often mentioned by parents and children when addressing research priorities, as it has an enormous impact on their quality of life.

A lot of research is being done in the field of supportive care, and a lot of improvements in care for children are being researched and developed. Unfortunately, not of all this knowledge gets implemented into clinical practice. This emphasizes the importance of evidence-based guideline development, which will be the focus of this thesis. Specifically, next to the guideline development, this thesis will focus on the translation of recommendations into practice, making recommendations available, applicable and usable for all clinicians and actually implementing these recommendations in clinical practice and improving quality of care and daily lives of children with cancer.

3. CLINICAL PRACTICE GUIDELINES

A clinical practice guideline (CPG) is defined as: "*a statement that includes recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options* [15]." Basically, a CPG is a summary of all available evidence regarding its topic, and provides clinicians with recommendations about the optimal care for patients. Keeping up to date with all new literature is not possible for clinicians or healthcare workers, and therefore having all available evidence in one, is essential. By assessing the available evidence on quality, and then reviewing the results and discussing its impact, considering benefits and harms, recommendations are made. The precise guideline developing process is provided further on.

CPGs are important in clinical practice because of numerous reasons. First of all, consistency of care results in better outcomes [16, 17] and is important to provide equal care to patients in different hospitals, regions and countries. Improving patients' health outcomes is obviously the most important advantage of CPGs. Other positive consequences are potential improvement of cost-effectiveness, providing a comprehensive overview for clinicians saving them time to stay up-to-date with literature, increasing awareness for clinicians and patients and exposing gaps in scientific knowledge [16, 17].

Usually, a search for literature regarding a topic for a CPG provides numerous citations, and performing meta-analyses and systematic reviews is necessary. The *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) methodology, elaborated on later, is very efficient and useful in making recommendations for topics with available evidence. However, for some topics such as pediatric oncology, very limited evidence is available and using the GRADE methodology to make an evidence-based recommendation is difficult.

Our challenge was to formulate recommendations based on none to very little evidence. Our vision throughout our guideline development process was that we explicitly aimed to provide recommendations even in absence of evidence, to establish good clinical practice and provide clinicians with a comprehensive guideline. My personal additional goal was to provide recommendations for clinicians in order to 'hands-on' improve their quality of care. We believe we cannot afford *not*

to make a recommendation. You cannot leave healthcare professionals, standing beside a patient, with a 'we have no recommendation due to limited evidence'. In my opinion, that is the strength of all the guidelines in our work.

For more detailed information on the history, limitations and effects of CPGs, mainly in pediatric oncology, I would recommend (*strong recommendation, expert opinion*) "The importance of evidence-based supportive care practice guidelines in childhood cancer—a plea for their development and implementation [16]." This thesis will focus more on the different subjects and contents of the guidelines and its meaning for quality of care.

Guideline development process – practical approach

Based on the high quality of the GRADE methodology, it was consistently used for all guideline development described in this thesis. A short overview of this method is provided, for further and more detailed information several articles are referred to. [18-20]

For every guideline topic, clinical questions were stated, a guideline panel was assembled, searches were performed and results were assessed. As this is different per topic, this is addressed in each chapter individually. A general, short overview of the GRADE guideline development methodology that we used – from study identification onwards –, is provided below.

After study identification, detailed information from each eligible study was extracted into evidence tables. The methodological quality of each single study was assessed and scored for risk of bias, using different tools depending on the types of studies [20, 21]. Then, all evidence was outlined in summary of findings tables. The quality of the total body of evidence per outcome was assessed by the GRADE approach [18, 19]. The data-extraction, risk of bias assessment and GRADE assessment were independently performed by two reviewers.

The GRADE evidence-to-decision framework was used to translate evidence into recommendations [19]. Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert evidence).

The GRADE terminology for evidence-based guidelines was used, such as 'we suggest' or 'we recommend' [18]. The wording 'we believe' was used to indicate recommendations that are based on expert opinion and group consensus, which is elaborated on below.

Grade methodology – advantages & challenges

A couple of advantages of the GRADE methodology are clear separation between quality of evidence and strength of recommendations, specific criteria for downgrading and upgrading quality of evidence ratings, transparent process on translating evidence to recommendations [18]. Using this method, GRADE provides a clear overview of the available evidence and *then* provides synopsis of the guidelines panel's discussion regarding this evidence, harms and benefits, opinions and experiences in a predefined, insightful and transparent way ('evidence-to-decision framework'). This two-step approach gives caregivers the opportunity, if needed, to adjust the recommendation for their specific patient. While still providing the caregivers with a recommendation, and not leave them without any, we also provide space for own interpretation and personal adjustment when necessary. With this framework, we provide clear insight in our decision-making, and this transparency is very important [19].

For some topics, no to very limited evidence was available. In order to solve this and still provide healthcare workers with clear recommendations, we used a slightly different wording for expert-opinion based recommendations. This was based on the 'White Paper' [22] by the international Pediatric Oncology Guidelines in supportive care (iPOG) Network, which provides us with wordings to use for expert-opinion based recommendations. We, as core group and guideline panel, found this explicit difference very important, in order to transparently show for which recommendations sufficient evidence is available, and for which there is too little. The wording 'we believe' was used to emphasize that these recommendations are based on expert opinion and group consensus.

4. CLINICAL PRACTICE GUIDELINES – IMPORTANCE OF USE & IMPLEMENTATION

To give an example of the importance of the use and implementation of the recommendations and guidelines, I would like to provide an overview of a study performed by Loeffen et al in 2015 [23]. In this study, they evaluated adherence to guidelines in different centers in the Netherlands (note that this took place *before* the opening of the Princess Máxima Center for pediatric oncology). In this study, a questionnaire regarding current supportive care practice was compiled, comprising 67 questions regarding supportive care practice. Concordance was observed for 11 of 67 practice items (16%) and discordance was observed for 50 of 67 practice items (75%) [23]. They showed that large variations existed in pediatric oncology supportive care practice, and they suggested that this could negatively influence care [23].

This study emphasizes the differences *within* a country, but we have reason to believe these differences are as large, or even larger, between all high- and middle-income countries. With the opening of the Princess Máxima Center and the centralization of care, we hope(d) to improve these discordances. This is, however, still an ongoing process and requires continued attention from all guideline developers, researchers and healthcare workers. Our core group and guideline panels are working on that, but we need more awareness and attention for not only the development of these guidelines, but also their implementation and adherence.

5. AIMS AND OUTLINE OF THIS THESIS

Local anesthetics during minor painful procedures

Management of needle-induced pain is important and relevant to all fields of pediatric medicine. Therefore, importantly, every child should receive any kind of Topical analgesia during needle-related procedures. There is a lack of evidence regarding which type of local anesthetic should be given to a child in a particular (clinical) situation as both types of drugs seem to be effective.

In **chapter 2**, our guideline entitled “A clinical practice guideline: Topical analgesia during needle-related procedures in children” is presented. The purpose of this clinical practice guideline was to establish a comprehensive overview of evidence

and to provide recommendations for clinical practice regarding the use of local anesthetics in reducing needle-induced pain during minor procedures in children.

In this guideline, we compared the use of two local anesthetics, i.e. EMLA® (Eutectic mixture of local anesthetics) and Rapydan®, in children (in general) who undergo a minor painful procedure. Children who are hospitalized or who visit the outpatient clinic frequently need to undergo minor needle-related procedures such as venapunctures, venous cannulation and accessing a central venous access port. These (repeated) procedures can be of great impact on quality of life and can cause high levels of distress, anxiety and non-compliance to therapies, even on longer term.

Restrictions in daily life

To prevent adverse health problems during anti-cancer treatment, such as infections and bleeding, restrictions in daily life have been defined for children with cancer related to school attendance, travelling with public transport, pets, hygiene measures and swimming. However, these restrictions can severely impair the quality of life of these children. Within the Netherlands, there is large variation in current supportive care practices, including restrictions in daily life [23]. Moreover, the majority of these recommendations regarding social restrictions for children with cancer are not evidence-based. Thus, critically reviewing and assessing the available evidence to formulate recommendations is of great importance. Guidance is necessary in order to provide the best possible care for these children, balancing cautiousness and restrictiveness.

In **chapter 3**, our guideline entitled “Less restrictions in daily life: a clinical practice guideline for children with cancer” is described. Our aim was to develop a clinical practice guideline regarding social restrictions in children with cancer by first establishing an overview of the available evidence and subsequently formulating recommendations for clinicians, children and their parents. As we expected evidence in this niche to be scarce, we explicitly aimed to provide recommendations even in absence of evidence, to establish good clinical practice and provide clinicians with a comprehensive guideline.

Blood transfusions

In **chapters 4 and 5**, guidelines on prophylactic platelet and red blood cell transfusions guidelines are outlined. Thrombocytopenia and anemia are frequently

occurring adverse effects of anti-cancer treatment, due to bone marrow suppression (resulting in anemia and thrombocytopenia) caused by chemotherapy. Both result in potentially severe symptoms in the child and can significantly impair their quality of life. To prevent severe side effects of anemia or to prevent bleeding due to a low platelet count, prophylactic platelet or red blood cell transfusions can be administered. However, a balance needs to be determined between unnecessary transfusions -and its potential adverse effects-, burden for the patient and costs; and preventing complications due to thrombocytopenia or anemia. It is therefore important that thresholds for prophylactic transfusions are determined precisely, again balancing cautiousness and restrictiveness.

In current clinical practice, the majority of recommendations regarding thresholds for administering platelet or red blood cell transfusions to children with cancer are not evidence-based and a clinical practice guideline was lacking. As children with cancer frequently receive these transfusions, critically reviewing and assessing the available evidence to formulate recommendations is of great importance.

Therefore, our aim was to develop a clinical practice guideline regarding prophylactic platelet and red blood cell transfusions in children with cancer. We aimed to achieve this by first establishing an overview of the available evidence and subsequently formulating recommendations for clinicians. We explicitly aimed to provide recommendations even in absence of evidence, to establish good clinical practice and provide clinicians with a comprehensive guideline.

Influenza

Respiratory viruses are the most common cause of infections in children and the burden of respiratory viruses in immunocompromised patients is becoming clearer [24, 25]. Influenza, as one of these respiratory viruses, is very common in both the normal population as in children with cancer. Children with cancer are more susceptible for the influenza virus, however much remains unknown about the specific course of infection in this population. [25-29] Mostly, the infection has a mild course, but can have several consequences for the child, e.g. hospitalization, interruption of chemotherapy and antibiotics or antiviral medication [25-29].

In **chapter 6**, an observational study (to strengthen the evidence base for our to be developed guideline) on influenza diagnoses in the Princess Máxima Center is

described. Knowledge regarding the incidence and the clinical course of influenza in children with cancer is limited. Our aim was to determine the incidence of laboratory-confirmed influenza in children with cancer and to analyze the course, clinical characteristics, and complications of these infections.

To prevent moderate and severe complications of an influenza infection in children with cancer, influenza prophylaxis is available through vaccination. Multiple studies have shown positive effects of influenza vaccination, but specific recommendations about offering the influenza vaccination to children with cancer and their families are lacking. Therefore, **chapter 7** covers the guideline on influenza prophylaxis by vaccination. Our aim was to develop a clinical practice guideline regarding influenza vaccination in children with cancer and their families by first establishing an overview of the available evidence and subsequently formulating recommendations for clinicians, children and their parents.

CONCLUSION AND DISCUSSION

In **chapter 8**, all results are summarized and discussed. Then, future research and implementation strategies will be discussed.

Closing statement

I hope to provide the reader insight in this whole process, and stimulate thoughts, opinions, and awareness about this topic. I hope your interest is sparked – enjoy reading.

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2

TOPICAL ANALGESIA DURING NEEDLE-RELATED PROCEDURES IN CHILDREN: A CLINICAL PRACTICE GUIDELINE

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ABSTRACT

Introduction

During intensive and long-lasting treatments, short-term or emergency care, children often undergo minor needle-related procedures (i.e. venapunctures, venous cannulation and puncture of central venous access ports). The use of topical analgesia topical analgesia before these procedures can reduce needle-related pain. There is, however, uncertainty about the type of local anesthetic (i.e. eutectic mixture of topical analgesia (EMLA®) or tetracaine-containing creams (e.g. Rapydan ®) that should be used. Therefore, a clinical practice guideline (CPG) was developed to establish a comprehensive, evidence-based overview and provide recommendations for clinical practice.

Methods

A comprehensive multidisciplinary panel was assembled, comprising 16 professionals and patient representatives in the Netherlands. A systematic literature review was performed and after dual appraisal of all articles, results were extracted and meta-analyses performed. The GRADE methodology was used to assess, extract and summarize the evidence. An in-person meeting was held to discuss the evidence, complete an evidence-to-decision framework and formulate recommendations.

Results

Ten randomized controlled trials comprising 1808 children formed the evidence base for the recommendations. We recommend the use of EMLA in children who need to undergo a minor needle-related procedure, with minimal application duration of 60 minutes (strong recommendation, very low quality evidence). We suggest the use of tetracaine-containing creams only when rapid cannulation/puncture (i.e. within 30-60 minutes) is required (weak recommendation, very low quality evidence).

Conclusion

In this CPG, we provide recommendations regarding the choice of local anesthetic for needle-induced pain during minor procedures in children. With these recommendations we aim to reduce procedural pain and thereby contribute to improving care for children.

1. INTRODUCTION

Children with cancer frequently need to undergo minor needle-related procedures such as venapunctures, venous cannulation and accessing a central venous access port. This also accounts for children with other types of diseases or for other types of care such as emergency treatment. These (repeated) procedures can be of great impact on quality of life and can cause high levels of distress, anxiety and non-compliance to therapies, even on long term (1-3). Management of needle-induced pain is important and relevant to all fields of pediatric medicine.

The use of topical analgesia before a needle-related procedure has been proven to reduce pain in children (2-4). Different types of topical analgesia are available and can be used safely. An eutectic mixture of topical analgesia (EMLA®) is the most commonly used pharmacological local anesthetic and consists of a mixture of lidocaine and prilocaine and can be applied as either cream (also available as a generic preparation as well, 2.5%/2.5%) or patch (25 mg/25mg) (5).

In addition, Rapydan®, a patch with a mixture of lidocaine, tetracaine (70 mg/70mg) and a heating element, or other tetracaine-containing creams such as Ametop® (4% containing tetracaine HCl) are also used (1). Both types of topical analgesia are effective by blocking nerve cell sodium influx and thus inhibiting depolarization and thereby conduction of the pain signal (5). EMLA® and tetracaine-containing creams have different characteristics and differ in for example costs and application duration. Tetracaine-containing creams are proven effective within 30-45 minutes after application, whereas EMLA® is proven effective after a minimum of 60 minutes of application (1-3).

Importantly, topical analgesia should be offered to every child before undergoing a minor needle-related procedure (4). However, there is a lack of evidence regarding which type of local anesthetic should be given to a child in a particular (clinical) situation as both types of drugs seem to be effective. Therefore, our aim was to develop a clinical practice guideline (CPG) regarding the use of topical analgesia in reducing needle-induced pain during minor procedures in children to establish a comprehensive overview of evidence and to provide recommendations for clinical practice.

2. METHODS

2.1 Guideline panel

A national, comprehensive multidisciplinary panel was assembled, comprising 16 professionals from the Netherlands. The panel included pediatric oncologists, general pediatricians, pediatric oncology researchers, a clinical psychologist, a child life specialist, a pediatric oncology nurse, a pediatric anesthesiologist, a hospital pharmacist, epidemiologists, guideline methodologists, and a patient and parent representative (see Supplemental Materials S1). Members were invited on the basis of their experience and knowledge on the topic. The core group (DS, DK, RM, LK, WT, EL) provided all the preparatory documents including methodology, study details and results.

Between 2019 and 2020, multiple in-person panel meetings were held to rank outcomes, discuss evidence and formulate recommendations.

2.2 Guideline scope

With this guideline, we aimed to develop a CPG regarding the use of topical analgesia in reducing needle-induced pain during minor procedures in children from 1-18 years. Non-pharmacological interventions were not included within the scope of this guideline.

2.3 Existing guidelines and clinical questions

Existing national and international guidelines on the use of topical analgesia in children published until November 2019 were searched (Guideline International Network (GIN) (6), National Institute for Health and Care Excellence (NICE) (7), International Pediatric Oncology Guidelines in supportive care Network (IPOG) (8), American Society of Clinical Oncology (ASCO) (9), Dutch Federation for pediatrics (NVK) (10)) and evaluated for the applicability and completeness of these guidelines (using the AGREE II checklist). In the absence of an applicable evidence-based guideline, a clinical question was defined by the core group. The main Patient-Intervention-Control-Outcome (PICO) question for this guideline was if, in children aged 1-18 years undergoing a minor needle-related procedure (P), tetracaine-containing creams or patches (I) are more effective than EMLA® cream or patches (C) on pain-intensity and other outcomes (O).

As no patients participated in this research, no ethics committee approval was required for the formation of this guideline and no informed consent was required.

2.4 Search strategy and selection criteria

An extensive systematic literature search (see Supplemental Materials S2) was performed. We searched the electronic databases PubMed, Embase and Cochrane CENTRAL (initial search September 24th 2019, top-up search December 2020).

Inclusion and exclusion criteria were defined by the core group. Only randomized controlled trials (RCTs) comprising participants aged 1-18 years old were included. Participants should have undergone a minor needle-related procedure, defined as venapuncture, venous cannulation or puncture of central venous access ports (in both outpatient and inpatient settings).

Studies were included that compared EMLA® cream or patch with a tetracaine-containing cream or patch. All different tetracaine-containing drugs (Ametop®, Rapydan®, other author-defined) and their possible mixtures were included in order to create a comprehensive overview. All application times were included, i.e. this was not limited to the manufacturers' recommended application time. When applicable, results were pooled by the researcher (DS).

2.5 Evidence selection and quality assessment

Study identification was performed independently by two reviewers (DS, DK). Initially titles and abstracts were screened, followed by full text assessment. Discrepancies were resolved by consensus. Detailed information from each eligible study was extracted into evidence tables. The methodological quality of each single study was assessed and scored for risk of bias. The Risk of Bias tool v2 from the Cochrane handbook was used (11).

All evidence was outlined in the summary of findings tables. The quality of the total body of evidence was assessed by the GRADE approach (12, 13). The data-extraction, risk of bias assessment and Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment were independently performed by two reviewers (DS, MT). Discrepancies were resolved by consensus or a third reviewer (EL).

Primary and secondary outcomes were defined and prioritized according to the GRADE system. The following outcomes were determined by the guideline panel: pain-intensity 1) self-reported, 2) by-proxy reported (doctors or caregivers) and 3) by-proxy reported (parents), first time success-rate of the procedure, adverse events and costs. The allocated hierarchy for the defined outcomes is shown in the Supplemental Materials S3.

2.6 Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations (13). Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert opinion). Final recommendations had to be unanimously supported by all panel members.

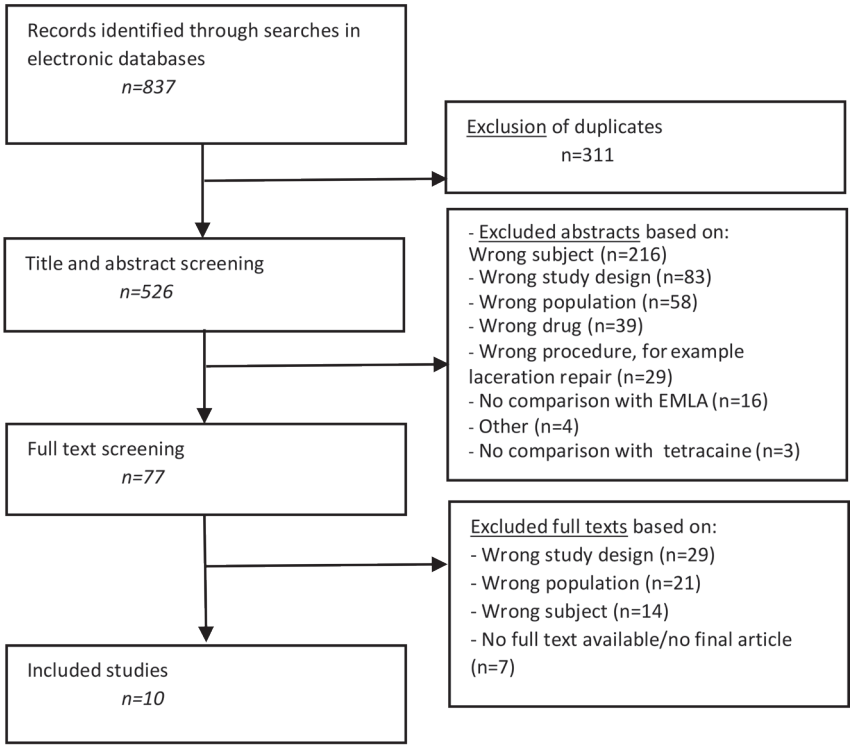
The GRADE terminology for evidence-based guidelines was used, such as 'we suggest' or 'we recommend'(12).

Within the overview of all recommendations , a color coding system was used to improve understandability and to emphasize the strength of the recommendations.

3. RESULTS

In total, 527 unique citations were identified in the literature search (March 2020) and in the search update in January 2023. 10 primary studies (all RCTs) were included with a total number of 1808 participants (see Figure 1). All primary study characteristics are shown in Table 1, and more extensively in Supplemental Materials S4 .

Figure 1: Flow diagram study selection



An overview of the included studies, the evidence tables and the GRADE assessments can be found in the Supplemental Materials S5. In table 1, the conclusions of evidence of the included studies are presented. In table 2, a list of all recommendations is shown.

Table 1: Primary study characteristics related to local anesthetic use prior to a minor painful procedure in children

Article	Intervention group	Control Group (EMLA)
Arendts, 2008 RCT (177 patients)	**Tetracaine** group (97 patients), no information dosage applied. Applied for 1 hour. Mean age 4.8 years (range 0-13)	**EMLA** group (80 patients), no information dosage applied. Applied for 1 hour. Mean age 4.9 years (range 0-12)
Arrowsmith, 2000 RCT (120 patients)	**Tetracaine** group (60 patients), no information dosage applied. Mean duration of application 2.04 hours (SD 1.0) Mean age 8.0 years (SD 4.0)	**EMLA** group (60 patients), no information dosage applied. Mean duration of application 1.93 hours (SD 1.0) Mean age 6.8 years (SD 4.0)

Table 1: *(continued)*

Article	Intervention group	Control Group (EMLA)
Bishai, 1999 RCCT (39 patients)	**Tetracaine** group (39 patients), no information dosage applied. Application duration 30 minutes (30 minutes placebo plus 30 minutes tetracaine) - Total group mean age 10.2 years (SD 3.7)	**EMLA** group (39 patients), no information dosage applied. Applied for 60 minutes. Total group mean age 10.2 years (SD 3.7)
Choy, 1999 RCT (34 patients)	**Tetracaine** group (17 patients), 1 gram applied. Application duration 30-45 minutes. - Median age 5 years (range 1-14)	**EMLA** group (17 patients), 2 grams applied on each site. Application duration at least 60 minutes. Median age 5 years (range 1-13),
Cozzi, 2017 RCT (339 patients)	**Lidocaine/tetracaine** (1:1 mixture of 70 mg lidocaine and 70 mg tetracaine) (167 patients), no information dosage applied. Application duration 60 minutes. Lidocaine/tetracaine 6.0 years (4.3-9.0 IQR)	**EMLA** group (172 patients), no information dosage applied. Applied for 30 minutes. Median age 6.0 years (4.0-9.0 IQR),
Lawson, 1995 RCT (94 patients)	**Tetracaine** group (47 patients), 1 gram applied. Mean application time 40.5 min (SD 1.9, range 35-45) Total group mean age 7.3 years (range 3-12)	**EMLA** group (47 patients), 2 grams applied. Mean application time 41.4 min (SD 2.4, range 35-45) Total group mean age 7.3 years (range 3-12)
Newbury, 2008 RCT (697 patients)	**Tetracaine** group (337 patients), on average 1.2 grams applied. 45 min of application. Mean age 6.9 years (SD 4.3)	**EMLA** group (342 patients), on average 2.9 grams applied. 90 min of application Mean age 7 years (SD 4.2)
Romsing, 1999 RCT (60 patients)	**Tetracaine** group (40 patients), 1 gram applied. Mean time of application 46.5 min (SD 5.6) No mean value, age range 3-15 years	**EMLA** group (20 patients), 2 grams applied. Mean time of application 60.4 min (SD 1.7). No mean value, age range 3-15 years
Soltesz, 2010 RCT (200 patients)	**Lidocaine/tetracaine** (70 mg lidocaine and 70 mg tetracaine), (100 patients) no information dosage applied. Median duration of application 35 minutes (25-75 percentile 30-42.5) Median age 7 (25-75 percentile 5-10)	**EMLA** group (100 patients), no information dosage applied. Median duration of application 35 minutes (25-75 percentile 30-45) Median age 4 (25-75 percentile 4 - 8.5)
Van Kan, 1997 RCT (66 patients)	**Tetracaine** group (34 patients), 1 gram applied. 30 minutes of application. Median age 6 (range 1-15)	**EMLA** group (32 patients), 2.5 grams were applied. 60 min of application. Median age 8 (range 1-15)

Table 2: Conclusions of evidence related to local anesthetic use prior to a minor painful procedure in children

Are tetracaine-containing creams or patches more effective as a local anesthetic than EMLA in children aged 1-18 years, undergoing a minor painful procedure such as venapuncture, central venous access port puncture or venous cannulation?	
3.1.1. Tetracaine cream vs EMLA® > 60 minutes	
Pain intensity, self-reported	**Quality of evidence**
Significantly lower pain scores in tetracaine group in one study. (14) No significant difference in one study. (15)	⊕◯◯◯ (2 studies) VERY LOW
Pain-intensity, by-proxy reported	**Quality of evidence**
Significantly lower pain scores in the tetracaine group in one study. (16) No significant differences in two studies. (15, 19)	⊕◯◯◯ (2 studies) VERY LOW
Pain intensity, by-proxy reported, parents	**Quality of evidence**
No significant differences between the groups. (15)	⊕⊕◯◯ (1 study) LOW
First time cannulation success-rate	**Quality of evidence**
No significant differences in three studies. (2, 3, 18) Pooled standardized mean difference not significant.*	⊕◯◯◯ (3 studies) VERY LOW
3.1.2. Lidocaine/tetracaine vs EMLA® > 60 minutes	
Pain intensity, self-reported	**Quality of evidence**
No significant differences between the groups.(19)	⊕⊕◯◯ (1 study) LOW
Pain-intensity, by-proxy reported	**Quality of evidence**
No significant differences between the groups. (19)	⊕◯◯◯ (1 study) VERY LOW
First time cannulation success-rate	**Quality of evidence**
Significantly higher success rate in lidocaine/tetracaine group.(19)	⊕◯◯◯ (1 study) VERY LOW
3.1.3 Tetracaine cream vs EMLA® < 60 minutes	
Pain intensity, self-reported	**Quality of evidence**
Significantly lower pain scores in the tetracaine group.(20)	⊕⊕⊕◯ (1 study) MODERATE
3.1.4 Lidocaine/tetracaine cream vs EMLA® < 60 minutes	
Pain-intensity, by-proxy reported	**Quality of evidence**
Significantly lower pain scores in lidocaine/tetracaine group. (1)	⊕⊕◯◯ (1 study) LOW
First time cannulation success-rate	**Quality of evidence**
No significant differences. (1)	⊕◯◯◯ (1 study) VERY LOW

**calculated by researcher*

All recommendations and their evidence-to-decision processes are discussed per subject. Only conclusions and important considerations of the guideline panel are shown. Recommendations are shown in table 3, full details are shown in the Supplemental Materials S6.

Table 3: Overview of recommendations regarding local anesthetic use prior to a minor painful procedure in children

Recommendation	Strength of recommendation	Quality of evidence
We recommend the use of EMLA cream or patch in children who need to undergo a needle-related procedure.	Strong	**VERY LOW** quality of evidence
We suggest the use of tetracaine-containing creams or patches in children when rapid cannulation or puncture (within **30-60 minutes**) is required.	Weak	**VERY LOW** quality of evidence

**The color coding in this table emphasizes the strength of the recommendation and shows if something is advised (green (strong) or yellow (moderate)) or discouraged (orange (moderate) or red (strong)).*

3.1 Recommendations

We recommend the use of EMLA (as standard of care) in children who need to undergo a minor procedure (strong recommendation, very low quality of evidence).

We suggest the use of tetracaine-containing creams or patches in children when rapid cannulation or puncture (within 30-60 minutes) is required (weak recommendation, very low quality of evidence).

3.2 Evidence

3.2.1 Tetracaine cream versus Emla® applied > 60 minutes

In total, seven studies reported on tetracaine cream versus EMLA® applied for more than 60 minutes. Two studies reported on self-reported pain scores, with significantly lower *self-reported* pain scores in the tetracaine group in one study (Romsing, 1999 (14)) versus no significant difference in another study (Bishai, 1999 (15)) (very low quality evidence). Three studies reported on by-proxy reported pain scores (either reported by doctors or nurses or by parents). Significantly lower doctor-reported pain scores were seen in the tetracaine group in one study (Arrowsmith, 2000 (16)) versus no significant difference in two studies (Choy 1999 (17), Bishai 1999 (15)). In addition,

no significant difference for pain scores *reported by parents* was reported in one study (low quality evidence) (15).

Three studies reported on first time cannulation success rate, for which no significant differences were seen (very low quality evidence) (Arendts 2008 (18), Newbury 2008 (3), van Kan 1997 (2)). After pooling the results of these studies, a total risk ratio (RR) of 1.03 [0.96,1.11] was calculated. Adverse events were discussed in two studies. Erythema was reported significantly more often in the tetracaine group (18), whereas blanching was reported significantly more often in the EMLA® group (15).

3.2.2 Lidocaine/tetracaine versus Emla® applied >60 minutes

One study reported on lidocaine/tetracaine (Rapydan®) versus EMLA® applied for more than 60 minutes (Cozzi, 2017 (19)). There were no significant differences for self-reported or by-proxy reported pain scores between the groups (very low to low quality evidence). A significantly higher first time cannulation success rate was found in the lidocaine/tetracaine group (n=158/171, 92.4%) compared to the EMLA® group (n=142/167, 85%), with an RR of 1.09 (95% CI 1.01-1.17, p=0.03) (very low quality evidence). Adverse events such as blanching or burn were reported, but did not differ significantly between groups.

3.2.3 Tetracaine versus Emla® applied < 60 minutes

One study reported on tetracaine versus EMLA® applied less than 60 minutes (Lawson, 1995 (20)), demonstrating significantly lower self-reported pain scores in the tetracaine group (moderate quality evidence). Significantly more erythema was seen in the tetracaine group.

3.2.4 Lidocaine/tetracaine versus Emla® applied < 60 minutes

One study reported on lidocaine/tetracaine versus EMLA® applied less than 60 minutes (Soltesz, 2010 (1)). In this study, significantly lower by-proxy reported pain scores were seen in the tetracaine group (low quality evidence). No significant difference was reported for first time success rate of cannulation (86% in EMLA group® versus 83% in lidocaine/tetracaine group) (very low quality evidence). Adverse events were not reported in this study.

3.3 Translating evidence into recommendations

3.3.1 Tetracaine-containing creams versus Emla applied >60 minutes

Benefits and harms were thoroughly discussed by the guideline panel. Some studies (14, 16) show a significant difference in pain scores in favor of the tetracaine-containing groups. In 3 other studies (15, 17, 19), for 6 outcomes (pain reported by proxy, self-reported) no significant differences in pain scores were reported. In one study (19), a significant difference in first time cannulation success rate was reported in favor of lidocaine/tetracaine 92.4% (n=158/171) and EMLA® 85% (n=142/167); RR 1.09 (95%CI 1.01-1.17), p=0.03 and a number needed to treat of 14. However, in 3 out of 4 studies (2, 3, 18), no significant differences in first time success rate of cannulation were reported.

Overall, there might be some effect in favor of tetracaine-containing creams, but we cannot consider it large. The main undesirable effects were considered adverse events of the anesthetic used: both tetracaine-containing creams and EMLA® have their adverse events, but they are small, temporary and self-limiting. In addition, the costs of tetracaine-containing creams are much higher than costs for EMLA®(21, 22), and this was also taken into an account in our recommendation.

Completing the evidence-to-decision framework, the guideline panel unanimously decided that there is no obvious superiority for tetracaine-containing creams or patches over EMLA®(when applied >60 minutes) for most outcomes.

3.3.2 Tetracaine-containing creams versus Emla applied <60 minutes

Two single studies (1, 20) showed significantly lower pain scores in the tetracaine-containing groups. In one study (1), the first time cannulation success rate was reported with no significant differences between the groups. The guideline panel unanimously felt that the evidence demonstrated in favor of tetracaine-containing creams and patches in the studies that compared tetracaine-containing creams or patches to EMLA® applied less than 60 minutes. However, we decided towards a *weak* recommendation because of the small number of included studies.

4. DISCUSSION

In children, needle-induced pain and distress is unnecessary and often avoidable. The use of a local anesthetic (dermal application) should be standard of care for every child undergoing a needle-related procedure, unless the intervention is required for emergency care. In this CPG, we formulated recommendations about the type of local anesthetic best applicable to a child in a clinical situation. Hereby, we aim to reduce procedural pain and thereby contribute to pain, fear and stress reduction in needle-related procedures.

For this study, we performed an extensive search in available literature and assessed all articles in the same manner using the GRADE methodology very strictly. Then, we assessed and evaluated all evidence with a multidisciplinary panel comprising all professionals involved in this type of care for children. In addition, we made an effort to show all our additional considerations in our evidence-to-decision framework in order to be as transparent as possible. For that manner, every caregiver can easily assess if our recommendation is applicable for his or her specific practice. Eventually, these recommendations were implemented in standard of care in the Princess Máxima Center for pediatric oncology in the Netherlands.

According to the identified evidence, tetracaine-containing creams are not superior to EMLA®, when applied for at least the minimal duration to be effective. There is no conclusive evidence that tetracaine-containing creams have a higher first-time cannulation success rate, as hypothesized often. (3, 19) However, it might be beneficial that the tetracaine-containing creams are effective within 30 to 45 minutes. For both types of topical analgesia, adverse events are transient and reversible and pain levels were comparable in the seven identified studies. Costs can differ between countries, but generally Rapydan® is more expensive than EMLA®. This should be taken into consideration for each country or institute separately.

The guideline panel identified some gaps in knowledge and future directions for research. To provide more guidance, there is need for more evidence about different types of topical analgesia . For example, children with cancer often undergo intensive and long-lasting courses of treatment with frequent needle-related procedures. Therefore, future studies should address the effectiveness of local anesthetic creams or patches in children undergoing repeated needle-related procedures. Future

studies should focus on, amongst others, longitudinal data collection to study the effects of local anesthetic use and pain-intensity over a longer period of time with repeated procedures. Also, the use and implementation non-pharmaceutical interventions to reduce pain are very relevant, but that is outside the scope of this guideline. This is very important and should always be considered besides pharmacological interventions.

In conclusion, when there is a time constraint and rapid cannulation or puncture is required within 30 to 45 minutes, tetracaine-creams are suggested as first choice. For all other elective, non-emergent needle-related procedures in children, EMLA® cream or patch is recommended, obviously used according to prescription (>60 minutes application). Future research should provide more evidence in order to strengthen these recommendations. Eventually, this will optimize care for children with cancer and thereby improve their short- and long-term quality of life.

Implementation of this evidence-based guideline can contribute to improving the quality of life of children with cancer. In addition, these recommendations will also provide a clear statement towards clinicians, children and parents and provides them guidance. However, it remains important to always consider the benefits and harms for a child individually.

SUPPLEMENTAL MATERIALS

Supplemental materials can be found online.

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3

LESS RESTRICTIONS IN DAILY LIFE: A CLINICAL PRACTICE GUIDELINE FOR CHILDREN WITH CANCER

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ABSTRACT

Purpose

In current clinical practice, recommendations regarding restrictions in daily life for children with cancer are often lacking or not evidence-based. Critically reviewing the evidence and formulating recommendations is therefore of great importance as social restrictions (e.g. swimming, school attendance, sports) can impair the quality of life of these children severely. Therefore, our aim was to develop a clinical practice guideline for clinicians, children and their parents regarding social restrictions in children with cancer.

Methods

A comprehensive multidisciplinary panel was assembled, comprising 21 professionals and patient representatives. A systematic literature review was performed, including dual appraisal of all citations. The GRADE methodology was used to extract, summarize and assess the evidence. Multiple in-person meetings were held to rank outcomes, discuss evidence, complete evidence-to-decision frameworks and formulate recommendations. Final recommendations were unanimously supported by all panel members.

Results

Six studies, including 758 children, formed the evidence base for the recommendations. Given the scarcity of the available evidence and various designs of studies in children with cancer, additional evidence was extracted from adult oncology guidelines, and shared expert opinions were utilized. In total, 14 recommendations were formulated of which multiple result in changes in current policy and standard of practice in the Netherlands. Topics covered in this guideline are swimming, having pets, visiting the zoo or farm, performing sports or high-velocity events, attending school or kindergarten, and use of public transport.

This guideline is not intended to provide recommendations for patients after end of treatment, for palliative care settings or for children undergoing a stem cell transplantation.

Conclusions

In this clinical practice guideline, we provide recommendations regarding restrictions in daily life in children with cancer. These include evidence-based recommendations and, in the absence of sufficient evidence, recommendations based on expert evidence. With these recommendations we provide guidance for clinicians, children and parents, and contribute to improving quality of life for children with cancer.

1. INTRODUCTION

Improving quality of life has become increasingly important in care for children with cancer. Due to improved survival rates there is an increased focus on morbidity and adverse effects of anti-cancer treatment [1, 2]. To prevent adverse health problems, such as infections and bleeding, social restrictions have been defined for children with cancer related to school attendance, travelling on public transport, pets, hygiene measures and swimming [3]. However, these social restrictions can potentially impair the quality of life of these children severely [4, 5].

Within the Netherlands, there is large variation in current supportive care practices, including social restrictions [6]. The majority of these recommendations regarding social restrictions for children with cancer are not evidence-based. Activities such as school attendance, swimming, visiting crowded places or performing sports are restricted without justified or well-founded reasoning – maybe even unnecessarily- , with potentially detrimental effects on quality of life.

Thus, critically reviewing and assessing the available evidence to formulate recommendations is of great importance. Guidance is necessary in order to provide the best possible care for these children, balancing cautiousness and restrictiveness.

Therefore, our aim was to develop a clinical practice guideline (CPG) regarding social restrictions in children with cancer by first establishing an overview of the available evidence and subsequently formulating recommendations for clinicians, children and their parents. We explicitly aimed to provide recommendations even in absence of evidence, to establish clinical consensus and provide clinicians with a comprehensive guideline.

2. METHODS

2.1 Guideline panel

A national, comprehensive multidisciplinary panel was assembled, comprising 21 professionals and patient representatives from the Netherlands. The panel included pediatric oncologists, pediatricians, a children's psychologist, a child life specialist, a surgeon, a pediatric infectious disease specialist, a patient representative, nurse

specialists, guideline specialists and several researchers (see Supplemental Materials S1). Members were invited on the basis of their experience and knowledge on the topic. Moreover, the patient and parent representative organization was involved, to make it as applicable, clear, and usable for the patients and parents as possible. The core group (DS, RM, DK, LK, WT, EL) provided all the preparatory documents including methodology, study details and results.

Between 2020 and 2022, multiple in-person panel meetings were held to rank outcomes, discuss evidence and formulate recommendations.

2.2 Guideline scope

With this guideline, our aim was to formulate recommendations regarding social restrictions in children with cancer aged 0-18 years. In addition, we explicitly aimed to provide recommendations even in absence of evidence, in order to provide recommendations for consistent and evidence-based clinical practice.

All recommendations are aimed at children with cancer receiving anti-cancer treatment with curative intent. These recommendations apply for out-patient settings, not for hospitalized patients. This guideline is not intended to provide recommendations for patients after end of treatment, for palliative care settings or for children undergoing a stem cell transplantation.

It was attempted to make recommendations as general as possible and applicable for everyone. However, some recommendations may not apply or should be adjusted for the readers' specific region or country.

2.3 Existing guidelines and clinical questions

Existing international guidelines on social restrictions published until November 2019 were searched (GIN [7], NICE [8], IPOG [9], ASCO [10]) and evaluated for the applicability and completeness of these guidelines. In the absence of an applicable evidence-based guideline for children with cancer, clinical questions were defined by the core group. An overview of all clinical questions is shown in the Supplemental Materials S2.

2.4 Search strategy and selection criteria

An extensive systematic literature search (see Supplemental Materials S3) was performed in collaboration with a medical librarian. We searched the electronic databases PubMed, Embase, Cochrane CENTRAL and CINAHL.

Inclusion and exclusion criteria were defined by the core group. Importantly, all children with cancer aged 0 to 18 years were included. Studies should have investigated any kind of social restriction. We only included controlled studies, applying a two-step approach by first including randomized controlled trials (RCTs) and in case of insufficient or inconclusive evidence other controlled and observational studies. Studies that only included children who had already underwent a stem cell transplantation were excluded, as we considered this a non-representative population.

It was agreed that when not enough studies were identified (n<5 per topic), we extrapolated from evidence-based guidelines in other pediatric patient populations (e.g. infectious diseases, hematology) or guidelines in adult oncology patients (applicability depending on clinical question).

2.5 Evidence selection and quality assessment

Study identification was performed independently by two reviewers. Initially titles and abstracts were screened, followed by full text assessment. Discrepancies were resolved by consensus after discussion between the two reviewers and a third, independent reviewer (EL).

Detailed information from each eligible study was extracted into evidence tables. The methodological quality of each single study was assessed and scored for risk of bias. For RCTs, the Risk of Bias tool v2 from the Cochrane handbook was used [11]. For non-RCT studies, we combined the risk of bias criteria for observational studies, as described in the Handbook of the International Guideline Harmonization Group [12], with specific aspects of the Cochrane RCT tool [11]. By combining these tools, we aimed to have the best possible tool to assess the risk of bias in our types of studies. These risk of bias assessment criteria for non-RCT studies are shown in Supplemental Materials S4.

All evidence was outlined in summary of findings tables. The quality of the total body of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [13, 14]. The data-extraction, risk of

bias assessment and GRADE assessment were independently performed by two reviewers (DS, DK). Discrepancies were resolved by consensus or a third reviewer (EL).

2.6 Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations [14]. Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert opinion). Final recommendations had to be unanimously supported by all panel members.

The GRADE terminology for evidence-based guidelines was used, such as 'we suggest' or 'we recommend'[13]. For the expert-based recommendations, the terminology from a recent paper published by the international Pediatric Oncology Guidelines in supportive care (iPOG) Network [15] was applied. The wording 'we believe' was used to emphasize that these recommendations are based on expert opinion and group consensus.

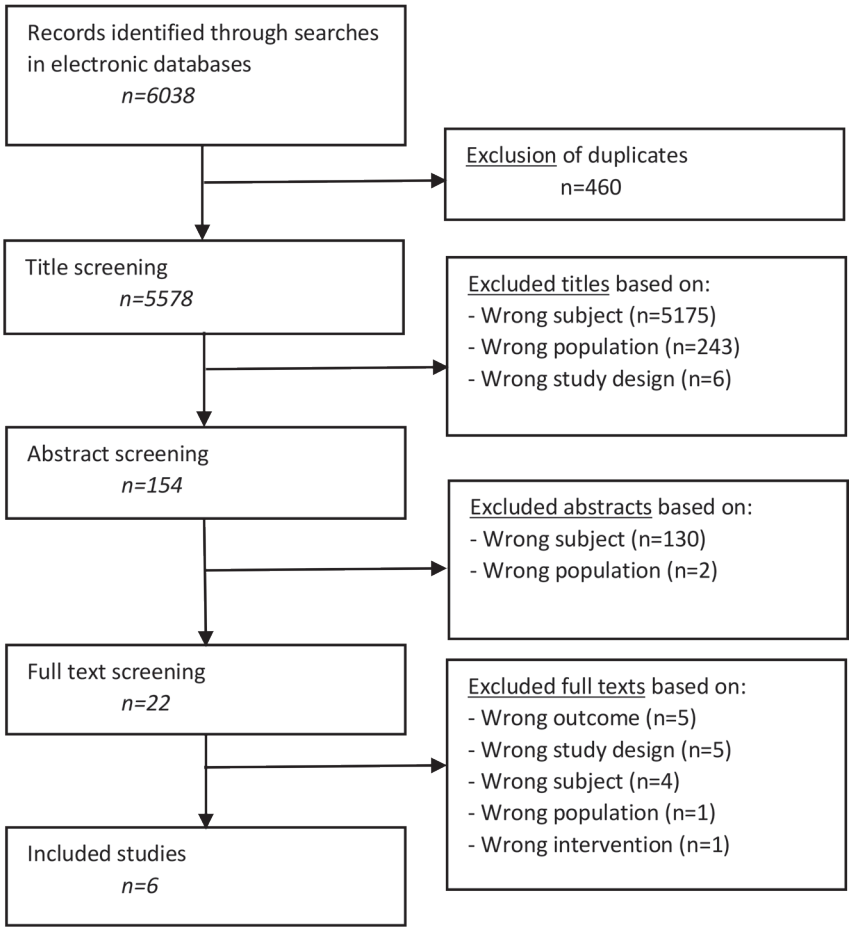
We also formulated good practice statements [16] for recommendations that were considered a part of good clinical practice, but are not specifically studied (because this is not achievable or not deemed necessary).

Within the overview of all recommendations (table 2), a color coding system was used to improve understandability and to emphasize the strength of the recommendations.

3. RESULTS

In total, 6038 unique citations were identified in initial literature search (September 2019) and two update searches (latest: February 2023). Six primary studies (2 RCTs, 2 retrospective cohort studies, 1 pre- and post- intervention study, 1 case-control study) were included with a total number of 758 participants (see Figure 1). All primary study characteristics are shown in Supplemental Materials S5.

Figure 1: Flow diagram study selection



An overview of the included studies, the evidence tables and the GRADE assessments can be found in the Supplemental Materials S6-7. In table 1, the conclusions of evidence of the included studies are presented. In table 2, a list of all recommendations is shown.

Table 1: Conclusions of evidence related to social restrictions in children with cancer

Conclusion of evidence	**Quality of evidence**
Bath toy use	
Significantly more bath toy use in group infected with *Pseudomonas* compared to the group without *Pseudomonas* infection.	⊕◯◯◯ (1 study (17)) **VERY LOW** quality of evidence
Bubble bath use	
Significantly more bubble bath use in group infected with *Pseudomonas* compared to the group without *Pseudomonas* infection	⊕◯◯◯ (1 study (17)) **VERY LOW** quality of evidence
Chlorhexidine use	
No significant differences in prevalence of infections were seen in the experimental bath wipes group versus the standard bath wipes group.	⊕⊕◯◯ (1 study (21)) **LOW** quality of evidence
Overall, no significant differences in prevalence of infections between patients with vs. without chlorhexidine bathing. Significantly lower prevalence of infections in patients with vs. without chlorhexidine bathing in specific age group 12-21 years.	⊕◯◯◯ (1 study (18)) **VERY LOW** quality of evidence
No significant differences in prevalence of infections were seen in the chlorhexidine bathing group versus the control group.	⊕⊕◯◯ (1 study (19)) **LOW** quality of evidence
Pets	
Restriction of pets at home was not significantly associated with a decreased risk of any type of infection.	⊕◯◯◯ (1 study (4)) **VERY LOW** quality of evidence
Social restrictions	
Restriction of social contact was not significantly associated with a decreased risk of any type of infection.	⊕◯◯◯ (1 study (4)) **VERY LOW** quality of evidence
Swimming	
No significant difference in prevalence of infections in swimmers group versus non-swimmers group. No significant difference in prevalence of infections in frequent swimmers group versus infrequent/non-swimmers group.	⊕◯◯◯ (1 study (22)) **VERY LOW** quality of evidence

Table 2: Overview of social restriction recommendations for children with cancer

	Recommendation	Strength of recommendation	Quality of evidence
#1	Bath toy use		
	We recommend against the use of bath toys that have a reservoir (in which water can be retained) or bath toys that cannot be dried thoroughly.	Strong	**VERY LOW** quality of evidence
#2	Bubble bath use		
2.1	We suggest not to use warm publically accessible bubble baths.	Weak	**VERY LOW** quality of evidence
2.2	We believe the use of a bubble bath at home is allowed, as long as the bath can be cleaned thoroughly and water is refreshed completely after every bath.	Weak	**EXPERT** opinion
#3	Chlorhexidine use		
	We suggest not to use chlorhexidine bathing or other bath wipes as it does not have an added value to basic hygiene measures.	Weak	**VERY LOW** quality of evidence
#4	Environmental factors (including sandbox)		
4.1	We recommend that children with cancer and neutropenia should avoid prolonged contact with environments that have high concentrations of fungal spores (i.e. construction or demolition sites, exposure to soil through gardening or digging, household renovation).	Strong	Adapted from ASCO guideline
4.2	We believe that children with cancer can play in the sandbox as long as they consider their regular hand hygiene.	Weak	**EXPERT** opinion
#5	Flowers		
	We strongly believe that indoor flowers or plants at home should be allowed.	Strong	**EXPERT** opinion
#6	Events with altitude or pressure differences		
	We believe that clinically stable children with cancer without neutropenia (i.e. neutrophil count $<0.5x10^9$/L) or thrombocytopenia (i.e. platelet count $<50x10^9$/L) can perform events with altitude or pressure differences, such as going on a plane or scuba diving in agreement with their treating physician.	Weak	**EXPERT** opinion
#7	Hygiene (general)		
	Proper hand hygiene should be performed by patients, caregivers and medical personnel.	Strong	GOOD PRACTICE STATEMENT
#8	Hygiene (personal)		
	We strongly believe that regular personal hygiene (regarding doing laundry, cleaning, renewing clothes) is sufficient for children with cancer and their households.	Strong	**EXPERT** opinion

Table 2: *(continued)*

	Recommendation	Strength of recommendation	Quality of evidence
#9	Pets, zoo and farm		
9.1	We suggest allowing to keep domestic pets in the households of children with cancer.	Weak	**VERY LOW** quality of evidence
9.2	We believe that children with cancer are allowed to go to the zoo or visit a farm.	Weak	**EXPERT** opinion
9.3	We believe that children with cancer should not clean (or play with or near) the litterbox or cages of their domestic pets.	Weak	**EXPERT** opinion
#10	Public transport		
10.1	We believe that children with cancer are allowed to use public transport or visit crowded places (i.e. big events such as visiting a concert or theater).	Weak	**EXPERT** opinion
10.2	We believe that it is not advisable for children with cancer with neutropenia to use public transport or visit crowded places when there is a higher incidence of viral infections and thereby a higher chance of getting infected.	Weak	**EXPERT** opinion
#11	School and kindergarten		
	We recommend allowing children with cancer to attend school or kindergarten irrespective of neutropenia (unless someone in their class or group has a contagious disease with potential severe consequences, e.g. varicella zoster).	Strong	**VERY LOW** quality evidence
#12	Sports and high-velocity events		
12.1	We strongly believe that children with cancer should be encouraged to exercise and perform sports.	Strong	**EXPERT** opinion
12.2	We believe that children with cancer with thrombocytopenia (i.e. platelet count <50x10^9/L) should not perform events with increased risk of bleeding (contact sports, high-impact or high-velocity events, events with risk of falling).	Weak	**EXPERT** opinion
#13	Swimming		
13.1	We suggest allowing children with cancer* to swim (irrespective of neutropenia).	Weak	**VERY LOW** quality of evidence
13.2	*We strongly believe that children with cancer with a non-tunneled central venous catheter such as PICC line should not swim.	Strong	**EXPERT** opinion
#14	Travelling abroad		
	We strongly believe that children with cancer can travel abroad, provided that they visit a country with a comparable health system and provided that the child is in good clinical health.	Strong	**EXPERT** opinion

The color coding in this table emphasizes the strength of the recommendation and shows if something is advised (green (strong) or yellow (moderate)) or discouraged (orange (moderate) or red (strong)).

All recommendations and their evidence-to-decision processes are discussed per subject. Given the extent of all recommendations, only conclusions and important considerations of the guideline panel are shown. Full details are shown in the Supplemental Materials S7.

3.1 Bath toy use

Recommendation 1. We recommend against the use of bath toys that have a reservoir (in which water can be retained) or bath toys that cannot be dried thoroughly. (STRONG recommendation, VERY LOW quality of evidence)

Evidence to decision. One case-control study [17] in children with cancer was identified. In this study [17], significantly more bath toy use was reported in the group infected with *Pseudomonas aeruginosa* compared to the group without *Pseudomonas aeruginosa* infection.

The guideline panel agrees that bath toys with a reservoir in which water can be retained should not be used in children with cancer. The still standing water in the reservoir, for example in the inside of a bath toy as in the included study, is a reservoir for several bacteria like *P. aeruginosa*, which can cause severe infections in these children. Also, toys that cannot be dried thoroughly are prone to colonization with bacteria and should therefore not be used.

Despite the very low quality of evidence, the panel decided to formulate a *strong* recommendation because of the expert opinions about the infectious risks.

It is not necessary to dispose all bath toys for (younger) children with cancer during their treatment. The panel agrees that if toys can be dried thoroughly and if there is no reservoir in which water can be retained, the toys are probably not an infectious risk and can be used safely. Note that this also accounts for sponges, towels and other items that become wet during showering or bathing.

3.2 Bubble bath use

Recommendation 2.1. We suggest not to use warm publically accessible bubble baths. (WEAK recommendation, VERY LOW quality of evidence)

Recommendation 2.2. We believe the use of a bubble bath at home is allowed, as long as the bath can be cleaned thoroughly and water is refreshed completely after every bath. (WEAK recommendation, EXPERT opinion)

Evidence to decision One case-control study [17] in children with cancer was identified. In this study [17], significantly more bubble bath use was reported in the group infected with *Pseudomonas* compared to the group without *Pseudomonas* infection.

The guideline panel believes the infectious risk in public bubble baths is relatively high because of the amount of people that enter the bubble baths, the constant high temperature of the bubble baths that form a good growth environment for bacteria and most importantly the fact that, for these publically accessible bubble baths, water is not frequently refreshed.

However, the guideline panel believes that if a private bubble bath can be cleaned properly before the use of the bath, and water can be completely refreshed, the use of a bubble bath at home (or at a vacation accommodation) is allowed.

3.3 Chlorhexidine use

Recommendation 3. We suggest not to use chlorhexidine bathing or other bath wipes as it does not seem to have an added value to basic hygiene measures. (WEAK recommendation, VERY LOW quality of evidence)

Evidence to decision. Two studies in children with cancer [18, 19] show inconsistent results regarding chlorhexidine bathing. Although one RCT [19] no overall significant differences in the prevalence of infections reported between patients with vs. without chlorhexidine bathing, there was a significantly higher rate of central line-related blood stream infection (CLABSI) infection in the chlorhexidine group aged 12-21 years. However, the validity of this outcome is difficult to assess due to several reasons (i.e. age groups not pre-defined, regular basic hygiene measures probably confounding). A non-randomized pre- and post-intervention study [18] showed no significant differences in prevalence of infections in the chlorhexidine bathing group versus the control group.

Also, a third study [20] on the use of chlorhexidine bath wipes, showed no significant differences in prevalence of infections.

With the current evidence the guideline panel does not see any added value for chlorhexidine bathing, and we consider it more of a burden to these children. Therefore, the panel suggests not to use chlorhexidine bathing as it does not seem to have an added value to basic hygiene measures.

3.4 Environmental factors (including sandbox)

Recommendation 4.1. We recommend that children with cancer and neutropenia should avoid prolonged contact with environments that have high concentrations of fungal spores (i.e. construction or demolition sites, exposure to soil through gardening or digging, household renovation). (STRONG recommendation, ASCO and IDSA guideline [21])

Recommendation 4.2. We believe that children with cancer can play in the sandbox as long as they consider their regular hand hygiene. (WEAK recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified. However, a recommendation by the ASCO and IDSA [21] guideline was used for the decision by the guideline panel. The guideline panel strongly agreed that the stated environmental sites [21], indeed could contain high levels of fungal spores and could therefore be a potential danger. Although this recommendation was not specifically made for children, we believe that it is also applicable to them.

The guideline panel specifically made a recommendation about playing in the sandbox, as this is a clinically relevant subject for parents and children. No evidence in pediatric oncology patients or other guidelines were identified. The guideline panel believes that children with cancer should be allowed to play in the sandbox, either at home, at the playground or at school, as long as they consider their regular hand hygiene.

3.5 Flowers

Recommendation 5. We strongly believe that indoor flowers or plants at home should be allowed. (STRONG recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.

The guideline panel believes that indoor flowers and plants at home should be allowed. We believe the risk of infection of just having plants or flowers in the house, is very minimal. The panel does suggest additional hygiene measures, such as refreshing the water of the flowers often, and proposes that the children do not play with or help cleaning the soil of the plants.

3.6 Events with altitude or pressure differences

Recommendation 6. We believe that clinically stable children with cancer without neutropenia (i.e. neutrophil count <0.5x10^9/L) or thrombocytopenia (i.e. platelet count <50x10^9/L) can perform events with altitude or pressure differences, such as going on a plane or scuba diving in agreement with their treating physician. (WEAK recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.
The guideline panel believes that children in a stable phase of their treatment without severe neutropenia or thrombocytopenia, should be allowed to perform these events, in accordance with their treating physician.

3.7 Hygiene (general)

Recommendation 7. Proper hand hygiene should be performed by patients, caregivers and medical personnel. (STRONG recommendation, GOOD PRACTICE STATEMENT)

Evidence to decision. The recommendation from the ASCO and IDSA [21] guideline was used, and expert opinions were discussed. The guideline panel strongly agrees that proper hand hygiene in concordance with local protocols is very important for patients, caregivers and medical personnel. We therefore formulated a recommendation in line with the recommendation from the ASCO and IDSA guideline.

3.8 Hygiene (personal)

Recommendation 8. We strongly believe that regular personal hygiene (regarding doing laundry, cleaning, renewing clothes) is sufficient for children with cancer and their households. (STRONG recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.
The guideline panel agrees that basic hygiene measures are sufficient for children with cancer. We believe that as long as the household is cleaned in a normal way, this is sufficient. There is no need to intensify (in frequency or in use of extra cleaning products) any of these personal hygiene measures such as cleaning the house or doing laundry.

3.9 Pets, zoo and farm

Recommendation 9.1. We suggest allowing to keep domestic pets in the households of children with cancer. (WEAK recommendation, VERY LOW quality of evidence)

Recommendation 9.2. We believe that children with cancer are allowed to go to the zoo or visit a farm. (WEAK recommendation, EXPERT opinion)

Recommendation 9.3. We believe that children with cancer should not clean (or play with or near) the litterbox or cage of their domestic pets. (WEAK recommendation, EXPERT opinion)

Evidence to decision. One study (observational study) in children with cancer was included for this clinical question [4], in which restriction of pets at home was not significantly associated with a decreased risk of any type of infection. The guideline panel agreed that any restriction in pets at home is not necessary. If children consider their regular hand hygiene after playing with or touching their pet, we see no reason why any other form of restriction should be advised. We believe risk of infection from a pet is minimal, considering adequate hand hygiene, and that the quality of life would decrease if there would be any form of pets restriction.

We also believe that children with cancer should be allowed to visit the zoo or farm. If the children remain at distance from the animals, we anticipated no problems regarding infectious risks. If the children, for example on a farm, touch the pets or feed them, they should again carefully consider their hand hygiene. However, we do suggest that children with cancer do not clean, play with or nearthe cages and/or litter boxes of the pets. We consider the infectious risk higher for these tasks, and it can easily – with no to minimal decrease in quality of life – be avoided by children with cancer.

Additionally, we also suggest that the pets of these children are regularly seen by a veterinarian and that they are in good health.

3.10 Public transport

Recommendation 10.1. We believe that children with cancer are allowed to use public transport or visit crowded places (i.e. big events such as visiting a concert or theater). (WEAK recommendation, EXPERT opinion)

Recommendation 10.2. We believe that it is not advisable for children with cancer with neutropenia to use public transport or visit crowded places when there is a higher incidence of viral infections and thereby a higher chance of getting infected. (WEAK recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.
The guideline panel agrees that there is no need to avoid public transport as long as basic hygiene measures such as hand hygiene are performed. Then, we believe the risk of infection remains minimal.

The guideline panel does feel that there is an exception for children with cancer and neutropenia, who should avoid the public transport or crowded places when there is a higher incidence of viral infections. In these months, there is a higher chance of getting infected. As the potential consequences of a viral infection can be big (for example, hospital admission because of fever, delay of chemotherapy or the need for antiviral medication), we believe the public transport should be avoided when there is a higher incidence of viral infections.

3.11 School and kindergarten

Recommendation 11. We recommend allowing children with cancer to attend school or kindergarten irrespective of neutropenia (unless someone in their class or group has a contagious disease with potential severe consequences, e.g. varicella zoster). (STRONG recommendation, VERY LOW quality evidence)

Evidence to decision. One study (observational study) in children with cancer was identified [4] which showed that restriction of social contact was not significantly associated with a decreased risk of any type of infection.

The guideline panel recognizes that the risk of infection at schools or kindergarten may be a concern to parents. However, we agree that going to school or kindergarten increases the quality of life of these children in such a way that it outweighs the harms of potential infections. Going to school is very important for the development of any child, also for children with cancer. It also has an important social aspect of seeing their friends and continuing with their life in the best possible way.

We strongly suggest that children stay at home when someone in their class or group has a contagious disease with potential severe consequences, e.g. varicella zoster. If this is the case, the guideline panel suggests that this will then be discussed by the treating physician for the specific patient to discuss the benefits and harms of going to school or kindergarten in that specific case.

3.12 Sports and high-velocity events

Recommendation 12.1. We strongly believe that children with cancer should be encouraged to exercise and perform sports. (STRONG recommendation, EXPERT opinion)

Recommendation 12.2. We believe that children with cancer with thrombocytopenia (i.e. platelet count <50x10^9/L) should not perform events with increased risk of bleeding (contact sports, high-impact or high-velocity events, events with risk of falling). (WEAK recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.
Firstly, the guideline panel strongly believes that children with cancer are allowed (and should be encouraged) to exercise and perform sports. It is always encouraged for children to perform sports and other physical activities. This greatly benefits their physical state and their quality of life.

However, the guideline panel feels that an exception needs to be made for children with thrombocytopenia (i.e. platelet count <50x10^9/L). In some types of activities, such as contact sports like boxing or rugby, high-impact or high-velocity events, and events with risk of falling, the risk of bleeding is too high when a child has thrombocytopenia. Therefore, these activities should be avoided in the event of thrombocytopenia. We suggest encouraging these children to perform activities that are safe, to ensure the positive effects of performing activities and sports.

3.13 Swimming

Recommendation 13.1. We suggest allowing children with cancer* to swim (irrespective of neutropenia). (WEAK recommendation, VERY LOW quality of evidence)

Recommendation 13.2. *******We strongly believe children with cancer with a non-tunneled central venous catheter such as PICC line should not swim. (STRONG recommendation, EXPERT opinion)

Evidence to decision. In one retrospective cohort study [22], no significant difference in prevalence of infections in the swimmers group versus the non-swimmers group and in the frequent swimmers group versus infrequent/non-swimmers group were reported. They report 34 infections in a total of 843 months (0.04% infection rate) in the swimmers group versus 13 infections in 506 months (0.025% infection rate), resulting in a risk ratio of 1.6 which they did not consider statistically significant (significance calculated based on 95% CI, but confidence intervals are not reported)[22].

Despite the lack of evidence, the guideline panel feels that an absolute restriction regarding swimming is not necessary. We believe not allowing the children to swim, would decrease their quality of life. The panel judged the benefits (improving quality of life) to outweigh the harms (minimal risks both infectious and dislocation wise).

For children with an external tunneled central venous catheter, swimming is therefore allowed, provided that the insertion site and dressings can be cleaned and dried thoroughly and that there is an unwounded skin (i.e. no needle in central venous access port) or sign of infection.

The guideline panel recognizes the fear for dislocation or problems with a central venous line from parents and children. Although not necessary, a suggestion is that the child can wear a wetsuit shirt (or a different type of tight shirt) so that the line is pushed against the body.

No studies investigated the risks of swimming in children with a non-tunneled line. The guideline panel believes that swimming with a non-tunneled line such as a peripheral inserted central catheter (PICC) line should not be allowed, given the increased infection risk for non-tunneled lines.

Regarding swimming location, the guideline panel believes that it should be possible to swim in all locations which are destined as swimming areas. For example, chlorinated water (including swimming lessons), the sea, or in open water, given that there is no general advice against this from the local authorities.

3.14 Travelling abroad

Recommendation 14. We strongly believe that children with cancer can travel abroad, provided that they visit a country with a comparable healthcare system and provided that the child is in good clinical health. (STRONG recommendation, EXPERT opinion)

Evidence to decision. No evidence in children with cancer was identified.
The guideline panel believes that children with cancer can travel abroad, provided that they visit a country with a comparable healthcare system as their own and provided that the child is in good clinical health. Note, this should always be a careful consideration for the child as an individual, and therefore this always needs to be discussed and allowed by the treating physician. It should not interfere with treatment and parents should carry a letter of the treating physician, in the event something happens when abroad.

4. DISCUSSION

In this clinical practice guideline, we provide evidence-based recommendations, expert-based recommendations and best practice statements regarding social restrictions in children with cancer. These recommendations provide guidance for clinicians, children and their parents and contribute to improving quality of life for children with cancer. As evidence-based recommendations for this area were lacking, this clinical practice guideline has the potential to greatly impact daily practice and therefore quality of care for children with cancer.

There is a major lack of evidence regarding the effects of social restrictions in children with cancer. We attempted multiple sensitive and broad literature searches, including other pediatric patient groups and adult oncology patients. Still the yield was low, and this is the most important limitation of this evidence-based guideline. In daily practice, healthcare providers and patients do not have the option to refrain

from discussing options and making a decision about care. Therefore, the guideline panel agreed that we should go to great lengths to formulate recommendations. Therefore, the guideline panel provided recommendations based on expert opinions. This directly contributes to improving practice and should be implemented more often in guidelines. Nevertheless, clearly more research is needed in this niche.

A strength of this guideline is that it is, to the best of our knowledge, the first guideline regarding this (broad) topic that addresses all these (different) subjects that are important to children and their parents, both evidence-based as expert-opinion based. Also, purposely attempted to formulate recommendations, even in absence of evidence, to not leave caregivers empty-handed. With that, we formulated insightful, recommendations for important topics within daily clinical practice for children with cancer. A limitation, besides the scarcity of evidence as mentioned earlier, can be attributed to the evidence-to-decision framework. Certain important topics are discussed in this framework, but that could also mean that other topics are not addressed evenly. However, given the transparency of the EtD-framework, it was attempted to fill it with as much information and considerations as possible, in order to make it as applicable as possible for other readers. It should also be noted that recommendations can be different per individual child per treatment per center, and this should always be considered by the treating physician when adapting the recommendations.

Then, shortly, we would like to address some barriers and facilitators. Note that these topics were not a part of the research but are addressed here because of its applicability, insight and use for guideline readers. We consider the evidence-to-decision frameworks as a facilitator due to its transparency and thereby adaptation possibilities to local context; also the variety in topics that are discussed in this guideline and the importance of these topics for patients are important facilitators. We consider the limited amount of evidence as the most important barrier in this guideline.

Throughout this process, it became clear how important current social restrictions are for children and their parents and how it affects their quality of life. This emphasizes the importance of the development of this guideline. Moreover our process underlined the importance of including patient representatives and their perspectives and for increasing the knowledge and awareness for this subject.

Implementation of this evidence-based guideline can contribute to improving the quality of life of children with cancer. For example, we recommend that children with external central venous catheters are allowed to swim, which until now was discouraged in the Netherlands. This is an example of an important change in current practice in the Netherlands, and an improvement in quality of life for these children. However, it remains important to always consider the benefits and harms for the individual child. This guideline can facilitate weighing these benefits and harms and balancing cautiousness and restrictiveness.

In conclusion, with effectuating this guideline, we aim to care and to contribute to improving the quality of life of children with cancer. These recommendations will play an important role in the daily lives of children with cancer and their parents, by establishing a balance between being cautious and thus protecting these vulnerable children for complications, and participating in 'normal' child life as much as possible.

SUPPLEMENTAL MATERIALS

Supplemental materials can be found online.

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4

PROPHYLACTIC PLATELET TRANSFUSIONS IN CHILDREN WITH CANCER: A GUIDELINE FOR CLINICAL PRACTICE

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ABSTRACT

Background

Platelet transfusions play an important role in supportive care in children with cancer. In current clinical practice, recommendations regarding thresholds for administering prophylactic platelet transfusions are often not evidence-based. Therefore, a clinical practice guideline (CPG) was developed to establish an overview of the available evidence and provide recommendations for clinicians.

Methods

A systematic literature review was performed, including dual appraisal of all citations. The GRADE methodology was used to assess, extract and summarize the evidence. When evidence in children with cancer was limited, additional evidence was extracted from adult cancer guidelines. A comprehensive multidisciplinary panel was assembled, comprising 23 professionals including a patients representative. Multiple in-person meetings were held to discuss evidence, complete evidence-to-decision frameworks and formulate recommendations.

Results

Three studies met our inclusion criteria, which included 1.454 children with cancer. The expert panel assessed all evidence and utilized this literature and shared expert opinions to formulate recommendations in a transparent manner. In total, 22 recommendations were formulated regarding prophylactic platelet transfusions in children with cancer for different situations and procedures. Thresholds for prophylactic platelet transfusions were recommended for children with cancer undergoing for example a lumbar puncture, line insertion and invasive diagnostic and therapeutic procedures.

Conclusion

In this CPG, we provide evidence-based and expert consensus-based recommendations regarding platelet transfusions in children with cancer. With these recommendations we aim to provide guidance for clinicians and to contribute to improving outcomes for children with cancer.

1. INTRODUCTION

Thrombocytopenia is a frequently occurring adverse effect of anti-cancer treatment, which may result in clinical symptoms in the child and impair their quality of life [1]. To prevent bleeding due to a low platelet count, prophylactic platelet transfusions can be administered. However, a balance needs to be determined between unnecessary transfusions -and its potential adverse effects [2] as well as costs- and preventing complications due to thrombocytopenia or anemia. It is therefore important that thresholds for prophylactic platelet transfusions are determined precisely, balancing cautiousness and restrictiveness.

In current clinical practice, the majority of the recommendations regarding thresholds for administering prophylactic platelet transfusions to children with cancer is not evidence-based and a clinical practice guideline was lacking. As children with cancer frequently receive prophylactic platelet transfusions, critically reviewing and assessing the available evidence and to formulate recommendations is of great importance.

Therefore, our aim was to develop a clinical practice guideline (CPG) regarding prophylactic platelet transfusions in children with cancer. We aimed to achieve this by first establishing an overview of the available evidence in medical literature and subsequently formulating recommendations for clinicians. We explicitly aimed to provide recommendations even in absence of evidence, to establish good clinical practice and provide clinicians with a comprehensive guideline.

2. METHODS

2.1 Guideline panel

A national, comprehensive multidisciplinary panel was assembled, comprising 23 professionals including a patient representative from the Netherlands. The panel included pediatric oncologists, a pediatric hematologist, a transfusion specialist, general pediatricians, a surgeon, an anesthesiologist, a patient representative, a pediatric oncology nurse, nurse specialists, pediatric intensive care specialists, a laboratory specialist, guideline specialists and several researchers (see Supplemental Materials S1). Members were invited on the basis of their experience and knowledge

on the topic. The core group (DS, DK, RM, LK, WT, EL) provided all the preparatory documents including methodology, study details and results. Between 2020 and 2022, multiple in-person meetings with the extended panel were held to rank outcomes, discuss evidence and formulate recommendations.

2.2 Guideline scope

This CPG includes recommendations regarding prophylactic platelet transfusions in children aged 0-18 years with cancer receiving anti-cancer treatment with curative intent. The guideline is not intended to provide recommendations for palliative care settings.

2.3 Existing guidelines and clinical questions

Existing published international guidelines on prophylactic platelet transfusions in children and adults were searched (GIN [3], NICE [4], iPOG [5], ASCO [6], FMS [7]) and evaluated for the applicability and completeness of these guidelines. In the absence of an applicable, complete or recent evidence-based guideline for children with cancer, clinical questions were defined by the guideline panel. An overview of all clinical questions is shown in the Supplemental Materials S2.

2.4 Compliance with ethical standards

As no patients participated in this research, no ethics committee approval was required for the formation of this guideline and no informed consent was required. Therefore, also, 'Human Ethics and Consent to Participate declarations' were not applicable. All guideline panel members and their functions can be found in Supplemental Materials S1. There was no conflict of interest.

2.5 Search strategy and selection criteria

An extensive systematic literature search (see Supplemental Materials S3) was performed in collaboration with a medical librarian. We searched the electronic databases PubMed, Embase and Cochrane CENTRAL. In- and exclusion criteria were predefined by the core group. Inclusion criteria were: 1) children with cancer, 2) aged 0-18 years, 3) undergoing a platelet transfusion at a certain threshold. Studies should have compared groups with different thresholds for platelet transfusions. Only controlled studies were included, applying a two-step approach by first including RCTs and in case of insufficient or inconclusive evidence other controlled studies.

It was agreed that in the absence of relevant studies, we would extrapolate from evidence-based guidelines in other pediatric patient populations (e.g. patients with hematological disorders) or guidelines in adult oncology patients (applicability depending on clinical question).

2.6 Evidence selection and quality assessment

Study identification was performed independently by two reviewers (DS, DK). Initially titles and abstracts were screened, followed by full text assessment. Discrepancies were resolved by finding consensus or a third reviewer (EL).

Detailed information from each eligible study was extracted into evidence tables. The methodological quality of each study was assessed and scored for risk of bias. For RCTs, the Risk of Bias tool v2 from the Cochrane handbook was used [8]. For non-RCT studies, we combined the risk of bias criteria for observational studies, as described in the Handbook of the International Guideline Harmonization Group [9], with specific aspects of the Cochrane RCT tool [8]. By combining these tools, we aimed to have the best possible tool to assess the risk of bias in our types of studies. These risk of bias assessment criteria for non-RCT studies are shown in Supplemental Materials S4.

All evidence was outlined in summary of findings tables. The quality of the total body of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [10, 11]. The data-extraction, risk of bias assessment and GRADE assessment were independently performed by two reviewers (DS, DK). Discrepancies were resolved by consensus or a third reviewer (EL).

2.7 Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations [11]. Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (EXPERT opinion). Final recommendations had to be unanimously supported by all panel members.

The GRADE terminology for evidence-based guidelines was used, such as ‘we suggest’ or ‘we recommend’[10]. For the expert-based recommendations, the

terminology from a recent paper published by the international Pediatric Oncology Guidelines in supportive care (iPOG) Network [12] was used. The wording 'we believe' was used to emphasize that these recommendations are based on expert opinion and group consensus.

Within the overview of all recommendations (table 2), a color coding system was used to improve understandability and to emphasize the strength of the recommendations.

3. RESULTS

In total, 9.345 unique citations were identified through literature search (September 2019) and two update searches (latest: February 2023). Three studies (1 RCT, 1 retrospective cohort study, 1 observational study) were included with a total number of 1.454 participants (see Figure 1). All primary study characteristics are shown in Supplemental Materials S5.

An overview of the included studies, the evidence tables and the GRADE assessments can be found in the Supplemental Materials S6. In table 1, the conclusions of evidence of the included studies are presented. In table 2, a list of all recommendations is shown.

Figure 1: Flow diagram study selection

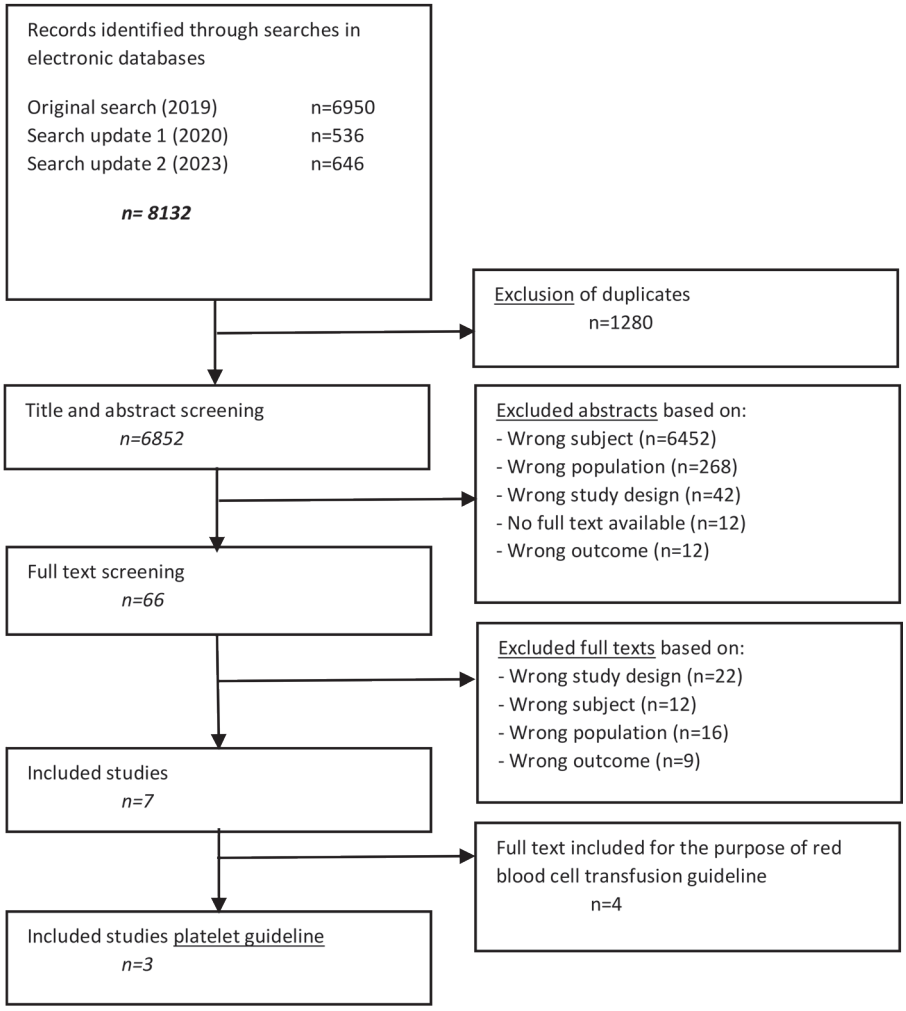

Table 1: Conclusions of evidence related to platelet transfusions in children with cancer

Conclusion of evidence	Quality of evidence
Children with cancer – in general (therapeutic versus prophylactic platelet transfusions)	
In one study, significantly less bleeding was observed in patients who received platelet transfusions prophylactically when platelet count fell <20 $\times 10^9$/L versus the group who received platelet transfusions therapeutically (i.e. when patients were bleeding).	⊕○○○ (1 study) **VERY LOW** QUALITY OF EVIDENCE
Lumbar puncture – severe hemorrhagic events	
In one study, no severe hemorrhagic events occurred in patients with different levels of platelet count.	⊕○○○ (1 study) **VERY LOW** QUALITY OF EVIDENCE
In one study, no severe hemorrhagic events (spinal hematoma) occurred in patients with different levels of platelet count.	⊕○○○ (1 study) **VERY LOW** QUALITY OF EVIDENCE
Lumbar puncture – influence on outcome material	
In one study, significantly more traumatic lumbar punctures were observed in the group with platelet count <20 $\times 10^9$/L compared to the group with platelet count >20 $\times 10^9$/L, <50 $\times 10^9$/L versus >50 $\times 10^9$/L and <100 $\times 10^9$/L versus >100 $\times 10^9$/L.	⊕○○○ (1 study) **VERY LOW** QUALITY OF EVIDENCE

Table 2: Overview of platelet transfusion recommendations for children with cancer

Recommendation	Strength of recommendation	Quality of evidence
Children with cancer – in general (therapeutic versus prophylactic platelet transfusions)		
Due to lack of evidence, a recommendation about prophylactic platelet transfusions in general in children with cancer cannot be made. However, if you do consider giving a prophylactic platelet transfusion, a platelet threshold of 10x10^9/L is sufficient. [7, 13, 14]	N/A	EXPERT opinion
Children with ALL		
We believe a platelet transfusion threshold of 10x10^9/L is sufficient for children with ALL during induction therapy.	Weak	EXPERT opinion
Children with AML (or APL)		
We believe a platelet threshold of 50x10^9/L is sufficient for children with APL or any other type of AML ***with*** coagulation abnormalities during induction therapy.	Weak	EXPERT opinion
We believe a platelet threshold of 20x10^9/L is sufficient for children with AML ***without*** coagulation abnormalities during induction therapy.	Weak	EXPERT opinion

Table 2: *(continued)*

Recommendation	Strength of recommendation	Quality of evidence
Children with sepsis		
We believe a platelet threshold of $10x10^9$/L is sufficient in children with cancer and sepsis.	Weak	EXPERT opinion
Bone biopsy (surgical)		
We believe a platelet threshold of $50x10^9$/L is sufficient for children with cancer who need a surgical bone biopsy for diagnostic purpose of a tumor.	Weak	EXPERT opinion
Bone marrow aspirate or biopsy		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need a bone marrow aspiration or biopsy.	Weak	EXPERT opinion
Broncho-alveolar lavage		
We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a broncho-alveolar lavage with use of a scope.	Weak	EXPERT opinion
Chest tube or drain elsewhere		
We believe a platelet threshold of $50x10^9$/L is sufficient for children with cancer who need a chest tube or drain insertion elsewhere.	Weak	EXPERT opinion
Dental extraction		
We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a dental extraction.	Weak	EXPERT opinion
Enema		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need an enema.	Weak	EXPERT opinion
Intramuscular injections		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need an intramuscular injection (including vaccination, provided that pressure is applied at the injection site for 10 minutes.	Weak	EXPERT opinion
Intubation		
We believe a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a non-urgent oral endotracheal intubation.	Weak	EXPERT opinion
We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer need a non-urgent nasal intubation.	Weak	EXPERT opinion
Line insertion or removal		
We believe a platelet threshold of $50x10^9$/L is sufficient for children with cancer who need a tunneled central venous line insertion or removal.	Weak	EXPERT opinion
We believe a platelet threshold of $10x10^9$/L is sufficient for children with cancer who receive an ultrasound-guided line insertion of a non-tunneled central line or peripherally inserted central catheter (PICC).	Weak	EXPERT opinion

Table 2: *(continued)*

Recommendation	Strength of recommendation	Quality of evidence
We believe a platelet threshold of 10x10^9/L is sufficient for children with cancer for removal of a non-tunneled central line or PICC.	Weak	EXPERT opinion
Lumbar puncture		
We suggest that a platelet threshold of 10x10^9/L is sufficient in children with cancer *without* leukemic blasts in their peripheral blood who need a lumbar puncture.	Weak	VERY LOW QUALITY evidence
We strongly believe a platelet threshold of 50x10^9/L should be maintained in children (with cancer) *with* leukemic blasts in their peripheral blood who need a lumbar puncture.	Strong	EXPERT opinion
Lymph node biopsy		
We believe a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a lymph node biopsy (both needle and excision biopsy).	Weak	EXPERT opinion
Major surgery (e.g. tumor resection)		
We believe a platelet threshold of 100x10^9/L is sufficient for children with cancer who need major surgery (e.g. tumor resection).	Weak	EXPERT opinion
Nasogastric tube insertion or removal		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need a nasogastric tube insertion or removal.	Weak	EXPERT opinion
Neurosurgery (including VP drain) or ocular surgery		
We believe a platelet threshold of 100x10^9/L is sufficient in children with cancer who need neurosurgery (including VP drain) or ocular surgery.	Weak	EXPERT opinion
PEG tube insertion and removal		
We believe a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a PEG tube insertion or removal.	Weak	EXPERT opinion
Rectal thermometer (probe) and administering rectal medication		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer with a rectal thermometer (probe) or for administering rectal medication.	Weak	EXPERT opinion
Skin biopsy (with biopsy punch)		
We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need to undergo a skin biopsy (with biopsy punch).	Weak	EXPERT opinion
Urinary catheter insertion		
We believe a platelet threshold of 20x10^9/L is sufficient in children with cancer who need a urinary catheter insertion.	Weak	EXPERT opinion

*The color coding in this table emphasizes the strength of the recommendation and shows if something is advised (green or yellow) or discouraged (orange or red).

[13] ASCO (2018) [14] NICE (2015) [7] FMS (2019)

3.1 Prophylactic platelet transfusions for children with cancer – general recommendation

Due to lack of evidence, a recommendation about prophylactic platelet transfusions in general in children with cancer cannot be made.

However, if you do consider giving a prophylactic platelet transfusion, we believe a platelet threshold of 10x10⁹/L is sufficient. [7, 13, 14] (EXPERT opinion)

Evidence to decision One RCT [15] in children with cancer was identified. Murphy et al (1982)[15] reported on a cohort of 56 children with acute leukemia (both lymphoblastic and myeloid) who were randomized to the therapeutic only strategy (transfusion when bleeding occurred) or to the prophylactic strategy (defined as platelet transfusion when morning platelet count was 20x10^9 or lower). This study showed more bleeding per patient-months in the therapeutic group, but did not show a difference in number of bleeds per patients, nor did they define the severity of the bleeds. This study was of very low quality due to important imprecision, i.e. a small population and very serious risk of bias i.e. unclear randomization and inclusion criteria, no patient characteristics and unclear outcome definitions. Hemorrhagic events in this study were defined as epistaxis not controlled by initial packing, gross gastrointestinal or genitourinary tract bleeding, any central nervous system bleeding, or any bleeding episode felt to be life-threatening. Most importantly, the severity of the bleeding episodes per study group was not specified and therefore conclusions cannot be drawn from this study.

Two studies in adult oncology patients [16, 17] (total patients n=991) and recommendations from ASCO [13], NICE [14] and FMS [7] guidelines were used as additional evidence. These two studies in adult oncology patients [16, 17] report no differences in severe hemorrhagic events and mortality between the therapeutic or prophylactic platelet transfusion groups (in adult oncology patients). This might suggest a therapeutic-only strategy. However, we question the use and extrapolation of results from adult studies in recommendations for children.

More evidence about the effects of prophylactic platelet transfusions in children with cancer in general is lacking. There remains a gap in knowledge due to lack of evidence (of good enough quality) in children with cancer and therefore, no recommendation can be formulated.

Therefore, the guideline panel is not able to make a recommendation on whether or not prophylactic platelet transfusions are needed. However, if you do consider administering your patient a prophylactic platelet transfusion, a threshold of 10x10^9/L is sufficient. We adapt these recommendations from the ASCO [13], NICE [14] and FMS [7] guidelines and it was unanimously supported by all guideline panel members.

3.2 Prophylactic platelet transfusion in children with cancer with specific indications

3.2.1 Prophylactic platelet transfusion at platelet level <50x109/L

During induction therapy, we believe a platelet threshold of 50x10^9/L is sufficient for children with 1) APL or 2) any other type of AML with coagulation abnormalities (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. However, three guidelines were used for the decision by the guideline panel.

In the NOPHO-DBH-AML (2012) [18] protocol a threshold of 50 x10^9/L is recommended for "children with AML, especially those with APL, or M4 or M5 AML, who have a high incidence of coagulation disturbances". The NICE guideline [14] advises a threshold of 50-75 x10^9/L for children with "any coexisting causes of abnormal haemostasis". The ASCO guideline [13] recommends a threshold of <10x10^9/L for patients receiving therapy for hematologic malignancies, but they acknowledge that higher thresholds are advisable for patients with coagulation abnormalities (eg, acute promyelocytic leukemia). The guideline panel strongly believes that for APL or any other type of AML with coagulation abnormalities, a higher threshold should be maintained, in line with the recommendations from NICE [14] and ASCO [13], and the NOPHO-DBH-AML-2012 protocol [18], because of the high incidence of coagulation disturbances.

3.2.2 Prophylactic platelet transfusion at platelet level <20x10^9/L

We believe a platelet threshold of 20x10^9/L is sufficient for children with AML without coagulation abnormalities during induction therapy (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. The guideline panel, together with an invited expert (prof. dr. G.J. L. Kaspers, Princess

Máxima Center for pediatric oncology) on this subject, believes that a prophylactic platelet transfusion is appropriate in this specific patient group. Based on years of experience with a threshold of 20x10^9/L during induction therapy for children with AML, the guideline panel believes that this threshold is sufficient. The guideline panel feels that after induction therapy, a prophylactic platelet transfusion is no longer necessary.

3.2.3 Prophylactic platelet transfusion at platelet level <10x10^9/L

We believe a platelet transfusion threshold of 10x10^9/L is sufficient for children with ALL during induction therapy (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. The ASCO [13], NICE [14] and FMS [7] guidelines recommend a threshold of 10x10^9/L. Also, the guideline panel believes that this threshold is sufficient, based on their experience. The guideline panel agrees that after induction therapy, with a lower chance of bleeding than during induction therapy, a prophylactic platelet transfusion might no longer be necessary.

We believe a platelet threshold of 10x10^9/L is sufficient in children with cancer and sepsis (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. The guideline panel used the "Surviving sepsis campaign [19]" as a base for their expert opinion. In this study, an expert panel developed recommendations for clinicians caring for children with septic shock and other sepsis-associated organ dysfunction. They suggest against prophylactic platelet transfusion based solely on platelet levels in non-bleeding children with septic shock or sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence. [19] The panel recognizes the importance of the recommendation this group formulated, but believes that a certain platelet threshold should be maintained in a pediatric oncology population. We believe that if the platelet count falls below 10x10^9/L in a child with cancer and sepsis, the risk of bleeding and other complications is higher. The panel does not see any evidence for a prophylactic platelet transfusion higher than 10x10^9/L, as also supported by the "Surviving sepsis campaign". [19]. Depending on individual circumstances a higher threshold can be considered in individual cases.

3.3 Prophylactic platelet transfusion prior to a procedure

3.3.1 Prophylactic platelet transfusion at platelet level <100x10⁹/L

We believe a platelet threshold of 100x10⁹/L is sufficient for children with cancer undergoing 1) major surgery (e.g. tumor resection) or 2) neurosurgery (including VP drain) or 3) ocular surgery (WEAK recommendations, EXPERT opinion).

Evidence to decision. For all groups, no evidence in children with cancer was identified.

The panel believes that a platelet threshold of 100x10^9/L is sufficient in children with cancer who need major surgery such as tumor resection, neurosurgery or ocular surgery, in line with recommendations from ASCO [13] and NICE [14]. These types of surgery are very invasive, have a long duration and a lot of potential bleeding sites with major clinical consequences. We believe that the potential consequences of bleeding during or after the procedure could be very harmful. In addition, the potential bleeding cannot be managed easily.

3.3.2 Prophylactic platelet transfusion at platelet level <50x10⁹/L

We strongly believe a platelet threshold of 50x10⁹/L should be maintained in children (with cancer) with leukemic blasts in their peripheral blood who need a lumbar puncture (LP). (STRONG recommendation, EXPERT OPINION).

Evidence to decision. Two observational studies [20, 21] in pediatric oncology patients were identified. These two studies with a total of 14.311 lumbar punctures, showed no severe hemorrhagic events. They reported a traumatic LP in 10-16% of all punctures, independent of the platelet count at time of puncture. However, the proportion between the groups divided per threshold is unclear, as well as the number of lumbar punctures performed at important diagnostic moments during therapy. The guideline panel strongly believes that a platelet threshold of 50x10^9/L is sufficient in children with cancer *with* leukemic blasts in their peripheral blood who need to undergo a lumbar puncture, also in line with the FMS guideline [7]. Because the incidence of a traumatic LP is rather high, and because of the possible consequences this traumatic LP has on intensifying further therapy (due to possibly interfering with CNS status), the guideline panel is comfortable in setting a higher

threshold for this specific circumstance than for a regular LP without leukemic blasts in peripheral blood.

We believe a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a non-urgent nasal intubation (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. The panel believes that a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a non-urgent nasal intubation. The nasal route of intubation is very narrow, well vascularized and can therefore bleed easily. When bleeding does occur, vision can get impaired and that might severely affect the intubation. In addition, the potential bleeding cannot be managed easily.

We believe a platelet threshold of 50x10^9/L is sufficient in children with cancer undergoing 1) broncho-alveolar lavage with use of a scope; 2) chest tube insertion or drain insertion elsewhere; 3) dental extraction; 4) lymph node biopsy (both needle and excision biopsy); 5) PEG tube insertion and removal; 6) surgical bone biopsy for diagnostic purpose of a tumor or 7) tunneled central venous line insertion or removal (WEAK recommendations, EXPERT opinion).

Evidence to decision. For all these subjects, no evidence in children with cancer was identified. Therefore, the guideline panel formulated recommendations based on expert opinions. These procedures are invasive and have bleeding potential. We believe that the possible consequences of bleeding during or after these procedures could be harmful and therefore a threshold of 50x10^9/L is considered sufficient, in line with recommendations from the FMS guideline [7].

3.3.3 Prophylactic platelet transfusion at platelet level <20x10^9/L

We believe a platelet threshold of 20x10^9/L is sufficient in children with cancer who need a urinary catheter insertion (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. Therefore, the guideline panel formed a recommendation based mainly on expert opinions together with an invited expert (A.J. Klijn, Wilhelmina Children's Hospital, Utrecht). We believe that the initial chance of bleeding due to this procedure will probably be small, but there are potential consequences of bleeding. However, the bleeding

cannot be recognized directly and most importantly not easily managed. Also, the inability of a child to relax during the insertion of the catheter can give a higher chance of bleeding and therefore a lower threshold was not chosen. The threshold of $20x10^9$/L is in line with the recommendation of the FMS guideline [7].

We believe a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a non-urgent oral endotracheal intubation (WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. Therefore, the guideline panel formed a recommendation based mainly on expert opinions. This oral route for intubation is more accessible, less vascularized and bleeds less easily than the nasal route for intubation. When bleeding does occur, vision can be maintained and would be less likely to affect the intubation and bleeding can be managed easily. Therefore, the guideline panel feels comfortable in lowering the threshold for non-urgent oral endotracheal intubation to $20x10^9$/L. This recommendation does not apply for (semi) urgent situations in which rapid intubation is required, as then the platelet transfusion is inferior to securing the airway swiftly.

3.3.4 Prophylactic platelet transfusion at platelet level <$10x10^9$/L

We believe a platelet threshold of $10x10^9$/L is sufficient for children with cancer who undergo 1) removal of a non-tunneled central line or PICC or 2) ultrasound-guided line insertion of a non-tunneled central line or PICC

(WEAK recommendation, EXPERT opinion).

Evidence to decision. No evidence in children with cancer was identified. Therefore, the guideline panel formed a recommendation based on expert opinions. For these procedures, the distance between the insertion site (skin entry) and the potential bleeding site is small, and potential bleeding can be managed quickly and easily. By choosing a threshold of <$10x10^9$/L, we prevent unnecessary platelet transfusions, still considering the benefits and harms of a possible bleeding episode due to the procedure.

We suggest that a platelet threshold of 10x10^9/L is sufficient in children with cancer without leukemic blasts in their peripheral blood who need a lumbar puncture (WEAK recommendation, VERY LOW QUALITY evidence).

Evidence to decision. The evidence in pediatric oncology patients for this recommendation is described in 3.3.2. In addition, the panel believes that a platelet threshold of 10x10^9/L is sufficient in children with cancer without blasts in their peripheral blood who need to undergo a lumbar puncture. We feel that a prophylactic transfusion threshold is necessary, because of the chance of severe hemorrhagic events. The FMS guideline [7] recommends a threshold of 20x10^9/L, but the guideline panel agrees to suggest a threshold of 10x10^9/L, also based on years of experience. For this recommendation certain circumstances were assumed, namely that the child is sedated [22] and therefore can lay completely still during the procedure. If this is not the case, a higher threshold of 50x10^9/L can be considered.

3.3.5 Prophylactic platelet transfusion not necessary

The guideline panel believes that a prophylactic platelet transfusion is not necessary in children with cancer undergoing 1) a bone marrow aspirate or biopsy; 2) a skin biopsy (with biopsy punch); 3) intramuscular injections; 4) enema; 5) nasogastric tube insertion or removal; 6) rectal thermometer probe and administering rectal medication (WEAK recommendations, EXPERT opinion).

Evidence to decision. For all these procedures, no evidence in children with cancer was identified. Therefore, the guideline panel formed a recommendation based mainly on expert opinions. We believe that the initial chance of bleeding due to these procedures is very small. In addition, the panel feels that the potential bleeding that occurs from the procedure, would be limited, can be easily recognized (as the bleeding is often visible or noticeable by the patient) and easily managed if necessary.

In summary, all thresholds for platelet transfusions are shown in table 3.

Table 3: Overview of thresholds for prophylactic platelet transfusions

1) Prophylactic platelet transfusion in general:

Prophylactic platelet transfusion at platelet level <50x10⁹/L
Children with APL or any other type of AML with coagulation abnormalities during induction therapy

Prophylactic platelet transfusion at platelet level <20x10⁹/L
Children with AML during induction therapy

Prophylactic platelet transfusion at platelet level <10x10⁹/L
Children with ALL during induction therapy
Children with cancer and sepsis

2) Prophylactic platelet transfusion prior to a procedure:

Prophylactic platelet transfusion at platelet level <100x10⁹/L
Major surgery (e.g. tumor resection)
Neurosurgery (including VP drain) or ocular surgery.

Prophylactic platelet transfusion at platelet level <50x10⁹/L
Broncho-alveolar lavage with use of a scope
Surgical bone biopsy for diagnostic purpose of a tumor
Chest tube or drain elsewhere
Children (with cancer) with leukemic blasts in their peripheral blood who need a lumbar puncture
Lymph node biopsy (both needle and excision biopsy)
PEG tube insertion and removal
Non-urgent nasal intubation
Inserting or removing tunneled central venous line
Dental extraction

Prophylactic platelet transfusion at platelet level <20x10⁹/L
Urinary catheter insertion
Non-urgent oral endotracheal intubation

Prophylactic platelet transfusion at platelet level <10x10⁹/L
Ultrasound-guided line insertion of a non-tunneled central line or PICC.
Removal of a non-tunneled central line or PICC
Lumbar puncture for children *without* leukemic blasts in their peripheral blood

Prophylactic platelet transfusion not necessary
Bone marrow aspirate or biopsy
Skin biopsy (with biopsy punch)
Intramuscular injections (for example vaccination)
Enema
Nasogastric tube insertion or removal
Rectal thermometer (probe) and administering rectal medication

4. DISCUSSION

In this clinical practice guideline, we provide evidence-based and expert opinion based recommendations regarding prophylactic platelet transfusions in children with cancer. These recommendations provide guidance for clinicians and contribute to improving quality of life for children with cancer. As evidence-based recommendations on this topic were lacking, this clinical practice guideline has the potential to greatly impact daily practice and therefore quality of care for children with cancer.

There is a major lack of evidence regarding the thresholds for prophylactic platelet transfusions in children with cancer. We attempted multiple broad literature searches, including other patient groups, such as children with bleeding disorders or adult oncology patients. Still the yield was low, and this is the most important limitation of this evidence-based guideline. However, the guideline panel agreed that we should go to great lengths to avoid not formulating a recommendation, as a CPG is now missing and of major importance for healthcare providers in their daily practice. With prophylactic platelet transfusions being administered so frequently in children with cancer and the potentially major consequences of bleeding, it is abundantly clear that more research is needed in this field of practice.

To our knowledge, this is the first CPG in children with cancer regarding prophylactic platelet transfusions, which attempted such a complete overview of all procedures and specific indications. The great effort that was made to provide recommendations, even in absence of evidence, is a great strength of this guideline. The use of expert opinion recommendations directly contributes to improving practice and should be implemented more often in guidelines when evidence is lacking.

Implementation of this guideline will hopefully contribute to improving the quality of life of children with cancer, through minimizing the number of platelet transfusions with its potential harms, costs and burden, while preventing bleeding. Many of these recommendations are based on expert-opinion, as we tried to provide as many guidance as possible. To provide optimal transparency, all precise considerations are reported in the evidence-to-decision framework. With that, a clinician can, together with patients and/or parents, always consider the benefits and harms for a child individually. We hope this guideline provides an aid in weighing these benefits and harms, balancing cautiousness and restrictiveness.

In conclusion, with effectuating the recommendations from this CPG, the guideline panel aims to improve care and to contribute to improving the quality of life of children with cancer. These recommendations will play an important role in current clinical practice and the demonstrated lack of evidence hopefully stimulate more research in this field of practice. Currently we are developing indicators to monitor the effect of this guideline.

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SUPPLEMENTAL MATERIALS

Supplemental materials can be found online.

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5

PROPHYLACTIC RED BLOOD CELL TRANSFUSIONS IN CHILDREN AND NEONATES WITH CANCER: AN EVIDENCE BASED CLINICAL PRACTICE GUIDELINE

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ABSTRACT

Background

Red blood cell (RBC) transfusions play an important role in supportive care in children and neonates with cancer. However, in current clinical practice evidence-based recommendations are lacking on when to administer prophylactic RBC transfusions. To address this gap, a clinical practice guideline (CPG) was developed to systematically review the available evidence and provide recommendations for clinicians.

Methods

A systematic literature review in 3 databases was conducted. The GRADE methodology was used to assess, extract and summarize the evidence. A multidisciplinary panel of 21 professionals was assembled to ensure comprehensive expertise. If there was insufficient evidence in children with cancer, additional evidence was gathered in general pediatric or adult oncology guidelines, or the panel utilized shared expert opinion to develop a comprehensive CPG. Multiple in-person meetings were conducted to discuss evidence, complete evidence-to-decision frameworks and formulate recommendations.

Results

Four studies including 203 children with all types of cancer, met the inclusion criteria. The expert panel assessed all evidence and translated it into recommendations. In total, 47 recommendations were formulated regarding RBC transfusions in children and neonates with cancer. For instance, specific thresholds for prophylactic RBC transfusions were recommended for children and neonates with cancer who have sepsis, are on ECMO or are undergoing radiotherapy.

Conclusion

This clinical practice guideline presents evidence-based recommendations regarding RBC transfusions in children and neonates with cancer. By providing these recommendations, we aim to guide clinicians and contribute to improving outcomes for children and neonates with cancer.

1. INTRODUCTION

Red blood cell (RBC) transfusions are important in the supportive care for children with cancer and those undergoing a hematopoietic stem cell transplantation (HSCT). These transfusions are often necessary due to anemia resulting from their underlying oncological disease or due to bone marrow depression during their anti-cancer treatment (13). Blood transfusions can significantly improve the quality of life of children and neonates with cancer. However, while transfusions are generally well tolerated, they are associated with adverse short- and long-term effects (such as volume overload, transfusion reactions, and iron overload (1, 2)). Thus, it is essential to strike a balance between unnecessary transfusions - and its adverse effects - and preventing complications caused by anemia.

Unfortunately, current clinical practice lacks evidence-based recommendations for administering RBC transfusions in children with cancer specifically. Given the frequency of these transfusions in these patients, it is crucial to critically review and assess the available evidence to develop accurate recommendations.

Therefore, our aim was to develop a clinical practice guideline (CPG) regarding RBC transfusions in children with all types of cancer in general and children with all types of cancer who are undergoing an HSCT. This CPG focuses on prophylactic RBC transfusions in children and neonates with cancer. We explicitly aimed to provide recommendations even in absence of evidence,, to establish good clinical practice and provide clinicians with a comprehensive guideline.

2. METHODS

2.1 Guideline panel

A national, comprehensive multidisciplinary panel was assembled, comprising 22 professionals and a patient representative. The panel included pediatric hemato-oncologists, pediatricians, a radiotherapist, a surgeon, a patient representative, nurse specialists, a pediatric intensive care specialist, a laboratory specialist, guideline specialists and several researchers (see Supplemental Materials S1). Members were invited on the basis of their experience and knowledge on the topic. The core group (DK, DS, RM, LK, WT, EL) provided all the preparatory documents including

methodology, study details and results. Between 2020 and 2022, multiple in-person meetings were held to rank outcomes, discuss the evidence and formulate recommendations.

2.2 Guideline scope

This CPG includes recommendations regarding prophylactic RBC transfusions in children with cancer aged 0-18 years receiving anti-cancer treatment with curative intent. This guideline was not intended to provide recommendations for palliative care settings or for cases of ongoing blood loss (e.g. emergency care, ongoing blood loss in gastro-intestinal tract, epistaxis). The guideline focuses on prophylactic RBC transfusions, symptoms can however influence the threshold for transfusion and clinical decision-making accordingly.

2.3 Existing guidelines and clinical questions

Existing international guidelines on prophylactic RBC transfusions were searched (latest search February 2023; National Institute for Health and Care Excellence (NICE), Guidelines International Network (GIN), American Society of Clinical Oncology (ASCO), international Pediatric Oncology Group (iPOG), Cancer Guideline Database) and evaluated for the applicability and completeness of these guidelines. Considering the absence of an applicable evidence-based guideline for children with cancer, clinical questions were formulated by the core group. An overview of the clinical questions is shown in the Supplemental Materials S2.

2.4 Search strategy and selection criteria

An extensive systematic literature search (shown in Supplemental Materials S3) was performed in collaboration with a medical librarian. We searched electronic databases PubMed, Embase and Cochrane CENTRAL.

In- and exclusion criteria were predefined by the core group. Importantly, all children and neonates with all types of cancer aged 0 to 18 years were included. Studies were included if groups with different thresholds for RBC transfusions were compared. We only included controlled studies, applying a two-step approach by first including RCTs but in case of insufficient or inconclusive evidence we included other controlled studies. It was agreed upon that when there were not enough studies identified, we would extrapolate from evidence-based guidelines in other pediatric patient

populations (e.g. benign hematology or cardiology) or guidelines in adult oncology patients (applicability depending on clinical question).

2.5 Primary evidence selection and quality assessment

Study identification was performed by title and abstract screening, followed by full text assessment, independently by two reviewers (DK, DS). Discrepancies were resolved by consensus.

Detailed information from each eligible study was extracted into evidence tables. The methodological quality of each single study was assessed and scored on risk of bias. For RCTs, the Risk of Bias tool v2 from the Cochrane handbook (3) was used. For non-RCT studies, we combined the risk of bias criteria for observational studies, as described in the Handbook of the International Guideline Harmonization Group (4), with specific aspects of the Cochrane RCT tool (3). By combining these tools, we aimed to have the best possible tool to assess the risk of bias in our types of studies. These risk of bias assessment criteria for non-RCT studies and the risk of bias results are shown in the Supplemental Materials S4.

All the evidence was collected in summary of findings tables. Per outcome, the quality of the total body of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (6). Data-extraction, risk of bias assessment and GRADE assessment were independently performed by two reviewers (DK, DS). Discrepancies were resolved by consensus.

2.6 Additional evidence selection and quality assessment

In anticipation of a lack of studies in childhood cancer patients, we searched for additional evidence. Guidelines on RBC transfusions in children without cancer or adults with cancer were searched in PubMed, Joint United Kingdom Blood Transfusion Services Professional Advisory Committee (JPAC), NICE, GIN, ASCO, iPOG and Dutch Federation of Medical Specialists (FMS). The quality of the guidelines was assessed according to the AGREE II (5) method. A guideline was eligible for inclusion if the AGREE II-score was 4 or higher (Supplemental Materials S5). The included single studies in those guidelines served as the evidence base for extrapolation. In addition, in case of lack of evidence, recommendations from high-quality guidelines are adopted.

2.7 Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations (6). Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert opinion). For all these expert opinion recommendations, evidence was considered 'weak', i.e. there was no topic in which expert opinion led to 'strong' recommendations. Final recommendations were unanimously supported by all panel members.

The GRADE terminology for evidence-based guidelines was used, such as 'we suggest' or 'we recommend' (6). For the expert-based recommendations, the terminology from a recent paper published by the international Pediatric Oncology Guidelines in supportive care (iPOG) Network (7) was used. The wording 'we believe' was used to emphasize that these recommendations are based on expert opinion and group consensus. A color-coding system was used to improve understandability and to emphasize the strength of the recommendations (54).

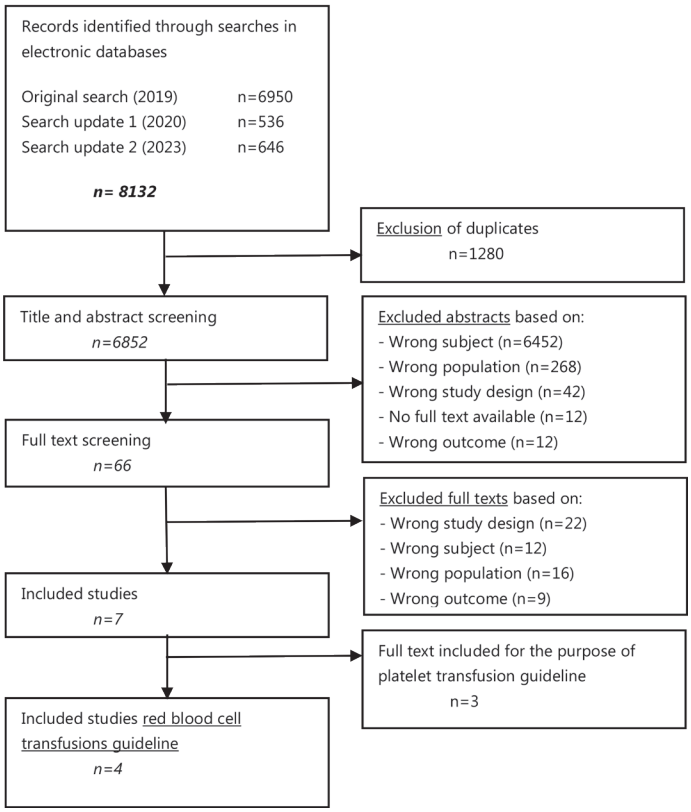
3. RESULTS

In total, 8132 unique citations were identified in initial literature search (September 2019) and two update searches (latest: February 2023), see flowchart.

Four primary studies (3 RCTs, 1 pre-post trial) were included with a total number of 203 participants (see Figure 1 in Supplemental Materials S6). All primary study characteristics and conclusions of evidence are shown in Supplemental Materials S6, including the inclusion and exclusion process. Moreover, seven (non childhood cancer) guidelines were included with a total of 43 different single studies. An overview of the included studies, the conclusions of evidence, the evidence tables and the GRADE assessments can be found in the Supplemental Materials S7. An overview of RBC transfusion recommendations for children and neonates with cancer are presented in Supplemental Materials S8. Within the overview of all recommendations, a color-coding system was used to improve understandability and to emphasize the strength of the recommendations. Below, all recommendations and

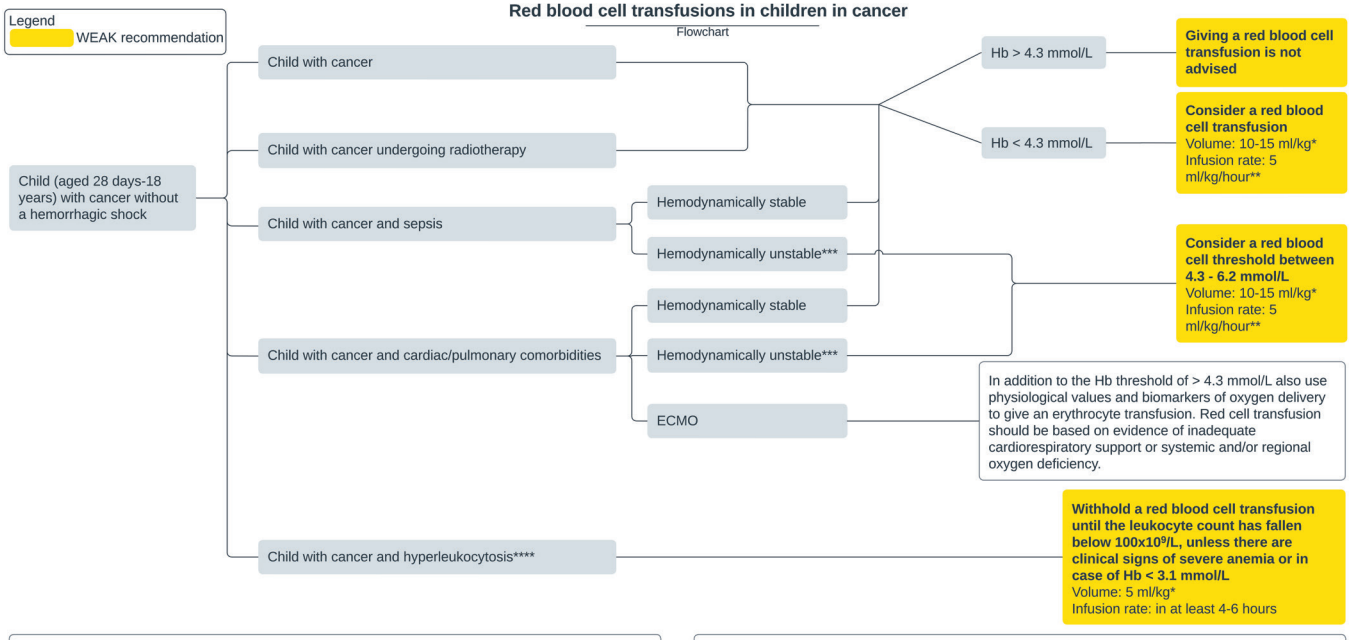
their evidence-to-decision processes are discussed per subject. Given the number of recommendations and the extent of the supporting materials, only conclusions and important considerations of the guideline panel are shown. Full details, including the evidence to decision frameworks, are shown in the Supplemental Materials S9. The results section is divided into the different circumstances in which we recommend a prophylactic RBC transfusion. An overview of the recommendations for scientific research is included in Supplemental Materials S10.

TABLE 1. Flowchart of the inclusion and exclusion process (including the interim updates).



The recommendations on RBC transfusions for children and neonates with cancer are visualized below (figure 1 and 2). These flowchart are also offered separately with measurements of Hb in g/dL.

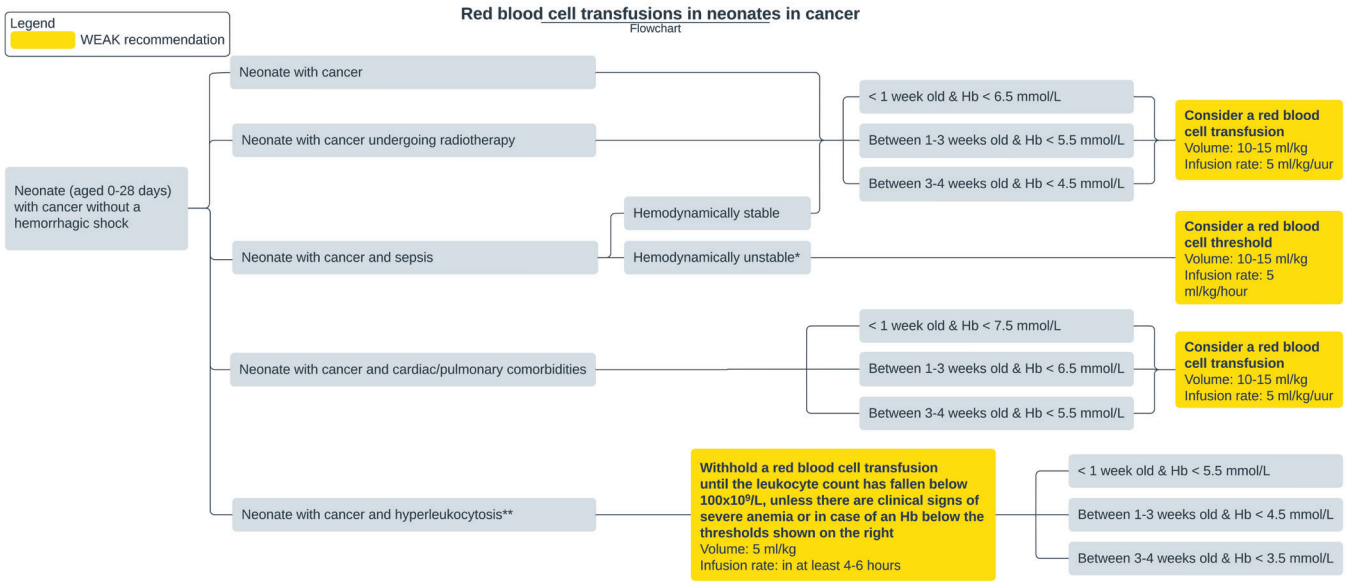
FIGURE 1. Flowchart of RBC transfusion recommendations for children with cancer.



Irradiated red blood cell transfusions in children with cancer
- In case of an HLA related product and donor:
  - a) Transfusion between 1st to 3rd degree relatives of cell-containing blood products;
  - b) HLA-compatible platelet concentrates.
- Granulocytes transfusions.
- Depending on the patient's immune status:
  - a) Intrauterine transfusion until 6 months after the due date;
  - b) Children with congenital combined immune deficiencies (e.g. SCID);
  - c) Acquired immune deficiencies such as:
    - Allogeneic stem cell transplantations up to 1 year after transplantation;
    - Autologous stem cell transplantations up to 6 months after transplantation;
    - After application of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) up to 1 year after transfusion.
  - d) Patients with prolonged T-cell depletion after medication;
    - Fludarabine or other T-cell depleting therapy as indicated by the pharmacist (up to 6 months after discontinuation of the therapy);
- Patients that recieve CAR-T cell therapy from 4 weeks before the leukapheresis until 1 year after the infusion. Unless otherwise described in the study protocol.

* With a maximum of 2 donor units (500-600 ml) per anemic episode.
** With a minimum of 3 hours.
*** E.g., use of inotropes, elevated lactate.
**** In cases where clinically significant hyperleukocytosis requires leukocytapheresis, a RBC transfusion may be utilized as replacement fluid to correct anemia in an isovolemic and controlled manner.

FIGURE 2. Flowchart of RBC transfusion recommendations for neonates with cancer.



* E.g., use of inotropes, elevated lactate.
** In cases where clinically significant hyperleukocytosis requires leukocytapheresis, a RBC transfusion may be utilized as replacement fluid to correct anemia in an isovolemic and controlled manner.

3.1 Prophylactic red blood cell transfusion in general

3.1.1 Prophylactic red blood cell transfusion in children with cancer

Recommendation 1.1.1. We suggest a hemoglobin (Hb) threshold of 4.3 mmol/L for RBC transfusion in children with cancer. (WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 1.1.2. We suggest <u>against</u> an Hb threshold of 3.7 mmol/L for RBC transfusion in children with cancer. (WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 1.1.3. We recommend <u>against</u> an Hb threshold of 3.1 mmol/L or lower for RBC transfusion in children with cancer. (STRONG recommendation, VERY LOW QUALITY evidence)
Recommendation 1.1.4. We suggest <u>against</u> an Hb threshold greater than 4.3 mmol/L for RBC transfusion in children with cancer. (WEAK recommendation, VERY LOW QUALITY evidence)

Evidence to decision. The comparison of an Hb threshold of 4.3 mmol/L to an Hb threshold greater than 4.3 mmol/L involved two pediatric oncology studies, one pediatric non-cancer study, and five adult non-cancer studies. Apart from significantly lower costs, there was no significant increased risk for mortality, morbidity, and transfusion-related complications with a threshold Hb of 4.3 mmol/L in comparison to an Hb threshold greater than 4.3 mmol/L in children with cancer (VERY LOW quality of evidence) (13, 14). From the guidelines that included single studies with children in general and adults, one adult study reported significantly higher mortality in the group with an Hb <4.3 mmol/L in comparison to an Hb >4.3 mmol/L in group (8), while another adult study reported significantly lower mortality in the group with an Hb <4.3 mmol/L in comparison to an Hb >4.3 mmol/L in group (12), while 6 other studies pediatric with cancer, pediatric, and adult studies reported no significant difference in mortality (11-16). Based on the available evidence, the panel concluded that there is likely no increased mortality risk. Additionally, two studies demonstrated fewer infections with an Hb threshold of 4.3 mmol/L compared to an Hb threshold greater than 4.3 mmol/L (12, 17). Furthermore, there was no significant increase in quality of life with a higher Hb threshold than 4.3 mmol/L (12). Considering these findings, the guideline panel determined that the benefits of maintaining an Hb threshold of 4.3 mmol/L compared to an Hb threshold greater than 4.3 mmol/L are likely substantial. Therefore, we suggest an Hb threshold of 4.3 mmol/L in children

with cancer. Moreover, no other study reported significant increase in benefits or harms from a higher Hb threshold, such as 5.0 mmol/L (12, 13, 15, 17, 18, 19, 20). Also, the guideline panel considered the potential risks of iron overload and increased costs associated with a higher Hb threshold and therefore, we suggest against adopting an Hb threshold greater than 4.3 mmol/L.

Regarding the comparison of an Hb threshold of 3.7 mmol/L to an Hb threshold greater than 3.7 mmol/L, no pediatric oncology studies were found. However, there were two adult non-cancer studies identified from the included guidelines. Pooled results indicated a significantly increased mortality risk in adult patients with an Hb threshold of 3.7 mmol/L in comparison to an Hb threshold greater than 3.7 mmol/L (8, 11). Similar to the previous comparison, no studies reported any potential benefit from an Hb threshold of 3.7 mmol/L. Therefore, we suggest against an Hb threshold of 3.7 mmol/L.

Regarding the comparison of an Hb threshold of 3.1 mmol/L to an Hb threshold greater than 3.1 mmol/L, no pediatric oncology studies were found. However, there were three adult non-cancer studies and one pediatric non-cancer study identified from the included guidelines. These studies consistently reported significantly higher mortality rates in hospitalized adults and children with an Hb of 3.1 mmol/L (8-11). Despite the low level of evidence, which is mainly derived from adult studies, the guideline panel strongly advised against offering this option due to the higher mortality rates.

3.1.2 Prophylactic red blood cell transfusion in neonates with cancer

Recommendation 1.2.1. We suggest an Hb threshold of 6.5 mmol/L for RBC transfusion in neonates with cancer when they are less than 1 week old. (WEAK recommendation, VERY LOW QUALITY evidence)

Recommendation 1.2.2. We suggest an Hb threshold of 5.5 mmol/L for RBC transfusion in neonates with cancer when they are between 1 and 3 weeks old. (WEAK recommendation, VERY LOW QUALITY evidence)

Recommendation 1.2.3.We suggest an Hb threshold of 4.5 mmol/L for RBC transfusion in neonates with cancer when they are between 3 and 4 weeks old. (WEAK recommendation, VERY LOW QUALITY evidence)

Evidence to decision. The incidence of cancer in neonates is exceedingly low. Despite this, it is crucial to provide recommendations for this specific patient group. Unfortunately, no pediatric oncology studies were identified to inform the guideline panel's decision. However, the Dutch Association of Medical Specialists (FMS) (21) developed a high-quality guideline addressing this matter, receiving an AGREE II-score of 6 out of 7. They provided recommendations primarily based on studies conducted in very low birth-weight infants (birth weight of 1500 grams or less). Although evidence specific to full-term and late-premature neonates (gestational age ≥ 32 weeks) is lacking, the FMS has adopted these thresholds for neonates in general. Considering the lack of evidence, the guideline panel decided to adopt the recommendations regarding neonates with cancer from the guideline of the FMS (2019).

3.2 Prophylactic red blood cell transfusion - sepsis

3.2.1 Prophylactic red blood cell transfusion in children with cancer during sepsis

Recommendation 2.1.1. We suggest an Hb threshold of 4.3 mmol/L for RBC transfusion in children with cancer during sepsis who are hemodynamically stable.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 2.1.2. We believe that for hemodynamically unstable children with cancer during sepsis and evidence of oxygen deficiency (e.g., use of inotropes, elevated lactate), an Hb threshold that ranges between 4.3 mmol/L and 6.2 mmol/L should be considered.
(EXPERT opinion)

Evidence to decision. Regarding children with cancer during sepsis who are hemodynamically stable, one pediatric non-cancer study and one adult non-cancer study were identified. Based on this limited evidence, there is no suggestions that there is an increased risk for mortality or morbidity with an Hb threshold of 4.3 mmol/L in comparison to an Hb threshold greater than 4.3 mmol/L in children and adults with sepsis who are clinically stable (18, 22). Furthermore, no studies reported any significant potential benefit from an Hb threshold greater than 4.3 mmol/L (18). Therefore, we suggest an Hb threshold of 4.3 mmol/L in children with cancer during sepsis who are hemodynamically stable. However, in hemodynamically unstable children with cancer during sepsis and evidence of oxygen deficiency (e.g., use of inotropes, elevated lactate), it is suggested to consider an Hb threshold ranging

between 4.3 mmol/L and 6.2 mmol/L as part of a comprehensive approach to improve oxygen delivery for children with unstable non hemorrhagic shock and evidence of oxygen debt (WEAK recommendation) (23).

3.2.2 Prophylactic red blood cell transfusion in neonates with cancer during sepsis

Recommendation 2.2.1. We suggest an Hb threshold of 6.5 mmol/L for RBC transfusion in neonates with cancer during sepsis when they are less than 1 week old.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 2.2.2. We suggest an Hb threshold of 5.5 mmol/L for RBC transfusion in neonates with cancer during sepsis when they are between 1 and 3 weeks old.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 2.2.3. We suggest an Hb threshold of 4.5 mmol/L for RBC transfusion in neonates with cancer during sepsis when they are between 3 and 4 weeks old.
(WEAK recommendation, VERY LOW QUALITY evidence)

Evidence to decision. These were no studies found on neonates with cancer during sepsis. There was no suggestion for an increased risk for mortality and morbidity in hemodynamically stable children and adults with sepsis with an Hb threshold of 4.3 mmol/L in comparison to an Hb threshold greater than 4.3 mmol/L (3.2.1 “Children with cancer during sepsis”) (18, 22, 23). Therefore we concluded that children with sepsis do not derive additional benefits from a higher Hb threshold compared to children without sepsis. Based on these findings, and the absence of direct evidence in neonates with sepsis, the guideline panel determined that the recommendations for neonates with cancer can be applied to neonates with cancer during sepsis as well (3.1.2 “Neonates with cancer”).

3.3 Prophylactic red blood cell transfusion - radiotherapy

3.3.1 Prophylactic red blood cell transfusion in children who undergo radiotherapy

Recommendation 3.1.1. We believe an Hb threshold of 4.3 mmol/L for RBC transfusion should be maintained in children with cancer who undergo radiotherapy
(EXPERT opinion)

Evidence to decision. No studies specifically addressing children with cancer undergoing radiotherapy were identified. Several other studies including adults with cancer concluded that there was no improvement in outcomes with an Hb threshold greater than 4.3 mmol/L (24, 25, 26, 27). Therefore, we suggest an Hb threshold of 4.3 mmol/L for RBC transfusion in children with cancer who undergo radiotherapy.

3.3.2 Prophylactic red blood cell transfusion in neonates who undergo radiotherapy

Recommendation 3.2.1. We believe an Hb threshold of 6.5 mmol/L for RBC transfusion should be maintained in neonates with cancer who undergo radiotherapy when they are less than 1 week old.
(EXPERT opinion)

Recommendation 3.2.2. We believe an Hb threshold for RBC transfusion of 5.5 mmol/L should be maintained in neonates with cancer who undergo radiotherapy when they are between 1 and 3 weeks old.

(EXPERT opinion)
Recommendation 3.2.3. We believe an Hb threshold for RBC transfusion of 4.5 mmol/L should be maintained in neonates with cancer who undergo radiotherapy when they are between 3 and 4 weeks old.
(EXPERT opinion)

Evidence to decision. No specific studies in neonates with cancer were identified. For the considerations of the recommendations we refer to 3.3.1 “Children with cancer who undergo radiotherapy”.

3.4 Prophylactic red blood cell transfusion - cardiac and pulmonary comorbidities

3.4.1 Prophylactic red blood cell transfusion in children with cancer with cardiac and/or pulmonary comorbidities

Recommendation 4.1.1. We suggest an Hb threshold of 4.3 mmol/L for RBC transfusion in children with cancer and cardiac and/or pulmonary comorbidities.
(WEAK recommendation, VERY LOW QUALITY evidence)

Recommendation 4.1.2. We believe that in case of a hemodynamically unstable child with cancer and pulmonary and/or cardiac comorbidities (e.g., use of inotropes, elevated lactate) a higher Hb threshold can be considered.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 4.1.3. For children on ECMO:

- ***In critically ill children on ECMO, there is insufficient evidence to recommend a specific RBC transfusion decision-making strategy using physiologic-based metrics and biomarkers.***
- ***In critically ill children on ECMO, we believe in using physiologic metrics and biomarkers of oxygen delivery in addition to Hb concentration to guide RBC transfusion. Administration of a RBC transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery.***

(EXPERT opinion)

Evidence to decision. No pediatric oncology studies were identified. Two pediatric non-cancer studies, and one adult non-cancer study were identified. The evidence gathered from these studies indicated that there is no increased risk for mortality, morbidity and hospital admission with an Hb threshold of 4.3 mmol/L compared to an Hb threshold greater than 4.3 mmol/L in children and adults with cardiac and pulmonary comorbidities (8, 18, 28). Studies comparing higher restrictive Hb thresholds (such as 5.0 mmol/L or 5.6 mmol/L) also did not report significant better outcomes regarding mortality, morbidity, quality of life, and admission to hospital (20, 29, 30). Therefore, the guideline panel decided to suggest an Hb threshold of 4.3 mmol/L in children with cancer and cardiac and pulmonary comorbidities. For hemodynamically unstable children with cancer and pulmonary and/or cardiac comorbidities, such as those requiring inotropes or exhibiting elevated lactate levels, considering an Hb threshold ranging between 4.3 mmol/L and 6.2 mmol/L. Regarding children on Extracorporeal Membrane Oxygenation (ECMO) the guideline panel decided to adopt the recommendations stated above from the Valentine (2018) guideline (31), AGREE-II score 5 out of 7.

3.4.2 Prophylactic red blood cell transfusion in neonates with cancer with cardiac and/or pulmonary comorbidities

Recommendation 4.2.1. We suggest an Hb threshold of 7.5 mmol/L for RBC transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are less than 1 week old.
(EXPERT opinion)
Recommendation 4.2.2. We suggest an Hb threshold of 6.5 mmol/L for RBC transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are between 2 and 3 weeks old.
(EXPERT opinion)
Recommendation 4.2.3. We suggest an Hb threshold of 5.5 mmol/L for RBC transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are between 3 and 4 weeks old.
(EXPERT opinion)

Evidence to decision. No pediatric oncology studies addressing this clinical question were found. However, the Dutch Association of Medical Specialists (FMS) (21) developed recommendations primarily based on studies conducted in very low birth-weight infants (birth weight of 1500 grams or less) who required respiratory support. Although evidence specific to full-term and late-premature neonates (gestational age ≥ 32 weeks) is lacking, the FMS has adopted these thresholds for neonates requiring respiratory support. Taking this into account, the guideline panel decided to adopt the recommendations regarding neonates with cancer and pulmonary and/or cardiac comorbidities from the guideline of the FMS (2019).

3.5 Prophylactic red blood cell transfusion - hyperleukocytosis

3.5.1 Prophylactic red blood cell transfusion in children with cancer during hyperleukocytosis

Recommendation 5.1.1. In children with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint until the number of leukocytes has fallen below 100 x 109 /L or in the presence of clinical symptoms of hyperleukocytosis
Recommendation 5.1.2. In children with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint, unless there are severe clinical signs of anemia or in case of an Hb below 3.1 mmol/L.

Recommendation 5.1.3. If needed, transfuse with a maximum of 5 ml/kg/4-6 hours. (EXPERT opinion)

Evidence to decision. No specific studies addressing this topic were identified. However, a study focusing on the management of hyperleukocytosis in children and adults with cancer provided relevant information. According to this study, the use of RBC transfusions in such cases should generally be avoided due to the potential increase in blood viscosity and the associated risk of leukostasis development or exacerbation, unless the patient exhibits symptoms of anemia (32). The guideline panel decided to take this into consideration in order to make a recommendation based on expert opinion. However, in cases where clinically significant hyperleukocytosis requires leukocytapheresis, a RBC transfusion may be utilized as replacement fluid to correct anemia in an isovolemic and controlled manner (33).

3.5.2. Prophylactic red blood cell transfusion in children and neonates with cancer during hyperleukocytosis

Recommendation 5.2.1. In neonates with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint until the number of leukocytes has fallen below 100 x 109 /L or in the presence of clinical symptoms of hyperleukocytosis.

Recommendation 5.2.2. In neonates with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint unless there are severe clinical signs of anemia or in case of an Hb below 5.5 mmol/L in neonates with cancer when they are less than 1 week old.

Recommendation 5.2.3. In neonates with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint unless there are severe clinical signs of anemia or in case of an Hb below 4.5 mmol/L for RBC transfusion in neonates with cancer when they are between 1 and 3 weeks old.

Recommendation 5.2.4. In neonates with cancer and hyperleukocytosis, we believe that a RBC transfusion should be given with restraint unless there are severe clinical signs of anemia or in case of an Hb below 3.5 mmol/L for RBC transfusion in neonates with cancer when they are between 3 and 4 weeks old.

Recommendation 5.2.5. If needed, transfuse with a maximum of 5 ml/kg/4-6 hours. (EXPERT opinion)

Evidence to decision. No specific studies addressing this topic were identified. For the considerations of the recommendations we refer to 3.5.1 "Children with cancer during hyperleukocytosis". The RBC thresholds were based on expert opinions.

3.6 Irradiated red blood cell transfusions

3.6.1 Irradiated red blood cell transfusions in children and neonates with cancer

Recommendation 6.1.1. We believe that irradiated blood products should be used in case of an HLA related product and donor:
a) Transfusion between 1st to 3rd degree relatives of cell-containing blood products;
(EXPERT opinion)
Recommendation 6.1.2. We believe that irradiated blood products should be used in case of granulocyte transfusions.
(EXPERT opinion)
Recommendation 6.1.3. We believe that irradiated blood products should be used depending on the patient's immune status:
a) During intrauterine transfusions until 6 months after the due date;
b) Children with congenital combined immune deficiencies (e.g. SCID);
c) Acquired immune deficiencies such as:

- ***Allogeneic stem cell transplantations up to 1 year after transplantation;***
- ***Autologous stem cell transplantations up to 6 months after transplantation;***
- ***After application of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) up to 1 year after transfusion.***

(EXPERT opinion)
Recommendation 6.1.4. We believe that irradiated blood products should be used in case of patients with prolonged T-cell depletion after medication:
a) Fludarabine or other T-cell depleting therapy as indicated by the pharmacist (up to 6 months after discontinuation of the therapy);
Recommendation 6.1.5. We believe that irradiated blood products should be used in case of patients that receive CAR-T cell therapy from 4 weeks before the leukapheresis until 1 year after the infusion. Unless otherwise described in the study protocol.
(EXPERT opinion)

Evidence to decision. There were no pediatric oncology studies identified. However, the Dutch Association of Medical Specialists (FMS) (21) developed a high-quality

guideline addressing this matter. The guideline drew its recommendations from a study of Kopolovic (2015) (34) and a survey amongst hemovigilance organizations worldwide. Considering the lack of evidence, the guideline panel decided to adopt the recommendations regarding irradiated blood products from the guideline of the FMS (2019) (21). The guideline panel added the indication for the use of CAR-T cells, based on the recommendations in the current study protocol (the pharmaceutical company that creates the CAR-T cells prescribed this period of irradiated blood products in a research context).

3.7 Low or high-volume red blood cell transfusions

3.7.1 Low or high-volume red blood cell transfusions in children with cancer

Recommendation 7.1.1. We suggest a transfusion volume of 10-15 ml/kg in children with cancer.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 7.1.2. We suggest against a transfusion volume of 20 ml/kg or higher in children with cancer.
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 7.1.3. We suggest a transfusion volume with a maximum of 2 donor units (between 500-600 ml) per anemic episode.
(EXPERT opinion)

Evidence to decision. No pediatric oncology studies were identified. In comparing a RBC transfusion volume of 10 ml/kg to a volume higher than 10 ml/kg, no studies including children were identified. However, one study involving neonates without cancer was identified. The limited evidence available suggests that there is no significant increase in morbidity associated with a transfusion volume of 10 ml/kg compared to a volume higher than 10 ml/kg (35). Regarding the comparison of a volume of 15 ml/kg to a volume higher than 15 ml/kg, again no studies including children were identified. However, two studies with neonates were identified. The available evidence suggests that there is no significant increase in mortality or morbidity associated with a transfusion volume of 15 ml/kg compared to a volume higher than 15 ml/kg (36, 37). One study involving children without cancer compared a RBC transfusion volume of 20 ml/kg to a volume higher than 20 ml/kg (38). The limited evidence available suggested that there is no significant difference in terms of mortality or morbidity when comparing a transfusion volume of 20 ml/kg to a

volume higher than 20 ml/kg (38). Additionally, the expert panel considered that a lower transfusion volume leads to reduced risk of volume overload and deemed this option as probably acceptable for all stakeholders. Therefore, we suggest in favor of a transfusion volume of 10-15 ml/kg, and suggest against the use of a volume of 20 ml/kg. The expert panel advises transfusing with a maximum of 2 donor units per anemic episode, which corresponds to a volume between 500-600 ml, based on shared expert opinion.

3.7.2 Low or high-volume red blood cell transfusions in neonates with cancer

Recommendation 7.2.1. We suggest a transfusion volume of 10-15 ml/kg in neonates with cancer
(WEAK recommendation, VERY LOW QUALITY evidence)
Recommendation 7.2.2. We suggest against a transfusion volume of 20 ml/kg or higher in neonates with cancer
(WEAK recommendation, VERY LOW QUALITY evidence)
Evidence to decision. For the considerations of the recommendations we refer to 3.7.1. “Low or high-volume RBC transfusion in children with cancer”.

3.8 Infusion rates of red blood cell transfusions

3.8.1 Infusion rates of red blood cell transfusions in children with cancer

Recommendation 8.1.1. We believe that the infusion rate of a RBC transfusion should be 5ml/kg/hour in children with cancer, with a minimum of 3 hours.
(EXPERT opinion)

Evidence to decision. There are no studies regarding infusion rates. However, JPAC (39) has provided a recommendation for an infusion rate of 5 ml/kg/hour in children, based on consensus, AGREE II-score of 4 out of 7. The guideline panel decided to adopt this recommendation, but added to the advice that a transfusion should take at least 3 hours, based on expert-opinions

3.8.2 Infusion Rates Of Red Blood Cell Transfusions In Neonates With Cancer

Recommendation 8.2.1. We believe that the infusion rate of a RBC transfusion should be 5ml/kg/hour in neonates with cancer.
(EXPERT opinion)

Evidence to decision. No specific studies were identified regarding infusion rates. However, the Dutch Association of Medical Specialists (21) has provided a recommendation for an infusion rate of 5 ml/kg/hour in neonates, based on consensus. The guideline panel decided to adopt this recommendation.

4. DISCUSSION

This clinical practice guideline comprises recommendations, in line with the GRADE methodology (6), regarding prophylactic RBC transfusions in children and neonates with cancer and has the potential to provide valuable guidance for clinicians in daily practice and contribute to improving quality of life for children and neonates with cancer worldwide.

The most notable limitation of this CPG is the substantial lack of evidence regarding appropriate thresholds for prophylactic RBC transfusions in children and neonates with cancer. To address this limitation, we conducted comprehensive and extensive literature searches, including exploration of RBC transfusion guidelines for children without cancer and (young) adults with cancer. Unfortunately the yield of relevant evidence was still remarkably low. However, the consensus among the guideline panel was unanimous in their determination to come up with recommendations even in the absence of adequate evidence from the literature. This was deemed essential, as healthcare providers in daily practice rely on practice guidelines to guide decision making regarding transfusions in their patients. Consequently, the guideline panel incorporated recommendations from existing high quality guidelines regarding RBC transfusions for adults with cancer and children in general in order to formulate recommendations based on the best available evidence. When such guidelines were unavailable, recommendations were constructed through expert consensus. We firmly believe that the incorporation of expert opinions serves as a valuable asset in enhancing clinical practice and should find more frequent implementation in the development of guidelines when evidence gaps exist*. Nevertheless, with prophylactic RBC transfusions being administered so frequently in children and neonates with cancer and the potential serious consequences of anemia, it is abundantly clear that further research in this field is imperative.

A second limitation of our guideline is the composition of the guideline panel, which consisted of experts from a national level. While this panel provided valuable insights and expertise, it is important to consider the applicability of this guideline to local contexts. However, we have provided extensive supplemental materials and evidence-to-decision frameworks that allow clinicians to assess the relevance and applicability of the guidelines to their specific settings. This approach empowers clinicians in other countries to make informed decisions based on the available evidence and adapt the recommendations as needed for their local context.

Implementation of this evidence-based guideline holds promise for enhancing the quality of life in children and neonates with cancer. With these evidence- and expert-based recommendations, we have endeavored to provide comprehensive and practical guidance. To ensure transparency, we have meticulously documented all the considerations in the evidence-to-decision frameworks. The inclusion of evidence-to-decision frameworks in this guideline provides clinicians with a valuable tool to assess the individual benefits and harms associated with different treatment options for each child and are making the decision-making process transparent. We sincerely hope that this guideline serves as a valuable tool in balancing the benefits and risks, promoting cautiousness and restrictiveness where appropriate.

In conclusion, through the effective implementation of the recommendations outlined in this CPG, the guideline panel aims to improve care provided to children and neonates with cancer and contribute to enhancing their quality of life. These recommendations hold significant importance in current clinical practice, and we hope that the lack of evidence in this area will serve as a stimulus for further research efforts. We are currently developing indicators to monitor the impact of this guideline and to facilitate continuous evaluation and improvement of care in this field.

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6

INCIDENCE AND CLINICAL COURSE OF INFLUENZA INFECTIONS IN CHILDREN WITH CANCER IN A DUTCH TERTIARY PEDIATRIC ONCOLOGY CENTER

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ABSTRACT

Introduction

Knowledge regarding incidence and clinical course of influenza infections in children with cancer is limited. Our aim was to determine the incidence of laboratory-confirmed influenza infections in children with cancer and to analyze the course, clinical characteristics and complications of these infections.

Methods

In a retrospective cohort study, all children undergoing treatment for cancer in the Princess Máxima Center for pediatric oncology and its shared care centers between October 1st 2018 and July 1st 2020 were screened for confirmed influenza infections. Clinical characteristics of these influenza infections were collected and analysed.

Results

58 children with cancer with a laboratory-confirmed influenza infection were identified. Given the Dutch incidence of childhood cancer (1195 diagnoses during study period), this accounts for an incidence of 4.9 influenza infections per 100 new childhood cancer diagnoses. Mean age at influenza diagnosis was 6.0 years (± 4.7 SD). In 22 patients (38%), a total of 35 interruptions or delays in chemotherapy were reported. Complications were seen in four patients (7%) and included two bacterial superinfections, one transient occurrence of drowsiness and one acute otitis media. Twenty-two (38%) patients were admitted to the hospital due to the influenza infection, with neutropenia (neutrophils <0,5 $x10^9$/L) significantly associated with hospitalization (OR 22.74, 95% CI 2.68-193.27, p=0,004). No influenza episode had a severe course or resulted in ICU admission or death.

Conclusion

In our cohort, under current restrictions and guidelines of supportive care, the incidence of influenza infections in children with cancer is relatively low and the course of the infections is generally mild.

INTRODUCTION

There is limited knowledge regarding influenza infections in children with cancer. In otherwise healthy children, influenza infection is an acute, self-limiting disease that usually results in mild, uncomplicated illness with respiratory complaints combined with symptoms such as fever, headache, and malaise (1-3). Earlier studies suggested that children with cancer could experience prolonged viral shedding and are more at risk for complications than otherwise healthy children (4-8).

Immunocompromised children, such as children receiving bone marrow suppressive therapy or hematopoietic stem cell transplantation are reported to bear the highest morbidity and mortality in influenza infections (2, 9). Complications include bacterial superinfections, progression to pneumonia, respiratory failure and increased mortality rates (8, 10). In children undergoing hematopoietic stem cell transplantation mortality associated with respiratory viruses ranges between 10 and 14% (9).

Thus, there might be a more severe course of influenza infections in children with cancer, as they are often immunocompromised, but specific information on children with cancer is lacking. The aim of this study was to determine the incidence of laboratory-confirmed influenza infections in children with cancer in a nationwide cohort and to describe this cohort extensively. We aimed to achieve better notion of the course of the infection in children with cancer, to analyse complications of this infection and to identify factors that might predispose to a severe course of the influenza infection.

METHODS

Study design and population

This retrospective study was performed in a Dutch cohort of pediatric oncology patients. These patients were treated as inpatients or outpatients at the Princess Máxima Center for pediatric oncology and its associated shared care hospitals, between October 1st, 2018 and July 1st, 2020. Since the opening of the Princess Máxima Center on May 18th, 2018, all Dutch children with cancer are referred to this hospital for diagnosis and treatment. For the diagnosis or treatment of influenza, patients are seen either in the Princess Maxima Center, or in one of the shared care centers.

In both cases, notes are written in the central electronic patient file of the Princes Maxima Center. Therefore, this cohort included all Dutch patients being treated for cancer in two consecutive influenza seasons (2018/2019 and 2019/2020).

Children aged 0-18 years with cancer (any type) receiving anti-cancer therapy were included. Children with non-oncological disease such as Fanconi anemia, myelodysplastic syndrome or aplastic anemia were excluded. All patients gave informed consent. The study was approved by the internal Biobank and Data Access Committee (PMCLAB2020.104) and the need for additional ethical approval was renounced.

Influenza infections

Laboratory-confirmed influenza infection was defined as identification of influenza using molecular diagnostics (polymerase chain reaction assays) in respiratory specimens (nasopharyngeal swab/ wash or tracheal aspirate). If a patient tested positive for an influenza infection multiple times, but with the same strain and in the same influenza season, these tests were considered to account for one influenza infection.

The patients with positive influenza tests were identified in two ways. First, all patients with a positive influenza test carried out in the Princess Máxima Center between October 2018 and July 2020 were identified from the records of the local Department of Medical Microbiology. Secondly, in order to include patients with their influenza infection diagnosed in a shared care hospital, the electronic patient records of all patients undergoing anti-cancer treatment in the Princess Máxima Center were string-searched for relevant terms, e.g. 'influenza' or anti-influenza drugs (oseltamivir, Tamiflu). The identified medical records where then closely reviewed in search of a laboratory confirmed influenza test and if necessary, shared care hospitals were contacted for additional information.

Incidence and demographics

Electronic patient records of children with laboratory-confirmed influenza infections were reviewed for demographic information and clinical course of infection. The exact overall number of children with cancer undergoing anti-cancer treatment during the study-period could not be retrieved as this was not documented. For this reason, the incidence was determined using the register for new cancer diagnoses

in the Netherlands from October 2018 till March 2020, which we retrieved from the Dutch Childhood Oncology Group (DCOG).

Statistical analyses

The differences between groups were evaluated using the Student's *t*- and Chi-squared ($\chi 2$) tests for continuous and categorical variables, respectively. Univariate and multivariate logistic regression analyses were used to identify factors that correlate with the need of hospitalization during an influenza infection. Possible factors tested were age, sex, diagnosis, treatment intensity, anemia and neutropenia and their odds ratio (OR) and 95% confidence interval (CI) were reported (11). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 26.0 for Windows (IBM Corp, Armonk, NY, USA).

RESULTS

We identified 67 influenza infections. Nine of these infections were excluded, as three children had two positive tests that counted as one influenza infection (with a maximum number of days between the positive test of 20 days) and six children had non-oncological diagnoses. Thus, 58 children with cancer and a laboratory-confirmed influenza infection were included. A flowchart of the inclusion process is shown in figure 1 in the appendix.

Incidence

A total of 1195 patients were diagnosed with childhood cancer from October 2018 till July 2020. As we identified 58 patients with influenza infections during this period, this accounted for an incidence of 4.9 influenza infections per 100 new childhood cancer diagnoses. Patients with hematological malignancies had a statistically significant higher incidence of influenza infections with 8.2 per 100 new diagnoses of hematological malignancies compared to neuro-oncology patients or patients with a solid tumor with in both groups 2.8 per 100 new diagnoses ($\chi 2(1)=9.6$; p=0.002 and $\chi 2(1)=12.0$; p=0.001 respectively). Patients with hematological malignancies were significantly more likely to get an influenza infection (OR=3.1 CI 1.78-5.33, p<0.001) compared to other childhood cancer patients (see table 1).

Table 1. Incidence per diagnosis group

	New diagnoses	Influenza infections	Incidence per 100 new diagnoses
Overall	1195	53	4,9/100 new diagnoses
Per Specific Diagnosis Group			
Hemato-oncology	451	37	8,2/100 new diagnoses
Neuro-oncology	319	9	2,8/100 new diagnoses
Solid tumors	425	12	2,8/100 new diagnoses

Patient characteristics

Patients acquired an influenza infection at a mean age of 6.0 years (SD ±4.7 years), with a median of 248 days (range 6-1076 days) between date of diagnosis and date of influenza infection. Most influenza infections were seen in males (55%). Five patients (9%) received a hematopoietic stem cell transplantation (HSCT) before diagnosis of influenza with a median of 193 days (range 33-494 days) between HSCT and influenza infection (see table 2). The most common symptoms of influenza were fever (86%), cough (81%) and rhinitis (79%). Symptoms did not differ significantly in patients with different cancer diagnoses groups. Fifty patients (86%) were treated with oseltamivir (Tamiflu®), as is standard policy as documented in our nationwide guideline on children with cancer. A complete overview of the demographic and clinical characteristics of patients with an influenza infection can be found in table 1A-B, appendix 1.

Laboratory characteristics

Patients had a median hemoglobin (Hb) level of 6.3 mmol/L (range 3.7-9.3 mmol/L), and 24 (41%) of patients were anemic (defined as an Hb <6 mmol/L for patients under 6 years, and an Hb < 6.5 mmol/L for patients 6 years and older) during their influenza infection. Patients had a median of 1.3 x10^9/L (range 0.0-14.3x10^9/L) neutrophils, and 14 (24%) of the children were in neutropenia (defined as neutrophils <0.5x 10^9/L or when neutrophils are not available leukocytes <1 x 10^9/L) at time of their influenza infection. CRP differed greatly with a median of 7.3 mg/L and a range of less than 0.5 to 147 mg/L (table 2).

Table 2. Patient Characteristics

Patient characteristics (n=58)		
Sex	**n**	**%**
Male	32	55
Female	26	45
Mean age at cancer diagnosis	**mean**	**range**
	6.0	1-16
Mean age at influenza infection	**mean**	**range**
	6.8	1-16
Days between cancer diagnosis and influenza infection	**median**	**range**
	248	6-1076
Cancer diagnosis	**n**	**%**
Hemato-oncology	37	64%
Neuro-oncology	9	16%
Solid tumor	12	21%
Hematopoietic stem cell transplantation (HSCT)	**n**	**%**
	5	9
Days between HSCT and influenza infection	**median**	**range**
	193	33-494
Type of influenza	**n**	**%**
Type A	53	91
Type B	2	3
Unknown	3	6
Laboratory characteristics		
	median	**range**
Hb (mmol/L)	6.3	3.7-9.3
Leukocytes (x10^9/L)	2.5	0.2-15.2
Neutrophils (x10^9/L)	1.3	0.0-14.3
CRP (mg/L)	7.3	<0.5-147.0
	n	**%**
Anemia*	24	41%
Neutropenia#	14	24%

** Anemia: patients up to 6 years: Hb <6 mmol/L and patients of 6 years and older: Hb < 6.5 mmol/L.*
 # Neutropenia: Neutrophils <0.5x 10^9/L or when neutrophils are not available Leukocytes <1 x 10^9/L

Delay in chemotherapy

In 22 patients (38%), a total of 35 interruptions or delays in chemotherapy occurred (table 2, appendix 2). The median number of days of delay in chemotherapy was 7 (range 3-30 days). An interruption of oral 6-mercaptopurine (6MP) occurred most often (n=16), with a median of 8 days (range 2-30 days). In one patient the start of the next phase of treatment was delayed with 4 days (acute lymphoblastic leukemia, 1st consolidation phase, (DCOG protocol ALL-11 protocol 1b).

Complications

Complications occurred in 4 of the 58 influenza infections (7%) and included two bacterial superinfections, one transient occurrence of drowsiness, and one acute otitis media. The bacterial superinfections comprised pulmonary symptoms and a positive blood culture for respectively *Paenibacillus provencensis* and *Streptococcus pneumoniae*.

Severe course of influenza infection

No patient required admission to the pediatric intensive care unit (PICU) because of the influenza infection and there was no mortality attributed to, nor related to influenza infection. Because there was no severe course of an influenza infection, risk factors related to a more severe course of influenza infection could not be explored.

Factors correlated with hospitalization

Twenty-two patients were admitted to the hospital because of the influenza infection. These patients did not differ significantly from non-hospitalized patients in demographic characteristics. However, patients that needed hospitalization did have significantly lower hemoglobin levels (t(50)=3.43, p=0.001) and lower leukocyte counts (t (48)=2.58, p=0.013) (see table 3).

Table 3. Laboratory characteristics in non-hospitalized and hospitalized children with influenza infections

Laboratory characteristics	Mean (±SD) in patients non-hospitalized	Mean (±SD) in patients hospitalized	T-test P value
Hb (mmol/L)	6.72 (±1.08)	5.59 (±1.25)	**0.001**
Leukocytes (x10^9/L)	4.35 (± 3.25)	2.16 (± 2.4)	**0.013**
Neutrophils (x10^9/L)	2.66 (±2.97)	1.12 (±1.78)	0.056
Lymphocytes (x10^9/L calculated*)	1.48 (± 1.13)	1.13(±0.94)	0.278
CRP (mg/L)	20.13 (±26.33)	34.07 (± 42.94)	0.199

***** *An approximation of lymphocytes of patients was calculated by subtracting the neutrophil count from the leukocyte count.*

Patients in neutropenia were significantly more likely to be hospitalized compared to patients that were not in neutropenia in both univariate (OR 20.67, 95% 3.89-109.88, p<0.001) and multivariate (OR 22.74, 95% CI 2.68-193.27, p=0.004) analyses. No other characteristics, such as type of cancer or treatment intensity, were correlated with hospitalization (see table 4).

Table 4. Multivariate analysis of factors predicting the need for hospitalization for influenza infection in pediatric patients receiving treatment for cancer.

Variable X	Complicated course		
	OR*	(95% CI)	P value
Gender			
Male	1		
Female	1,86	(0,396-8,70)	0,43
Age			
0 to <4 years	1		
4 to <10 years	4,46	(0,50-40,13)	0,18
10 to <18 years	6,89	(0,69-69,20)	0,10
Type of cancer			
Neuro-oncology	1		
Hematology-oncology	0,84	(0,05-13,12)	0,90
Solid tumors	2,56	(0,19- 34,99)	0,48
Treatment intensity			
ITR 2	1		
ITR 3	0,48	(0,04-5,67)	0,56
ITR 4	0,16	(0,01-2, 65)	0,20
Normal range Hb	1		
Anemia	2,97	(0,58-15,17)	0,19
Normal range neutrophils Neutropenia*	1		
	22,74	(2,68-193,27)	***0,004***

** Odds ratio in multivariate logistic regression analysis*
In this analysis the number of patients were 52, as in 6 patients the laboratory characteristics were not known. The multivariate analysis for only the demographics factor (with n=58) showed no significant correlations
** Anemia: patients up to 6 years: Hb <6 mmol/L and patients of 6 years and older: Hb < 6,5 mmol/L*
** Neutropenia: Neutrophils <0,5 x 10^9/L or when neutrophils are not available Leukocytes <1 x 10^9/L*

DISCUSSION

In this study, we explored incidence, clinical characteristics and course of influenza infections in children with cancer. We examined 58 influenza infections in children with cancer (incidence 4.9 influenza infections / 100 new oncological diagnoses). Patients with hematological malignancies showed the highest risk to develop an influenza infection compared to other childhood cancer patients. Influenza infections had a mild course, but their impact was notable as chemotherapy was postponed frequently and many patients were hospitalized.

It is difficult to compare incidence to other studies, as the limited studies performed differed in measurements and study size. Previous studies reported incidence rates such as 32%, 5.7 influenza infections per 1000 patients per year, or as 38% of all respiratory viruses (which occurred in 42%) in children with cancer (6, 7). The low incidence rates of our study could be the result of ongoing advances in supportive care, focus on (antiviral) immune- and chemo prophylaxis, and lifestyle of patients. In 2020, the COVID-19 pandemic resulted in a complete lockdown in the Netherlands from March till June. As most influenza infections occur in the winter and the study period was almost completed, the COVID-19 pandemic is expected to have had little effect on this study. Our study showed that patients with hematological malignancies bear significantly more risk for influenza infection compared to patients with other malignancies. Higher incidence in patients with hematological malignancies is also seen in other studies (4, 8). This could have an iatrogenic cause as therapy for haematological malignancies is more aimed at inducing myelosuppression, and consist of a longer extent and intensity than treatment for neuro-oncological diagnoses or solid tumors (12).

In our study, a mild course of influenza infection was seen in children with cancer which was comparable to the course of influenza infections in otherwise healthy children (3). Complications of influenza infections were not frequent in our study and this number of complications is relatively low in comparison to other studies in children with cancer with complication rates up to 17% and 30% (7, 8). During our study period, no patients were admitted to the intensive care. The burden of influenza in our study seems low and one might argue if precautionary measures are needed. However, results of previous studies show that complications of influenza infections in children with cancer can be serious and can lead to admission to the intensive care unit with numbers ranging from 7-17% the (4, 7, 8, 13, 14). Precautionary measures taken in Dutch hospitals, such as relatively rapid use of antiviral agents (86% received oseltamivir) and rapid use of broad-spectrum antibacterial in patients with neutropenia and fever, might explain this difference.

No mortality was related to influenza infection in our study. This is comparable with earlier studies which reported mortality rates between 0% to 5% (7, 8, 13), as most of these studies were not able to single out influenza related mortality.

Chemotherapy was postponed in 38% of cases. Previous studies showed comparable rates of influenza related delay in chemotherapy (4, 8). It remains unclear if this has an adverse influence on cancer outcomes, as we could not yet evaluate the impact on overall survival and anti-cancer treatment outcomes.

We found neutropenia to be correlated with significantly more hospitalization due to influenza infections. This correlation is partially explainable by our guidelines to hospitalize all patients with fever in neutropenia. Yet, an earlier study by Carr et al. did also report neutropenia as a risk factor for serious complications such as hypotension or respiratory failure in patients with influenza infections (8). Thus, as neutropenia in our study is only correlated with hospitalization, it might be a possible factor for identification of patients at risk of a more severe course of influenza infection.

We recognized three important limitations. First, calculation of the incidence of influenza infections per new oncological diagnoses in the Netherlands does not include all children with cancer being treated at a certain timepoint. This results in an overestimation of incidence of influenza infections, as not all children undergoing treatment were taken into an account. Second, this relatively small study has a retrospective design and is thus limited in the detection of clinical symptoms of children included in our study period. For example, children with a possible influenza infection but without a fever could have been not tested and thus left out. In addition, electronic patient records of shared care centers were not thoroughly searched, and thus more influenza infections could have been missed. This may result in an underestimation of the incidence. Third and last, the influenza vaccination status of patients could not be retrieved from their medical records, which is an important limitation of this study. However, in the period studied influenza vaccination was not routinely recommended in the Netherlands, so probably the number of vaccinated children was low (15).

With this retrospective cohort study, we have created an overview of occurrence and clinical impact of influenza infections in children with cancer. Further prospective studies with longer study periods are needed to confirm our findings. If in the future we would be able to find clear risk factors for a severe course of an influenza infection, we could develop a more risk adapted treatment and vaccination plan per patient group or even individual patient, which could reduce burden of influenza infections in children with cancer.

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7

INFLUENZA VACCINATION IN CHILDREN WITH CANCER: A CLINICAL PRACTICE GUIDELINE

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ABSTRACT

Background

For children with cancer, influenza prophylaxis is available through vaccination. This aims to prevent moderate and severe complications of an influenza infection, such as hospitalization, chemotherapy delay, bacterial superinfections, progression to pneumonia or respiratory failure. Specific recommendations about offering influenza vaccination to children with cancer and their families are lacking. Therefore, our aim was to develop a clinical practice guideline (CPG) regarding influenza vaccination in children with cancer and their families.

Methods

A systematic literature review was performed, including dual appraisal of all citations. The GRADE methodology was used to select, extract, assess, and summarize the evidence. A comprehensive multidisciplinary panel was assembled, comprising 17 professionals and a patient representative. Multiple in-person meetings were held to rank outcomes, discuss evidence, complete evidence-to-decision frameworks and formulate recommendations. Final recommendations were unanimously supported by all panel members.

Results

Four controlled studies, including 166 children, formed the evidence base for the recommendations. These studies showed no statistical significant difference in incidence of influenza infections in vaccinated children versus unvaccinated children (2% (n = 2/100) versus 6.8% (n = 11/161), RR 0.29 [0.07-1.29], 1 study, very low quality of evidence), but did report a longer duration of admission to hospital (4 days versus 5.1 days, 1 study, very low quality of evidence) and longer postponement of scheduled chemotherapy (0.5 days versus 4.5 days) in unvaccinated children (1 study, very low quality of evidence). No minor or severe adverse events were reported (2 studies, very low to low quality of evidence). The level of seroprotection ranged from 33-89% (4 studies, very low quality of evidence).

Based on the evidence and expert opinion, we suggest to provide influenza prophylaxis through vaccination to children with cancer yearly, except for children who are undergoing a stem cell transplantation (weak recommendation). For this

group, it is suggested that their caregivers and/or household members receive the yearly vaccination.

Conclusions

In this clinical practice guideline, we provide recommendations regarding influenza vaccination in children with cancer. With these recommendations we provide guidance for clinicians, children and parents, and contribute to improving quality of life for children with cancer.

1. INTRODUCTION

Respiratory viruses are the most common cause of infections in children and the burden of respiratory viruses in immunocompromised patients is becoming more evident [1, 2]. Influenza, as one of these respiratory viruses, is very common in both the normal population and in children with cancer. Children with cancer are more prone to a symptomatic influenza virus infection [3], however studies concerning the course of infection in children with cancer are lacking. Mostly, the infection seems to have a mild course [1], nevertheless it can have several negative consequences for the child, e.g. hospitalization, interruption of chemotherapy and the need for antibiotics or antiviral medication.

Severe complications of an influenza virus infection in immunocompromised children can occur, such as bacterial superinfections, progression to pneumonia or respiratory failure [4, 5]. To prevent all these negative effects, influenza prophylaxis is available through vaccination. This inactivated vaccine is proven safe, also in children with cancer, and shows a 70-90% efficacy in the general population when the vaccine has a good antigenic match with the epidemic virus [1]. Multiple studies have shown the positive effects of influenza vaccination [6], but specific recommendations about offering the influenza vaccination to children with cancer and their families were lacking.

Therefore, our aim was to develop a clinical practice guideline (CPG) regarding influenza vaccination in children with cancer and their families by first establishing an overview of the available evidence and subsequently formulating recommendations for clinicians, children and their parents.

2. METHODS

2.1 Guideline panel

A comprehensive multidisciplinary panel was assembled, comprising 17 Dutch professionals. The panel included pediatric oncologists, pediatricians, pediatric infectious disease specialists, a clinical microbiologist, a patient representative, nurse specialists, and guideline specialists (see Supplemental Materials S1). Members were invited on the basis of their experience and knowledge on the topic. The core group

(DS, MT, RM, ED, MW, LK, WT, EL) provided all the preparatory documents including methodology, study details and results.

Multiple in-person panel meetings were held to rank outcomes, discuss evidence and formulate recommendations. This guideline is developed in collaboration with a patient and parent representative organization, to make it as applicable, clear, and usable for patients and parents as possible.

2.2 Guideline scope

This CPG regarding influenza vaccination includes recommendations for children with cancer aged 6 months- to 18 years.

2.3 Existing guidelines and clinical questions

Existing international guidelines on influenza vaccination in children with cancer published until October 2023 were searched (GIN [7], NICE [8], IPOG [9], ASCO [10]) and evaluated for the applicability and completeness of these guidelines. In the absence of an applicable evidence-based guideline for children with cancer, clinical questions were defined by the core group. An overview of all clinical questions is shown in the Supplemental Materials S2.

2.4 Search strategy and selection criteria

An extensive systematic literature search (see Supplemental Materials S3) was performed (original search Marc 2020, update October 2023). We searched the electronic databases PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL).

In- and exclusion criteria were defined by the core group. Importantly, all children with cancer aged 6 months to 18 years were included. Studies should have investigated any kind of influenza vaccination. We only included controlled studies, applying a two-step approach by first including randomized controlled trials (RCTs) and in case of insufficient or inconclusive evidence other controlled studies.

2.5 Evidence selection, data extraction and quality assessment

Study identification was performed independently by two reviewers. Initially titles and abstracts were screened, followed by full text assessment. Discrepancies were resolved by consensus.

Detailed information from each eligible study was extracted into evidence tables, including the risk of bias assessment. For RCTs, the Risk of Bias tool v1 from the Cochrane handbook was used [11]. For non-RCT studies, we the risk of bias criteria for observational studies, as described in the Handbook of the International Guideline Harmonization Group [12], with specific aspects of the Cochrane RCT tool [11] (see Supplemental Materials S4). By combining these tools, we aimed to have the best possible tool to assess the risk of bias in our types of studies.

Furthermore, all evidence was outlined in summary of findings tables. The quality of the total body of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [13, 14]. The data-extraction, risk of bias assessment and GRADE assessment were independently performed by two reviewers (DS, MT). Discrepancies were resolved by consensus or a third reviewer (EL).

2.6 Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations [14]. Within this framework, for every clinical question the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert evidence). Final recommendations had to be unanimously supported by all panel members.

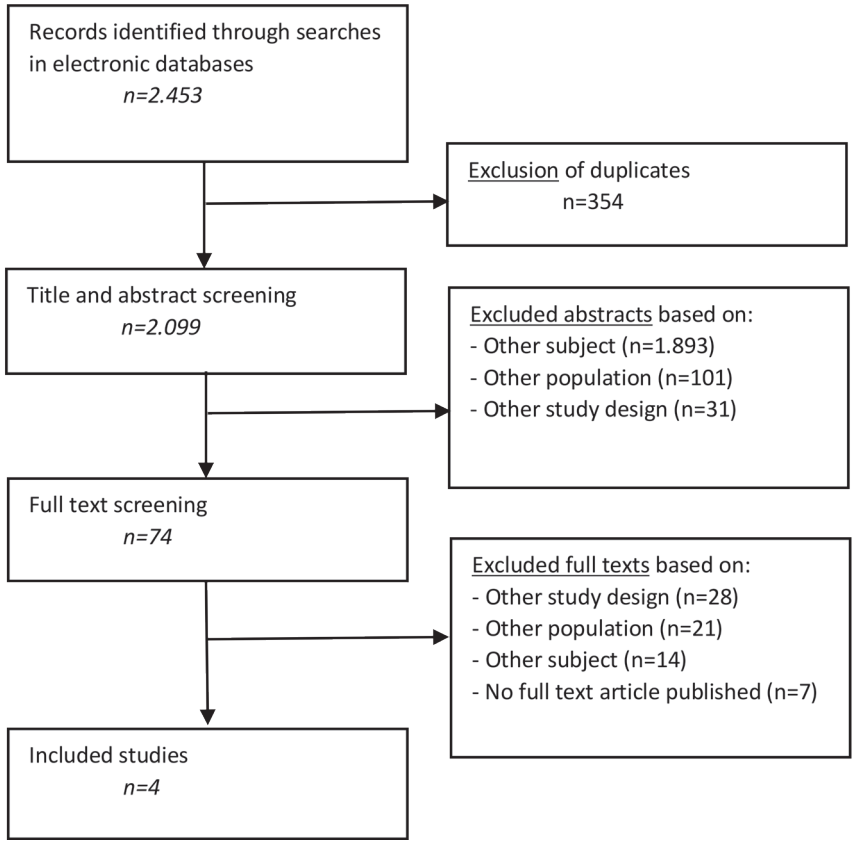
The GRADE terminology for evidence-based guidelines was used, such as ‘we suggest’ or ‘we recommend’[13]. For the expert-based recommendations, the terminology from a paper published by the international Pediatric Oncology Guidelines in supportive care (iPOG) Network [15] was used. The wording ‘we believe’ was used to emphasize that these recommendations are based on expert opinion and group consensus.

Within the overview of all recommendations (table 2), a color coding system was used to improve understandability and to emphasize the strength of the recommendations.

3. RESULTS

In total, 2099 unique citations were identified in the literature search and update (March 2020, October 2023). Four studies (1 RCT and 3 CCT) were included with a total number of 166 participants (see Figure 1). Characteristics of included studies are shown in Supplemental Materials S4 and S7.

Figure 1: Flow diagram study selection



An overview of the included studies, the evidence tables, GRADE assessments and evidence-to-decision frameworks can be found in the Supplemental Materials S5-6. In table 1, the conclusions of evidence are presented. In table 2, a list of all recommendations is shown.

Table 1: Conclusions of evidence related to influenza vaccination in children with cancer

What is the effect of influenza vaccination in children with cancer on influenza-like symptoms, secondary infections and other outcomes compared to children with cancer without influenza vaccination?	
Laboratory-confirmed influenza infections	**Quality of evidence**
No significant differences were reported in the number of influenza infections in vaccinated children with cancer compared to unvaccinated children with cancer.	⊕◯◯◯ (1 study)[17] VERY LOW
Admission to the hospital (influenza related)	**Quality of evidence**
The mean hospital admission length (in days) was lower in vaccinated children with cancer compared to unvaccinated children with cancer. Statistical significance was not reported.	⊕◯◯◯ (1 study) [17] VERY LOW
Delay or dose reduction of anti-cancer treatment	**Quality of evidence**
The mean delay of anti-cancer treatment (in days) was lower in vaccinated children with cancer compared to unvaccinated children with cancer. Statistical significance was not reported.	⊕◯◯◯ (1 study) [17] VERY LOW
Minor adverse events related to influenza vaccination	**Quality of evidence**
Significantly more runny nose or congestion was reported in vaccinated children with cancer compared to unvaccinated children with cancer as a minor adverse event. Note that these patients received the vaccine *intranasally.*	⊕⊕◯◯ (1 study) [16] LOW
There were no significant differences in vomiting, tiredness, headache, fever, cough or sore throat between vaccinated and unvaccinated children with cancer.	⊕⊕◯◯ (1 study) [16] LOW
In vaccinated children with cancer, in 4/100 fever within 24 hours of vaccination was reported.	⊕◯◯◯ (1 study) [17] VERY LOW
Major adverse events related to influenza vaccination	**Quality of evidence**
No serious adverse events occurred in both vaccinated children with cancer and unvaccinated children with cancer. **with intranasal vaccine.*	⊕⊕◯◯ (1 study) [16] LOW
No serious adverse events occurred in both vaccinated children with cancer and unvaccinated children with cancer.	⊕◯◯◯ (2 studies) [17, 18] VERY LOW
Influenza immunity - Seroprotective response (postvaccination HI titre ≥40)	**Quality of evidence**
In vaccinated children with cancer, seroprotection was achieved in 33-63% for H1N1 influenza virus (3 studies [3, 17, 18]), in 38-55% for H3N2 influenza virus (2 studies [3, 17]), and in 41-43% for influenza B-strain virus (2 studies [3, 17]).	⊕◯◯◯ (3 studies) [3, 17, 18] VERY LOW
In intranasal-vaccinated children with cancer, seroprotection was achieved in 78% for H1N1 influenza virus, in 89% for H3N2 influenza virus, and in 44% for influenza B-strain virus.	⊕⊕◯◯ (1 study) [16] LOW

Table 2: Overview of recommendations regarding influenza vaccination for children with cancer

Recommendation	Strength of recommendation	Quality of evidence
We suggest offering the yearly influenza vaccination to children with cancer undergoing anti-cancer treatment.	Weak	**VERY LOW** quality of evidence
We suggest **not** to offer the yearly influenza vaccination to children with cancer who underwent a stem-cell transplantation.	Weak	**VERY LOW** quality of evidence
We suggest offering the yearly influenza vaccination to caregivers and/or household members of children with cancer undergoing cancer-treatment who cannot receive the vaccination themselves.	Weak	**EXPERT OPINION**

*The color coding in this table emphasizes the strength of the recommendation and shows if something is advised (green or yellow) or discouraged (orange or red).

All recommendations and their evidence-to-decision processes are discussed per subject. Given the extent of all recommendations, only conclusions and important considerations of the guideline panel are shown. Full details are shown in the Supplemental Materials S6.

3.1 Recommendation.

We suggest offering the yearly influenza vaccination to children with cancer undergoing anti-cancer treatment, excluding children with cancer who underwent a stem-cell transplantation (see recommendation 3.2). (WEAK recommendation, VERY LOW quality of evidence)

Evidence. Four studies [3, 16-18] reported on the effect of influenza vaccination regarding both clinical effects [17] and levels of seroprotection in children with cancer [3, 16, 18]. One study used an intranasal vaccine (Halasa 2011, [16]), the three other studies used intramuscular vaccination [3, 17, 18].

Seroprotection levels. In general, in these four studies, the level of seroprotection ranged from 33-89%. Specific seroprotection numbers per virus, per study, can be found in Table 1.

Clinical effects. One study (controlled clinical trial (CCT)) [17] showed no statistically significant difference in incidence of influenza in vaccinated children with cancer compared to unvaccinated children with cancer; 2% in vaccinated children (n = 2/100) versus 6.8% (n = 11/161) in unvaccinated children (RR 0.29 [0.07-1.29]) (very low

quality evidence). However, mean length of influenza-related hospital admission in vaccinated children was 4 days as compared to 5.1 days in unvaccinated children (statistical significance not reported). Moreover, the mean delay in delivery of scheduled chemotherapy in vaccinated children was 0,5 day versus 4,5 days in unvaccinated children (statistical significance not reported).

Minor adverse events were reported by the study of Halasa et al. (RCT) [16], i.e. significantly more runny or congested nose after intranasal vaccine. Kotecha et al. (CCT) [17], reported fever within 24 hours in 4 out of 100 vaccinated patients as a minor adverse event. Three studies reporting on severe adverse events, among which Guerin et al. (CCT) [18], identified none [16-18].

Evidence to decision. *Clinical effects.* In one study, there is no effect of vaccination on the occurrence of influenza infection in children with cancer. However, differences are described regarding other factors, such as admission to the hospital and delay of chemotherapy. The guideline panel considers these negative consequences of an influenza infection as very important and it therefore takes a big part in the evidence-to-decision making process.

Seroprotection levels. The included studies [3, 16-18] show that children with cancer are able to achieve an antibody response to vaccination. The guideline panel believes that this level of immunity might protect the child from getting an influenza infection.

Taking everything into account, the panel agreed that the benefits (preventing possible negative consequences of an influenza virus infection) weigh against the potential harms (adverse events) and costs of a yearly influenza vaccination. Therefore, we feel that vaccination is a good way of maximally preventing influenza virus infections. It should be noted that this intervention is an addition to other measures such as hygiene, vaccination of hospital personnel and isolation measures; the vaccine does not replace any of these measures.

3.2 Recommendation.

We suggest <u>not</u> to offer the influenza vaccination to children with cancer who underwent a stem-cell transplantation. (WEAK recommendation, VERY LOW quality of evidence)

Evidence. In the study of Guerin et al [18], 28 children who underwent an HSCT were included. Of those, 14 received the influenza vaccination, which they received after a median of 171 days (IQR 76-336) after HSCT. Seroprotection was achieved in 62,5% (5/8 patients, data were unavailable for 6 patients) and zero major adverse events were described.

Evidence to decision. The guideline panel defines HSCT recipients as a specific subgroup. For this patient group, we suggest not to offer a yearly vaccination, because of their possible inability to make an antibody response as a result of their repressed immune system. We believe the evidence in this study is important and strengthens the idea that vaccinations can be given safely in this patient group, but this study is very small (28 patients), therefore data is too limited and does not report on any clinical effects (as the focus of this study was mostly on seroprotection levels). We did not decide towards vaccination based on this one study, in this vulnerable patient group. More evidence in this specific patient group is necessary to decide towards vaccination or not.

3.3. Recommendation.

We suggest offering the influenza vaccination to caregivers and/or household members of children with cancer undergoing cancer-treatment who cannot receive the vaccination themselves. (WEAK recommendation, EXPERT OPINION)

Evidence to decision. No evidence was identified. However, the guideline panel suggests that caregivers and/or household members of children with cancer should receive an influenza vaccination. In this way they can optimally protect the patient who cannot receive the vaccination themselves. This 'cocoon' effect was proven effective in neonates and significantly reduced the risk of influenza-related morbidity in one study [19].

In general, it should be noted that this intervention is an addition to other measures such as hygiene, vaccination of hospital personnel and isolation measures; the vaccine does not replace any of these measures.

4. DISCUSSION

In this clinical practice guideline, we provide evidence-based recommendations regarding influenza vaccination in children with cancer. As evidence-based recommendations for this area were lacking, these recommendations provide guidance for clinicians, children and their parents or caregivers and contribute to improving quality of life for children with cancer. With these recommendations, we hope to provide a clear overview and a tool that can be used in clinical practice. To our knowledge, this is the first study to provide such recommendations for children with cancer regarding influenza vaccination.

There remains a lack of evidence regarding influenza vaccination in children with cancer. With only 4 included articles, the yield from the literature search was low, and this is the most important limitation of this evidence-based guideline. However, the guideline panel agreed that we should go to great lengths to avoid not formulating a recommendation, as healthcare providers and patients in daily practice do not have the option to refrain from discussing options and making a decision about care. This directly contributes to improving practice and should be implemented more often in guidelines. In our opinion, further research should focus on the clinical effects of influenza vaccination, both protective and adverse events, in order to further strengthen the evidence base for this recommendation. Also, it would be interesting to see the effect of vaccinating caregivers and house hold members, instead of the child with cancer. This might benefit mainly children undergoing an HSCT. Clearly, more research is needed in this niche.

An important discussion that remains, is how well do seroprotection levels actually protect the child from getting an influenza virus infection. This is a core discussion that was held on the importance of both seroprotection levels and clinical effects. In our opinion future studies should not focus only on serum titers, but also to the clinical effect of the vaccination. We discussed both topics separately in order to address them equally, and in the end balanced all results together. In the evidence-to-decision framework, both topics are addressed separately in order to provide transparency. We believe both topics are important, and the combination of the two resulted in the formulation of the recommendations as they are.

We discussed a couple of specific subgroups in the decision-making process. For children who are too sick to receive the vaccine, we decided that this is a consideration that should be taken for each child individually by their physician. There were no reasons to believe that children in a specific diagnosis group would benefit more from this vaccine. Therefore, we did not make any subgroup considerations based on diagnosis groups.

To our beliefs, implementation of influenza vaccination for children with cancer is feasible. There is a good infrastructure via the general practitioner and costs are reimbursed by healthcare insurance. Although we are aware that in some countries, this may be more difficult, but we do encourage implementation of this guideline.

Implementation of this evidence-based guideline will hopefully contribute to improving the quality of life of children with cancer. In addition, these recommendations will also provide a clear statement towards caregivers, children and parents and provides them guidance. However, it remains important to always consider the benefits and harms for each child individually. We hope this guideline provides an aid in weighing these benefits and harms, balancing cautiousness and restrictiveness.

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8

SUMMARY & GENERAL DISCUSSION

8.1 SUMMARY

This thesis provides insights in guideline development for supportive care in children with cancer, its strengths and limitations and an overview of current gaps in knowledge. Accordingly, it shows the work that was performed by four separate guideline panels resulting in five evidence-based guidelines on important supportive care topics in pediatric oncology. Together, more than 50 evidence-based and expert evidence based recommendations were made in this thesis, of which the most important ones are described in this summary. For all recommendations, I would like to refer to the individual chapters.

Chapter 2 concerns our guideline entitled: 'Topical analgesia during needle-related procedures in children'. During intensive and long-lasting treatments, short-term treatments or emergency care, children often need to undergo minor needle-related procedures (i.e. venapunctures, venous cannulation and puncture of central venous port). From previous studies we knew that the use of local anesthetics before these procedures reduced needle-related pain. There was, however, uncertainty about the type of local anesthetic that should be used, i.e. eutectic mixture of local anesthetics (EMLA®) or tetracaine-containing creams such as Rapydan®. Therefore, a clinical practice guideline (CPG) was developed to establish a comprehensive overview of evidence and to provide recommendations for clinical practice.

Ten randomized controlled trials comprising 1.808 children formed the evidence base for the recommendations. The guideline panel agreed that every child should receive any kind of local anesthetic before undergoing a needle-related procedure and that it should be implemented in their treatment as early as possible. When choosing the kind of local anesthetic, we recommend the use of EMLA® in children who need to undergo a minor needle-related procedure. We suggest the use of tetracaine-containing creams only when rapid cannulation/puncture (i.e. within 30-60 minutes) is required.

Chapter 3 concerns 'Less restrictions in daily life: a clinical practice guideline for children with cancer'. In current clinical practice, recommendations regarding restrictions in daily life for children with cancer are often lacking or not evidence-based. Critically reviewing the evidence and formulating recommendations is therefore of great importance as social restrictions (e.g. limiting swimming, school

attendance, sports) can impair the quality of life of these children severely. Therefore, our aim was to develop a clinical practice guideline for clinicians, children and their parents regarding social restrictions in children with cancer.

Six studies, including 758 children, formed the evidence base for the recommendations. Given the scarcity of the available evidence and various designs of studies in children with cancer, shared expert opinions were utilized. In total, 14 recommendations were formulated of which multiple have resulted in changes in policy and standard of practice in the Netherlands. Topics covered in this guideline are swimming, having pets, visiting the zoo or farm, performing sports or high-velocity events, attending school or kindergarten, and use of public transport.

One of the key recommendations of this guideline is the allowance for children with a tunneled, central venous line to swim, whereas they were not allowed earlier. This restriction had a huge impact on the quality of life of these children, as frequently reported by patients and parents. Quality of life has been a very important argument in balancing the harms and benefits for each recommendation, and was decisive in most discussions.

In **chapters 4 and 5**, guidelines on prophylactic platelet and red blood cell transfusions are outlined. Thrombocytopenia and anemia are frequently occurring adverse effects of anti-cancer treatment, due to bone marrow suppression (resulting in thrombocytopenia and anemia). This may result in potentially severe symptoms in the child and can significantly impair their quality of life. To prevent bleeding due to a low platelet count or severe side effects of anemia, prophylactic platelet or red blood cell transfusions can be administered. A balance needs to be determined between preventing complications due to thrombocytopenia or anemia versus unnecessary transfusions – and its potential adverse effects–, burden for the patients, and costs. It is therefore important that thresholds for prophylactic transfusions are determined.

Prophylactic platelet transfusions (**chapter 4**): in total, three studies including 1.454 children with cancer formed the evidence base for the recommendations. The expert panel assessed all evidence and used this to formulate recommendations in a transparent manner. Given the scarcity of the available evidence, the panel also utilized shared expert opinion to formulate a comprehensive CPG. In total, 22 recommendations were formulated regarding prophylactic platelet transfusions

in children with cancer. Thresholds for prophylactic platelet transfusions were recommended for children with cancer undergoing for example a lumbar puncture or line insertion, and for children with cancer and sepsis.

Prophylactic red blood cell transfusions (**chapter 5**): in total, four studies including 203 children with cancer formed the evidence base for the recommendations. The expert panel assessed all evidence and translated it, transparently, into recommendations. In total, 34 recommendations were made regarding red blood cell transfusions in children and neonates with cancer. For example, thresholds for prophylactic red blood cell transfusions were recommended for children and neonates with cancer and sepsis or undergoing radiotherapy.

Compared to earlier clinical practice, these recommendations led to noteworthy changes in policy. For example, less prophylactic platelet transfusions before insertion of feeding tube or intramuscular injection; and less prophylactic red blood cell transfusions in children with sepsis or undergoing radiotherapy.

In **chapter 6**, an observational study on children with cancer and influenza is described, to strengthen the evidence base for our guideline in **chapter 7**. Knowledge regarding incidence and clinical course of influenza in children with cancer is limited and of importance to the development of the guideline. In this retrospective cohort study, we included all children diagnosed with cancer in the Netherlands between October 1st 2018 and July 1st 2020 who had tested positive for influenza virus in a respiratory sample.

In all, 58 children with cancer with a laboratory-confirmed influenza were identified. Given the Dutch incidence of childhood cancer (1.195 diagnoses during study period), this accounted for an incidence of 4.9 influenza virus infections per 100 newly childhood cancer diagnoses. Median age at influenza diagnosis was 5 years (range 1-16). In 22 patients (38%) a total of 35 interruptions or delays in chemotherapy were reported. Complications were seen in two patients (3%) and included one transient occurrence of drowsiness and one acute otitis media. Twenty-two patients (38%) were admitted to the hospital due to the influenza virus infection, with neutropenia (neutrophils <0,5 x10^9/L) significantly associated with hospitalization. No influenza episode had a severe course, i.e. resulting in ICU admission or death. Thus, in our Dutch cohort of children who underwent treatment for cancer, the incidence of

influenza virus infections was relatively low and the course of the infection was generally mild.

Chapter 7 covers the guideline on influenza prophylaxis by vaccination. In order to prevent complications of an influenza infection such as hospitalization, chemotherapy delay or bacterial superinfections, prophylaxis is available through vaccination. Multiple studies have shown positive effects of influenza vaccination in healthy children and adults, but specific recommendations about offering the influenza vaccination to children with cancer and their families are lacking. Therefore, our aim was to develop a CPG regarding influenza vaccination in children with cancer and their families by establishing an overview of the available evidence and formulating recommendations for clinicians, children and their parents.

Four studies, including 166 children, formed the evidence base for the recommendations. These studies showed no statistical significant difference in incidence of influenza infections in vaccinated children versus unvaccinated children ((n = 2/100) versus 6.8% (n = 11/161), RR 0.29 [0.07-1.29]), but did report a longer duration of admission to hospital (4 days versus 5.1 days) and longer postponement of scheduled chemotherapy (0.5 days versus 4.5 days) in the non-vaccinated patients. No minor or severe adverse events were reported. The level of seroprotection ranged from 33-89%. The guideline development working group suggests to provide influenza prophylaxis through vaccination to children with cancer yearly, except for children who are undergoing a stem cell transplantation. For this group, we suggest that caregivers who are in daily contact with the child with cancer, receive the yearly vaccination.

Remain calm. This is not an attack.

One might easily confuse these recommendations for an attack against doctors' and other caregivers' perspectives or their years of experience. Naturally we do not discard the value of their knowledge and experience. However, it is impossible to keep up with the literature and sometimes studies can be disregarded – too old, too small, etc. We formulated an as solid as possible base for these recommendations and encourage caregivers to take advantage of this, even though they might have recommended parents and children otherwise previously. As said earlier, deviating from a recommendation might be perfectly reasonable for a specific patient. We do not want to impose our will on clinicians; we just want to provide them with insights and guidance for decision making.

Note that there is a difference between weak recommendations ('we suggest') and strong recommendations ('we recommend'). For *strong* recommendations, the evidence or arguments are considered that strong, valuable or important that the guideline panel group strongly recommends (in favor or against) a certain intervention. For weak recommendations, there are arguments in a certain direction, but are not that strong that they are *strongly* recommended. With these, as said earlier, we want to provide insights and guidance. With the right arguments or in specific patients groups, deviating from a recommendation is reasonable.

Personally, I think it is important to emphasize that the recommendations described in this thesis are not set in stone and can be subject to change over the years when new evidence emerges (as guidelines should be). We aim to provide guidance for now, but maybe time and developments in medical care will catch up on us. We will keep on learning and improving, and that means changing the recommendations if necessary.

8.2 TO RECOMMEND OR NOT TO RECOMMEND

For the local anesthetics guideline (chapter 2) and influenza guideline (chapter 7), multiple studies were identified which served as a solid evidence base. After all results were assessed and discussed in the guideline panel, we formulated clear recommendations regarding these topics and they were implemented in clinical care almost directly. It was fairly straight forward, rules were easy and after a couple of moves the game was decided; like a game of checkers.

For the other topics on daily life restrictions and blood transfusions, due to a lack of evidence, this shifted towards expert-evidence based recommendations . While this resulted mostly in suggestions (weak recommendations) rather than strong recommendations, I believe that as a guideline panel we learned the most from this process. Interesting discussions of weighing pros and cons were held, important clinical questions were answered *and* gaps in knowledge were recognized and documented. Also, this gave us the opportunity to involve patient and parent representatives more in the whole process; in prioritizing the topics and in the actual formation of the recommendations. Like in a decent game of "30 Seconds", there was a lot of (*semi*-regulated) discussion, probably more questions than answers were raised, we were set back at times (like throwing '2' in 30 Seconds) and boundaries

were sought (everyone that plays this game can relate). It was a very different form of guideline development, and a very different level of playing this game (the game representing evidence-based guideline development, not 30 Seconds). Throughout this process, we encountered equalities with (features of) games such as 'Risk', the prison in 'Monopoly' or '*Mens Erger Je Niet'* ('Ludo' in English, but that does not cover the joke). However, in the end, everybody won.

All game-metaphors aside (definitely not the last ones – sorry), we did actually learn to play the game. We formed teams with professionals from many different specialties and included parents and patients in order to encompass every angle and point of view. We played by the rules, being the GRADE methodology, while sometimes we had to define new rules to play by (referring to how to handle lack of evidence). Besides, we offer caregivers, patients and parents a transparent view in our playbook. In the end, the guidelines and their recommendations are well-discussed, solid and strong. Guess we all won, then.

That's the name of the game

In this thesis, there is a division into two groups. There were guidelines that had a solid evidence base and for which we made evidence-based recommendations. For the other group, in lack of evidence, we mainly discussed expert opinions and little evidence that was available. If my thesis would have focused on this last group, I would have named my thesis "Fantastic recommendations and where to find them?", "You had me at recommend", or "To evidence and beyond". It was a lovely challenge and pleasure to make that extra step and to formulate recommendations when no evidence was available, to discover and push the boundaries and limitations of traditional evidence-based guideline development (without compromising methodological rigor).

To illustrate the difference in amount of work, amount of consensus or discussion and work-related events, I performed a small retrospective analysis. The comparison entailed guidelines in which we had evidence as a solid base (i.e. influenza guideline and local anesthetics guideline), versus guidelines that consisted mostly of expert opinion recommendations (i.e. restrictions in daily life, prophylactic platelet transfusions). First, significantly more meetings were held (11 versus 3), more emails were sent (288 versus 43) and more discussion was held (not measurable) regarding these topics with little to no evidence. Also, the time investment the whole guideline panel had to put in, was much bigger (22 hours plus reading time versus 6 hours plus

reading time). In conclusion, there was an inverse correlation between work put into the guidelines and the size of its evidence base.

During these 22+ hours, a lot of opinions and arguments were discussed by many different experts. Instead of stating "expert opinion" behind the recommendation, I would like to state: "based-on-very-much-opinions-of-very-experienced-and-smart-doctors-and-healthcare-workers-who-discussed-these-results-endlessly-and-truly-believe-this-is-the-best-way-to-go-and-have-trust-in-this-recommendation-and-really-believe-this-is-the-best-option". 'Expert opinion' feels like one expert *thinks* or *guesses* that this is a good idea and that we just adapted that. On the contrary, behind every 'expert opinion' goes (endless) discussion with the whole working group weighing all the pros and cons. With that, we used the little evidence that was available and if possible extrapolated evidence from other populations or studies combining different expert opinions based on years of experience. You, as a reader, might be familiar with the term 'expert opinion'. However, therefore we deliberately chose to use the term 'expert *evidence'* in our guidelines, in line with the White Paper by Dupuis et al [3]. With this term, we hope to make the recommendations more powerful and emphasize the importance of the experts' opinions. This phrasing emphasizes that expert evidence is also based on knowledge and experience, and not solely based on the opinion of one expert. Therefore, I also plea for the use of 'expert evidence' instead of 'expert opinion' in guideline development.

In addition, I believe we should advocate for making expert evidence more attractive. This, because I think the general opinion of clinicians is that an expert opinion would not be good enough. But in the event that there is not enough evidence, it is the only thing that is left and a second-best option to guide clinicians who take care of a child and need guidance in their work. Taking that hands-on mentality in mind, I think it is important to include expert evidence based recommendations in guidelines rather than provide 'no recommendation possible' in the absence of evidence from clinical studies. Therefore, I plea for these guidelines to be recognized as complete, well-developed and solid – *because* of the expert opinion or expert evidence recommendations and not *despite* of them. Naturally, this should not be mistaken for a plea to disregard evidence from clinical studies. If available, this always comes first.

8.3 STRENGTHS & LIMITATIONS

The overall strengths of the guidelines we developed are: 1) the very consistent and transparent way of assessing the evidence and translating it into recommendations, 2) the involvement of the guideline panel members in the Princess Máxima Center and shared care hospitals in order to stimulate direct implementation (and the commitment of all these guideline panel members who did all this voluntarily), 3) the involvement of parents and patient representatives (elaborated on further in 'Better together') and 4) the addressing of important topics that play a huge role in the life of children with cancer and their parents and have a great impact on their quality of life.

In my opinion, one of the strengths regarding the more expert evidence based guidelines is that we provided recommendations for clinicians in order to 'hands-on' improve their quality of care. We cannot afford *not* to make a recommendation, as healthcare professionals do not have the option to refrain from making a decision about care. You cannot leave them, standing beside a patient, with a 'we have no recommendation due to limited evidence'. We explicitly aimed to provide recommendations even in absence of evidence, to establish good clinical practice and provide clinicians with a comprehensive guideline. The guideline panel agreed to go to great lengths to avoid not formulating a recommendation, and in my opinion, that is the strength of all the guidelines in our work. In our opinion, this directly contributes to improving practice and should be implemented more often in guidelines. In addition, we documented all of our arguments and discussions to provide transparency. We stimulate using these arguments in deciding for the individual patient, and deviating from them – with good reasoning – is completely supported.

Better together

Also, working together with patient and parent representatives is a great strength within the development of these guidelines. Throughout this whole process, it became clear how important these topics are for children and their parents and how it affects their quality of life. This emphasizes the importance of the development of these guidelines and underlines the importance of including patient representatives and their perspective in the guideline panels.

We want to emphasize the role of parent and patient participation and shared decision making in pediatric oncology. The guideline on 'restrictions in daily life' is a perfect example of this. At the outpatient clinic, together with parents and patients, benefits and harms of a restriction can be discussed. The transparency that we offered can be very useful (also in different contexts). Our recommendations provide guidance, but are open for discussion and can be implemented differently per individual patient. These topics, when applicable, may stimulate shared decision making and open the discussion with parents and patients.

Even better ('Limitations')

The fact that there was little to no evidence available is obviously one of the most important limitations of these guidelines. There is a major lack of evidence regarding the effects of restrictions in daily life and blood transfusions in children with cancer. Despite multiple broad literature searches, including other patient groups and adult oncology patients, the yield was low. This is the most important limitation of this evidence-based guideline. Clearly, more research is needed in this niche. Therefore, research gaps were identified and recommendations for further research will be discussed further on.

Also, the guideline panel members were all assembled from Dutch centers and hospitals. This made the communication and implementation easier, but an international guideline panel would have given more support internationally. To cover this, we provided clear insights in our arguments and discussion, in order for every caregiver to read and assess the considerations. Then, they can decide whether it is applicable to their context and patient as well, or if they want to deviate. Thereby, we hope to get international support for the recommendations in order to provide the same quality of care for children across the world, when applicable.

8.4 FUTURE PERSPECTIVES

Evidence-based guidelines result in consistency of care which results in better outcomes [1, 2]. It is important to provide equal care to patients in different hospitals, regions and countries. Improving patients' health outcomes, including quality of life, is obviously the most important advantage of evidence-based guideline development. Other positive consequences are potential improvement of cost-

effectiveness, providing a comprehensive overview for clinicians saving them time to stay up-to-date with literature, increased awareness for clinicians and patients and to expose gaps in scientific knowledge. We need to weigh the benefits against the harms and acknowledge that developing evidence-based guidelines, in whichever part of care, is very important and will help us improve quality of care.

I believe that we should focus on creating and developing evidence-based guidelines now, and then continue building on that in the future and update them. The limitation lies in terms of money and time. It is very time consuming to make these guidelines precisely, and it needs to be a solid base to continue building on.

My proposal to solve this problem, would be to create a dedicated pool of trained professionals. We have experienced that the GRADE methodology is complicated, but once the professionals are familiar with it, it works perfectly. I think a larger cohort of professionals nationwide should be trained in this evidence-based guideline development method. Then, if a guideline proposal is made or guidance is requested for a certain subject, a guideline panel can be composed from this pool. Such a pool will have a couple of benefits. Firstly, all guideline development ideas and proposals will be centralized and everybody will know that a group is developing those recommendations. Also, and very importantly, all the groups will use the same method of guideline development. This will contribute to the understandability of the recommendations and their strength among all users of the guideline.

If only

If only there was a tool that could take over all this work of performing an extensive search, collecting all data and make a summary of the evidence. In a couple of years, we will amusingly memorize people (like me), who did all this work by themselves and not use any form of artificial intelligence (AI). Maybe, in the future, AI tools could help us with collecting all the evidence and thereby drastically decrease that work load. However, I do believe that – for now and in the future – the human perspective is always decisive. The process 'from evidence to recommendation' is very important and should be always done by professionals in the specific field of interest. Nevertheless, I do believe that in the whole data collection process, AI – in any form – can play an important role that will make guideline development like this more accessible.

Even Better (Part 2)

Communication-wise, I believe a guideline should provide all discussions and arguments transparently, maybe in bullet points below the recommendation. Then, other clinicians know what the recommendation is based on, and if they believe those arguments would apply for their patients as well. Now, this is described in the evidence-to-decision framework, but not highlighted as in this example below.

WEAK recommendation, EXPERT EVIDENCE	**We believe that a prophylactic platelet transfusion is not necessary in children with cancer undergoing a bone marrow aspirate or biopsy.**
No studies were found regarding this topic, therefore we exceeded to expert evidence.	
General information:	Children with cancer frequently undergo bone marrow aspirates or biopsies. In the Netherlands, these procedures happen when the child is sedated.
Arguments:	We believe that the initial chance of bleeding due to this procedure is very small. In addition, the panel feels that the potential bleeding that occurs from the procedure, would be limited, can be easily recognized (as the bleeding is often visible or noticeable by the patient) and easily managed if necessary. This recommendation was based on expert opinion (n=23) and years of experience in centers in the Netherlands.

This is a short example, but for this matter, clinicians can quickly see the arguments that the recommendation is based on and they can easily check if this accounts for their patients too.

I believe that the biggest win can be made in communication towards clinicians and patients regarding expert evidence, and this example makes the recommendation process more insightful for the readers. Maybe, we could invite experts from the communication department in optimizing the best way to visually show the recommendation, to make it attractive to read, and to make sure it reaches all the persons it should reach. Communication is and will be key.

8.5 GAPS IN KNOWLEDGE & RESEARCH RECOMMENDATIONS (BASED ON THIS THESIS)

With respect to gaps in knowledge, a couple of recommendations for specific future research can be made. Almost all recommendations regarding blood transfusions and restrictions in daily life had very little to no evidence and for all its topics, more evidence

is wanted and needed. As naming each of them is not doable and not relevant here, the most important recommendations for future research are listed below.

- **Prophylactic platelet transfusions in children with cancer**. Deciding towards either the prophylactic or therapeutic strategy can have a lot of consequences, and should preferably be done if based on high quality research in our specific population.
  We suggest a randomized controlled trial in children with cancer, randomized to either the prophylactic (proposing a threshold of $10x10^9$/L) or therapeutic (thus no prophylactic transfusions) strategy group. Then, outcomes such as quality of life, severe hemorrhagic events, adverse events of platelet transfusion, hospitalization and costs etc. should be measured. Once we have a high-quality study with a large number of patients and a sufficient follow up, we might have arguments to change the strategy of administering platelet transfusions.
- **Evaluation of specific threshold of prophylactic platelet transfusions.** For many procedures, a prophylactic platelet transfusion is advised. We lowered some specific thresholds in our recommendations, but maybe more thresholds can be lowered in the upcoming years. With regards to cost effectiveness and late effects, it is important to minimize the number of (unnecessary) transfusions.
- **Swimming with tunneled line.** Despite little evidence, this was a topic with much discussion in the guideline panel and also during implementation. We changed current policy in the Netherlands regarding this topic, i.e. now these children are allowed to swim which they were not before, and it is important to follow up on the results and infectious outcomes. This is a very important topic for children and parents, so there is definitely need for more research.
- **Influenza incidence and course of infection.** With our small study in the Princess Máxima Center, we already gained knowledge on the incidence of influenza in children with cancer and the usual mild course of infection. We would propose a larger cohort study or RCT, preferably international, with longer follow up to be able to determine more precisely what the course of infection is in children with cancer (and its impact on hospital admission, delay of chemotherapy, etc). In addition, we would want to see what vaccination does for these children, this should be documented more carefully to assess if vaccination actually changes the clinical course of infection.

In addition, I also have a couple of general research recommendations;

- **New clinical questions for guideline development.** I believe everyone should be able to raise their clinical question for a guideline, ranging from nurse to professor to child life's specialist. Especially the caregivers who are close to children and their parents, will have very good ideas of which questions are raised by them and what they find important (for example 'are we allowed to have a Christmas tree?')
  I hope to achieve a kind of list in which nurses, patients and doctors can rank the importance of some kind of topics, to assess what is really relevant in clinical practice for everyone. Maybe, yearly table-sessions can be held or a dedicated email address where healthcare workers or parents and patients can send their ideas to. We might increase involvement through the use of social media, in which patients or parents can send in their own ideas or questions.
- **Participation of patients and parent representatives.** We already learned so much from their involvement, and we can definitely learn more. During the discussions in the guideline panel groups, the input of our representatives has always been very useful. Especially regarding 1) the shared weighing of pros and cons and keeping quality of life from a patients' perspective in mind 2) the wording used in the recommendations and 3) ultimately the communication of the recommendations towards parents and patients. I believe it is important to involve patient representatives throughout the whole process: as early as possible in defining clinical questions and as long as possible in being involved in the implementation process.
- **Implementation and communication.** We all know that big goals are yet to be achieved within the field of implementation. We should investigate how we can implement our recommendations optimally, and develop indicators to see concordance and discordance to the recommendations, and clinical implications hereof. These indicator projects are up and running, but I hope to see them roll out even wider throughout the whole field of supportive care and beyond.

IMPROVING QUALITY OF LIFE

It was described throughout this thesis and discussion, but – in my opinion – it deserves a special subheading.

Throughout the whole guideline process, quality of life (QoL) was one of the most important considerations. In discussing the benefits and harms of a recommendation, we always discussed the importance and role of QoL for that specific topic. I am very proud of this (small) contribution to improving quality of life.

NOW WHAT?

Our recommendations and guidelines have been published on multiple platforms. The 'restrictions in daily life' and 'blood transfusions' have been published nationally (*Richtlijnen database*). Here, they are accessible for everyone and can be used in clinical practice. A couple of our peer-reviewed articles have been published in Supportive Care and Cancer, and there they are available for international caregivers. All the other guidelines have been submitted to peer reviewed journals. We promoted these recommendations extensively, both nationally and internationally through presentations at congresses. Also, we communicated the introduction of the new guidelines through various platforms via the Princess Máxima Center, to also inform our patients and parents.

After finishing this thesis, I will continue to promote these guidelines and their implementation. In addition, I hope to be working on more guidelines, because of their importance, also in general pediatric practice. I hope to advocate for this type of research and spread my enthusiasm along with it.

CLOSING STATEMENT

In conclusion, with effectuating all evidence-based recommendations and expert evidence based recommendations as described in this thesis, we aim to improve care and to contribute to improving quality of life of children with cancer. These recommendations will play an important role in the daily lives and treatment of children with cancer and their parents, by establishing a balance between being cautious and thus protecting these vulnerable children for complications, and participating in 'normal' child life as good as possible.

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APPENDICES

NEDERLANDSE SAMENVATTING (DIT PROEFSCHRIFT)

In Nederland krijgen er jaarlijks circa 600 kinderen de diagnose kanker. De meest voorkomende diagnoses zijn leukemie (30%), hersentumoren (20-25%) en lymfomen zoals Hodgkin lymfoom (11%). Van alle kinderen die de diagnose kanker krijgen, is een derde jonger dan 5 jaar. De behandeling bestaat uit verschillende onderdelen zoals chemotherapie, immuuntherapie, maar bijvoorbeeld ook bestraling of operatie(s). Vaak is langdurige behandeling nodig; zo duurt de behandeling van een hoog-risico leukemie 3 jaar.

De overleving van kinderen met kanker is de afgelopen jaren flink verbeterd. In de jaren 1990 was de 5-jaars overleving nog 73%, in 2020 was dit al 83%. Er wordt veel – terecht en heel belangrijk – onderzoek gedaan naar nieuwe methodes van behandeling om deze overleving nóg hoger te maken. Tegelijkertijd is het ook belangrijk om onderzoek te doen naar *Supportive Care* (ondersteunende zorg) en alles wat daarbij komt kijken zoals misselijkheid, bloedtransfusies, infecties, voeding en pijn. Tijdens de behandeling van kanker zijn er verschillende bijwerkingen die kunnen zorgen voor verminderde kwaliteit van leven bij kinderen. Alle verschillende therapieën hebben verschillende bijwerkingen. Zo kan chemotherapie bijvoorbeeld leiden tot misselijkheid, maar ook tot het verliezen van het haar en het vatbaar worden voor infecties en bloedingen door lage witte bloedcellen of lage bloedplaatjes.

In dit proefschrift wordt veel gesproken over *Supportive Care*. Ik zou dit willen beschrijven als de zorg rondom de behandeling voor kinderkanker. Denk daarbij dus aan de al eerder beschreven onderwerpen zoals bloedtransfusies, leefregels, infecties en pijn. Een belangrijk middel om deze zorg te verbeteren is het ontwikkelen van *evidence-based* richtlijnen. Dit zijn richtlijnen die gebaseerd zijn op de huidige literatuur en de nieuwste onderzoeken. Hierin is de balans belangrijk tussen de voor- en nadelen, en bijvoorbeeld de kwaliteit van leven en het risico op infecties of bloedingen. Zo kunnen we als zorgverleners de juiste aanbevelingen opstellen en daarmee streven naar dat de zorg overal hetzelfde is.

Om deze richtlijnen te maken hebben we de GRADE methode gebruikt. Dit is een methode om alle conclusies uit de literatuur te halen, deze te beoordelen en met een gevarieerde groep professionals te bespreken en te vertalen naar aanbevelingen.

Dit proefschrift levert inzichten in richtlijnontwikkeling binnen *Supportive Care* voor kinderen met kanker, met bijbehorende sterke punten en beperkingen en een overzicht van kennislacunes. Hierin beschreven vindt u het werk van vier verschillende multidisciplinaire richtlijngroepen, dat geresulteerd heeft in 5 verschillende *evidence-based* richtlijnen over belangrijke onderwerpen voor kinderen, ouders en zorgverleners binnen de kinderoncologie.

In totaal zijn er meer dan 50 evidence-based en expert-opinion based aanbevelingen gemaakt in dit proefschrift. De belangrijkste hiervan worden beschreven in deze samenvatting, voor een volledig overzicht van alle aanbevelingen verwijs ik graag naar de bijbehorende individuele hoofdstukken.

In **hoofdstuk 2** wordt onze richtlijn over lokale anesthetica (verdovende middelen op de huid) rondom een prikprocedure bij kinderen beschreven. Tijdens zowel langdurige en intensieve behandelingen als spoedeisende zorg, is er vaak noodzaak voor een pijnlijke procedures zoals bloed prikken (venapunctie), een infuus prikken of, specifiek bij kinderen met kanker, een Port-A-Cath® (PAC, een kastje onder de huid waardoor de kinderen chemotherapie krijgen) aanprikken. Uit eerdere studies weten we dat het gebruiken van lokale anesthetica om de huid te verdoven, de pijn die kinderen ervaren door deze procedures vermindert. Er bleef echter onduidelijkheid over welk middel het beste gebruikt kon worden (bijvoorbeeld EMLA® of crèmes of pleisters met tetracaine, zoals Rapydan®). Daarom hebben wij deze richtlijn gemaakt, waarin we een uitgebreid maar inzichtelijk overzicht hebben gemaakt van de beschikbare literatuur en aanbevelingen die daaruit voortkomen, voor kinderen, ouders en zorgverleners.

Tien gerandomiseerde studies met daarin 1.808 kinderen dienden als *evidence* (bewijs) voor deze richtlijn. De richtlijn groep concludeerde als eerste dat elk kind een vorm van lokale anesthetica moet krijgen alvorens het ondergaan van een pijnlijke procedure zoals eerder beschreven. Dit moet zo vroeg mogelijk in hun behandeling worden gestart en moet standaard zorg zijn voor alle kinderen. Wanneer er een keuze gemaakt moet worden over *welk* lokaal anestheticum moet worden gekozen, zijn de volgende aanbevelingen gemaakt: we raden het gebruik van EMLA® aan in kinderen die een pijnlijke procedure moeten ondergaan zoals eerder beschreven. Tetracaine-bevattende crèmes of pleisters worden aanbevolen als de procedure snel uitgevoerd dient te worden, dat wil zeggen tussen 30-60 minuten.

Hoofdstuk 3 gaat over de richtlijn *Leefregels bij kinderen met kanker*. In de huidige praktijk zijn de aanbevelingen rondom de leefregels bij kinderen met kanker niet gebaseerd op literatuur (*evidence*). Gezien de enorme impact van deze leefregels (denk aan zwemmen, naar school gaan, sporten) op de kwaliteit van leven van de kinderen, is het erg belangrijk dat deze aanbevelingen kritisch worden bekeken. Ons doel was dus om een uitgebreid maar inzichtelijk overzicht te creëren voor kinderen met kanker, hun ouders en zorgverleners.

Zes studies met daarin 758 kinderen dienden als *evidence* (bewijs) voor deze richtlijn. Bij erg weinig studies bij kinderen met kanker, werd ook de gedeelde *expert opinion* van de professionals in onze richtlijn groep gebruikt. In totaal werden er 14 aanbevelingen gemaakt, waarvan er meerdere al geresulteerd hebben in beleidsveranderingen binnen de zorg in Nederland. Onderwerpen die zijn beschreven in deze richtlijn zijn onder andere zwemmen, het hebben van huisdieren, naar de dierentuin of kinderboerderij gaan, het uitvoeren van sporten of activiteiten met een hoge snelheid, naar school of naar het kinderdagverblijf gaan en het gebruik van het openbaar vervoer.

Eén van onze belangrijkste aanbevelingen in deze richtlijn is het toestaan van zwemmen voor kinderen met een getunnelde, centraal veneuze lijn waar dit eerder niet toegestaan was. Deze leefregel had grote impact op de kwaliteit van leven van de kinderen, zoals vaak teruggehoord van ouders en kinderen. Zo konden zij bijvoorbeeld niet naar zwemles, maar ook niet zwemmen met leeftijdsgenoten of op vakantie zolang de behandeling duurde, soms wel 3 jaar. Dit was dus ***niet*** gebaseerd op literatuur, alleen op eigen redenatie en 'gezond verstand'. Kwaliteit van leven was een belangrijk meetellend argument in het afwegen van de voor- en nadelen rondom dit onderwerp, en was doorslaggevend in de meeste discussies. Deze aanbeveling heeft de meeste impact gehad, en tegelijkertijd is er ook de meeste discussie rondom geweest (zowel binnen de werkgroep als daarbuiten).

In **hoofdstukken 4 en 5** worden de richtlijnen over profylactische transfusies van bloedplaatjes (trombocyten) en rode bloedcellen (erytrocyten) beschreven. Trombocytopenie (te weinig bloedplaatjes) en anemie (te weinig rode bloedcellen) zijn veel voorkomende bijwerkingen van de behandeling tegen kanker door het onderdrukken van het beenmerg. Dit kan leiden tot potentieel ernstige symptomen bij kinderen met kanker en heeft daarmee ook impact op hun kwaliteit van leven.

Om ernstige bijwerkingen van deze trombopenie en anemie te voorkomen kan een profylactische transfusie worden gegeven. Er moet echter een balans bewerkstelligd worden tussen het voorkómen van complicaties door deze lage celgetallen, en het voorkómen van onnodige transfusies en de potentiële nadelen daarvan zoals de last voor patiënten, kosten etc. Het is daarom belangrijk dat deze transfusie grenzen precies worden bepaald en beschreven.

Profylactische trombocyten transfusies (**hoofdstuk 4**): in totaal werden er 3 studies gebruikt als *evidence* met daarin 1.454 kinderen met kanker. De richtlijn groep heeft alle resultaten van deze studies besproken en gebruikt om aanbevelingen mee te maken. Bij erg weinig *evidence* bij kinderen met kanker, werd ook de gedeelde *expert opinion* van de professionals in onze richtlijn groep gebruikt. In totaal werden er 22 aanbevelingen gemaakt over grenzen van een profylactische trombocyten transfusie bij kinderen met kanker. Deze grenzen werden beschreven in bepaalde groepen zoals kinderen met sepsis (bloedvergiftiging) of met een bepaald type kanker, en beschreven rondom een bepaalde procedure, bijvoorbeeld voorafgaand aan het ondergaan van een lumbaal punctie (ruggenprik) of het inbrengen van een lijn.

Profylactische erytrocyten transfusies (**hoofdstuk 5**): in totaal werden er 4 studies gebruikt als *evidence* met daarin 203 kinderen met kanker. De richtlijn groep heeft alle resultaten van deze studies besproken en gebruikt om aanbevelingen mee te maken. Bij erg weinig *evidence* bij kinderen met kanker, werd ook de gedeelde *expert opinion* van de professionals in onze richtlijn groep gebruikt. In totaal werden er 34 aanbevelingen gemaakt over grenzen van een profylactische erytrocyten transfusie bij kinderen met kanker. Deze grenzen werden beschreven in bepaalde groepen zoals kinderen met sepsis of kinderen die radiotherapie (bestraling) ondergaan.

In **hoofdstuk 6** wordt een observationele studie beschreven over kinderen met influenza (griepvirus) in het Prinses Máxima Centrum. De resultaten in deze studie zijn in hoofdstuk 7 gebruikt om te dienen als *evidence*. De huidige kennis over de incidentie (het vóórkomen) en het beloop van influenza in kinderen met kanker is zeer beperkt en dit was nodig voor het ontwikkelen van de richtlijn. Echter, eerst, hebben we gekeken naar een groep kinderen in het Prinses Máxima Centrum en bijbehorende ziekenhuizen die kinderen met kanker behandelen, die influenza hadden tussen Oktober 2018 en Juli 2020.

Bij 58 kinderen werd de diagnose influenza bevestigd middels laboratorium onderzoek. De huidige incidentie in Nederland voor het vóórkomen van kanker op de kinderleeftijd is 1195 nieuwe diagnoses tijdens de periode oktober 2018 tot juli 2020. Daarmee waren er dus 4.9 influenza diagnoses per 100 nieuwe kankerdiagnoses. De gemiddelde leeftijd voor het krijgen van influenza was 5 jaar (met een spreiding tussen de 1-16 jaar). In 22 patiënten (38%) was er 35 keer een onderbreking van de chemotherapie of uitstel hiervan beschreven. Complicaties werden beschreven bij 2 patiënten (3%) en waren één patiënt met tijdelijke sufheid en één patiënt met een acute otitis media (middenoor ontsteking). Er werden 22 patiënten (38%) opgenomen in het ziekenhuis met influenza, waarvan neutropenie (te lage neutrofielen; een bepaalde witte bloedcel) significant geassocieerd was met opname in het ziekenhuis. Geen enkele influenza episode leidde tot een ernstig beloop, intensive care opname of overlijden. Dus, in onze groep kinderen in Nederland die behandeling voor kanker onderging, is het vóórkomen van influenza infecties relatief laag en het beloop van dit virus is relatief mild.

Tenslotte behelst **hoofdstuk 7** de richtlijn over het voorkómen van influenza door middel van de griepvaccinatie. Door griepvaccinaties kunnen bijwerkingen van influenza zoals opname in het ziekenhuis, uitstel van chemotherapie en bacteriële superinfecties worden beperkt. Meerdere studies hebben een positief effect laten zien van de griepvaccinaties, maar specifieke aanbevelingen over griepvaccinatie bij kinderen ontbreken tot op heden. Daarom was ons doel om een *clinical practice guideline* te maken, waarin we een uitgebreid maar inzichtelijk overzicht hebben gemaakt van de beschikbare literatuur en aanbevelingen die daaruit voortkomen, voor kinderen, ouders en zorgverleners.

Vier studies met daarin 166 kinderen dienden als *evidence* (bewijs) voor deze richtlijn. Deze studies lieten geen statistisch significant verschil zien in de incidentie van influenza in gevaccineerde kinderen met kanker vergeleken met ongevaccineerde kinderen met kanker (2% (n=2/100) versus 6.8% (n=11/161), RR 0.29 [0.07-1.29]). Wél lieten deze studies zien dat ongevaccineerde kinderen langer in het ziekenhuis moesten blijven (4 dagen versus 5.1 dagen) en dat er langer uitstel van chemotherapie was (0.5 versus 4.5 dagen). Er werden geen bijwerkingen gerapporteerd van de vaccinatie. In het bloed werden antistoffen gevonden die varieerden tussen 33-89%. De belangrijkste aanbeveling van deze studie is dat we aanbevelen dat kinderen met kanker jaarlijks hun influenza vaccinatie krijgen, met uitzondering van kinderen die

een stamceltransplantatie ondergaan. Voor deze laatste groep raden we vaccinatie van de mensen in hun huishouden aan.

Concluderend, zijn deze richtlijnen al een mooie stap in de goede richting over deze onderwerpen die belangrijk zijn voor kinderen met kanker en hun ouders. Maar, met de verbeterende overleving voor kinderen met kanker, wordt de *Supportive Care* steeds belangrijker. Ook de impact op de kwaliteit van leven van deze kinderen is heel erg belangrijk, en heeft daarom ook in alle aanbevelingen een groot aandeel gehad.

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LIST OF PUBLICATIONS

Published:

An Evidence-Based Guideline for Red Blood Cell Transfusions in Children with Cancer
Demi Kruimer, Debbie Stavleu, Renée Mulder, Leontien Kremer, Wim Tissing, Erik Loeffen
Support Care Cancer. 2024 Nov 4;32(11):766.

Complementary and alternative medicine modalities used to treat adverse effects of anti-cancer treatment among children and young adults: A systematic review and meta-analysis of randomized controlled trials
Dana C. Mora, Grete Overvåg, Miek C. Jong, Agnete E Kristoffersen, Debbie C. Stavleu, Jianping Liu, Trine Stub
BMC Complement Med Ther. 2022 Apr 2;22(1):97.

Less Restrictions in Daily Life: A Clinical Practice Guideline
Debbie Stavleu, Renée Mulder, Demi Kruimer, Leontien Kremer, Wim Tissing, Erik Loeffen
Support Care Cancer. 2024 Jun 8;32(7):419.

Topical Analgesia During Needle-Related Procedures in Children: a Clinical Practice Guideline
Debbie Stavleu, Renée Mulder, Demi Kruimer, Maarten Mensink, Leontien Kremer, Wim Tissing, Erik Loeffen
Archives of Disease in Childhood, 2025;0:1–5

Parental Opinions on Medical Decision-Making in Adolescence: A Case-Based Survey
Debbie Stavleu, Peter de Winter, Xandra Veenstra, Karlijn van Stralen, David De Coninck, Koen Matthijs, Jaan Toelen.
J Dev Behav Pediatr. 2022 Jan 1;43(1):17-22.

Pijnvrij prikken: EMLA of Rapydan voor een prikprocedure?
D.C. Stavleu, W.J.E. Tissing, M.O. Mensink, P. Leroy, E.A.H. Loeffen. Praktische Pediatrie, September 2020

In submission:

An Evidence-Based Guideline for Influenza Vaccination in Children with Cancer
Debbie Stavleu, Mirre Thomas, Renée Mulder, Leontien Kremer, Wim Tissing, Erik Loeffen

Incidence and Clinical Course of Influenza Infections in a Dutch pediatric oncology center
Mirre Thomas en Debbie Stavleu, Marianne van de Wetering, Yvette Loeffen, Wim Tissing, Erik Loeffen

Prophylactic Platelet Transfusions in Children with Cancer: A Clinical Practice Guideline
Debbie Stavleu, Renée Mulder, Demi Kruimer, Leontien Kremer, Wim Tissing, Erik Loeffen

PhD PORTFOLIO

Name PhD student: Debbie Stavleu
PhD training period: September 2019 – September 2023
Promotor: Prof. dr. W.J.E Tissing, prof. dr. L.C.M Kremer
Co-promotor: dr. E.A.H Loeffen

Courses

- Algemene Didactiek en het Ontwerpen van Onderwijs, UMC Utrecht ihkv BKO
- Professioneel gedrag (professioneel gedrag beoordelen en feedback geven), UMC Utrecht ihkv BKO
- Online presenteren, UMC Utrecht (Online)
- Meta-analysis – Boerhaave nascholing LUMC, Leiden
- Start to Supervise - Rijksuniversiteit Groningen, Groningen (Online)
- Scientific Illustrations in Cell Biology - Graduate School of Medical Sciences, Groningen (Online)
- Introduction to Teaching - Rijksuniversiteit Groningen, Groningen (Online)
- Influencing styles & Conflict management – Career Services UU, Graduate School of Life Sciences, Utrecht
- Manage your supervisor – Career Services UU, Graduate School of Life Sciences, Utrecht
- Stress management (Happy PhD student) - Graduate School of Medical Sciences, Groningen (Online)
- Peer-to-peer support - Graduate School of Medical Sciences, Groningen (Online)
- Managing your PhD - Graduate School of Medical Sciences, Groningen (Online)
- EMWO - Basic course for clinical investigators (BROK®) course and certificate
- Presentation skills - Graduate School of Medical Sciences, Groningen (Online)
- KNAW Samenweten: Buiten je boekje (Hoe reik ik als wetenschapper effectief uit naar niet-wetenschappers? En hoe plaats ik mijn onderzoek in brede maatschappelijke context?)
- Scientific Writing - Graduate School of Medical Sciences, Groningen (Online)
- Ethics of Research and Scientific Integrity for Researchers - Graduate School of Medical Sciences, Groningen (Online)
- Research Data Management Awareness workshop – Graduate School of Medical Sciences, Groningen (Online
- Medical Statistics – Graduate School of Medical Sciences, Groningen

- EBRO training (evidence-based guideline development), Kennisinstituut van de Federatie Medisch Specialisten, Utrecht

Presentations at (inter)national conferences, symposia or meetings

- Heilige Huisjes, Congres Nederlandse Vereniging voor Kindergeneeskunde, Juni 2024, Papendal
- An Evidence-Based Guideline for Social Restrictions in Children with Cancer | ISLCCC 2023 (Atlanta, poster presentation)
- An Evidence-Based Guideline for Social Restrictions in Children with Cancer | SIOP 2022 (Barcelona, poster presentation)
- An Evidence-Based Guideline Blood Transfusions in Children with Cancer | SIOP 2022 (Barcelona, poster presentation)
- Guideline development in Supportive Care: Social Restrictions in Children with Cancer | NAFKAM Congress 2022 (Tromsø, invited oral presentation)
- An Evidence-Based Guideline for Platelet and Red Blood Cell Transfusions in Children with Cancer | ISLCCC 2022 (Utrecht, poster presentation)
- Evidence-based guideline development: Blood transfusions in Children with Cancer – NVB-TRIP Congress, Ede
- Social Restrictions in Children with Cancer: an Evidence-Based Guideline – Amsterdams Kinder Symposium, Amsterdam
- An Evidence-Based Guideline for Platelet Transfusions in Children with Cancer | SIOP 2021 (Online, e-Poster presentation & discussion)
- An Evidence-Based Guideline for Social Restrictions in Children with Cancer | SIOP 2021 (Online, e-Poster presentation & discussion)
- Choice of Local Anesthetic in Reducing Needle-Induced Pain during Minor Procedures in Children: a Clinical Practice Guideline - MASCC 2021 (online presentation)
- Choice of Local Anesthetic in Reducing Needle-Induced Pain during Minor Procedures in Children: a Clinical Practice Guideline - SIOP congress 2020 (Online, e-Poster)

Supervising

- Supervising master thesis, medical student VUmc School of Medical Sciences (Irradiation of blood products after fludarabine administration in children with acute myeloid leukemia)
- Supervising master thesis, medical student University of Groningen (Influenza infections in children with cancer)

Teaching

- Teaching activities WKZ, teach master students during internship pediatrics
- Supportive care: what can we do to optimize quality of live during this intensive treatment? (including differences between High income and Low and middle income countries (focus on guideline development) – International Summerschool Princess Máxima Center for pediatric oncology, Utrecht
- Guideline development workshop, minor pediatric oncology (bachelor students) - Princess Máxima Center for pediatric oncology, Utrecht
- Guideline development – International Summerschool Princess Máxima Center for pediatric oncology, Utrecht

Other

- Week of Science Lustrum committee Princess Máxima Center
- Initiation and editorial board on "Quality of Life magazine" in Princess Máxima Center
- Organizing activities for Quality of Life group (sport activities, quizzes, bingo) in Princess Máxima Center
- Applied for "Prijs voor de Jonge Onderzoeker 2021" with my PhD project "Game changers: evidence-based guideline development in pediatric oncology"
- Organisation committee "Dag van de Wetenschap" and activities In Princess Máxima Center
- "Slimme gasten WKZ/UMCU" – providing education to children in elementary schools on being a scientist.

ABOUT THE AUTHOR

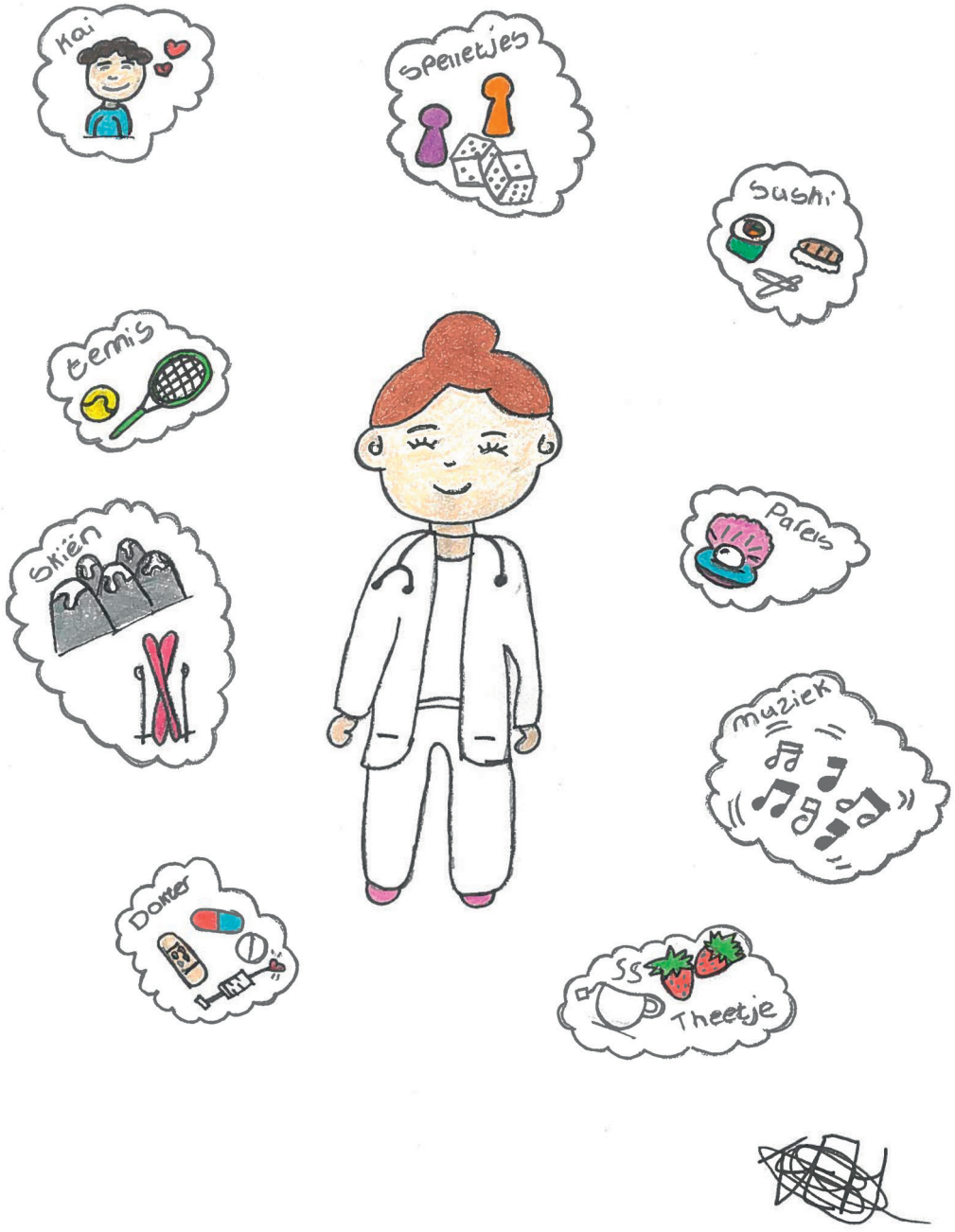
Debbie Celine Stavleu was born on March 9th 1996 in Leiden, the Netherlands. After finishing pre-university education (VWO) in Oegstgeest, she started medical school in Amsterdam in 2013. Up and through 2019, relevant medical internships in pediatrics were performed in VUmc, Spaarne Gasthuis and the Princess Máxima Center.

In 2019, she started as a PhD candidate in this center within supportive care research. Debbie was seated in two research groups, supportive care group and late effects group, and attended several conferences in Tromso, Barcelona and Atlanta. During four years, together with the core group and all guideline panels, five evidence-based guidelines were published and implemented in the Princess Máxima Center and nationwide. In addition, Debbie was - very enthusiastically - involved in several side projects. Also, she was involved in providing bachelor and master students with education in the Princess Máxima Center and WKZ and she started her UTQ (university teaching qualification). After the PhD duration, she worked as a pediatric resident in the Maasstad hospital in Rotterdam. During this period, she continued her work on the pediatric oncology guidelines (awareness and implementation), and also initiated new guideline development projects for general pediatric practice.

Debbie lives in Bodegraven with her boyfriend Kai.

Debbie was inspired by people such as Derek Shepherd from Grey's Anatomy ("It's a beautiful day to save lives") and Harvey Specter from Suits ("Work until you no longer have to introduce yourself"). Otherwise, she was inspired by patients such as Ella and Bram and their parents.

PS. If you don't feel like reading this part, the drawings on the right page define my most important characteristics; drawn by Fenne Habold.


Kai
Spelletjes
Sushi
Tennis
Skiën
Paard
Muziek
Donor
Theetje

DANKWOORD

Ik had dit niet  gekund.

Of dit het langste dankwoord is dat je ooit hebt gelezen? Waarschijnlijk wel. Maar ik heb het heerlijk gevonden om uitgebreid de tijd te nemen om de mensen te bedanken die belangrijk voor mij zijn geweest en nog steeds zijn. De meeste mensen die mij inmiddels kennen (en waarschijnlijk ook de mensen die mij nog niet zo goed kennen) zouden weten dat ik het liefst een deel 2 van mijn boekje had gemaakt, geheel gewijd aan mijn dankwoord. Ik vind het heerlijk om te schrijven – soms grappig en scherp – maar ook om oprecht de mensen te bedanken die zoveel voor mij betekend hebben. Hoewel de meesten wel weten wat ik ze wil zeggen, heb ik het hier toch nog met heel veel plezier opgeschreven. Ga er maar goed voor zitten, kruip lekker onder een dekentje, popcorn erbij, *lights out* in 3...2....1...

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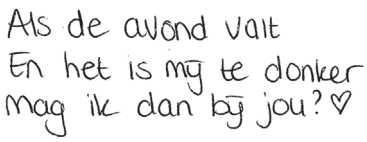
Allerliefste **Kai**,



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