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Prophylactic levofloxacin in pediatric neutropenic patients during autologous hematopoietic stem cell transplantation

Hafez HA, Yousif D, Abbassi M, Elborai Y, Elhaddad A. Prophylactic levofloxacin in pediatric neutropenic patients during autologous hematopoietic stem cell transplantation.

Abstract: Background: Using fluoroquinolone prophylaxis in pediatric neutropenic patients is a controversial issue due to the concern about emergence of resistant strains in addition to the lack of pediatric studies. This study was performed to assess the effectiveness of levofloxacin prophylaxis in pediatric patients during autologous stem cell transplantation.
Methods: This was an observational study of pediatric patients who underwent autologous stem cell transplantation, comparing patients who received levofloxacin prophylaxis to historical controls.
Results: A total of 96 patients were included (46 patients in the control group and 50 patients received levofloxacin). The median duration till onset of first fever was 11 d in the control group as compared to 15 d in patients who received levofloxacin ($p \leq 0.001$). The incidence of infectious complications was higher in patients without levofloxacin (4/46) than those with levofloxacin (1/50). The median duration of empirical antibiotic use was 10 d in the levofloxacin group compared with 14 d in the control group ($p < 0.001$).
Conclusion: Levofloxacin prophylaxis delayed first spike of fever, decreased the incidence of septic complications, and shortened the duration of empiric antibiotic use, but its impact on emergence of resistant organisms should be closely monitored.

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Bacterial sepsis continues to be a leading cause of morbidity and toxic deaths in children receiving intensive therapy for hematological malignancies and for those undergoing hematopoietic stem cell transplantation (HSCT) (1).

The incidence of bacteremia during the neutropenic period post-HSCT ranges from 21% to 34% and 21% to 58% for patients undergoing autologous and allogeneic transplant, respectively (2–4). In most studies, gram-positive bacteria are the predominant pathogen. Bloodstream infections are an independent predictor of mortality after HSCT (5, 6). Delayed antibiotic initiation until bacteriological documented infection is associated with high risk of infection-related complications and mortality, so prophylactic and/or empiric antibiotic administration is mostly used. In HSCT recipients, sequential antibiotic regimens might be used, a prophylactic regimen on onset of neutropenia and an empiric regimen on onset of fever (7).

Studies of the use of prophylactic antibiotics in neutropenic adult oncology patients conducted over the last 30 yr have consistently shown efficacy in reducing the incidence of fever and microbiologically documented bacterial infections, but individually the studies have failed to show an effect on overall survival (8).

The investigation of the use of prophylactic antibiotics in children with cancer has been much more limited. Overall benefit of prophylactic antibiotic use in febrile neutropenic pediatric patients was previously demonstrated (9). A retrospective study in pediatric cancer patients undergoing HSCT both autologous and allogenic showed no difference in febrile episodes with fluoroquinolone prophylaxis than without, but there was significantly lower bacteremia in the prophylaxis

group (3). A pilot study of ciprofloxacin prophylaxis for pediatric patients receiving delayed intensification therapy for acute lymphoblastic leukemia showed a significant reduction in hospitalization, intensive care admission, and bacteremia compared to historical controls (10). In another study in acute myeloid leukemia pediatric patients, the only benefit of fluoroquinolone prophylaxis was the reduction in gram-negative bacteremia (11).

The Infectious Disease Society of America guidelines published in 2010 for the use of antimicrobial agents in neutropenic patients recommended prophylaxis for high-risk patients with expected durations of prolonged and profound neutropenia (ANC < 100 cells/μL) for more than seven d (12).

The main concern related to the prophylactic use of antibiotics remains the development of resistant organisms. Accordingly, transplant centers using fluoroquinolone prophylaxis are advised to institute surveillance measures to monitor for rates of vancomycin-resistant enterococci (VRE), *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and fluoroquinolone-resistant gram-negative organisms, as well as monitor antibiotic usage patterns (13).

Due to lack of evidence in the literature, this study was conducted to assess the effect of levofloxacin prophylaxis on the prevention of bacterial infection during profound neutropenia in pediatric patients undergoing autologous HSCT and to evaluate the effect of levofloxacin use on duration of antibiotic use and duration of hospitalization.

Patients and methods

This was an observational study with an historical control group conducted at the Bone Marrow Transplantation (BMT) units of the CCHE (Children Cancer Hospital, Egypt) and El-Sheikh Zayed Specialized Hospital in Cairo, Egypt. The study started in October 2010 till December 2012 in CCHE, and the historical control data were collected from patient files in El-Sheikh Zayed Specialized Hospital and CCHE, who underwent HSCT from September 2008 to October 2010. Prior to the opening of the Bone Marrow Transplant (BMT) Unit in CCHE in late 2009, CCHE patients had BMT performed in El-Sheikh Zayed Specialized Hospital. The study population consisted of pediatric patients (age below 18 yr) with hematologic or solid malignancies that underwent autologous peripheral stem cell transplantation, using the same myeloablative chemotherapy and following the same guidelines for infection control and treatment of infection in both institutions. Institution review board approval was obtained at both institutions. The collected data were stored in a password-protected database.

Levofloxacin prophylaxis was started as a part of the standard prophylactic antimicrobial regimen in both sites since October 2010 at a dose of (10 mg/kg/d for patients ≥5 yr with maximum 750 mg/d and 10 mg/kg/dose twice daily for those <5 yr with maximum 500 mg/d); both groups received the exact prophylactic antimicrobial regimen.

Levofloxacin administration was initiated in the study group from the beginning of the conditioning regimen till the first documented spike of fever. Patients in both the study and control groups were kept on general prophylactic measures which were oral acyclovir (750 mg/m^2/d, from day −10), oral fluconazole (6 mg/kg/d, from day −1), and oral trimethoprim-sulfamethoxazole (TMP-SMX) (2.5 mg/kg twice daily; till day −2, then resumed after engraftment).

Infection control measures, including handwashing policies and isolation procedures, remained constant and similar throughout the study period at both sites. Patients were kept in HEPA-filtered rooms till engraftment (ANC of >0.5 × 10^9/L and platelet count of >20 000 × 10^9/L for two consecutive days). Prophylaxis was continued until neutropenia resolved (rising ANC more than 500 cells/μL) or until first spike of fever (temperature, ≥38°C) or any other evolving sign of infection. Patients were physically examined daily for clinical signs of infection, and neutropenic fever was treated with empirical broad spectrum antibiotics (pipracillin/tazobactam and amikacin or cefoperazone/sulbactam and amikacin) according to the antimicrobial guidelines use in neutropenic patients in each institution.

Appropriate blood samples were sent for microbiological examination (culture and sensitivity). Antibiotics were continued until neutrophil recovery and infection resolved. If blood cultures were positive or a source of fever was identified, antimicrobial treatment was tailored accordingly.

The primary end point of the study was the occurrence of fever requiring empirical antibacterial therapy during neutropenia. Fever occurrence, laboratory results, antibacterial administration, and bacterial cultures were recorded.

Any infectious complications such as septic shock and death from infection, microbiologic features as causative organisms isolated during infection, source of infection, resistant strains, the duration of antibiotic use, frequency of antifungal administration, total duration of hospitalization

during the transplant period, and any documented signs of levofloxacin toxicity were also recorded and compared.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows. Continuous variables were analyzed as mean values ± standard deviation (SD) or median (range) as appropriate. Rates and proportions were calculated for categorical data. For categorical variables, results were compared using chi-square (χ^2) tests and Fisher's exact test when appropriate. Comparisons among continuous variables with normal distribution were analyzed by Student's *t*-test, while continuous variables without normal distribution were analyzed by the Mann–Whitney *U*-test. Kaplan and Meier procedure was used to analyze the time to first fever spike and comparisons between the two groups was made using the log-rank test. p-value of ≤0.05 was considered statistically significant.

Results

Clinical features of the study population

A total of 96 patients underwent autologous HSCT were included, 50 of which received prophylactic levofloxacin (the study group) and 46 patients did not receive levofloxacin prophylaxis (the control group). The demographic characteristics and clinical features, including age, diagnosis and conditioning regimen, were comparable between the two groups (Table 1).

Clinical febrile episodes

During the observation period of infection, Kaplan and Meier procedure was used to analyze the time to first fever spike, where 96% of the study group patients were fever free during the first week, and 62% remained fever free during the second week with median duration of 15 d from beginning of the conditioning chemotherapy (95% CI = 14–16), while in the control group patients, 67.4% were fever free during the first week and only 13%

Table 1. Demographic characteristics and clinical features of the patients' groups and their p-value showing no statistically significant difference in baseline characteristics (number [percentage] or median [range])

Factor Sample size (N)	Study group (with levofloxacin) N = 50	Control group (without levofloxacin) N = 46	p-value
Median age (range)	4.0 (1.1–16.0)	5.0 (1.5–17.0)	0.085
Gender (%)			
Male	32 (64.0)	34 (74)	0.295
Diagnosis (%)			
High-risk neuroblastoma	42 (84)	41 (89.1)	0.762
Hodgkin's lymphoma	7 (14)	5 (10.86)	
Wilms' tumor	1 (2)	0	
Remission status before SCT (%)			
CR	28 (56)	28 (61)	0.802
VGPR or PR	22 (44)	18 (39)	
Type of conditioning (%)			
BU/ALK	40 (80)	41 (89)	
CEM	3 (6)	0	
CMV	7 (14)	5 (11)	0.304
Laboratory values			
White blood cells $\times 10^3$ (cells/μL)	4.3 (2.1–9.9)	4.7 (2.4–14.9)	0.422
Absolute neutrophil count (ANC) (cells/mL)	2300 (315–7500)	2450 (98–9800)	0.565
Hemoglobin (g/dL)	11.2 (7.7–13.7)	11.0 (8.5–13.4)	0.292
Platelets $\times 10^3$ (cells/μL)	273 (118–2450)	234.5 (42–664)	0.017
Alanine aminotransferase (U/L)	28 (11–114)	32 (12–234)	0.145
Aspartate aminotransferase (U/L)	34 (15–104)	30 (12–134)	0.847
Total bilirubin (mg/dL)	0.6 (0.2–1.1)	0.5 (0.1–1.7)	0.386
Direct bilirubin (mg/dL)	0.1 (0.2–0.8)	0.1 (0–0.4)	0.481
Serum creatinine (mg/dL)	0.4 (0.2–0.6)	0.5 (0.2–0.9)	0.911
Urea (mg/dL)	20 (6–43)	23 (5–40)	0.339
Blood urea nitrogen (mg/dL)	10.5 (5–20)	12 (4–18)	0.482
History of prior infectious complications (%)	30 (60.0)	35 (76.1)	0.092

SCT, stem cell transplantation; CR, complete remission; VGPR, very good partial remission; PR, partial remission; BU\ALK, busulfan and melphalan; CMV, cyclophosphamide, melphalan, and etoposide; CEM, carboplatin, etoposide, and melphalan.

remained fever free through the second week with a median duration of 11 d (95% CI = 7–15). When the median duration of fever-free days of both groups was compared using the log-rank test, the difference was found to be statistically significant ($p < 0.001$) (Fig. 1).

The relative risk for clinically documented febrile episode in patients not receiving levofloxacin to patients receiving levofloxacin was 2.1 (95% CI is 1.4–3.2).

Microbiological data

The frequency of microbiological documented bacteriological infections was nearly the same in both groups, 30% in group A and 30.4% in group B, and when compared using chi-square test, the difference was found to be non-significant ($p = 0.963$).

The difference was in the type of organism isolated, where gram-negative infections in the study group were less than in the control group (6% vs. 15%); however, this difference was found to be statistically insignificant using the chi-square test ($p = 0.089$). Assessing the prevalence of resistant gram-negative organisms, there was no difference in the occurrence of extended-spectrum b-lactamase (ESBL) infection between the two groups (three cases in each group). For isolated gram-positive resistant bacteria, there was one case with MRSA in the study group and two cases in the control group: one with MRSA and another with vancomycin-resistant enterococcus (VRE).

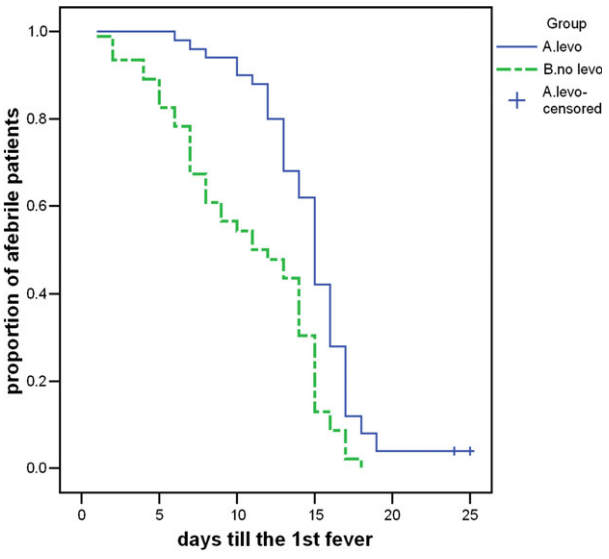

Fig. 1. Duration of fever-free days among patients of both groups analyzed using Kaplan and Meier procedure showing the proportion of febrile patients throughout the observation period, where two patients of the levofloxacin group remained afebrile till the end of the observation period (levo-censored) representing 2% of the whole patients. The difference in the median duration of fever-free period compared using the log-rank test, was statistically significant ($p < 0.001$).

Infectious complications and mortality

In the control group, four patients developed gram-negative septicemia (8.7%) and two of them died because of uncontrolled infection, while in the study group, only one patient developed sepsis (2%) with no reported mortality. When the frequency of infection-related mortality compared between the two groups using Fisher's exact test, the difference was non-significant (p-value = 0.227) (Table 2).

Duration of antibiotic administration and hospitalization

Levofloxacin prophylaxis significantly reduced the duration of empiric antibiotic administration. The median duration of empiric antibiotic use in the study group patients was 11 d compared to 14 d in the control group ($p < 0.001$). The frequency of empirical antifungal use was much higher in the control group patients (98%) as compared to the study group (46%) and was found to be statistically significant using the chi-square test ($p < 0.001$). The duration of hospitalization was also significantly reduced with levofloxacin prophylaxis, where the median duration of hospitalization in the study group was 24 d compared to 28 d for the control group ($p < 0.001$).

There were no documented signs of levofloxacin toxicity especially tendonitis nor infusion reactions observed during the study.

Discussion

This is the first study in pediatric neutropenic patients to document the superiority of levofloxacin-containing prophylactic regimens in delaying the onset of fever, minimizing the days of antibiotic use and duration of hospitalization.

This is highly important because bacterial infections continue to be a leading cause of morbidity and toxic death in children undergoing HSCT. Data from adult studies are contradicting, some suggest that antibiotic prophylaxis decreases the incidence of infection-related deaths in patients receiving intensive myelo-suppressive therapy while others find no effect on mortality; however, antibiotic prophylaxis in pediatric patients is largely unstudied (14, 15).

Table 2. Comparison of microbiological data and infectious complications of the studied patients represented as number (percentage) or median (range)

Factor	Study group N = 50	Control group N = 46	p-value
Bacteremia (%)			
Positive blood culture	15 (30)	14 (30.4)	0.963
Gram positive	12 (24)	7 (15)	
Gram negative	3 (6)	7 (15)	0.089
Resistant gram negative	3 (6)	3 (6.5)	
Resistant gram positive	1 (2)	2 (4.3)	
Chest infiltrates (%)	7 (14)	7 (15.2)	0.866
CVL infection (%)	11 (22)	9 (19.5)	0.806
Sepsis (%)	1 (2)	4 (8.7)	0.191
Infection-related deaths (%)	0	2 (4.34)	0.227
Median duration of empiric antibiotic use (days)	10 (0–22)	14 (7–23)	<0.001*
Total duration of hospitalization (days)	24 (20–36)	28 (22–40)	<0.001*
Frequency of empiric antifungal usage	23 (46.0)%	45 (97.8)%	<0.001*
Mean duration of engraftment after SCT (days)	11.6 ± 1.1	11.4 ± 2.1	0.598

*Statistically significant difference.

Recent clinical practice guidelines recommend quinolone prophylactic use in acute leukemia patients receiving intensive remission-induction, post-remission consolidation, or salvage induction therapy and hematopoietic stem cell transplant recipients, when the duration of profound neutropenia is at least seven d (12), while the lack of data for levofloxacin use in children and young people limited the recommendation for use or avoidance during periods of neutropenia.

Hence, this study was performed to assess the effect of levofloxacin prophylaxis in pediatric patients with profound neutropenia following autologous stem cell transplantation aiming to prevent the infectious complications.

Our findings regarding the delay of the first febrile episode were reported by many other studies in adults, where Bucaneve et al. (16) in their large meta-analysis (GIMEMA infection program) to evaluate levofloxacin prophylaxis in 760 adult neutropenic cancer patients (mainly acute leukemia and stem cell transplantation) showed a lower incidence of fever in patients receiving levofloxacin compared with the placebo group (65% vs. 85%, respectively, $p = 0.001$), and an updated review carried out by Gafter-Gvili et al. (17) in 2012 found that antibiotic prophylaxis resulted in a significant decrease in the occurrence of fever and mortality among quinolone subgroups (26 trials, 4205 participants; RR 0.74, 95% CI 0.65–0.84). In addition, the study by Garnica et al. (18) in 2013 assessed the effects of quinolone prophylaxis in high-risk neutropenic patients and found that febrile episodes occurred later in the course of neutropenia for patients receiving prophylaxis (median 4 vs. 2 d after the first day of neutropenia, $p < 0.001$).

All the available meta-analyses have shown a reduction of microbiologically documented infections in patients who have received antibacterial prophylaxis (14, 19). In our study, although no impact was demonstrated on the frequency of bacteriological documented infections (30% in each group), a reduction in the gram-negative infection was observed with levofloxacin prophylaxis but was not statistically significant (6% vs. 15%, $p = 0.089$). Bucaneve et al. demonstrated a significant reduction in the rates of microbiologically documented infections with prophylactic levofloxacin (22% vs. 39%), with a striking decrease in gram-negative bacteremia (6% vs. 14% in the placebo group). Gram-positive infections were also reduced (12% of infections in the levofloxacin group vs. 18% in the placebo group) (20). A retrospective study was carried out by Saito et al. (21) examining the effect of discontinuation of levofloxacin-based antibacterial prophylaxis on the risk of bacteremia and found that the incidence of blood stream infections increased significantly upon discontinuation of prophylaxis (from 10.0% to 20.3% ($p < 0.0001$), with a significant increase in gram-negative bacteremia upon discontinuation of prophylaxis (from 20.5% to 40.5% $p < 0.001$). Garnica et al. also proved the same reduction in bacteremia with ciprofloxacin prophylaxis in his study (22% vs. 33%, $p = 0.04$) (18).

This study was not able to document difference in mortality rates between the two groups. However, mortality benefit associated with fluoroquinolones prophylaxis is inconsistent throughout the literature. Some studies reported impact of prophylaxis on the mortality rate as in the Leibovici et al. (22) large meta-analysis, the average death rate in patients not receiving prophylaxis was 5%, while in the group of patients receiving prophylaxis mortality was 3%. A retrospective study conducted by the St. Jude group on antibiotic prophylaxis in 78 consecutive pediatric patients with acute myeloid leukemia undergoing chemotherapy showed a significant reduction in incidence and mortality by septicemia after prophylaxis with intravenous cefepime or intravenous vancomycin associated with oral ciprofloxacin (23). In the current study, 8.5% of patients without levofloxacin prophylaxis developed gram-negative septicemia and 4%

infection-related mortality, compared to no infection-related mortality in patients with levofloxacin prophylaxis; however, this difference was not statistically significantly different. On the other hand, Saito et al. and Chong et al. (21, 24) reported a similar infection-related mortality rates among those who received and did not receive quinolone prophylaxis. These variable results could be due to the fact that mortality rate among patients with neutropenia is influenced by factors unrelated to prophylaxis, such as the response to empirical antibiotic therapy, the severity of underlying disease, and the presence of comorbidities.

The main concern over the use of prophylactic antibiotics remains the emergence of antibiotic resistance, as quinolone use has been associated with MRSA, multidrug-resistant *Escherichia coli*, and *Pseudomonas aeruginosa* (25). In previous trials that reported resistance data, patients who received fluoroquinolones developed no more infections with pathogens resistant to the drug than patients who received placebo (RR, 1.04; 95% CI, 0.73–1.5) (16, 19). In this study, there were not enough data to conclude the impact of prophylaxis on emergence of the levofloxacin-resistant strains. However, the microbiological data documented no difference between the two groups in prevalence of resistant gram-negative organisms such as ESBL. A similar observation by Chong et al. (24) showed no significant increase in ESBL-producing *E. coli* during the period of prophylaxis. In contrast with the previous data, a single-center study demonstrated an increased rate of resistance in allogenic transplant recipients receiving levofloxacin prophylaxis (26). However, none of the trials reporting higher incidence of resistance had evidence that quinolone resistance was associated with increased infection-related mortality rates.

This study investigated other outcome measures that demonstrated the beneficial effects of levofloxacin in terms of reduction in duration of empiric antibiotic and antifungal exposure and the total length of hospital stay, both of which might have an impact on reduced toxicity and cost. The empiric regimen of antibiotics usually contains an aminoglycoside, and the empiric antifungal added after prolonged fever is amphotericin B. Both agents are known for their high toxicity profile, in addition to the need for monitoring aminoglycoside use. These findings were also reported by Garnica et al. (18) as the mean duration of hospitalization was shorter in the ciprofloxacin group (22 vs. 24 d, $p = 0.002$), and the mean duration of antibiotic therapy was significantly reduced (8 vs. 11 d, $p < 0.001$).

In conclusion, this is the first study in pediatrics to provide evidence that prophylaxis with levofloxacin in pediatric patients with autologous stem cell transplantation is effective in delaying febrile episodes, reducing empiric antibiotic use and reducing the total duration of hospital stay. However, this study is limited by the fact that the control group was historical, the patient number was limited and the observation length was not long enough to properly evaluate the effect of levofloxacin prophylaxis on the emergence of resistance.

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Authors' contributions

Hanafy Ahmed Hafez: Designed the study, analyzed the data, and drafted the manuscript; Dalia Yousif: Collected and analyzed data, contributed to the manuscript draft; Maggie Abbassi: contributed with intellectual input for the results interpretation and discussion and reviewed the final version of the manuscript; Yasser Elborai: Designed the study, analyzed the data and contributed with intellectual input for the discussion and reviewed the final version of the manuscript; Alaa Elhaddad: Contributed with intellectual input for the discussion and reviewed the final version of the manuscript. All authors read and approved the final manuscript.

References

1. Gratwohl A, Brand R, Frassoni F et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Transpl 2005: 36: 757.
2. Castagnola E, Faraci M, Moroni C et al. Bacteremias in children receiving hemopoietic SCT. Bone Marrow Transpl 2008: 41: S104.
3. Mullen CA, Nair J, Sandesh S, Chan KW. Fever and neutropenia in pediatric hematopoietic stem cell transplant patients. Bone Marrow Transplant 2000: 35: 59.
4. Castagnola E, Bagnasco F, Faraci M et al. Incidence of bacteremias and invasive mycoses in children undergoing allogeneic hematopoietic stem cell transplantation: a single center experience. Bone Marrow Transpl 2008: 41: 339.
5. Cappellano P, Viscoli C, Bruzzi P, Van Lint MT, Pereira CAP, Bacigalupo A. Epidemiology and risk factors for bloodstream infections after allogeneic hematopoietic stem cell transplantion. New Microbiol 2007: 30: 89.
6. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. Bone Marrow Transpl 2007: 40: 63.

7. Guthrie KA, Yong M, Frieze D, Corey L, Fredricks DN. The impact of a change in antibacterial prophylaxis from ceftazidime to levofloxacin in allogeneic hematopoietic cell transplantation. Bone Marrow Transpl 2010: 45: 67.
8. Hammond SP, Baden LR. Antibiotic prophylaxis for patients with acute leukemia. Leuk Lymphoma 2008: 49: 183.
9. Castagnola E, Boni L, Giacchino M et al. A multicenter, randomized, double blind placebo-controlled trial of amoxicillin/clavulanate for the prophylaxis of fever and infection in neutropenic children with cancer. Pediatr Infect Dis J 2003: 4: 359.
10. Yousef AA, Fryer CJH, Chedid FD, Abbas AAH, Feliman SK, Khattab TM. A pilot study of prophylactic ciprofloxacin during delayed intensification in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2004: 43: 637.
11. Felsenstein S, Orgel E, Rushing T, Fu C, Hoffman JA. Clinical and microbiologic outcomes of quinolone prophylaxis in children with acute myeloid leukemia. Pediatr Infect Dis J 2015: 34: e78.
12. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011: 52: e56.
13. Ng ES-T, Liew Y, Earnest A, Koh LP, Lim S-W, Hsu LY. Audit of fluoroquinolone prophylaxis against chemotherapy-induced febrile neutropenia in a hospital with highly prevalent fluoroquinolone resistance. Leuk Lymphoma 2011: 52: 131.
14. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005: 142: 97.
15. Kimura S, Akahoshi Y, Nakano H et al. Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of randomized controlled trials. J Infect 2014: 69: 13.
16. Bucaneve G, Micozzi A, Menichetti F et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005: 353: 977.
17. Gafter-Gvili A, Fraser A, Paul M et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 2012: 1: CD004386.
18. Garnica M, Nouér S, Pellegrino FLPC, Moreira BM, Maiolino A, Nucci M. Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance. BMC Infect Dis 2013: 13: 356.
19. Van de Wetering MD, de Witte MA, Kremer LCM, Offringa M, Scholten RJPM, Caron HN. Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: a systematic review of randomised controlled trials. Eur J Cancer 2005: 41: 1372.
20. Cullen M, Steven N, Billingham L et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005: 353: 988.
21. Saito T, Yoshioka S, Iinuma Y et al. Effects on spectrum and susceptibility patterns of isolates causing bloodstream infection by restriction of fluoroquinolone prophylaxis in a hematology–oncology unit. Eur J Clin Microbiol Infect Dis 2008: 27: 209.
22. Leibovici L, Paul M, Cullen M et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer 2006: 107: 1743.
23. Kurt B, Flynn P, Shenep JL et al. Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. Cancer 2008: 113: 376.
24. Chong Y, Yakushiji H, Ito Y, Kamimura T. Clinical impact of fluoroquinolone prophylaxis in neutropenic patients with hematological malignancies. Int J Infect Dis 2011: 15: e277.
25. Rangaraj G, Granwehr BP, Jiang Y, Hachem R, Raad I. Perils of quinolone exposure in cancer patients: breakthrough bacteremia with multidrug-resistant organisms. Cancer 2010: 116: 967.
26. Therriault BL, Wilson JW, Barreto JN, Estes LL. Characterization of bacterial infections in allogeneic hematopoietic stem cell transplant recipients who received prophylactic levofloxacin with either penicillin or doxycycline. Mayo Clin Proc 2010: 85: 711.