Clinical Trial

Risk-adapted approach for fever and neutropenia in paediatric cancer patients — A national multicentre study

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Antibiotics;
Risk assessment model

Abstract  Background: In this national multicentre study, we examined the safety of reducing antibiotics in selected paediatric cancer patients with febrile neutropenia.

Methods: Patients with signs of a bacterial infection and/or abnormal vital signs indicating sepsis were considered high risk and received antibiotic therapy. Remaining patients were allocated to low- or medium risk, depending on their interleukin-8 level. Low-risk patients did not receive any antibiotics and were discharged from the hospital after having been afebrile for 12 h. Medium-risk patients were re-evaluated after 72 h of antibiotic treatment and, in selected patients, antibiotics were stopped.

Results: Two hundred thirty-three febrile neutropenic episodes in 141 paediatric cancer patients were included in the study. Sixty-four episodes were classified high risk (28%), 122 medium risk (52%), and 47 (20%) low risk. In the medium-risk group, antibiotics were stopped after 72 h in 50 in 122 episodes (41%). Median duration of antibiotic treatment and hospital
admission was significantly lower in low- and medium-risk episodes with early discharge. No failures were observed in the medium-risk group with early discharge. In the low-risk group, six failures were observed (12.8%), due to coagulase-negative staphylococci-positive blood cultures and recurrent fever. Conclusion: We showed that it is safe to shorten antibiotic treatment to 72 h in selected medium-risk patients with febrile neutropenia, regardless of the neutrophil count. The safety of withholding antibiotics in selected low-risk paediatric cancer patients with febrile neutropenia requires further investigation, using more suitable definitions for safety. Reduction in hospital admissions allows children with cancer more time at home and consequently improves their quality of life.

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1. Introduction

Infectious complications are still a major cause of morbidity and mortality in paediatric cancer patients. Since delaying antibiotic treatment until the focus of infection has been identified may have rapid lethal consequences, standard care for paediatric cancer patients presenting with febrile neutropenia is hospital admission for empirical treatment with broad-spectrum intravenous antibiotics. Usually, patients are not discharged until fever has resolved and the absolute neutrophil count (ANC) has recovered, which normally takes at least 5–7 d [1].

However, in only 20–30% of paediatric cancer patients with febrile neutropenia is an actual bacterial infection documented [1–3]. Besides bacterial infection, there are many other potential inducers of fever, including viral infections, transfusion of blood products, cytostatic drugs, the malignancy itself, and mucositis. These other causes do not require antibiotics, implying that there is considerable overtreatment in paediatric cancer patients with febrile neutropenia. This overtreatment comes with extra hospital admissions and invasive medical procedures that affect quality of life for both children and their families [4]. In addition, it leads to increased healthcare costs [5], emergence of resistant pathogens [6], negative side-effects of antibiotics, and nosocomial infections [7].

Previously, we have examined the feasibility of withholding antibiotics in adult and paediatric cancer patients with febrile neutropenia by using a risk assessment model based on objective clinical parameters (i.e. blood pressure, heart rate, and respiratory rate) in combination with the infectious biomarker interleukin-8 (IL-8) [8]. IL-8 is a cytokine with powerful chemotactic activity for neutrophils and is released from monocytes, endothelial cells, and many other cells in response to IL-1, tumour necrosis factor and lipopolysaccharides [9]. IL-8 levels have been shown to increase much earlier than CRP levels, and increased levels can be detected even before onset of fever [10,11].

By using this risk assessment model, we demonstrated that it was safe to withhold antibiotics in selected cancer patients who are at low risk for bacterial infection [8]. However, this was a monocentre study, including only a small group of paediatric cancer patients.

In addition to examining the safety of withholding antibiotics in low-risk patients, as previously described, we expanded the risk assessment model, by examining the safety of shortening antibiotic therapy in a selected group of medium-risk patients. In the current study, we examined the safety and feasibility of this expanded risk assessment model in a large group of paediatric cancer patients with febrile neutropenia in a multicentre setting.

2. Patients and methods

2.1. Patients

Outpatient paediatric cancer patients presenting with fever and chemotherapy-induced neutropenia were eligible for inclusion in the study. Fever was defined as a single body temperature (measured at the axilla) >38.5 °C, or two or more recordings of >38.0 °C during a 6-h period. Neutropenia was defined as ANC <0.5 × 10⁹/l [12] or, if not available, leucocytes <1.0 × 9/l. Patients who had received antibiotics other than the usual prophylactic antibiotic treatment strategies (i.e. selective gut decontamination, Pneumocystis jiroveci prophylaxis, or group Viridans streptococcus prophylaxis (pheneticillin 50 mg/kg/d in three doses orally)) or had undergone allogeneic stem cell transplantation in the previous month were excluded from the study.

All patients underwent a physical examination at presentation. In addition to routine blood counts, diagnostic blood cultures were performed and a plasma sample was taken to measure the plasma IL-8 concentration at presentation with febrile neutropenia and 12–24 h later.
2.2. Study design

This prospective multicentre study was performed in a total of six hospitals in the Netherlands (University Medical Centre Groningen (UMCG), Academic Medical Centre (AMC) Amsterdam, Free University Medical Centre (VUMC) Amsterdam, Erasmus Medical Centre Rotterdam, Leiden University Medical Centre (LUMC), and Isala Klinieken Zwolle) from June 2006 until January 2012. Medical ethics committees of every participating hospital approved the study protocol. The study was registered at www.trialregister.nl, trial ID number NTR3165. All patients and/or their parents, dependent on age, gave written informed consent for participation.

2.3. Risk assessment model

The new expanded risk assessment model based on clinical parameters and IL-8 is shown in Fig. 1. Patients who presented with signs of a local bacterial infection and/or abnormal vital signs indicating sepsis were allocated to the high-risk group. Abnormal vital signs indicating sepsis were defined as systolic blood pressure less than $-2$ standard deviation (SD) below normal for age and sex or heart rate and respiratory rate higher than $+2$ SD above normal for age and sex, see Supplementary Table 1. These patients were admitted immediately and received intravenous broad-spectrum antibiotic treatment.

The remaining patients were allocated to the medium- or low-risk group based on their plasma IL-8 level (determined at admission and after 12–24 h). Patients with two subsequent plasma IL-8 levels below the cutoff value (60 ng/l) were classified as low risk. In low-risk patients, antibiotics were withheld, and they were discharged after 12 h of afebrile observation.

If the first or second IL-8 measurement was above the cut-off value, the patient was classified as medium risk. Medium-risk patients were admitted and intravenous broad-spectrum antibiotics were started. New in this risk assessment model, compared to the one of Oude Nijhuis et al. [8], was the re-evaluation of medium-risk patients after 72 h of antibiotic treatment. If after 72 h of antibiotic treatment, a patient had been afebrile for at least 24 h, with no clinical signs of infection (defined by signs of local bacterial infections and/or abnormal vital signs indicating sepsis), and blood cultures were still negative, antibiotics were stopped and the patient was discharged. If one of the above-mentioned criteria was not met, antibiotics were continued according to the standard care for paediatric cancer patients with febrile neutropenia.

Following discharge, low- and medium-risk patients with early discharge were contacted daily by the research physician or nurse until day 8 of the study protocol.

![Fig. 1. The risk assessment model of the interleukin-8 (IL-8) study. Note: HF: heart frequency, RF: respiratory frequency, RR: blood pressure, and iv: intravenous.](image-url)
2.4. Laboratory methods

Plasma IL-8 concentrations were measured using the solid-phase, two-site chemiluminescent immunometric assay according to the manufacturer’s instructions (Immulite 1000, Diagnostic Products Corporation, Los Angeles, CA). The lower detection limit of the assay is 5 ng/l. The result of this IL-8 determination was available within 30 min. The cut-off value was based on our previous study results and set at 60 ng/l [8,13].

2.5. Outcome

The primary outcome of this study was the safety of the risk assessment model in the low- and medium-risk groups.

In the low-risk group, the safety of withholding antibiotics in low-risk paediatric cancer patients with febrile neutropenia was investigated. Failure was defined according to the previous multicentre study in paediatric febrile neutropenia was investigated. Failure was defined according to the previous multicentre study in paediatric and adult patients [8], as one of the following situations: a) recurrent fever (defined by development of fever after a 24-h afebrile period until day 5 after inclusion); b) isolation of a bacterial pathogen from the blood cultures in patients classified as low risk; and c) persistent fever (defined by body temperature >38.5°C for at least 12 h between 48 and 72 h after inclusion in the study). A failure consequently lead to re-admission to the hospital and start of antimicrobial treatment.

In the medium-risk group, we studied the safety of discharge 72 h after start of antibiotics. Failure in the early discharge medium-risk group was defined as one of the following situations: a) isolation of a bacterial pathogen from the blood cultures in patients classified as low risk; and b) recurrent fever (defined by development of fever after a 24-h afebrile period until day 5 after inclusion).

A serious adverse event, defined by death or cardiac and/or respiratory support on the intensive care unit (ICU) attributable to infection during the first 5 d after inclusion in patients who were classified as low- or medium risk with early discharge, was determined to be an absolute reason for immediate cessation of the study.

Secondary outcomes of this study were bacteraemia, duration of fever, duration of neutropenia, duration of antibiotic treatment, duration of hospitalisation, and complications (i.e. admission to the ICU or death of the patient).

2.6. Statistical analysis

Patients’ characteristics in each risk group were compared using chi-square analysis (sex and malignancy) or Kruskal–Wallis test (age). Power analysis was performed at the design stage of the study. The primary outcome of the study was safety of the risk assessment model. Safety was defined as a failure rate of ≤10% in the medium-risk group with early discharge, and 95% confidence intervals were computed according to the efficient-score method corrected for continuity [14]. Using an alpha level of 5% and a power of 80%, it was estimated that at least 35 experimentally treated medium-risk patients were required in the case of 0 failures; at least 54 experimentally treated medium-risk patients in the case of 1 failure; and 70 experimentally treated medium-risk patients in the case of 2 failures [15]. Assuming 20% of all episodes would be medium risk with experimental treatment, a total of 175, 270, or 350, respectively, inclusions would be needed.

It was possible to enroll patients several times. To account for possible correlations between episodes within the same patient, a generalised estimating equation (GEE) [16] was fitted for characteristics of the febrile neutropenic episodes (temperature and laboratory measures) and the secondary outcomes (duration of fever, duration of neutropenia, duration of intravenous antibiotic treatment, and duration of hospitalisation). The adjusted mean for each risk group with their corresponding sandwich standard error and confidence intervals were computed. GEE is a well-known statistical methodology used in the analysis of data that are correlated within subjects such as data provided in this study. Failure to incorporate correlation of responses can give an incorrect estimation of regression model parameters, particularly in case where such correlations are large and lead to incorrect conclusions concerning the research question. Standard approaches such as analysis of variance are inadequate because covariance among the observations is ignored.

In all analysis performed in this article, a two-sided P-value of <0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics 18. To fit the GEE model, SPSS version 18 was used.

3. Results

3.1. Patient characteristics

During the study period, 247 febrile neutropenic episodes were included in 148 patients. Fourteen febrile neutropenic episodes were excluded because of protocol violations, i.e. administration of antibiotics in (possible) low-risk episodes, discharge of patients classified as low risk without having been afebrile for at least 12 h, or withholding second IL-8 measurement in potentially low-risk episodes. Finally, 233 febrile neutropenic episodes were included in 141 paediatric cancer patients. One hundred sixty-five episodes were included in 141 paediatric cancer patients. Ninety patients were enrolled only once, whereas 51 were enrolled more than once: 31 had 2 episodes and 20 had ≥3 episodes (median 1, range 1–6). Patient
Episodes of febrile neutropenia occurred in 5 in 64 high-risk episodes (8%, 95% confidence interval [CI] 1.2–14.3%). No deaths occurred in the high-risk episodes and all patients recovered without sequelae.

3.2. Low-risk group
In 47 of 233 febrile neutropenic episodes (20%), IL-8 levels were below the cut-off both at presentation (median 25, range 5–56 ng/l) and after 12–24 h (median 21, range 5–47 ng/l), and were, therefore, classified as low risk. In these episodes, patients did not receive any antibiotics and were discharged after having been afebrile for at least 12 h (after median 3 d, range 0–11 d).

In the low-risk group, six failures were observed (12.8%, 95% CI 4.8–25.7%). In three low-risk episodes, the initial blood culture became positive (after median 2 d, range 2–3 d). In all three cases, the cultured pathogens were coagulase-negative *staphylococci* (CNS). All three patients had not yet met the criterion of being afebrile for at least 12 h, and, therefore, were still in the hospital. Antibiotics were started immediately after the cultures became positive. No complications occurred in any of the three patients, and patients recovered completely.

In three other low-risk episodes, patients were readmitted within 5 d after inclusion because of recurrent fever (all three at day 5 after inclusion). Antibiotics were started promptly in these patients,

### Table 1
Characteristics of patients included in the study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>141</td>
</tr>
<tr>
<td>Sex – male (%)</td>
<td>69 (49%)</td>
</tr>
<tr>
<td>Age at diagnosis – median (range)</td>
<td>5 (0–17)</td>
</tr>
</tbody>
</table>

### Table 2
Characteristics of the febrile neutropenic episodes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes (total 233)</td>
<td>64 (28%)</td>
<td>122 (52%)</td>
<td>47 (20%)</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.8 (38.7–39.0)</td>
<td>38.8 (38.7–39.9)</td>
<td>38.6 (38.4–38.8)</td>
<td>0.157</td>
</tr>
<tr>
<td>Hb mmol/l – mean (95% CI)</td>
<td>5.23 (4.99–5.46)</td>
<td>5.24 (5.03–5.45)</td>
<td>5.19 (4.86–5.51)</td>
<td>0.967</td>
</tr>
<tr>
<td>Leucocytes × 10⁹ – mean (95% CI)</td>
<td>0.61 (0.44–0.77)</td>
<td>0.50 (0.37–0.63)</td>
<td>0.91 (0.69–1.12)</td>
<td>0.007</td>
</tr>
<tr>
<td>Neutrophils × 10⁹ – mean (95% CI)</td>
<td>0.18 (0.13–0.23)</td>
<td>0.19 (0.15–0.23)</td>
<td>0.17 (0.13–0.22)</td>
<td>0.805</td>
</tr>
<tr>
<td>Thrombocytes × 10⁹ – mean (95% CI)</td>
<td>54.4 (40.2–68.5)</td>
<td>71.8 (53.8–89.7)</td>
<td>88.5 (57.8–119.2)</td>
<td>0.081</td>
</tr>
<tr>
<td>CRP ng/l – mean (95% CI)</td>
<td>80.2 (59.2–101.2)</td>
<td>61.6 (45.6–77.7)</td>
<td>35.2 (24.7–45.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval.
regardless of IL-8 levels. No bacterial infection was identified in any of these patients neither on initial admission nor during re-admission, and no clinical complications occurred.

Overall, no severe adverse events were observed in the low-risk group.

### 3.3. Secondary outcomes

Bacteremia was found in 37 episodes (15.9%). The majority of the bacteremias, namely 81% (30 in 37), was caused by Gram-positive bacteria, mainly *Streptococcus* spp. (14 in 37 [38%]) and CNS (11 in 37 [30%]). Most positive blood cultures were identified in high-risk episodes (16 in 64, 25%) and medium-risk episodes with complete antibiotic therapy (18 in 72, 25%). The sensitivity of the new expanded risk assessment model for predicting bacteremia was 92% (34 in 37, 95% CI 79–98%). Specificity, positive predictive value, and negative predictive value were 48% (94 in 196, 95% CI 41–55%), 26% (34 in 136, 95% CI 18–33%), and 97% (94 in 97, 95% CI 90–99%), respectively.

Duration of fever and duration of neutropenia were significantly higher in the high- and medium-risk groups with complete antibiotic treatment than in the early-discharged medium- and low-risk groups (see Table 3). No antibiotics were given to patients in the low-risk group (except for the three patients with CNS-positive blood cultures and the three patients with recurrent fever). Intravenous antibiotic therapy was given for a mean duration of 8.7 and 9.2 d in high- and medium-risk groups with complete antibiotic treatment. The mean duration of hospitalisation was 12.0 and 11.2 d in the high- and medium-risk groups with complete antibiotic treatment, compared to 4.7 and 3.6 d in the early-discharged medium- and low-risk groups (p < 0.001). The outcome variables for initial febrile neutropenic episodes only (n = 141) showed similar results, see Supplementary Table 3.

### 4. Discussion

In this study, we examined the safety of reducing antibiotic treatment in paediatric cancer patients with febrile neutropenia, by using our expanded risk assessment model, in a prospective, multicentre setting in the Netherlands. By using this new expanded risk assessment model, based on objective clinical parameters in combination with the infectious marker IL-8, we distinguished three risk groups for bacterial infection: high-, medium- and low risks. In 97 of 233 included febrile neutropenic episodes (41%), patients benefited from the risk assessment model by shortening or even withholding antibiotic treatment and shortening of the hospital stay. We showed that it is safe to shorten antibiotic treatment to 72 h in selected medium-risk patients with febrile neutropenia, regardless of the neutrophil count. The safety of withholding antibiotics in selected low-risk paediatric cancer patients with febrile neutropenia was not shown to be safe and requires further investigation, using more suitable definitions for safety.

It is well known that paediatric cancer patients with febrile neutropenia are a heterogeneous group of patients concerning the risk of complications during febrile neutropenia, with only a small part of patients developing serious infectious complications. In the past decade, many studies have been performed examining various risk factors for predicting bacterial infection in paediatric cancer patients with febrile neutropenia, including patient characteristics, laboratory measures and infectious biomarkers [13,17–25]. Some studies did examine initial or step down outpatient or oral antibiotic therapy [26–32]. However, results are largely varying and none has been fully validated. In 2012, Lehrnbecher et al convened a panel of paediatric cancer and infectious diseases experts and developed an evidence-based guideline for the empiric management of febrile neutropenia in paediatric cancer patients [33]. They strongly recommended antibiotics should be

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**Table 3**

<table>
<thead>
<tr>
<th>Secondary end-points.</th>
<th>High risk</th>
<th>Medium risk - antibiotics continued after 72 h</th>
<th>Medium risk - antibiotics stopped after 72 h</th>
<th>Low risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) (total 233)</td>
<td>64 (27)</td>
<td>72 (31)</td>
<td>50 (21)</td>
<td>47 (20)</td>
<td>0.031</td>
</tr>
<tr>
<td>Bacteremia – n (%)</td>
<td>16 (25)</td>
<td>18 (25)</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of fever (d) – mean (95% CI)</td>
<td>4.1 (3.0–5.2)</td>
<td>4.8 (4.0–5.5)</td>
<td>1.6 (1.4–1.8)</td>
<td>1.8 (1.5–2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of neutropenia (d) – mean (95% CI)</td>
<td>8.8 (6.5–11.2)</td>
<td>7.2 (5.8–8.6)</td>
<td>6.5 (4.6–8.3)</td>
<td>5.6 (3.5–7.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>Duration of intravenous antibiotic treatment (d) – mean (95% CI)</td>
<td>8.7 (7.6–9.9)</td>
<td>9.2 (8.3–10.2)</td>
<td>3.5 (3.3–3.7)</td>
<td>0.6 (0.0–1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of hospitalisation (d) – mean (95% CI)</td>
<td>12.0 (8.7–15.3)</td>
<td>11.2 (9.2–13.1)</td>
<td>4.7 (4.3–5.1)</td>
<td>3.6 (2.8–4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications – n (%)</td>
<td>5 (8)</td>
<td>5 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** CI: confidence interval.
discontinued in patients who are clinically well with negative blood cultures at 48 h, who have been afebrile for at least 24 h and who have evidence of marrow recovery. Moreover, they also recommended that in low-risk patients, discontinuation of empiric antibiotics may be considered at 72 h when blood cultures are still negative and patients have been afebrile for at least 24 h, irrespective of marrow recovery, as long as careful follow-up is ensured. This (weak) recommendation was based on one randomised controlled trial in a monocentre study in Chile in 1997 who randomly assigned low-risk patients to either stopping or continuing antibiotics on day 3 irrespective of bone marrow status and found no difference in outcome and no infectious deaths [34]. In the present study, we examined the safety of shortening antibiotic treatment in selected febrile neutropenic episodes, regardless of the neutrophil count, in a prospective multicentre setting. Medium-risk patients were re-evaluated after 72 h of antibiotic treatment; if a patient had been afebrile for at least 24 h, there were no signs of infection, and blood cultures were still negative, antibiotics were stopped and the patient was discharged, irrespective of the ANC. No failures (defined by positive blood cultures or relapse fever) were observed in this group.

Our study was designed to extend the concept of reducing antibiotics even further. Antibiotics were withheld completely in selected patients with low-risk febrile neutropenia. Oude Nijhuis et al. previously stated that it was safe to withhold antibiotics in a group of cancer patients aged 0–77 years in a single-centre study [8]. In the present study, we examined the safety of withholding antibiotics in a multicentre setting, including only children with febrile neutropenia. Twenty percent of all febrile neutropenic episodes were classified as low risk and as such they did not receive any antibiotics. They were discharged after having been afebrile for at least 12 h. In these patients, two problems were encountered, leading to a failure rate of 12.8%. Firstly, in three episodes classified as low risk (6.4%), patients were discharged at day 2, but developed relapse fever with 5 d of admission. They were re-admitted and were started on intravenous antibiotics promptly. No bacterial infections were documented in these patients and importantly no complications occurred either during the initial admission or during re-admission periods. Non-documented viral infections were most likely to have been the cause of (relapse) fever. In the study of Oude Nijhuis et al., relapse fever was not seen in low-risk patients [8]. However, both paediatric and adult cancer patients were then included, whereas the present study included only paediatric cancer patients. It has been described that viral infections are seen more often in paediatric than in adult cancer patients [2] which may be the cause of the higher rate in relapse fevers in the present study.

The second problem encountered in the low-risk group comprised CNS cultured from blood, which occurred in three febrile neutropenic episodes (6.4%). These patients were still in the hospital at the time of the positive blood culture, since they had not been afebrile for at least 12 h, and appropriate antibiotics were started promptly. No other clinical signs of infection were observed, and no complications occurred. In the Netherlands, the majority of paediatric cancer patients have indwelling central venous access catheters, from which blood cultures are usually obtained. CNS are commensal skin organisms that often contaminate blood cultures [35]. The positive predictive value of blood cultures drawn from an indwelling central venous catheter has been shown to be lower than from a peripheral venous puncture [36]. The question arises whether the CNS grown in blood cultures of our three low-risk paediatric cancer patients was caused by contamination, local infection of the intravascular device, or true bacteremias. However, the normally low-virulent CNS can be threatening in paediatric cancer patients with febrile neutropenia, and, therefore, may have to be regarded as an actual bloodstream infection in these patients, especially when there has been taken only a single blood culture, if an alternative source of infection is not identified [37].

Since our definition of safety is a failure rate of ≤10%, and in our study, we observed a failure rate of 12.8% (95% CI 4.8–25.7%) in the low-risk group, we have to conclude that withholding antibiotics in selected paediatric cancer patients with febrile neutropenia have not been proven to be safe. Perhaps, completely withholding antibiotics in paediatric cancer patients with febrile neutropenia who were selected low risk according to our risk assessment model is simply not safe. However, our definitions of failure may also have been too stringent; particularly, to define re-admission due to relapse fever, a failure seems to be too stringent. We propose in the next study to define failure in the low-risk group as isolation of a bacterial pathogen from the blood cultures in patients classified as low risk. Moreover, for safety reasons, patients in the low-risk group presenting with recurrent fever need to be readmitted, but no antibiotics should be started and the event should not be called a failure until blood cultures become positive.

We are aware that our study has limitations. Although the setting of the present study was multicentre, the majority of patients were included in one centre. Difficulties in implementation of the study, including obtaining approval of the local ethics committees and introducing the laboratory measurement of IL-8, lead to a considerable delay in some of the hospitals and as a result reduced the number of patients they were able to include during the study period. Nevertheless, the prospective origin of the study plus the substantial number of febrile
neutropenic episodes included are important strengths of this study. The actual number of inclusions eventually was even higher than were strictly needed from the power analysis. The time period that we had estimated in advance that would be needed to recruit the number of patients needed turned out to be longer than was actually needed, since there were zero failures in the experimentally treated medium-risk patients. We did decide to continue the study to further fortify our findings.

It would be interesting to examine in future studies whether it is possible to optimise our risk assessment model further. Possibly, the addition of another biomarker may be useful. Although CRP was significantly different among the risk groups in our study, it is not useful in the risk assessment model because of the widespread values. Procalcitonin has been described to be a promising diagnostic marker for the detection of bacterial infection in paediatric cancer patients, particularly when measured serially [13,38–43].

In conclusion, our results show that by using a risk assessment model based on objective clinical parameters in combination with plasma IL-8, antibiotic over-treatment in paediatric cancer patients with febrile neutropenia may be reduced considerably. It was shown to be safe to shorten antibiotic treatment in selected medium-risk febrile neutropenic paediatric cancer patients, regardless of the neutrophil count. The safety of withholding antibiotics in selected low-risk febrile neutropenic paediatric cancer patients requires further investigation, using more suitable definitions for safety.

It is important to develop new methods to safely reduce antibiotic overtreatment in paediatric cancer patients with febrile neutropenia, as reduction in hospital admissions allows children with cancer more time at home and consequently improves their quality of life.

Conflict of interest statement

None declared.

Role of the (funding) sources

The study was supported by the KiKa foundation. The work of K.G.E. Miedema has been supported by the ODAS foundation. Siemens supported the study by providing the Immulite 1000 at the various participating centres.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.10.065.

References


