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Original Article

Levofloxacin Prophylaxis Versus no Prophylaxis in Acute Myeloid Leukemia During Post-Induction Aplasia: a Single Center Study

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Abstract. ***Background:*** **Acute myeloid leukemia (AML) patients are at high risk of infections during post-induction neutropenia. Recently, the role of antibacterial prophylaxis has been reconsidered due to concerns about the emergence of multi-resistant pathogens. The aim of the present study was to evaluate the impact of avoiding prophylaxis on the rate of induction death (primary endpoint), neutropenic fevers, bloodstream infections (BSIs), resistant pathogens BSIs and septic shocks (secondary endpoints).**

Methods: We performed a retrospective single-center study including 373 AML patients treated with intensive induction chemotherapy, divided into two groups according to levofloxacin prophylaxis given (group A, gA) or not (group B, gB).

Results: Neutropenic fever was observed in 91% of patients in gA and 97% in gB (OR 0.35, IC95% 0.08 – 1.52, p=0162). The rate of BSIs was 27% in gA compared to 34% in gB (OR 0.69, 0.38 – 1.25, p=0.222). The induction death rate was 5% in gA and 3% in gB (OR 1.50, 0.34 – 6.70, p=0.284). Fluoroquinolones (FQ) resistant pathogens were responsible for 59% of total BSIs in gA and 22% in gB (OR 5.07, 1.87 – 13.73, p=0.001); gram-negative BSIs due to multi-drug resistant organisms were 31% in gA and 36% in gB (OR 0.75, 0.15 – 3.70, p=0.727).

Conclusions: Despite its limitations (retrospective nature, single-center, different cohort size), the present study showed that avoiding levofloxacin prophylaxis was not associated with an increased risk of induction death. The cumulative incidence of neutropenic fever was higher in non-prophylaxis group, while no difference was observed for BSIs. In the prophylaxis group we observed a higher incidence of FQ-resistant organisms.

Keywords: acute myeloid leukemia, levofloxacin prophylaxis, bloodstream infections, induction death, antibiotic resistance.

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Introduction. Bacterial infections are a major cause of morbidity and mortality in patients with acute myeloid leukemia (AML) during neutropenia following induction chemotherapy.[1] According to the Infectious Diseases Society of America (IDSA) guidelines,[2] the risk of infections in neutropenic patients is classically divided into high (prolonged profound neutropenia >7 days) and low risk (neutropenia expected to resolve within 7 days). AML patients treated with intensive induction chemotherapy are expected to have long aplasia periods (neutrophils count < 500/mm^3) lasting between 15 and 25 days, placing them at high risk for infections.

The use of antibacterial prophylaxis has been the standard of care since 2005 when Bucaneve et al. published a prospective randomized trial showing that prophylactic treatment with levofloxacin was effective in preventing febrile episodes and bacteremia in neutropenic patients with cancer.[3] In 2007 antibacterial prophylaxis with fluoroquinolones (FQ) was recommended by the European Conference on Infections in Leukemia (ECIL) group for high-risk neutropenic patients.[4] However, in recent years concerns have been raised about the worldwide emergence of multi-drug resistant (MDR) pathogens.[5] As previously reported, the incidence of MDR gram-negative bacteria has increased among AML patients during subsequent consolidation chemotherapy.[6] In the era of increasing antibiotic resistance, understanding antibacterial prophylaxis's real efficacy is of utmost importance. Randomized controlled and observational trials after 2006 report possible benefits of FQ prophylaxis on febrile neutropenia and bloodstream infections (BSI) rate but not on overall mortality.[7,8] More recently, some international guidelines still recommended FQ prophylaxis in patients who are at high risk for febrile neutropenia (National Institute for Health and Care Excellence – NICE,[9] German Society of Hematology and Medical Oncology – DGHO,[10] American Society of Clinical Oncology - ASCO and IDSA,[11] National Comprehensive Cancer Network – NCCN).[12] By contrast, Australian guidelines gave a low level (grade C) of recommendation for antibacterial prophylaxis in high-risk patients;[13] similarly, the European Society for Medical Oncology (ESMO) guidelines on the management of febrile neutropenia discourage the use of antimicrobial, including FQ, for prophylaxis.[14] In 2017 the ECIL group analyzed the emergence of antimicrobial resistance in gram-negative rods and questioned the recommendations for FQ prophylaxis, underscoring the need for up-to-date, evidence-based data on local epidemiology.[7]

Following these considerations, the aim of the present study was to evaluate the impact of avoiding antibacterial prophylaxis on infections and early mortality rates in AML patients during post-induction aplasia.

Material and Methods. This retrospective analysis was conducted at the Department of Oncology and Hematology AOU. Città della Salute e della Scienza of Turin, Italy. All consecutive adult patients with AML (excluding acute promyelocytic leukemia) diagnosed between June 2001 and March 2019 and treated with intensive induction chemotherapy were enrolled in the study. Patients treated until December 2016 received antibacterial prophylaxis with levofloxacin 500 mg QD during post-induction aplasia, as common past practice in our center. Considering the locally increased incidence of FQ-resistant and extended-spectrum beta-lactamase (ESBL) producing gram-negative bacteria during consolidation chemotherapy and based on the worldwide emergence of multi-resistant pathogens, from 2017, we decided to discontinue the administration of FQ prophylaxis. Consequently, for the study analysis, patients have been divided into two groups on the basis of antibacterial prophylaxis administration: group A included patients who received levofloxacin from June 2001 to December 2016, and group B those who did not, from January 2017 to March 2019.

All patients were treated with intensive induction regimens containing cytarabine arabinoside and anthracyclines.[15] Different doses of cytarabine were administered depending on the chemotherapy schedule: high doses in fludarabine-based regimens[16,17] and standard doses in a 7 + 3-like scheme.[18] Chemotherapy was administered through a central venous catheter (CVC, Hohn, or Picc). Patients presenting at diagnosis with infectious fever were excluded from the analysis. Neutropenic fever was defined as a temperature ≥ 38.0°C during post-induction aplasia. In all febrile patients, empirical antibiotics were promptly started; the approach remained similar for both analyzed periods and involved a broad-spectrum antibiotic therapy with a beta-lactam mostly associated with an aminoglycoside. CVC-related BSIs

(CR-BSI) were defined by differential time to positivity (DTP) criteria: growth of microbes from a catheter blood sample should precede by at least 2 hours microbial growth detected in a blood sample obtained from a peripheral vein.[19] The definition of septic shock was established according to the 2016 Sepsis and Septic Shock Consensus Definitions.[20] Early induction death was defined as all-cause mortality during the induction cycle, referred to as the period from the first day of chemotherapy until the post-induction bone marrow revaluation within a maximum of 35 days.

When there were two bacteremia episodes in patients, to assess the incidence of resistant organisms, both were

counted. All bacteria specimens isolated from blood cultures were considered, including the multiple specimens detected in polymicrobial BSI. Data about colonized rectal swabs and their impact on BSI in hospitalized patients were available from 2017 when we started weekly testing for colonization with ESBLs and carbapenem-resistant Enterobacteriaceae (CRE). For all the isolates, MALDI-TOF MS analysis was used for bacterial identification, and antimicrobial susceptibility testing was carried out using Microscan WalkAway plus System (Beckman Coulter, Brea, CA, USA), according to the manufacturer's instructions. Mastdiscs® combi Carba plus disc system (Mast Group Ltd, Bootle, UK) was used to characterize carbapenemase producers when meropenem MIC was >0.125 μg/ml. Carbapenem resistance genes were detected using the Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA). ESBL-E production was confirmed by standard test (NBC 46, Beckman Coulter, Brea, California, USA). Antimicrobial susceptibilities were interpreted according to EUCAST.

Statistical analysis. The study's primary endpoint was the rate of induction death; secondary endpoints were the rate of neutropenic fever, BSI, and septic shock. An additional objective was to assess the potential role of FQ prophylaxis on the emergence of antibiotic resistance, particularly the incidence of FQ-resistant organisms and MDR gram-negative pathogens. The median and standard deviation for continuous variables and percentage for discrete variables were used to describe the sample. Mann-Whitney test for continuous and Fisher exact test for categorical variables were used to compare patients and disease characteristics between the study groups. The effect of omitting antibacterial prophylaxis on the induction death rate, neutropenic fever, BSI, and septic shocks was estimated using four logistic regression models adjusted for age, gender, cytarabine doses (> or < 1g/m^2), duration of aplasia (≤ 15 days; 15 < days < 20; ≥ 20 days) and genetic risk stratification (favorable, intermediate or adverse).[15] Results are presented as Odds Ratio (OR). The cumulative incidence of fever and BSI was calculated in patients receiving or not levofloxacin prophylaxis, applying competing risk analysis with death and progression disease as competing events. The Gray test compared cumulative incidence curves between the two study groups. The Kaplan-Meier curves were estimated to depict overall survival (OS) in patients with or without prophylaxis and compared by log-rank test.

Results

Patient characteristics. A total of 373 AML patients with a median age of 56 (range 18-76) years, of whom 55% were males, were included in the present study. Complete remission (CR) was achieved in 267 patients (72%), while 84 were resistant (22%), and 22 died (6%) during induction. The group receiving levofloxacin prophylaxis (group A) included 315 patients, while the group not receiving prophylaxis (group B) included 58 patients. The different periods of observation (16 years vs. 1.5 years) were responsible for the group sizes. The median age at diagnosis was different in the two groups (55 vs. 60 years in group A and B, respectively, p=0.0025). Patients' characteristics are summarized in **Table 1**.

Table 1. Patients' characteristics compared in the study groups.

	Levofloxacin prophylaxis (Group A)	No levofloxacin prophylaxis (Group B)	p value
Patients, n°	315	58	
Median age, yr (range)	55 (18-76)	60 (21-75)	0.0025
Age distribution, n° (%)			
18-40 yr	57 (18)	5 (9)	
40-60 yr	140 (44)	20 (34)	0.013
60-76 yr	118 (38)	33 (57)	
Male sex, n° (%)	174 (55)	31 (53)	0.886
ELN-2017 Risk, n° (%)			
Favorable	21 (7)	3 (5)	
Intermediate	142 (45)	24 (41)	0.745
Adverse	152 (48)	31 (54)	
Chemotherapy, n° (%)			
7+3-like	253 (80)	49 (85)	
HD-ARAC	61 (19)	2 (3)	<0.001
Other	1 (1)	7 (12)	
Complete Remission, n° (%)	226 (72)	41 (71)	0.875

Abbreviations: ELN: European LeukemiaNet, HD-ARAC: high-dose cytarabine.

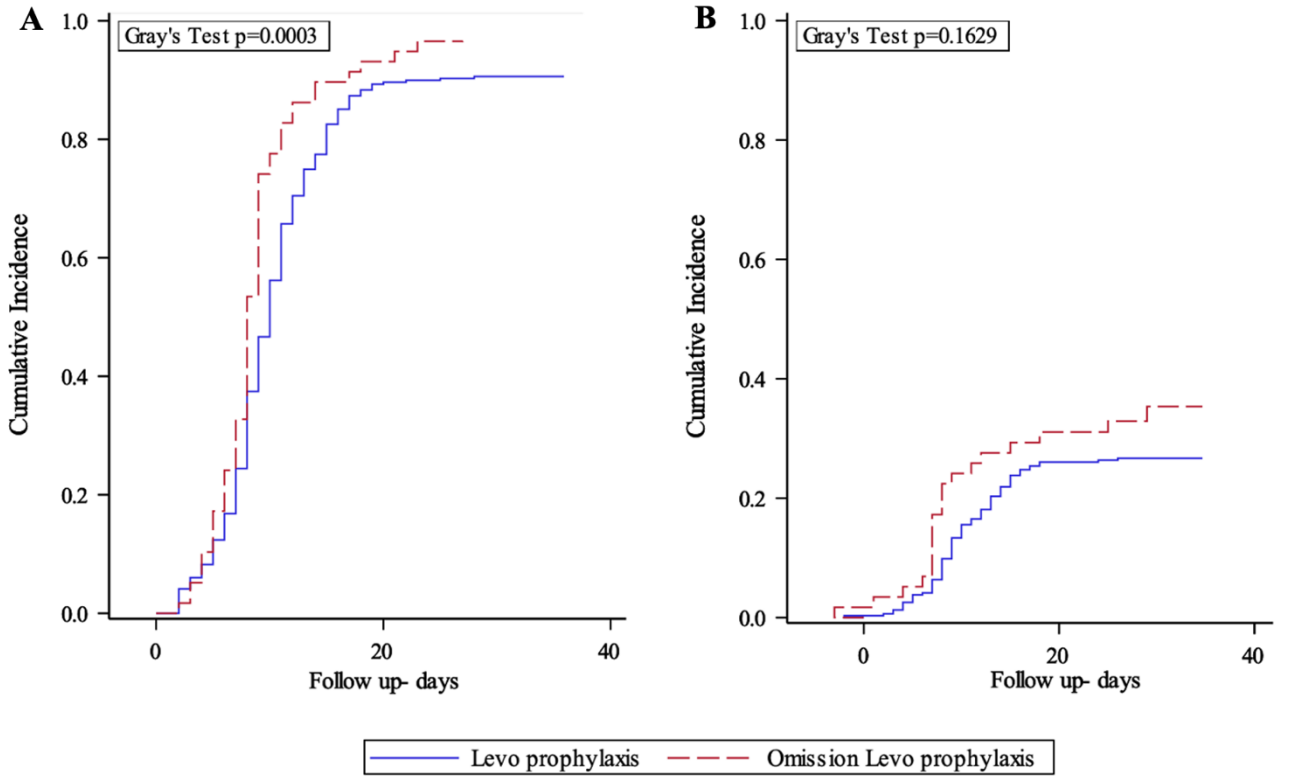

Figure 1. Cumulative incidence of fever (A) and BSI (B) at 35 days as a function of levofloxacin prophylaxis.

Efficacy of FQ prophylaxis. A total of 286 patients (91%) developed at least one episode of neutropenic fever in group A and 56 patients (97%) in group B (OR 0.35, IC95% 0.08 – 1.52, p=0.162). Among febrile patients, neither clinical infections nor microbiological isolates (fever of unknown origin - FUO) were found in 36% (n=104) of patients in group A and 23% (n=13) in group B. A clinical infection was diagnosed in 43% (n=123) of patients in group A (n=69 pneumonia, n=32 enterocolitis, n=22 other clinical infections) and 75% (n=42) of patients in group B (n=15 pneumonia, n=22 enterocolitis, n=5 other clinical infections). Overall, 84 patients (27%) in group A and 20 patients (34%) in group B had at least one episode of bacteremia (OR 0.69, IC95% 0.38 – 1.25, p=0.222). CVC-related BSIs were documented in 1% (n=3) of febrile patients in group A and 5% (n=3) in group B. Of note, a higher cumulative incidence (CI) of neutropenic fever during the 35 days after induction chemotherapy was observed in patients who did not receive levofloxacin prophylaxis (96.6 vs 90.6%, p=0.0003; **Figure 1A**) while the CI of BSI did not differ significantly between the two groups (26.7% in group A vs. 35.3% in group B, p=0.163; **Figure 1B**). A septic shock was recorded in 15 (5%) febrile patients in group A vs. 4 (7%) in group B (OR 0.68, IC95% 0.22 – 2.11, p=0.499). Among them, 4 patients in group A and no patients in group B required an intensive care unit (ICU) admission. Mortality due to septic shock was 75% in the prophylaxis group (n=11) and 25% in the non-prophylaxis group (n=1). The induction death rate was comparable in both groups, being 5% (n=16) in group A and 3% (n=2) in group B (OR 1.50, IC95% 0.34 – 6.70, p=0.284). Kaplan-Meier OS curves are shown in **Figure 2**. **Table 2** summarizes the overall results.

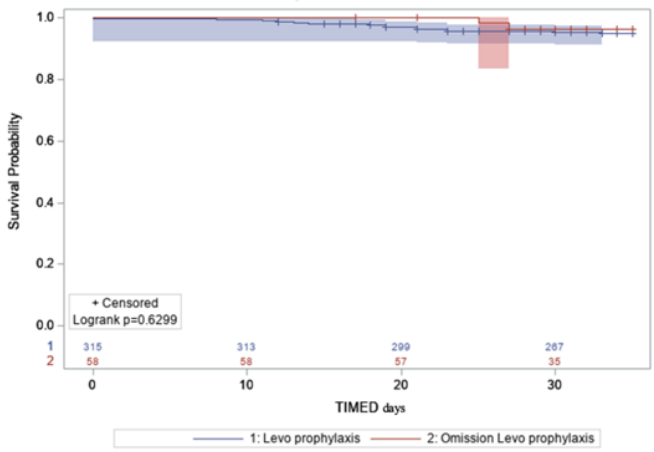

Figure 2. Kaplan-Meier overall survival curves based on levofloxacin prophylaxis.

A multivariate regression analysis did not show any impact of levofloxacin prophylaxis on the incidence of neutropenic fever (OR 0.62, IC95% 0.13 - 2.97, p=0.552), bloodstream infection (OR 0.75, IC95% 0.39 - 1.48, p=0.410), septic shock (OR 0.73, IC95% 0.20 - 2.66, p=0.632) and induction death (OR 1.39, IC95% 0.27 - 7.21, p=0.696), see **Table 3**. A prolonged duration of aplasia (more than 20 days) was associated with an increased risk of neutropenic fever (OR 6.07, IC95% 1.58 - 23.31, p= 0.009). Patients in the adverse genetic risk category showed an increased risk of induction death (OR 11.46, IC95% 2.45 – 53.62, p=0.002). Increasing

Table 2. Primary and secondary endpoints compared in patients with and without levofloxacin prophylaxis.

N° (%)	Levofloxacin prophylaxis (Group A)	No levofloxacin prophylaxis (Group B)	OR (IC95%), p value
PATIENTS	**315**	**58**	
Induction death	16 (5)	2 (3)	1.50 (0.34 – 6.70), p=0.284
Neutropenic fever	286 (91)	56 (97)	0.35 (0.08-1.52), p=0.162
Bloodstream infection (BSI)	84 (27)	20 (34)	0.69 (0.38 – 1.25), p=0.222
1 BSI	76	14	
2 BSI	8	6	
Septic shock	15 (5)	4 (7)	0.68 (0.22-2.11), p=0.499
TOTAL EPISODES OF BSI	**92**	**26**	
Gram-positive	63 (68)	15 (58)	
Gram-negative	28 (30)	10 (38)	0.66 (0.27 – 1.60), p=0.355
Polymicrobial	1 (2)	1 (4)	
FQ Resistant bacteria	55 (59)	6 (22)	5.07 (1.87 – 13.73), p=0.001
Gram-negative MDR	9 (31)	4 (36)	
ESBL-E	2	3	
CRE	3	1	0.75 (0.15 – 3.70), p=0.727
Pseudomonas aeruginosa MDR	2	0	
Stenotrophomonas maltophilia MDR	2	0	

Abbreviations: FQ: fluoroquinolones, MDR: multi-drug resistant, ESBL-E: extended-spectrum beta-lactamase enterobacteriaceae, CRE: carbapenem-resistant Enterobacteriaceae.

Table 3. Association between the omission of levofloxacin prophylaxis and study endpoints in a multivariate regression model.

	Odds Ratios (IC95%)			
	Neutropenic Fevers	**Bloodstream Infections**	**Septic Shocks**	**Induction Deaths**
Levofloxacin prophylaxis	0.62 (0.13-2.97)	0.75 (0.39-1.48)	0.73 (0.20-2.66)	1.39 (0.27-7.21)
Age	1.09 (0.81- 1.47)	1.25 (1.03-1.51)	1.11 (0.77-1.60)	1.64 (1.02-2.62)
Gender (M)	2.07 (0.96-4.47)	1.19 (0.74-1.91)	0.77 (0.29-2.01)	0.79 (0.29-2.17)
Adverse ELN-2017 Risk	1.26 (0.57-2.81)	0.76 (0.47-1.23)	9.05 (2.01-40.70)	11.46 (2.45-53.62)
Ara C > 1g/m²	1.51 (0.42-5.49)	1.76 (0.95-3.26)	1.54 (0.45-5.31)	1.45 (0.41-5.17)
Days of aplasia				
> 15	1.29 (0.51-3.26)	1.20 (0.60-2.39)	0.29 (0.06-1.48)	0.42 (0.10-1.76)
> 20	6.07 (1.58-23.31)	1.48 (0.77-2.83)	0.79 (0.26-2.39)	0.44 (0.12-1.55)

Abbreviations: ELN: European LeukemiaNet, Ara C: cytarabine arabinoside.

age was associated with early mortality (OR 1.64, IC95% 1.02 – 2.62, p=0.040) and BSI occurrence (OR 1.25, IC95% 1.03 - 1.51, p=0.023).

Role of FQ prophylaxis on antibiotic resistance. Considering the 118 positive blood cultures, 120 bacterial isolates have been detected, 93 in group A and 27 in group B. Two fungal bloodstream infections (candidemia) were not included in the analysis.

Gram-positive bacteria accounted for 67% (n=80) of the BSI, while gram-negative organisms were identified in the remaining 33% (n=40) of BSI. **Table 4** summarizes the frequency and the characteristics of bacterial bloodstream isolates.

Overall, FQ resistance was observed in 51% (n=61) of all bacteria; 55% (n=44) of gram-positive pathogens, 43% (n=17) of gram-negative bacteria, and 55% (n=16) of Enterobacteriaceae were FQ-resistant. MDR organisms (ESBLs, CRE, and non-fermented MDR bacilli) represented 31% (n=13) of all gram-negative bacteria.

When comparing the characteristics of bacterial bloodstream isolates in prophylaxis and non-prophylaxis groups, gram-negative bacteria were found in 31% (n=29, of which 1 in a polymicrobial BSI) of patients in group A vs. 41% (n=11, of which 1 in a polymicrobial BSI) in group B (OR 0.66, IC95% 0.27 – 1.60, p=0.355). Overall, FQ-resistant pathogens were responsible for 55 BSI (59%) in group A and 6 (22%) in group B (OR 5.07, IC95% 1.87 – 13.73, p=0.001). Gram-positive FQ-resistant bacteria were 63% (n=40) in group A and 25% (n=4) in group B, while FQ resistance was observed in 52% (n=15) and 18% (n=2) of gram-negative pathogens in group A and B, respectively. Bacteremia due to gram-

Table 4. Frequency and characteristics of bacterial bloodstream isolates.

Bacterial Bloodstream Isolates N° (%)			
Gram Positive	**80 (67)**	**Gram Negative**	**40 (33)**
Staphylococci	**56 (70)**	**Enterobacteriaceae**	**29 (73)**
CoNS	51	Escherichia Coli	18
S. epidermidis	31	ESBL	2
S. haemolyticus	7	Klebsiella Pneumoniae	8
S. hominis	5	ESBL	2
S. xylosus	1	KPC	4
S. spp (others)	7	Enterobacter cloacae	3
Staphylococcus aureus	5	**Non-fermentant bacilli**	**8 (20)**
MRSA	4	Pseudomonas Aeruginosa	6
MSSA	1	MDR	2
Enterococci	**10 (13)**	Stenotrophomonas maltophilia	2
E. spp	1		
E. faecalis	1		
E. faecium	8		
VRE	2		
Streptococci	**9 (11)**	**Others**	**3 (7)**
S. mitis	6	Aeromonas spp	1
S. bovis	1	Ochrobactrum spp	1
S. agalactiae	1	ESBL	1
S. spp (others)	1	Cupravidus pauculus	1
Bacilli	**5 (6)**		
Corynebacterium spp	4		
Bacillus spp	1		

Abbreviations: CoNS: coagulase-negative staphylococci, MRSA: methicillin-resistant staphylococcus aureus, MSSA: methicillin-sensible staphylococcus aureus, VRE: vancomycin-resistant enterococci, ESBL-E: extended-spectrum beta-lactamase enterobacteriaceae, KPC: Klebsiella pneumoniae carbapenemase-producing, MDR: multi-drug resistant.

negative resistant organisms (ESBLs, CRE, and non-fermenting MDR bacilli) was 31% (n=9) in group A and 36% (n=4) in group B (OR 0.75, IC95% 0.15 – 3.70, p=0.727).

Data on rectal swabs colonization with resistant bacteria were only available from patients in the non-prophylaxis group since routine testing was started in 2017. Twenty-two percent of the patients (n=13/58) had a colonized rectal swab, 12 of which with an ESBL-producing organism and 1 with a KPC. Of them, 23% (n=3/13) developed a bloodstream infection due to the same pathogen.

Discussion. In the last few years, the emergence of MDR pathogens has become an increasing worldwide problem, and the large-scale use of antibiotic drugs has been questioned.[7] Consequently, defining the role of antibacterial prophylaxis has become a major concern in the era of antimicrobial resistance, particularly in endemic MDR environments.

The present study explored the impact of avoiding FQ prophylaxis during post-induction neutropenia in AML patients. Noteworthy, we found no significant influence of prophylaxis omission on induction death. Also, we did not observe a significant difference in febrile neutropenia rate between patients receiving or not levofloxacin prophylaxis, even if a trend towards a higher number of neutropenic fevers was observed in patients who did not receive it (97% vs. 91%). The CI of neutropenic fever was significantly higher in patients without prophylaxis, partially due to the difference in the time to fever, which was shorter in patients not receiving prophylaxis.

Interestingly, FUO episodes were more common in the group receiving prophylaxis, while a clinical infection was diagnosed more frequently in the other group. Although we can debate if the absence of antibacterial prophylaxis could translate into an increased incidence of clinically diagnosed infections, more likely, these data reflect the diagnostic advances made in recent years to reduce FUO incidence and increase infectious disease diagnoses. In the present study, avoiding levofloxacin prophylaxis was not associated with an increased incidence of BSI. Even though a numerically higher frequency of BSI (34% vs. 27%) and gram-negative isolates (41% vs 31%) was present in the non-prophylaxis group, the difference lacked statistical significance. The frequency of septic shocks did not differ significantly between the two groups. Interestingly, we observed that septic shock mortality decreased from 75% in the prophylaxis group to 25% in the non-prophylaxis group. Although we cannot exclude a role of prophylaxis, this difference is probably due to our improvements in the management of septic patients.

Another objective was to assess the potential impact of FQ prophylaxis on the emergence of antibiotic resistance, an issue on which only a few and contrasting data are available. As expected, the use of FQ prophylaxis was associated with a significant increase in the incidence of FQ-resistant bacteria. Indeed, among

patients receiving levofloxacin prophylaxis, almost 60% of the bacterial bloodstream isolates were FQ resistant, in contrast to only about 20% of the bacteria in the non-prophylaxis group (63% vs. 25% in gram-positive and 52% vs. 18% in gram-negative in group A and B, respectively). No significant difference was observed in the ESBL-producing organisms and CRE incidence among the two groups. However, since modifying the epidemiological environment requires months or even years, these data need to be considered preliminary. To fully address this issue, it would be important to evaluate the incidence of resistant pathogens also in the subsequent consolidation cycles.

The increased rate of patients colonized with resistant pathogens reported worldwide is considered a direct consequence of wrong antibiotic prescriptions and the extensive use of antibacterial prophylaxis.[21] Positive rectal swabs are an important risk factor for BSI in neutropenic patients, and their increase should be considered when balancing the potential benefits of FQ prophylaxis in this setting.[22] In our study, 22% of patients from the available data had a colonized rectal swab, mostly from ESBL organisms. Importantly, almost a quarter of them experienced a related bacteremia due to the same pathogen.

Conclusions. In the present study avoiding levofloxacin prophylaxis did not increase induction mortality and did not have a significant impact on infectious outcomes, even if a trend towards an earlier onset of neutropenic fever was observed. Although limited by its retrospective nature, the different periods, and the different sizes of the confronted groups, the present analysis included a large and homogeneous cohort of patients in terms of diagnosis (AML), treatment (intensive chemotherapy), and site of observation (single center). The results are concordant with the most recently published metanalyses addressing this issue[7,8] and support the non-use of FQ prophylaxis, especially in settings of endemic MDR spread.

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