Ciprofloxacin *versus* colistin prophylaxis during neutropenia in acute myeloid leukemia: two parallel patient cohorts treated in a single center

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ABSTRACT

Patients undergoing intensive chemotherapy for acute myeloid leukemia are at high risk for bacterial infections during therapy-related neutropenia. However, the use of specific antibiotic regimens for prophylaxis in afebrile neutropenic acute myeloid leukemia patients is controversial. We report a retrospective evaluation of 172 acute myeloid leukemia patients who received 322 courses of myelosuppressive chemotherapy and had an expected duration of neutropenia of more than seven days. The patients were allocated to antibiotic prophylaxis groups and treated with colistin or ciprofloxacin through 2 different hematologic services at our hospital, as available. The infection rate was reduced from 88.6% to 74.2% through antibiotic prophylaxis (*vs.* without prophylaxis; P=0.04). A comparison of both antibiotic drugs revealed a trend towards fewer infections associated with ciprofloxacin prophylaxis (69.2% *vs.* 79.5% in the colistin group; P=0.07), as determined by univariate analysis. This result was confirmed through multivariate analysis (OR: 0.475, 95%CI: 0.236-0.958; P=0.041). The prophylactic agents did not differ with regard to the microbiological findings (P=0.6, not significant). Of note, the use of ciprofloxacin was significantly associated with an increased rate of infections with pathogens that are resistant to the antibiotic used for prophylaxis (79.5% *vs.* 9.5% in the colistin group; P<0.0001). The risk factors for higher infection rates were the presence of a central venous catheter (P<0.0001), mucositis grade III/IV (P=0.0039), and induction/relapse courses (*vs.* consolidation; P<0.0001). In conclusion, ciprofloxacin prophylaxis appears to be of particular benefit during induction and relapse chemotherapy for acute myeloid leukemia. To prevent and control drug resistance, it may be safely replaced by colistin during consolidation cycles of acute myeloid leukemia therapy.

Introduction

Bacterial infections are the most common cause of treatment-related mortality in patients with neutropenia after chemotherapy, particularly when the expected duration of neutropenia is seven or more days.[1-3] Patients with acute myeloid leukemia (AML) are at a particularly high risk. In addition to disease- and therapy-induced myelosuppression, disease-related conditions, such as alteration of the host defenses secondary to infiltration of the bone marrow and therapy-induced side effects (such as mucositis or diarrhea after breakdown of the mucosal barrier), further contribute to the high risk of infections.[4]

Fluoroquinolone has partially replaced the previous use of non-absorbable antibiotics, such as colistin/polymyxin B and oral vancomycin, for the prophylaxis of neutropenia-related infections. Initially, this was based on better tolerance for fluoroquinolone rather than on a proven decrease in the infection rate.[5-11] Although subsequent double-blind, placebo-controlled, randomized trials have shown a decrease in the infection rates,[12,13] evidence of significant benefits of fluoroquinolones in preventing infection-related mortality is still limited to meta-analyses.[14] Nevertheless, fluoroquinolones have been included in some, but not all, guidelines for the treatment of neutropenic AML patients.[1,3,15]

The prevention and control of drug-resistant and multidrug-resistant pathogens are becoming increasingly challenging. Widespread antibiotic prophylaxis may promote the development of drug resistance. In addition, fluoroquinolones are increasingly being linked to serious side-effects, thus leading the Food and Drug Administration (FDA) to raise concerns regarding their use and to introduce the term Fluoroquinolone-associated Disability.[16] Thus, the use of antibiotic prophylaxis in afebrile neutropenic AML patients remains controversial.[17]

Here, we report a single-institution analysis comparing the effects and benefits of two common antibiotic prophylaxis regimens, colistin and ciprofloxacin, in a cohort of AML patients with a high risk of chemotherapy-induced neutropenic infections.

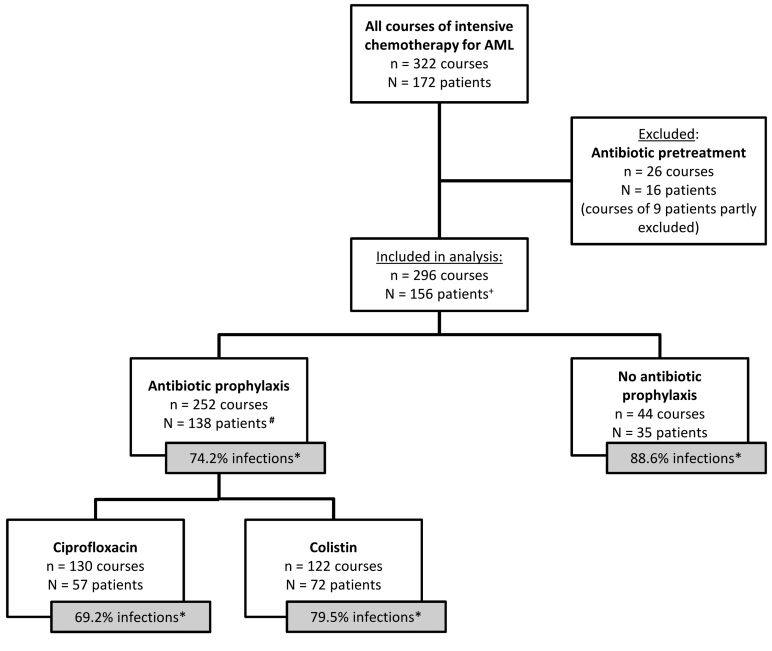
Methods

Patients

A total of 172 consecutive patients with AML who received inpatient, intensive chemotherapy in the Department of Medicine A of the University Hospital of Muenster, Germany, and were at risk of developing chemotherapy-induced neutropenia lasting more than seven days, were included in this retrospective analysis. All patients provided written informed consent prior to the initiation of the anti-leukemic therapy. Approval for this analysis was obtained from the Ethics Board of the Westfalian Wilhelms-University Muenster, Germany, and the Physicians Chamber of Westphalia-Lippe, Germany (approval number 2015-695-f-S).

On the basis of service availability, all patients were allocated to one of two different physician services within the same department; one treatment team used oral colistin, and the other administered ciprofloxacin. Individual patients' characteristics (e.g. disease status, treatment regimen) had no influence on his/her assignment to each treatment group. All other therapies and supportive care were provided to both groups, according to identical institutional guidelines.

Intensive induction or consolidation chemotherapy and an expected duration of neutropenia of more than seven days were prerequisites for eligibility in this study. Neutropenia was defined as a neutrophil count less than $<0.5x10^9$ cells/L, and leukocytopenia was defined as a leukocyte count less than $1.0x10^9$ cells/L when differential leukocyte counts were not available.



* Infection rates are based on treatment courses
+ Patients can occur in both groups with individual treatment courses (N = 18 patients)
# 9 patients switched between both antibiotic groups

Figure 1. Flow chart displaying the treatment courses administered and the patient numbers (n,N). AML: acute myeloid leukemia.

Prophylactic regimen

Patients received antibiotic prophylaxis simultaneously with the start of chemotherapy. Upon hematologic recovery (<0.5x10^9 neutrophils/L or >1.0x10^9 leukocytes/L), prophylaxis was stopped.

Patients in the colistin group were given 8 million IU daily, divided into four doses. Patients in the ciprofloxacin group were given 500 mg twice daily. Both drugs were taken orally. In addition, both groups received prophylaxis for *Pneumocystis jirovecii* pneumonia with 960 mg of trimethoprim-sulfamethoxazole twice daily for two days *per* week.

Table 1A. Patients' baseline characteristics.

Characteristics	All patients (n=156)	Without prophylaxis (n=35)	Ciprofloxacin (n=57)	Prophylaxis Colistin (n=72)	P
Age at first treatment					0.299
Mean ± SD	58.1±13.9	54.5±15.6	57.1±14.0	59.2±13.3	
Median (IQR)	60 (49-69)	60 (47.2-65)	56 (48-67)	62 (54.5-69)	
Range	18-85	18-76	18-84	19-85	
Sex, n (%)					0.672
Male	85 (54.5)	19 (54.3)	33 (57.9)	39 (54.2)	
Female	71 (45.5)	16 (45.7)	24 (42.1)	33 (45.8)	
FAB classification, n (%)					0.683
M0	13 (8.3)	2 (5.7)	6 (10.5)	5 (6.9)	
M1	14 (9.0)	3 (8.6)	3 (5.3)	7 (9.7)	
M2	42 (26.9)	14 (40.0)	15 (26.3)	18 (25.0)	
M3	2 (1.3)	8 (22.9)	2 (3.5)	0 (0.0)	
M4	41 (26.3)	0 (0.0)	15 (26.3)	20 (27.8)	
M5	28(18.0)	6 (17.1)	9 (15.8)	15 (20.8)	
M6	6 (3.9)	1 (2.9)	3 (5.3)	2 (2.8)	
M7	1 (0.6)	1 (2.9)	0 (0.0)	0 (0.0)	
Undetermined	9 (5.8)	0 (0.0)	4 (7.0)	5 (6.9)	
Therapy stage, n (%)					0.609
Induction	133 (85.3)	18 (51.4)	28 (49.1)	41 (56.9)	
Consolidation	14 (9.0)	12 (34.3)	23 (40.4)	26 (36.1)	
Relapse	9 (5.8)	5 (14.3)	6 (10.5)	5 (6.9)	
Charlson comorbidity index at first treatment, n (%)					0.576
2	87 (55.8)	21 (60.0)	34 (59.6)	41 (56.9)	
3	35 (22.4)	10 (28.6)	13 (22.8)	12 (16.7)	
4	18 (11.5)	2 (5.7)	5 (8.8)	11 (15.3)	
≥5	16 (10.3)	2 (5.7)	5 (8.8)	8 (11.1)	
Number of courses analyzed (%)					0.076
1	84 (53.9)	16 (45.7)	26 (45.6)	41 (56.9)	
2	27 (17.3)	5 (14.3)	10 (17.5)	13 (18.1)	
3	20 (12.8)	4 (11.4)	6 (10.5)	12 (16.7)	
4	18 (11.5)	6 (17.1)	10 (17.5)	5 (6.9)	
5	7 (4.5)	4 (11.4)	5 (8.8)	1 (1.4)	
Prophylactic regimen, n (%)					
Without antibiotic prophylaxis	35 (22.4)	–	–	–	–
With antibiotic prophylaxis	138 (88.5)				
Ciprofloxacin	57 (36.5)				
Colistin	72 (46.2)				
Switch between prophylaxes	9 (5.8)				

FAB: French-American-British classification; SD: standard deviation; IQR: Interquartile range; n: number.

Table 1B. Status at the time of treatment group allocation: the treatment courses according to therapy stage.

Treatment course (%)	Induction (n=148 courses)	Consolidation (n=129 courses)	Relapse (n=19 courses)
1st*	126 (85.1)	0	0
2nd	21 (14.2)	26 (20.2)	0
3rd	1 (0.7)	53 (41.1)	3 (15.8)
4th	0	31 (24.0)	4 (21.1)
5th	0	19 (14.7)	8 (42.1)
6th	0	0	2 10.5)
10th	0	0	1 (5.3)
11th	0	0	1 (5.3)

**Includes courses of double-induction; n: number.*

End points used in the analysis

The primary end point was a clinically documented infection requiring empirical antibacterial therapy, which was defined as the presence of at least two of the following criteria: a) fever during neutropenia (oral temperature above 38.3°C in a single measurement or ≥ 38.0°C in measurements taken over at least one hour); b) clinical signs of infections (e.g. hypotension, tachypnea, or tachycardia); and c) laboratory (e.g. an increase in C-reactive protein or procalcitonin levels) or microbiological findings. Because antibiotic prophylaxis may interfere with the culture results, microbiological findings were not mandatory because this would have resulted in under-reporting of infections.[13]

The secondary end points were microbiological findings (positive culture results), an infection-related need for intensive care medicine, and mortality as a result of any type of infection.

Statistical analysis

Distributions of patient baseline characteristics in both prophylactic groups were compared using χ^2 tests for categorical variables and Mann-Whitney U tests for the continuous variables.

The differences between groups were analyzed through statistical methods capable of modeling repeated measurements. Here, generalized estimation equations (GEEs) were applied.

All statistical analyses were performed with IBM SPSS Statistics for Windows, v.22.0 (IBM Corp., Armonk, NY, USA) and SAS software (v.9.4, for Windows, SAS Institute Inc., Cary, NC, USA).

A detailed description of Materials and Methods is included in the *Online Supplementary Appendix*.

Results

Patients' characteristics

A total of 172 patients received 322 treatment courses with at least one chemotherapy course per stay (Figure 1). Courses with antibiotic treatments prior to the start of chemotherapy (n=26) were excluded, and the data for 296 treatment courses (156 patients) were used for the subsequent analyses. The patients' baseline characteristics at the first treatment course are presented in Table 1A. During a total of 44 courses (14.9%) antibiotic prophylaxis was not administered in 35 patients, mostly at the request of the patient. However, this group of patients was also analyzed and separately compared with patients who received prophylaxis. The remaining 138 patients received antibiotic prophylaxis over 252 treatment courses: 72 patients received colistin (in 122 courses), and 57 patients received ciprofloxacin (in 130 courses). Nine patients switched treatment group (5.8% crossover) mainly due to capacity reasons of one team and to ensure continuation of chemotherapy.

Patients received a median of 3 treatment courses. A complete standard therapy usually included 3-5 courses per patient (1-2 induction courses and 2-3 consolidation courses). Deviations from standard therapy were mostly due to courses outside of the study period, the need for allogeneic stem cell transplantation, death, or exclusion of courses with antibiotic pre-treatment.

Induction therapy accounted for 50.0% of all treatments, followed by consolidation (43.6%) and relapse (6.4%) treatments. This distribution was similar between the colistin and ciprofloxacin groups (Table 1B).

Infection rates

In the absence of antibiotic prophylaxis, clinically documented infections occurred significantly earlier (P=0.0001) (*Online Supplementary Figure S1*) and more often (88.6% *vs.* 74.2%) with prophylaxis (Table 2). Infections during col-

Table 2. Infection-related data.

	Prophylaxis (n=252 courses)		Without prophylaxis (n=44 courses)
	Ciprofloxacin (n=130)	Colistin (n=122)	
Onset of infection, median in days	15.5	13.0	10.0
Infection, n (%)	90 (69.2)	97 (79.5)	39 (88.6)
Induction, n (%)[a]	55 (88.7)	63 (96.9)	19 (90.5)
Consolidation, n (%)[a]	29 (48.3)	28 (54.9)	15 (83.3)
Relapse, n (%)[a]	6 (75.0)	6 (100)	5 (100)
Infection with detection of pathogen, n (%)	39 (30.0)	42 (34.4)	22 (50.0)
Gram-positive	31	27	15
Gram-negative	7	18	9
Fungal	1	3	2
Viral	4	2	1
Resistant to prophylaxis	31	4	-
Infection with multidrug-resistant pathogen, n (%)	4 (3.1)	6 (4.9)	2 (4.5)
Vancomycin-resistant *Enterococcus*	2	5	1
Extended-spectrum-betalaktamase	1	1	0
Pseudomonas aeruginosa	1	0	1
Mucositis (grade III/IV), n (%)	34 (26.2)	21 (17.2)	9 (20.5)
Central venous catheter, n (%)	71 (54.6)	74 (60.7)	27 (61.4)
Need for intensive care, n (%)	5 (3.8)	5 (4.1)	4 (9.1)
Infection-related	5	4	4
Length of hospital stay, median, days	29.0	32.0	29.0
Death during hospital stay, n (%)[b]	3 (5.1)	6 (8.5)	3 (20.0)
Infection-related	3	6	3

[a]*Percentage of infections in each treatment group according to therapy stage (induction, consolidation, or relapse);* [b]*percentage of patients (not treatment courses); n: number.*

Table 3. Infection rates in the entire patient cohort (prophylaxis and no prophylaxis): univariate GEE analysis of 296 treatment courses (156 patients).

	N	Estimated risk of infection in % (95% CI)	P
Prophylaxis			
No	44	89.7 (78.2-95.5)	0.0403
Yes	252	77.6 (72.0-82.5)	
Sex			
Male	170	84.7 (77.2-88.8)	0.0420
Female	152	73.6 (64.6-81.0)	
Central venous catheter			
No	128	57.5 (46.8-67.7)	<0.0001
Yes	194	91.9 (86.7-95.2)	
Mucositis (grade III/IV)			
No	254	76.3 (70.1-81.6)	0.0111
Yes	67	93.7 (82.6-97.9)	
Therapy stage			
Induction	167	93.4 (87.7-96.5)	<0.0001
Consolidation	133	56.4 (46.1-66.2)	
Relapse	22	89.1 (65.0-97.3)	
		OR (95% CI)	P
Charlson index (*per* point)		0.8682 (0.6861-1.0985)	0.2391
Age (*per* year)		0.9927 (0.9716-1.0143)	0.5018

GEE: generalized estimation equation; CI: confidence interval; OR: odds ratio; N: number.

istin prophylaxis were observed in 79.5% of courses compared with 69.2% of courses in the case of ciprofloxacin prophylaxis (*P*=0.0727). Patients who received ciprofloxacin prophylaxis developed infections on day 15 (median), which was later than the time at which patients developed infections in the colistin group (median on day 13; *P*=0.0266) (*Online Supplementary Figure S2A*) The median length of hospital stay was substantially influenced (*P*=0.0283, GEE model) by the choice of prophylaxis (32 *vs.* 29 days in the colistin and ciprofloxacin groups, respectively). However, ciprofloxacin had no effect on the probability of discharge without infection (ciprofloxacin *vs.* colistin; *P*=0.0747) (*Online Supplementary Figure S2B*).

The highest infection rates were observed during the induction and relapse reinduction courses (96.9% and 100% in the colistin group compared with 88.7% and 75.0% in the ciprofloxacin group). In contrast, infections occurred less frequently during consolidation courses (54.9% with colistin and 48.3% with ciprofloxacin; *P*<0.0001). Approximately one-quarter (26.2%) of the patients who received ciprofloxacin suffered from mucositis, compared with 17.2% in the colistin group (*P*=0.1683). Central venous catheters were used in slightly over half of the courses in both groups (54.6% in the ciprofloxacin *vs.* 60.7% in the colistin group).

Microbiological findings

In cases of infection, the detection rate of isolated microorganisms was similar in both prophylactic groups (30.0% in the ciprofloxacin group *vs.* 34.4% in the colistin group; *P*=0.6436) (Table 2). In the colistin group, most of the micro-organisms were Gram-positive bacteria (64.3%), followed by Gram-negative bacteria (42.9%). The use of ciprofloxacin caused a clear shift towards Gram-positive pathogens (79.5% *vs.* 17.9% Gram-negative).

The frequency of multidrug-resistant bacteria was not significantly different between the groups (4.9% in the colistin group *vs.* 3.1% in the ciprofloxacin group; *P*=0.4727). Although vancomycin-resistant *enterococci* appeared more often in the colistin group (5 *vs.* 2 courses; *P*=0.6667), multidrug-resistant *Pseudomonas aeruginosa* was not observed in this group (compared with 1 isolate in the ciprofloxacin group). Notably, the rate of pathogens with resistance to the assigned prophylactic drug was significantly higher in the ciprofloxacin group (79.5%, 31 of 39 *vs.* 9.5%, 4 of 42 in the colistin group; *P*<0.0001).

Concerning the microbiologic milieu on both wards, results of routine monitoring display a similar spectrum of germs, especially concerning resistant pathogens. In detail, ciprofloxacin-resistance was predominantly found in samples with *E. coli* and *Pseudomonas aeruginosa* (approx. 40%), colistin-resistant bacteria have not become evident in significant quantity.

Outcome

The need for intensive care was reduced by the application of prophylaxis (4.0% of patients who received prophylaxis *vs.* 9.1% who did not receive prophylaxis; *P*=0.2747), but there was no difference between the two prophylactic agents (3.8% of patients who received ciprofloxacin *vs.* 4.1% who received colistin; *P*=0.9245). Although there was a trend, mortality was not significantly influenced by the application of prophylaxis (7.0% mortality among patients who received prophylaxis *vs.* 20.0% among patients who did not receive prophylaxis; *P*=0.4219) or the type of prophylaxis (5.1% in the ciprofloxacin group *vs.* 8.6% in the colistin group; *P*=0.2857). All cases of death were described as infection-related (Table 3).

Risk factors for infections

After the use of either antibiotic, the infection rate decreased from 88.6% to 74.2% (*P*=0.0403) (Table 2). Furthermore, the presence of a central venous catheter, mucositis, and induction/relapse therapy were associated with increased infection rates in the univariate analysis of the entire cohort (all *P*<0.05) (Table 3). The same parameters were significantly associated with infections in the univariate analysis of patients who received antibiotic prophylaxis (Table 4). Among these risk factors, only the incidence of mucositis increased the infection rates [odds ratio

Table 4. Infection rates among patients treated with antibiotic prophylaxis: univariate GEE analysis of 252 treatment courses (138 patients).

	N	Estimated risk of infection in % (95% CI)	P
Prophylaxis			
Colistin	122	81.4 (73.7-87.2)	0.0727
Ciprofloxacin	130	71.4 (62.2-79.0)	
Sex			
Male	133	81.3 (73.9-86.9)	0.0531
Female	119	70.6 (61.0-78.6)	
Central venous catheter			
No	107	52.9 (42.0-63.0)	<0.0001
Yes	145	91.5 (85.6-95.1)	
Mucositis (grade III/IV)			
No	196	72.3 (65.6-78.1)	0.0039
Yes	55	93.4 (82.2-97.8)	
Therapy stage			
Induction	127	93.1 (86.8-96.5)	<0.0001
Consolidation	111	51.8 (41.5-62.0)	
Relapse	14	85.3 (57.1-96.2)	
		OR (95% CI)	P
Charlson index (*per* point)		0.8894 (0.6995-1.1308)	0.3386
Age (*per* year)		0.9957 (0.9733-1.0185)	0.7077

GEE: generalized estimation equation; CI: confidence interval; OR: odds ratio; N: number.

Table 5. Infection rates among patients treated with antibiotic prophylaxis: multivariate GEE model of 252 treatment courses (138 patients).

	Estimated risk of infection in % (95% CI)	OR (95% CI)	P
Type of prophylaxis			0.0405
Ciprofloxacin	83.1 (70.3-91.1)	0.475 (0.236-0.958)	
Colistin	91.2 (83.8-95.4)		
Sex			0.0969
Male	90.1 (82.7-95.2)	1.867 (0.902-3.864)	
Female	83.9 (71.6-91.5)		
Central venous catheter			0.3157
Yes	91.3 (81.6-96.2)	2.183 (0.573-3.086)	
No	82.8 (65.3-92.5)		
Mucositis (grade III/IV)			0.0045
Yes	94.7 (84.5-98.3)	6.229 (1.773-21.883)	
No	74.1 (65.8-80.9)		
Age (*per* year)		1.002(0.975-1.029)	0.9099
Charlson score (*per* point)		0.818 (0.609-1.100)	0.2047
Therapy stage			0.0757
Induction or relapse	74.2 (54.9-87.2)	0.163 (0.042-0.637)	
Consolidation	94.6 (86.9-97.9)		

The reference categories are in bold. GEE: generalized estimation equation; CI: confidence interval; OR: odds ratio.

(OR) 6.229, 95% confidence interval (CI) 1.773-21.883; *P*=0.0045] in multivariate analysis, whereas prophylaxis with ciprofloxacin significantly decreased (0.4475, 95%CI: 0.236-0.958; *P*=0.0405) the infection rate in the multivariate analysis (Table 5).

Furthermore, a subgroup analysis of different disease stages (induction, relapse, and consolidation) was performed. Here, prophylaxis with ciprofloxacin was independently associated with decreased infection rates only during the induction or relapse courses (OR 0.097, 95%CI: 0.017-0.556; *P*=0.0038) and not during the consolidation courses (OR 0.650, 95%CI: 0.285-1.481; *P*=0.2941) (Table 6). In contrast, mucositis was a significant predictor of infection in the consolidation courses (OR 4.398, 95%CI: 1.593-12.141; *P*=0.0089) but marginally missed significance in the induction/relapse courses (OR 5.357, 95%CI: 0.759-37.843; *P*=0.0511).

Discussion

We report the results of a retrospective, single-institution analysis comparing the effects and benefits of two common antibiotics, colistin and ciprofloxacin, that were administered prophylactically in a cohort of AML patients at high risk of infection due to chemotherapy-induced neutropenia. Although the comparison was not based on a prospective randomization, the allocation of the patients to the 2 different prophylactic drugs was random, and all other therapy and supportive care was provided to both groups according to identical institutional guidelines.

First, our data confirm that antibiotic prophylaxis is advantageous in preventing febrile neutropenia compared with no prophylaxis. Limiting allocation to courses without prophylaxis was neither planned nor random. Despite this and the small size of this group, it is remarkable that

Table 6. Influence of the therapy regimen/disease stage on the infection rates among patients treated with antibiotic prophylaxis (multivariate GEE model).

	Induction or relapse (N=125 patients, n=141 courses)			Consolidation (N=61 patients, n=110 courses)		
	Estimated risk of infection in % (95% CI)	OR (95% CI)	*P*	Estimated risk of infection in % (95% CI)	OR (95% CI)	*P*
Type of prophylaxis						
Ciprofloxacin	93.4 (71.9-98.7)	0.097 (0.017-0.556)	0.0038	65.6 (42.5-83.1)	0.650 (0.285-1.481)	0.2941
Colistin	99.3 (93.7-99.9)			74.6 (55.2-87.4)		
Sex						
Male	97.1 (84.4-99.5)	1.839 (0.541-6.250)	0.3354	62.6 (39.8-80.9)	1.998 (0.834-4.785)	0.1274
Female	98.4 (89.2-99.8)			77.0 (57.4-89.2)		
Central venous catheter						
Yes	95.6 (89.1-99.0)	0.380 (0.021-6.962)	0.4279	76.9 (46.2-92.8)	1.975 (0.519-7.509)	0.3559
No	98.7 (77.7-99.9)			62.7 (47.7-75.6)		
Mucositis (grade III/IV)						
Yes	99.1 (90.8-99.9)	5.357 (0.759-37.843)	0.0511	83.2 (61.2-94.0)	4.398 (1.593-12.141)	0.0089
No	95.2 (78.1-99.1)			53.0 (35.6-69.7)		
Age (*per* year)		1.036(0.-989-1.086)	0.0991		0.994 (0.959-1.031)	0.7602
Charlson score (*per* point)		0.710 (0.510-0.988)	0.2349		0.855 (0.582-1.257)	0.4226

The reference categories are in bold. GEE: generalized estimation equation; CI: confidence interval; OR: odds ratio; N, n: number.

this finding was not dependent on the agent that was chosen and is in accordance with previous observations.[12,13] Second, the application of ciprofloxacin decreases the infection rates in the induction and relapse courses more than colistin. This result is in accordance with some previous studies comparing fluoroquinolones with non-absorbable agents, although none of these studies investigated ciprofloxacin *versus* colistin in a high-risk cohort of AML patients.[7,11]

Concerning microbiological findings, the type of prophylaxis did not influence the infection rates, but the application of ciprofloxacin induced a shift from Gram-negative to Gram-positive organisms in the microbiological findings, as previously described.[18,19] The effects of fluoroquinolones on the incidence of Methicillin-resistant *Staphylococcus aureus* (MRSA) have been described previously.[20,21] Furthermore, patients without antibiotic prophylaxis and those who received colistin presented with a similar spectrum of micro-organisms, which may be explained by the lack of systemic activity of colistin and its narrower spectrum compared with ciprofloxacin.

The type of prophylaxis did not significantly influence major clinical events, such as the requirement for intensive care or infection-related mortality. Thus, our results are in accordance with other studies showing a slight but insignificant trend towards lower mortality rates in patients who received antibiotic prophylaxis (*vs.* no prophylaxis) and in those who received ciprofloxacin (*vs.* colistin).[12,13] However, based on the observed mortality rates in this study, a 5-fold increase in the number of patients would have been necessary to reveal statistically significant differences. Because of the limited AML incidence, no study to date has overcome this obstacle, and statistically significant differences in mortality rates have been observed only in larger meta-analyses.[14,22,23]

However, we found a significant difference in the number of pathogens that were resistant to the applied prophylaxis. Prophylaxis-resistant pathogens were identified more frequently in patients treated with ciprofloxacin (79.5% *vs.* 9.5% with colistin). This result may raise concerns regarding the general usage of broad-spectrum antibiotics such as fluoroquinolones for prophylaxis. Because these drugs are part of the standard therapy for many other infections, a prior application can considerably impair their efficacy in this context. Thus, it is more likely that an even broader empiric regimen may be chosen if an infection occurs.[17]

In our study, no relevant differences in the rates of multidrug-resistant pathogens were observed, and only vancomycin-resistant enterococci were observed at non-significant levels in the colistin group. However, the choice of prophylaxis must also be taken into account with regard to the development of multidrug-resistant organisms, which are an increasing challenge in the health care system.[24-28] Consequently, a reduction of the likelihood of infections in neutropenic cancer patients must be weighed against the additional effects of drug resistance on the morbidity and mortality of hospital-acquired infections.[24,29-32] Notably, patients who received ciprofloxacin prophylaxis were discharged earlier than patients who received colistin prophylaxis. Because the time to infection was also prolonged for patients who received ciprofloxacin prophylaxis, these data suggest a clinically meaningful benefit of ciprofloxacin prophylaxis.

In addition to antimicrobial prophylaxis, two other factors influenced the infection rates: the use of a central venous catheter and the incidence of mucositis. Both factors are potential ports of entry for bacterial invasion into the bloodstream and have been described previously.[4] However, only mucositis emerged as an independent predictor of a higher infection rate, particularly in patients receiving consolidation therapies.

The influence of prophylaxis clearly differed between the induction/relapse and consolidation courses. Although the choice of prophylactic agent was an independent parameter for lower infection rates in the induction/relapse courses, the infection rates in the consolidation courses were predominantly influenced by mucositis. This result may be explained by the observation that patients are at a higher risk at the time of primary diagnosis or relapse because they previously suffered from functional neutropenia for an unknown period of time due

to overt leukemia. Furthermore, the differences in the chemotherapy protocols used for induction and consolation may also play a role. Some limitations of this study deserve discussion. First, although other factors disturb the mucosal barrier, this analysis was limited to mucositis. Second, the duration of neutropenia was not included in the analysis, thus, a potential association with the differences in the induction or consolidation courses could not be revealed. Third, this analysis can provide only suggestions for antibiotic prophylaxis in a cohort of selected high-risk patients but cannot provide general recommendations. Antimicrobial resistance is influenced by an individual patient's characteristics as well as hospital/environmental conditions. The data from this analysis enable a hypothesis to be made, and further prospective trials are warranted.

In summary, ciprofloxacin prophylaxis appears to be of particular benefit during induction and relapse chemotherapy for AML, but it may be safely replaced by colistin during consolidation cycles of AML therapy. The selection of prophylactic agents should take into account variables such as therapy stage (induction/relapse *vs.* consolidation), the risk of developing mucositis, and the local distribution of resistant pathogens.

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