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*Published in:*  
Pediatric blood & cancer

*DOI:*  
[10.1002/psc.27504](https://doi.org/10.1002/psc.27504)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2019

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

ten Berg, S., Loeffen, E. A. H., van de Wetering, M. D., Martens, D. H. J., van Ede, C. M., Kremer, L. C. M., & Tissing, W. J. E. (2019). Development of pediatric oncology supportive care indicators: Evaluation of febrile neutropenia care in the north of the Netherlands. *Pediatric blood & cancer*, 66(2), [27504].  
<https://doi.org/10.1002/psc.27504>

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# Development of pediatric oncology supportive care indicators: Evaluation of febrile neutropenia care in the north of the Netherlands

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## Funding information

KWF Kankerbestrijding, Grant/Award Number: RUG 2013-6345

Sanne ten Berg and Erik A. H. Loeffen contributed equally to this work.

## Abstract

**Introduction:** Febrile neutropenia (FN) is a common complication of the intensive treatment strategies used in pediatric oncology. By close adherence to high-quality guidelines, which can be evaluated by indicators, the burden of FN can potentially be reduced.

**Objectives:** The aims of this study were tripartite—(1) to develop structure, process, and outcome indicators, (2) to evaluate the implementation of the Dutch Childhood Oncology Group (DCOG) guideline on FN, and (3) to produce baseline measures on local quality of FN care (in the north of the Netherlands).

**Methods:** Seven indicators derived from the DCOG guideline were developed. Regarding structure indicators, we gathered information from all local centers providing care for children with cancer ( $n = 9$ ). Regarding process and outcome indicators, we collected individual patient data from one academic and two shared-care hospitals. Children (<18 years) were included if they had been diagnosed with cancer in 2014 or 2015 and had suffered from FN.

**Results:** Six out of nine hospitals used the DCOG guideline on FN and three hospitals used an outdated supportive care handbook. Regarding individual patient data, we included 119 FN episodes in 59 patients. All FN episodes without focus were initially treated with guideline-based antibiotics. Of all FN episodes, 18.5% resulted in intensive care unit (ICU) admittance. Cumulative incidence of death during FN was 1.74%.

**Conclusion:** Adherence to the DCOG guideline at the individual patient level was excellent. However, indicators concerning mortality and ICU admittances showed that FN still has devastating consequences. Subsequently, we will implement these indicators nationwide in order to improve FN care.

## KEYWORDS

clinical practice guidelines, febrile neutropenia, indicators, pediatric oncology, supportive care

## 1 | INTRODUCTION

Cure rates of children with cancer have increased from 20% in the 1960s to a current survival of 80% in developed countries.<sup>1,2</sup> This substantial increase is mainly due to higher specific diagnostic tools

and more intensive types of therapy. The drawback of these therapies is the association with relatively higher rates of treatment-related morbidity and mortality.<sup>3</sup> A recent Canadian study showed that one in every four deaths in children with acute lymphoblastic leukemia (ALL) was related to treatment.<sup>4</sup> The major cause for treatment-related

Abbreviations: ALL, acute lymphoblastic leukemia; BAL, broncho-alveolar lavage; CI, confidence interval; CPG, clinical practice guideline; DCOG, Dutch Childhood Oncology Group; EPR, electronic patient records; FN, febrile neutropenia; HRCT, high-resolution computed tomography; ICU, intensive care unit; MREC, medical research ethics committee

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mortality is febrile neutropenia (FN) and associated infections.<sup>5,6</sup> A possible way to lower the burden of FN is by optimizing supportive care and by close adherence to corresponding high-quality guidelines.

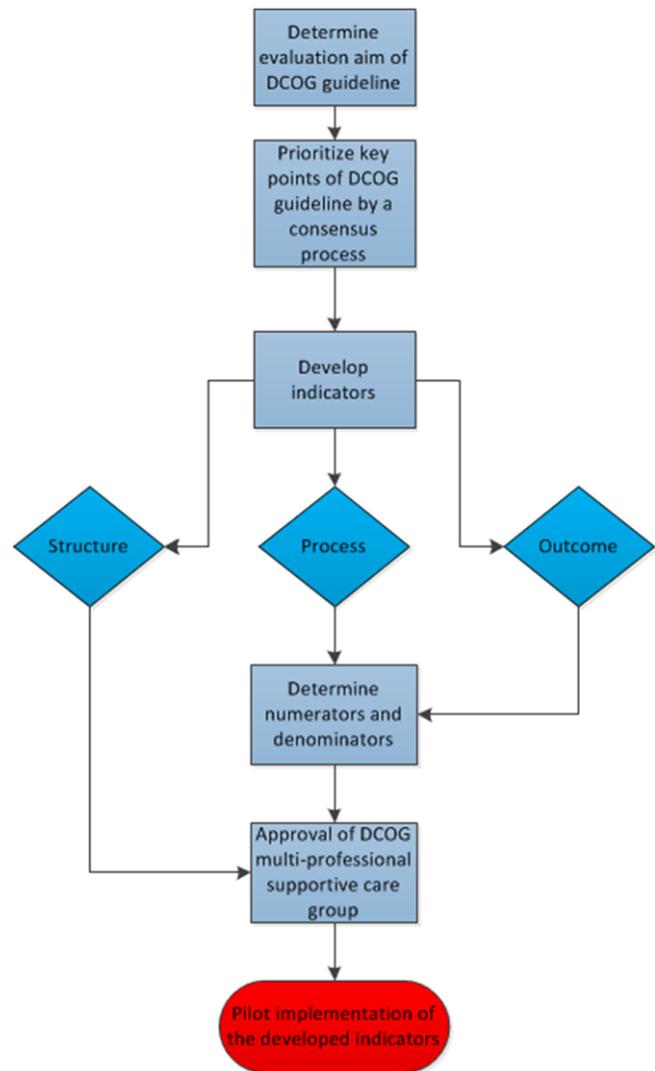
Clinical practice guidelines (CPGs) are guidelines based on a systematic appraisal of the best available evidence, and can assist practitioners' decision making in order to limit practice variation and to improve clinical care.<sup>7,8</sup> Currently, only few international high-quality pediatric oncology supportive care guidelines exist. Among those are CPGs on FN and on nausea and vomiting.<sup>9,10</sup> In the Netherlands, guidance for supportive care is provided by the Dutch Childhood Oncology Group (DCOG) guidelines, which are based on the available international CPGs combined with local expert consensus. Nevertheless, despite the existence of these guidelines, a recent survey showed that 75% of examined supportive care was discordant in the Netherlands.<sup>11</sup> This might imply suboptimal care, which may result in increased morbidity and mortality.<sup>12</sup> Therefore, it is of the utmost importance to adequately implement guidelines, and evaluate this by means of indicators.<sup>13</sup>

Indicators are measurable items and are used as guides to monitor, evaluate, and improve the quality of patient care, clinical support services, and organizational function that affect patient outcomes.<sup>13,14</sup> Three types of indicators have been identified, which denote attributes of settings in which care occurs (structure), activities and processes that belong to giving and receiving care (process), and states of health or events that follow care (outcome).<sup>14</sup> The development of indicators is ideally done in line with evidence-based recommendations or by a systematic review of available literature, but can also be accomplished by a (multi-) expert consensus process.<sup>14</sup> The main objectives of this study focusing on FN were (1) to develop structure, process, and outcome indicators derived from the DCOG guidelines on FN, and (2) to perform a first implementation of these indicators in the north of the Netherlands.

## 2 | METHODS

### 2.1 | Indicator development

Figure 1 shows a flowchart of the development of indicators. A multidisciplinary project group, consisting of two pediatric oncologists (W.J.E.T., M.D.W.), a pediatric epidemiologist (L.C.M.K.), and two clinical researchers (E.A.H.L., S.B.), prioritized the main topics of the DCOG guideline on FN using a simple consensus process (see Supplementary Material S1 for a full list of extracted recommendations). Due to the retrospective nature of this study, we had to consider whether information needed for the indicators was documented and therefore available. If not, those recommendations could not be used to develop indicators. Firstly, structure indicators were developed to gather information on the use of the DCOG FN guideline to verify whether hospitals met the basic conditions. Secondly, process indicators were developed to evaluate the provided supportive care. Thirdly, outcome indicators were used to measure important undesirable outcomes of FN. For rate-based indicators, numerators and denominators were determined. After development, the DCOG multiprofessional supportive care working group (10 professionals including



**FIGURE 1** Flowchart of the development of indicators

pediatric oncologists, nurses, and an epidemiologist) approved the indicators.

### 2.2 | Data collection

This study was performed in the northern part of the Netherlands. This area comprises nine hospitals providing care to children with cancer. Concerning the structure indicators and one process indicator, all centers were included. With regard to the process and outcome indicators, individual patient data were collected in three centers—University Medical Center Groningen (academic hospital, primary pediatric oncologic treatment center), Medical Center Leeuwarden, and Isala Zwolle (the latter two are secondary hospitals providing pediatric oncology shared care). Eligible patients for individual patient data collection were all children (<18 years at diagnosis) diagnosed with cancer between January 1, 2014 and December 31, 2015, and who were treated in the participating centers. Data collection took place in August 2017; thus, most included patients had (nearly) finished treatment.

To evaluate the structure and process indicators, a questionnaire was completed by pediatricians who provided local care for children

with cancer in all nine hospitals. To gather information for the outcome indicators (ie, the individual patient data), electronic patient records (EPR) in the three participating hospitals were consulted by the main researcher (S.B.). In order to identify patients who were admitted for an episode of FN, we checked the laboratory records of eligible children. As it is standard care for children with cancer who present with fever in the hospital to have a blood culture drawn (to identify possible causal microorganisms), we used these blood cultures to identify febrile episodes. We then checked whether these febrile episodes were neutropenic (neutrophils  $< 500/\mu\text{L}$ , or when not determined, leukocytes  $< 1000/\mu\text{L}$ ). "Admission" was defined as "a hospitalization in which an episode of FN occurs," to also include children who were not primarily hospitalized for FN but did develop fever during admission.

For the included patients, we extracted basic demographic factors from the EPR—gender, date of birth, diagnosis, date of diagnosis, and treatment protocol. Additionally, variables that describe the characteristics of the FN episode were extracted—antibiotics used, additional testing performed, and occurrence of complications (defined as intensive care unit [ICU] admittance and inpatient death). In case of different local FN protocols, we would compare the findings between the three hospitals. In addition, all identified deviations from the DCOG guideline as well as all episodes with a complication were further investigated individually in a qualitative manner.

## 2.3 | Statistical analyses

Results are presented in a descriptive manner. Rate-based indicators are presented in percentages. Possible differences between hospitals, if any, were analyzed by means of a chi-squared test. Confidence intervals (95% CI) were computed according to the Wilson method as small numbers of successes and/or failures were anticipated.<sup>15</sup> Statistical analyses were performed using Stata Statistical Software, Release 15 (StataCorp LLC, College Station, TX).

## 2.4 | Ethical approval

The local medical research ethics committee (MREC) of the University Medical Center Groningen judged that this study did not fit the scope of the Medical Research Involving Human Subjects Act according to the Declaration of Helsinki; thus, it was not obligatory to seek formal approval of the MREC.

## 3 | RESULTS

In all, seven indicators were developed (Table 1). The operationalized structure indicators concerned the local recommendation on antimicrobial policy of FN. With regard to the process indicators, we evaluated the administered antibiotics in FN episodes without bacterial focus, which means no source of infection at the onset of fever (DCOG guideline—monotherapy with ceftazidim) and the conduction of additional testing in neutropenic children under antibiotics with persistent ( $>96$  h since onset) fever (DCOG guideline—performance of high-resolution computed tomography [HRCT] thorax and, if indicated, broncho-alveolar lavage [BAL] just after 96 h).<sup>16</sup> In other words, one

**TABLE 1** The developed structure, process, and outcome indicators

Structure Indicators	
Indicator 1	Having a general recommendation on the antimicrobial policy of FN in children with cancer <ol style="list-style-type: none"> <li>1. No recommendation</li> <li>2. Verbal agreement</li> <li>3. Written recommendation in own document system</li> <li>4. According to the DCOG guideline</li> </ol>
Indicator 2	Is the recommendation according to the DCOG guideline? <ol style="list-style-type: none"> <li>1. Yes</li> <li>2. No</li> </ol>
Process indicators	
Indicator 3	Percentage of febrile neutropenia episodes without microbial focus, which are treated with ceftazidim
Numerator	The number of FN episodes without microbial focus, for which patients received ceftazidim according to the DCOG guideline
Denominator	All episodes of FN without microbial focus
Indicator 4	Percentage of febrile episodes in neutropenia with persistent fever without focus ( $>96$ h), in which an HRCT or BAL was performed
Numerator	The number of persistent FN episodes without microbial focus, in which an HRCT/BAL was performed
Denominator	All persistent FN episodes without microbial focus
Outcome indicators	
Indicator 5	The percentage of clinical FN episodes in children with cancer, in which a patient is admitted to the ICU
Numerator	The number of clinical FN episodes in children with cancer, in which a patient is admitted to the ICU
Denominator	All clinical FN episodes
Indicator 6	Cumulative incidence of children with cancer who die during a clinical FN episode
Numerator	The number of children with cancer who die during a clinical FN episode
Denominator	The total number of children with cancer diagnosed between January 1, 2014 and December 31, 2015, with the children with cancer who die not during a clinical FN episode as competing interest
Indicator 7	The percentage of clinical FN episodes of which patients have died
Numerator	The number of clinical FN episodes of which patients have died
Denominator	The total number of clinical FN episodes

of both equals success. For numerators and denominators, see Table 1. With regard to outcome indicators, we registered ICU admittance and inpatient mortality, the latter being interpreted with two indicators—one focusing on cumulative incidence of death during FN (with death not during FN as competing event) in children with cancer and one focusing on mortality rate in febrile neutropenic episodes.

**TABLE 2** Characteristics of the patients who suffered from one or more FN episodes

	n (%)
Patients	59 (100)
Sex	
Male	37 (62.7)
Female	22 (37.3)
Median age at diagnosis in years (minimum-maximum)	5 (0-17)
Deceased	3 (5.1)
Diagnosis group	
Hematological	41 (69.5)
Solid	13 (22.0)
Brain	5 (8.5)
Number of total FN episodes per hospital	119 (100)
UMCG	88 (74.0)
Medical Center Leeuwarden	18 (15.2)
Isala Zwolle	13 (10.9)
Relapsed disease	10 (16.9)
Number of FN episodes per patient	59 (100)
1	26 (44)
2	18 (30.5)
3	8 (13.6)
4	3 (5.1)
5	3 (5.1)
6	1 (1.7)
Number of ICU admittances	22 (100)
With focus	6 (27.3)
Without focus	16 (72.7)

### 3.1 | Structure indicators (all hospitals)—indicators 1 and 2

Six (including all three hospitals where individual patient data were collected) out of nine hospitals stated they were using the DCOG guideline on FN for local care recommendations. The three remaining hospitals stated their local recommendations for FN conformed to the workbook *Supportive Care Pediatric Oncology* written by the DCOG in 2005. All nine hospitals however stated that their first choice of antibiotics in episodes without focus was ceftazidim (in line with DCOG guideline recommendation).

### 3.2 | Process indicators—indicators 3 and 4

A total of 181 children were diagnosed with cancer between January 1, 2014 and December 31, 2015 in the north of the Netherlands, of whom 30 had died (16.6%) at the moment of data collection. In total, 119 FN episodes occurred in 59 patients, ranging from one to six episodes (median 2) per patient (see Table 2 for characteristics). Three of the 59 included patients had died during an FN episode, one in a shared-care hospital and two in the academic hospital.

Of the 119 FN episodes, 108 were without focus. These were all (100%; 95% CI 0.97-1.00) treated with ceftazidim according to the DCOG guideline. Furthermore, 14 episodes of persistent fever (>96 h) occurred, in which we found that a timely HRCT thorax and/or BAL was performed in 12 of the 14 episodes (85.7%; 95% CI 0.6-0.96). In both cases where additional testing deviated from the DCOG guideline, the HRCT and/or BAL was performed 2 days over time without any registered reason for delay. Both patients were (since fever onset) admitted to the academic hospital; thus, transfer from a shared-care hospital could not have caused the delay.

### 3.3 | Outcome indicators—indicators 5, 6, and 7

Of all 119 episodes of FN, 22 (18.5%; 95% CI 0.13-0.26) resulted in ICU admittance, of which 16 were without focus at the onset of the fever. In all 22 episodes, the children were initially admitted with fever to the academic hospital (only hospital with a pediatric ICU in the area). We could not determine whether this was related to the severity of the FN episodes (this was not studied).

Of the 181 children diagnosed with cancer, three died during FN admission. Correspondingly, the cumulative incidence of death during FN was 1.74% (indicator 6). In addition, this means that three of 119 FN episodes resulted in death (2.5%; 95% CI 0.01-0.07) (indicator 7).

We tried to elucidate the cause of death for these three children. Diagnoses were ALL (n = 1), mixed phenotype acute leukemia (n = 1), and osteosarcoma (n = 1). One patient died in a shared-care hospital (second episode of FN) due to a fulminant *Escherichia Coli* sepsis, before pediatric intensivists of the academic hospital arrived onsite to transfer the child to the ICU. Two patients died in the academic hospital; one patient (fourth episode) died of *E. Coli* sepsis, and for the other patient (fifth episode) the cause of death remains unknown (negative blood cultures, no approval of parents for autopsy).

## 4 | DISCUSSION

In this study, we developed indicators to evaluate the quality of care concerning FN episodes in children with cancer. We found that six out of nine hospitals in the north of the Netherlands use the appropriate DCOG guideline on FN. Furthermore, the recommendation of this guideline to use monotherapy with ceftazidim in episodes without focus was accurately adhered to, and the recommendation to perform additional testing in prolonged fever episodes was largely adhered to. However, FN still puts a large burden on medical, social, and financial aspects; in our cohort of 181 children with cancer, 119 admissions because of FN episodes occurred. Additionally, one in five FN episodes resulted in ICU admission and one in 40 FN episodes resulted in death.

### 4.1 | Implementation of the DCOG guideline

Overall, it can be said that the DCOG guideline on FN is implemented quite successfully, as it has been shown in the three largest hospitals that if hospitals indeed use the DCOG guideline for guidance, the adherence is excellent considering the choice of antibiotics in FN episodes without focus (100%).

Six out of nine hospitals used the DCOG guideline for guidance. The other three used an outdated workbook (published in 2005), in which the recommendation on the use of antibiotics in febrile episodes without focus was ceftazidim as well. Even though we did not perform a formal analysis of which recommendations were used in certain hospitals and whether these recommendations differed from the new guidelines or not, there is a risk of suboptimal care as these guidelines are outdated and new guidelines are already in use.

In our study, ICU admission occurred in 18.5% of all episodes. Comparable studies are scarce, but we found that in adults with cancer, 14% of episodes with FN resulted in ICU admittance.<sup>17</sup>

Furthermore, cumulative incidence of death during an FN episode was 1.74% in our cohort. In a study on infection-related deaths in children with ALL, the mortality rate due to sepsis was 2.4%.<sup>6</sup> With this information being given, we may draw the conclusion that the quality of care with regard to the outcomes of FN in the north of the Netherlands is comparable to that found in the (sparsely available) literature. Naturally, this study only provided us with baseline measurements, which will be repeated to evaluate quality of care over time.

## 4.2 | Limitations

We chose a balanced approach of rigorous and pragmatic indicator development. Therefore, this study can be seen as a practice example of how to develop high-quality indicators and produce baseline measurements in a relatively short period of time. However, the content of these indicators might differ from those that are developed using more rigorous and time-consuming methods.

Another limitation is the nature of retrospectively acquired data. While this study benefits from the advantages of this type of data collection (eg, instant availability), data were restricted to those already collected by routine clinical care. Therefore, in a follow-up project, we will identify the variables needed in the EPR and structurally collect prospective data.

As some of the included patients had relapsed before data collection, we worried this might introduce bias and hence limit generalizability. Therefore, we performed a sensitivity analysis wherein all FN episodes that occurred during relapse ( $n = 12$ ) were removed, which did not change our findings meaningfully.

In addition, we only included the three largest centers for individual patient data collection; we did not perform this in the six smaller centers. There might have been admissions due to FN in these centers that we were not aware of. If anything, this would mean that our identified incidence (and thus burden) of FN might even be an underestimation.

Lastly, this first implementation was only done in the north of the Netherlands, which is a relatively small area. Thus, it might be possible that the nationwide quality of the provision of supportive care differs from that in our findings.

## 4.3 | Recommendations for future use of indicators in FN

The developed indicators have been shown to be useful and can therefore be implemented nationally (and internationally). In the

Netherlands, all children with cancer will predominantly be treated at the Princess Máxima Center for Pediatric Oncology (opening mid-2018) in collaboration with shared-care centers. To evaluate and compare the quality of care in all the hospitals involved in treating children with FN, measuring these indicators will be important. However, using our methods, this will be costly in terms of both time and money, as every single patient with an FN episode has to be selected by hand. Therefore, we recommend saving all the information needed for these indicators electronically, automatically, and nationally. Furthermore, it will be important that guidelines be linked to the EPR. An automated program should be interwoven with the EPR to stimulate care based on current guidelines and to evaluate the indicators. This program might also facilitate necessary checks (eg, "is the patient indeed febrile?"). Moreover, we should develop a learning cycle to get insight on why some children suffer from (major) adverse effects while others do not. This will be essential in order to improve the quality of supportive care in children with cancer.

## 5 | CONCLUSION

This study on the implementation of indicators for FN served as a baseline measurement of quality of care. We found that guidelines are suboptimally implemented: three out of nine hospitals used an outdated workbook. The relatively high rates of mortality and ICU admissions show that FN still puts great burden on children with cancer.

Ideally, these indicators should be implemented nationwide in the Netherlands and all the information needed for these indicators should be saved nationally and electronically in order to keep track of changes in quality of care concerning FN. Also, we would like to repeat this study in 5 years and expand it to all Dutch hospitals caring for children with cancer, to get a more comprehensive overview and to identify any improvements or deteriorations. In addition, this study serves as a practical example of a rigorous but pragmatic method of development of indicators and we encourage this to be replicated in other fields of (pediatric) medicine as well.

## ACKNOWLEDGMENTS

We would like to thank Nynke Zwart for providing a list of all the children diagnosed with cancer in the north of the Netherlands. We would also like to thank local pediatricians for completing the questionnaire. The project "Towards evidence-based guidelines for supportive care in childhood oncology" is supported by the Alpe d'HuZes Foundation (Dutch Cancer Society; RUG 2013-6345).

## CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** ten Berg S, Loeffen EAH, van de Wetering MD, et al. Development of pediatric oncology supportive care indicators: Evaluation of febrile neutropenia care in the north of the Netherlands. *Pediatr Blood Cancer*. 2019;66:e27504. <https://doi.org/10.1002/pbc.27504>