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Clinical Trial

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

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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

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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.

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 $<0.5 \times 10^9$/l [12] or, if not available, leucocytes $<1.0 \times 9^9$/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.