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Original Article

# Clinical efficacy of cycling empirical antibiotic therapy for febrile neutropenia in pediatric cancer patients

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ABSTRACT

*Background:* Febrile neutropenia (FN) is the main treatment-related cause of mortality among children with cancer, as the prolonged use of broad-spectrum antibiotics can lead to antibiotic resistance in these patients. Antibiotic cycling has been reported to limit the emergence of antibiotic-resistant bacteria among adult patients. However, no studies have evaluated pediatric patients with FN.

*Methods:* Between September 2011 and February 2014, 126 pediatric cancer patients were admitted to our center for chemotherapy and/or hematopoietic stem cell transplantation and were included in this study.

Retrospective and prospective data collection were performed before and after antibiotic cycling, respectively. Between September 2011 and November 2012 (before antibiotic cycling was implemented), intravenous cefpirome was used as the empirical therapy for FN. Between December 2012 and February 2014 (after antibiotic cycling was implemented), the monthly antibiotic cycling involved intravenous piperacillin-tazobactam (PIPC/TAZ), intravenous meropenem or ciprofloxacin (CPFX), and intravenous cefepime in that order. For children aged ≥13 years, the monthly cycling involved intravenous PIPC/TAZ, and CPFX was administered.

*Results:* The detection rates for extended-spectrum β-lactamase producers in blood and stool culture samples decreased significantly after the implementation of antibiotic cycling (0.33/1000 patient-days vs 0/1000 patient-days, $p = 0.03$; 1.00/1000 patient-days vs 0/1000 patient-days, $p < 0.01$; respectively).

*Conclusion:* Antibiotic cycling was associated with a decreased emergence of multidrug-resistant microbes.



## 1. Introduction

Febrile neutropenia (FN) is one of the most common adverse events among patient receiving chemotherapy for cancer, and these patients have a high risk of developing serious infectious diseases after infection with various microbes [1].

The definition of FN from the Infectious Disease Society of America guidelines is generally used to identify patients who should receive empirical antibiotic therapy [2], and FN is associated with a mortality rate of 75% before the introduction of empirical antibiotic therapy [3]. The recent use of empirical antibiotic therapy for all patients with FN has been associated with a lower mortality rate, and the Infectious Disease Society of America recommended monotherapy with a broad-spectrum antibiotic in this setting (e.g., ceftazidime, imipenem-cilastatin, cefepime (CFPM), or piperacillin-tazobactam (PIPC/TAZ)) [2]. Pediatric cancer patients with FN frequently received prolonged broad-spectrum antibiotic treatment until their neutrophil counts recover to ≥500 cells/mm$^3$ and/or their infection resolves. Therefore, pediatric cancer patients with FN have a high risk of serious infections caused by antibiotic-

*Abbreviations:* FN, febrile neutropenia; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

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resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and extended-spectrum β-lactamase (ESBL) producers. Raymond et al. [4] have reported that antibiotic cycling can reduce the rates of bacteremia and infection-related mortality, and also control the emergence of antibiotic-resistant microbes in intensive care units. Antibiotic cycling has also subsequently been reported to limit the emergence of antibiotic-resistant bacteria among adult patients with FN [5–8]. However, no studies have evaluated pediatric patients with FN. Therefore, the present study evaluated the efficacy of cycling empirical antibiotic therapy for FN among pediatric cancer patients by analyzing blood culture-positive rates and the frequencies of antibiotic-resistant microbes before and after antibiotic cycling.

## 2. Patients and methods

### 2.1. Patients and samples

This study was performed in a pediatric ward at Kyushu University Hospital, and included 126 pediatric cancer patients who were admitted for chemotherapy and/or hematopoietic stem cell transplantation between September 2011 and February 2014. Patients who develop fever (axillary temperature of ≥38.0 °C for 1 h) and severe neutropenia (absolute neutrophil count of $<0.5 \times 10^9$/L) after chemotherapy or hematopoietic stem cell transplantation were included [2]. Patients with multiple FN events were eligible for the study. The study's protocol was approved by the ethics committee of Kyushu University Hospital. Two sets of blood samples were obtained from the patients using a peripheral blood and central venous catheter, and 3 mL of blood was inoculated into dedicated small culture bottles (appropriate for pediatric patients), which were then tested using a BACTEC™FX culture system (Becton Dickinson and Company, Tokyo, Japan). If just one of the 2 bottles of blood culture tested positive, we diagnosed bacteremia. Stool samples were obtained and cultured using 5% sheep blood agar (Becton Dickinson and Company). Nasal swabs were obtained and cultured using a BD BBL Culture Swab™ PLUS system (Becton Dickinson and Company). Blood, stool and nasal swab samples were obtained at the time of FN onset. Data before antibiotic cycling were collected retrospectively, whereas data after antibiotic cycling were collected prospectively. However, during both periods, some cases failed to undergo nasal swab and/or stool culture; thus the number of these culture was fewer than that of blood culture. All isolates were identified using the VITEK system (bioMerieux Japan, Tokyo, Japan), and their antibiotic susceptibilities were determined using the Clinical and Laboratory Standards Institute breakpoints [9].

### 2.2. Treatment protocol

Between September 2011 and November 2012 (before the antibiotic cycling was implemented), 69 eligible patients were admitted to the hospital (14,988 patient-days). During this period, intravenous cefpirome (CPR, every 8 h, 160 mg/kg/day) was used as the empirical therapy for FN. Between December 2012 and February 2014 (after the antibiotic cycling was implemented), 57 eligible patients were admitted to the hospital (16,202 patient-days). For children aged <13 years, the monthly antibiotic cycling involved intravenous PIPC/TAZ (every 6 h, 360 mg/kg/day), intravenous meropenem (MEPM, every 8 h, 120 mg/kg/day), and intravenous CFPM (every 8 h, 150 mg/kg/day) in that order. For children aged ≥13 years, the monthly cycling involved intravenous PIPC/TAZ, ciprofloxacin (CPFX, every 12 h, 10 mg/kg/day), and intravenous CFPM in that order (Fig. 1).

The antibiotics were administered using a central venous catheter as soon as possible after obtaining the blood samples, and were continued until the absolute neutrophil count recovered and/or the infection resolved. Prophylactic antibiotics were not used before or after the antibiotic cycling was implemented, and there were no differences in the standard precautions against FN. Data regarding the antibiotic treatments were obtained from the electronic medical records system at Kyusyu University Hospital. The defined daily doses per 1000 patient days before and after the implementation of antibiotic cycling were calculated as previously described [10].

### 2.3. Statistical analyses

Statistical differences were tested using the Fisher's exact test, and a $p$-value of <0.05 was considered statistically significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

## 3. Results

### 3.1. Patient characteristics

The patients' clinical characteristics are shown in Table 1. When we compared the groups from before and after the antibiotic

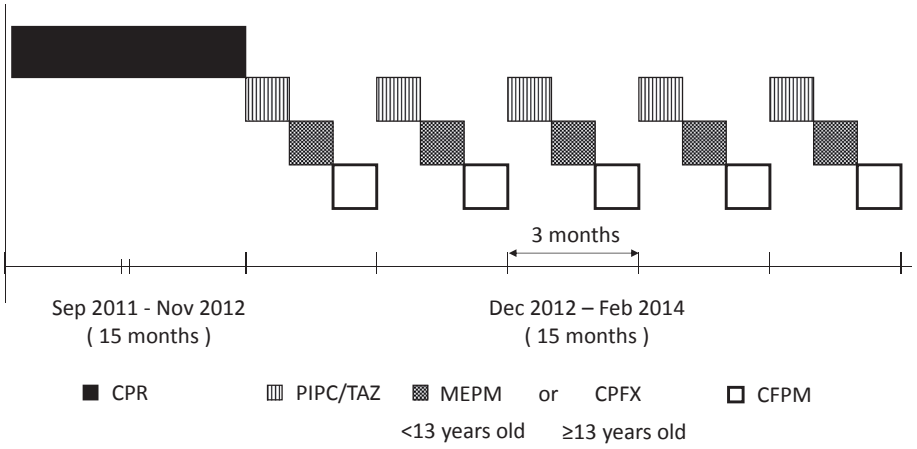


**Fig. 1.** Scheme for empirical treatment of febrile neutropenia. Antibiotic cycling was performed between December 2012 and February 2014 using the indicated antibiotics as empirical therapy. We used MEPM for children aged <13 years and used CPFM for children aged ≥13 years. CPR: cefpirome, PIPC/TAZ: piperacillin-tazobactam, MEPM: meropenem, CFPM: cefepime, CPFX: ciprofloxacin.