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Efficacy of antibiotic short course for bloodstream infections in acute myeloid leukemia patients with febrile neutropenia: A retrospective comparative study

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SUMMARY

Objectives: There is no specific recommendation about antimicrobial treatment length for documented infections in chemotherapy induced febrile neutropenia (FN). Practices have changed along time in our center regarding length of antibiotic treatment. The aim of this study was to compare long versus short antibiotic course for bloodstream infection (BSI) treatment in acute myeloid leukemia (AML) patients during FN.

Methods: This monocentric retrospective comparative study included all consecutive BSI episodes among AML patients with FN for 3 years (2017–2019). Episodes were classified regarding the length of antibiotic treatment, considered as short course if the treatment lasted ≤ 7 days, except for nonfermenting bacteria and *Staphylococcus aureus* or *lugdunensis* for which the threshold was ≤ 10 days and ≤ 14 days, respectively. The primary outcome was the number of BSI relapses in both groups within 30 days of antibiotic discontinuation.

Results: Among 71 AML patients, 104 BSI episodes were included; 48 (46%) received short course treatment. Only 8 (7.6%) BSI episodes relapsed within 30 days of antibiotic discontinuation, 5 having received short course treatment. No association was found between risk of relapse and short course of antibiotic treatment ($p = 0.37$). The only risk factor significantly associated with BSI relapse was neutropenia duration ($p = 0.005$).

Conclusion: Antibiotic short course seemed as effective as prolonged treatment for BSI in AML patients during FN, with very few relapses at day 30. These encouraging findings should be confirmed through prospective studies.

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Abbreviations: AML, acute myeloid leukemia; AMR, antimicrobial resistance; ANC, absolute neutrophil count; AT, antibiotic treatment; BALANCE, bacteremia antibiotic length actually needed for clinical effectiveness; BSI, bloodstream infection; CoNS, coagulase negative staphylococci; ESBL-E, extended spectrum beta-lactamase enterobacteriaceae; EUCAST, european committee on antimicrobial susceptibility testing; FN, febrile neutropenia; GCSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IDSA, infectious disease society of america; IQR, inter-quartile range; LMR, logistic mixed regression; R/R, relapsed or refractory; RCT, randomized control trial; FUO, fever of unknown origin.

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Introduction

Emergence of antimicrobial resistance (AMR) is a major public health concern, leading to prolonged illness and increasing health cost and mortality.¹ By 2050 there would be 10 million people dying every year due to AMR if the resistance rise were to follow the actual trend.² Resistance to antibiotics is closely related to their consumption.

Antibiotics are widely prescribed among patients with hematologic malignancies during chemo-induced febrile neutropenia (FN), especially patients suffering from acute myeloid leukemia (AML) as they are highly susceptible to infections.³ Bloodstream infections (BSI) are found in 10 to 30% of FN episodes, associated with

a worse prognosis and higher mortality.^{4–6} Multi-Drug Resistant (MDR) bacteria are particularly frequent among this population, responsible for 16% of the BSI among MDR-colonized patients.⁷ Infections due to MDR bacteria are an independent risk factor for mortality.^{8,9} Shortened courses of antibiotic treatment (AT) could have an impact among this population, with an expected benefit at both individual and collective levels.

However, guidelines remain unclear regarding the length of AT in FN patients with documented infections. They indicate a minimal duration of treatment or a large range, without considering bacteria species or site of infection.^{3,10,11} The pursuit of AT until neutrophil recovery is also still a matter of debate. In 2017, French experts have proposed shorter courses of AT in the general population based on a literature review, which was carried out with the goal of reducing antibiotic consumption.¹² The review also highlighted a lack of data in literature about the length of AT in several areas, including microbiologically documented infections among FN patients.

Based on experts' recommendations for the general population,¹² practices in our cancer center changed in 2018 reducing the length of AT from 10–14 days to ≤ 7 days except for non-fermenting enterobacteriaceae and *Staphylococcus aureus* and *Lugdunensis*. The aim of this study was consequently to compare the efficacy of short and long course AT on BSI among AML patients during FN. We chose to focus on AML patients because they represented a homogeneous cohort, reducing bias and allowing inter-individual comparisons.

Methods

Setting and patients

This monocentric, comparative, retrospective study was conducted in a 1200-bed tertiary care center (University Hospital of Poitiers, France) from January 1st of 2017 to December 31st of 2019.

Each BSI episode was included when occurring in patients aged ≥ 18 years old and presenting AML during chemo-induced FN. Patients receiving intensive and non-intensive chemotherapy, *i.e.* hypomethylant agents and low dose aracytin could be included. Fever was defined as a single oral temperature measurement of ≥ 38.3 °C or a temperature of ≥ 38 °C sustained over a 1 h period. Neutropenia was defined by an absolute neutrophil count (ANC) < 500 cells/mm³ occurring after chemotherapy.³ BSI was considered as the detection of a pathogen in at least one blood culture. An exception was made for coagulase negative *Staphylococci* (CoNS) and other potential skin contaminants, for which two different positive blood cultures were required. As part of routine practice in our center, all medical files were reviewed by an infectious disease specialist to rule out contamination.

When a patient presented successive positive blood cultures with different bacteria, several BSI episodes could be included independently if: (i) blood cultures were separated for at least 24 h; (ii) there was at least one negative blood culture between them; (iii) there was no ongoing effective AT on the second bacteria when it occurred. Otherwise, it was considered as a single polymicrobial BSI. An included patient who presented BSI with the same bacteria within 30 days of antibiotic discontinuation could not be included a second time. In fact, this episode was considered as a relapse.

Other exclusion criteria were as follow: absence of fever when sampling blood culture, AT fewer than 4 days (considered too short to assess efficacy), no effective AT 48 h after the first positive blood culture, death before antibiotic discontinuation, need of surgery in addition to medical treatment, necessity of protracted course of AT for central nervous system or endovascular infections, patients undergoing hematopoietic stem cell transplantation.

Of note, in our center antibiotic prophylaxis is not part of routine protocol, even in discharge of neutropenic patients. Posaconazole is used as antifungal prophylaxis during induction. The first-line AT for FN is piperacillin-tazobactam or cefepime. In the case of persistent fever in a patient with neutropenia ≥ 7 days receiving AT, a sinus/thorax CT is performed to rule out invasive fungal disease.¹³ If CT shows signs of invasive fungal disease, anti-mold azoles are administered, if not, anti-yeast echinocandin is prescribed. If there is no microbiological or clinical documentation, the decision to stop AT when fever persists is left to the discretion of the physician in charge of the patient.

Data collection

Collected data included: chemotherapy treatment phase, comorbidities, duration of neutropenia, use of Granulocyte Colony Stimulating Factor (G-CSF), intake of corticosteroids (> 10 mg per day of prednisone equivalent, or > 700 mg of total dose, as described in¹⁴), history of infection with resistant bacteria, *i.e.* extending spectrum beta-lactamase enterobacteriaceae (ESBL-E) or *P. aeruginosa* resistant to ≥ 3 antibiotics categories, date of the first positive blood culture, isolated bacterial species, antibiotic susceptibility testing, sites of infection (Table 1), transfer to intensive care unit (ICU), date of death. None of the patients in our center received fluoroquinolone prophylaxis.

First-line AT for FN followed IDSA guidelines and was secondarily adapted to BSI documentation³. Short-course durations followed French experts' guidelines for the general population.¹²

To calculate length of AT, days of treatment were considered only if the antibiotic was appropriate after the first positive blood culture. Treatment was considered appropriate if (i) susceptibility was proven *in vitro* according to EUCAST recommendations,¹⁵ (ii) diffusion was considered good on the infected site *in vivo*, and (iii) plasmatic concentration level, if measured, was 8 to 10-fold the minimal inhibitory concentration.

Outcomes

BSI episodes were classified in two groups according to length of appropriate AT. A short course was considered ≤ 7 days, except for nonfermenting bacteria and *Staphylococcus aureus* or *Lugdunensis* for which the thresholds were ≤ 10 days and ≤ 14 days, respectively.

The primary outcome was to compare the number of BSI relapses in both groups within 30 days of antibiotic discontinuation. Secondary outcomes included comparison of mortality rate within 30 days of antibiotic discontinuation. Distribution of bacteria responsible for BSI and risk factors for BSI relapses were assessed.

Statistical analysis

Standard descriptive statistics, such as median, proportions, range, and inter-quartile range (IQR), were used to summarize the data. Logistic mixed regression (LMR) was used to evaluate the random effect of different episodes and subjects. In the absence of a significant random effect, t-test or Mann-Whitney U-test and χ^2 -test or Fischer's exact test were used to compare categorical variables and continuous variables as needed; otherwise, simple LMR was performed. Univariate and multivariate analysis with logistic mixed effect regression were performed to identify risk factors related to BSI relapses at day 30. As random effects, we had intercepts for subjects and episodes, as well as by-subject and by-episode random slopes. Values of $p < 0.05$ were considered statistically significant.

Table 1
Diagnostic criteria for different infective sites among AML patients presenting BSI in FN.

Retained diagnosis	Site	Diagnostic criteria
Primary BSI	None	No clinical symptom nor radiological sign of infection
CRBSI	Catheter	As defined in IDSA guidelines ²⁰
Digestive translocation	GI tract	Digestive symptoms (diarrhea, intense abdominal pain, severe mucositis) and/or Radiological signs of GI inflammation or infection (colitis, abscess)
Urinary tract infection	Urinary tract	Bacteria isolated on urine culture (with appropriate threshold described in ²⁹ independently of leucocyte count in these neutropenic patients) and/or Evocative clinical symptoms (lumbar pain, dysuria) and/or Compatible radiological signs (pyelonephritis, prostatitis)
Cellulitis or soft tissues abscess	Skin and soft tissues	Evocative clinical symptoms (erythema, inflammatory oedema) and/or Radiological signs of soft tissues abscess
Pneumoniae	Lungs	Bacteria isolated from lower respiratory tract sample (with appropriate threshold according to the type of sample ⁽³⁰⁾) and/or Evocative clinical symptoms (dyspnea, cough, expectorations) and/or Compatible radiological signs

BSI: bloodstream infection; AML: acute myeloid leukemia; FN: febrile neutropenia; CRBSI: catheter-related bloodstream infection; GI: gastro-intestinal

Table 2
Initial characteristics of BSI episodes among 104 AML patients with chemo-induced FN.

	Short treatment (n = 48)	Long treatment (n = 56)	p
Chronic kidney disease (n, %)			1
No	45 (93.8)	53 (94.6)	
Stage 1	1 (2.1)	0	
Stage 2	0	0	
Stage 3	2 (4.2)	3 (5.4)	
Corticosteroid treatment (n, %)	1 (2.1)	1 (1.8)	0.67
Treatment phase (n, %)			0.88
Induction	21 (43.8)	22 (37.9)	
Consolidation	13 (27.0)	15 (26.8)	
SalvageNon intensive chemotherapy	11 (22.9)3 (6.3)	15 (26.8)3 (5.4)	
History of MDR bacteria infection (n, %)	3 (6.3)	5 (8.9)	0.89
Severity (n, %)			0.008
No	45 (93.8)	39 (69.6)	
Transfer to intensive care unit	3 (6.3)	9 (16.1)	
Duration of neutropenia (median in days, IQR)	23.5 (15–29)	24 (14–32)	0.28
Duration of fever (median in days, IQR)	3 (2–7)	7.5(3–14)	0.02
Duration of antibiotic treatment (median in days, IQR)	6 (6–7)	11 (9.5–14)	< 0.001

BSI: bloodstream infection; AML: acute myeloid leukemia; FN: febrile neutropenia; MDR: multi-drug resistant; IQR: inter-quartile range

Ethical approval

The study respected the commitment to conformity with reference methodology MR-004 (declaration number 2211250v0 23/01/2019), French data protection authority (declaration numbers 2085881 and 2211250v0) and is registered in ClinicalTrials.gov (ID: NCT04910698).

Results

Description of the population and initial characteristics

Over three years, a total of 104 BSI episodes were included among 71 AML patients with chemo-induced FN (Fig. 1); 48 (46%) episodes were treated with short-course antibiotic and 56 (54%) with long course. The length of AT was left to the physician's discretion and followed the global trend of reducing antibiotic consumption; indeed, short-course treatment was delivered in 29%, 50% and 55% of the cases in 2017, 2018, and 2019, respectively. Patients from the two groups were comparable regarding comorbidities, treatment phase, duration of neutropenia, distribution of bacteria, and origin of infection (Table 2). However, fever lasted longer in the long course group (8 days vs 3 days; $p = 0.005$). Transfers

to ICU were also more frequent in the long course group (12 vs 2%; $p = 0.006$). Of note, patients admitted in ICU seemed to have a longer fever period than others (median of 8 days vs 4 days), but it was not statistically significant ($p = 0.76$).

Epidemiology and distribution of BSI

Among total population, BSI were caused mainly by enterobacteriaceae (42%), CoNS (21%), streptococci (13%), and non-fermenting bacteria (9%) (Fig. 2). There were no *S. aureus* nor *S. lugdunensis* in our study. In 65% of the cases, patients presented neither clinical symptoms nor radiological signs of infection, and the final diagnosis was primary BSI. Distribution of bacteria responsible for primary BSI was similar to that of the whole cohort.

A history of infection with resistant bacteria was found in 5 patients, who presented in total 8 BSI episodes. Three patients had a BSI episode with the same resistant bacteria that they were carrying. None of them experienced a BSI relapse. Among 44 BSI episodes due to enterobacteriaceae, 10 (23%) were ESBL-E and 2 (5%) had hyperproduced cephalosporinase. Regarding BSI due to *P. aeruginosa*, 78% ($n = 7/9$) of the strains were wild-typed.

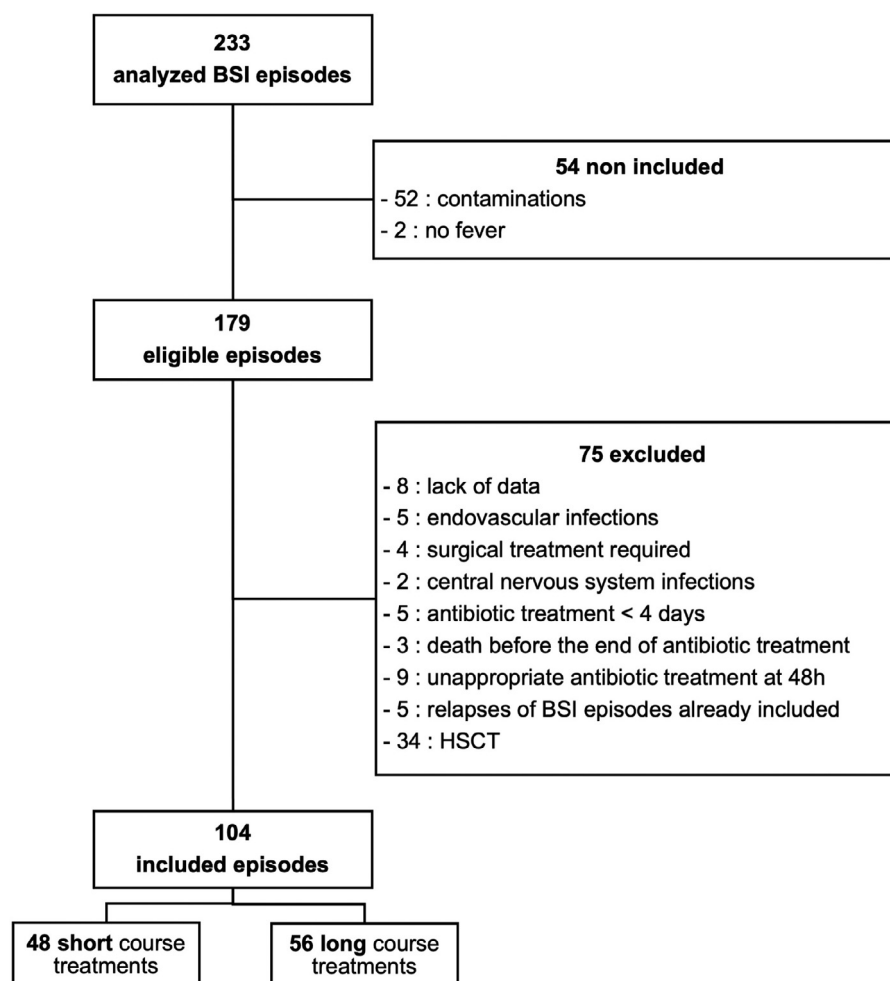


Fig. 1. Flowchart of bloodstream infection (BSI) episodes among acute leukemia patients (AML) hospitalized for febrile neutropenia.

Table 3

Assessment of risk factors for BSI relapses among AML patients in FN, univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Short treatment	6.96	0.94–512.70	0.37	4.57	0.68 – 30.70	0.11
Chronic kidney disease	0.92	0.78–1.07	0.28			
Duration of neutropenia	1.03	1.01–1.05	0.005	1.04	1.01–1.06	0.003
Remaining fever when stopping AT	0.43	0.008–24.4	0.68	0.48	0.05–4.83	0.53
Use of GCSF	0.096	0.0035–26.5	0.42			
Duration of fever	0.98	0.81–1.18	0.81			
Primary BSI	1.31	4.32 – 3.99	0.63			

BSI: bloodstream infection; AML: acute myeloid leukemia; FN: febrile neutropenia; GCSF: Granulocyte colony-stimulating factor; AT: antibiotic treatment; OR: odds ratio; CI: confidence interval

Risk factors for BSI relapses and mortality

A total of 7 patients presented 8 (7.7%) relapsing BSI episodes within 30 days of antibiotic discontinuation; 5 episodes received short-course treatment. Univariate analysis found no correlation between risk of relapse and short-course AT ($p = 0.37$) (Table 3). The only risk factor significantly associated with BSI relapse in multivariate analysis was duration of neutropenia ($p = 0.006$). The median length of neutropenia was 45 days (IQR = 28–92) among relapsing episodes, versus 22.5 days (IQR = 14–30) among non-relapsing BSI ($p = 0.005$).

Among 8 relapsing BSI, 7 were due to enterobacteriaceae (only one ESBL-E), and one was due to CoNS. Most of the relapsing BSI were primary BSI (88%). Of note, 88% of the relapsing BSI ($n = 7/8$)

occurred in patients having a refractory or relapsed (R/R) AML, vs 38% among non-relapsing episodes ($n = 36/96$) (not significant in multivariate analysis, $p = 0.05$).

The mortality rate at 30 days after AT discontinuation was 7.7%; 2 out of the 8 patients received short-course treatment. Only one death was considered of infectious origin and received long-course AT.

When discontinuing AT, 17 patients were still febrile (8 in the short-course group, 9 in the long-course group). Among them, 11 had another etiology for persistent fever: 5 had suspected invasive fungal disease, 5 had another simultaneous microbiological or clinical documentation, one had thrombosis. Only one of them belonging to the long treatment group had BSI relapse ($p = 0.53$).

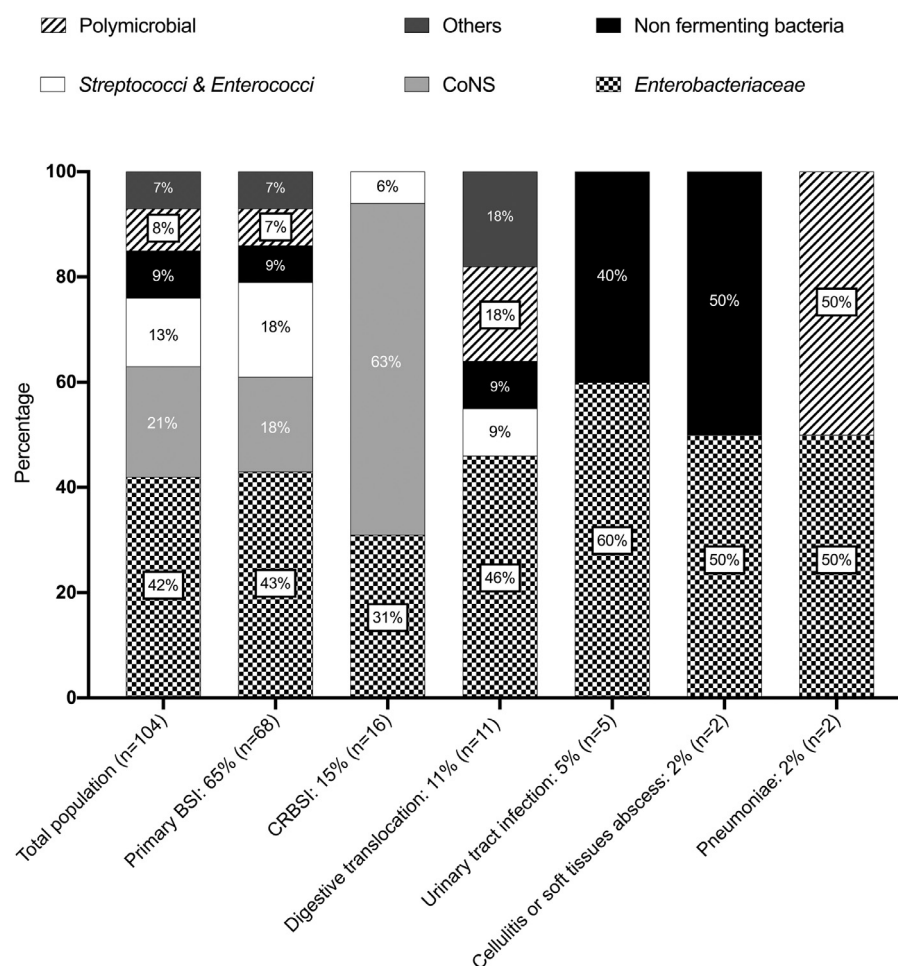


Fig. 2. Distribution of bacteria responsible for bloodstream infection (BSI) episodes among acute leukemia patients (AML) hospitalized for febrile neutropenia. CoNS: coagulase-negative staphylococci; CRBSI: catheter-related bloodstream infection.

Discussion

In our study, the relapse rate of BSI within 30 days of antibiotic discontinuation and the mortality rate at 30 days in AML patients with FN were not associated with short-course AT. The only risk factor for relapsing BSI in multivariate analysis was the duration of neutropenia. Although not statistically significant, most of the relapsing BSI cases were due to enterobacteriaceae and occurred among patients presenting relapsed or refractory (R/R) AML.

Cohorts of AML patients assessing BSI relapse rate are scarce. The only study we found focused on BSI relapses among acute leukemia patients receiving more than one cycle of chemotherapy, including 78% AML.¹⁶ The relapse rate was 28.3%, but the period from index BSI to the relapse was not specified and not all the patients (92%) were neutropenic. Gram-negative bacteria represented 73% of relapsing-BSI vs 56% of non-relapsing BSI. At multivariate analysis, receiving more than 4 courses of chemotherapy and having ESBL *E. coli* BSI were risk factors for relapsing BSI. Duration of neutropenia and rate of R/R malignancy were not specified.

Immunosuppression is considered as a risk factor for relapsing BSI in general population.¹⁷ In our study, patients who had longer neutropenia had a higher risk of relapsing BSI. Given that there is a risk to relapse a recent BSI for each day of neutropenia, cumulative risk becomes higher for prolonged neutropenia. A long-duration of neutropenia (> 9 days with ANC < 1000 cells/mm³) was associated with a higher risk of BSI among autologous HSCT patients,¹⁸ but no data are available concerning relapsing BSI.

Most of our patients presenting relapsing BSI had R/R AML. Unfavorable outcome of the underlying disease leads to successive courses of chemotherapy, longer duration of neutropenia at times without any neutrophil recovery, which is indirectly linked to higher risk of BSI relapse. In the literature, R/R malignancy is considered as a risk factor for BSI among pediatric cancer patients,¹⁹ but no data are available about relapsing BSI.

In our study, mortality rate was 7.7% at 30 days. Few data are available, ranging from 10 to 15% among acute leukemia patients^{16,20}; we found no data focusing on mortality rate for AML patients with BSI.

Optimal duration for BSI treatment is still in debate, whether patients are immunocompromised or not, except for CRBSI, for which guidelines have been recently published.²¹ A recent literature review suggested that short-course AT is not related to a higher risk of treatment failure for uncomplicated BSI.¹² A systematic review in 2011 included randomized control trials (RCT) comparing the efficacy of shorter versus longer AT for common infections in ICU. A sub-group analysis on patients presenting BSI ($n = 155$) found no significant difference between short-course (5–7 days) and long-course (7–21 days) treatment, regarding clinical cure, microbiological cure and survival.²² However, the bacteria responsible for BSI were not detailed. A pilot study called BALANCE (Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness), assessing the feasibility of a RCT comparing 7-day versus 14-day AT for BSI in ICU, found encouraging results.²³ Although immunocompromised patients have been excluded from the analysis,

an international multicenter BALANCE study is ongoing, planning on including over 3600 patients.²⁴

In our study, patients transferred in ICU belonged more frequently belonged to the long-course treatment group. This was probably linked to the gravity of the situation, since discontinuation of antibiotics for an unstable patient or a patient suffering from severe infection was not an easy decision to make for the physician. Likewise, remaining fever probably discouraged physicians from stopping antibiotics; this potential confounder could explain the higher rate of episodes with prolonged fever in the long-course group. Nevertheless, persistent fever when discontinuing AT was not related to a higher risk of BSI relapse in our study. We could draw a parallel with the AntibioSTOP study, which showed that discontinuation of AT at day 5 might be safe in the case of fever of unknown origin (FUO) for hematological patients suffering from FN, regardless of the evolution of fever.²⁵ This practice has not yet been recommended by ECIL, which advised 48 h of apyrexia to stop AT for FUO in FN patients, irrespective of neutrophil count, supported by the results of the How long study.²⁶

Fewer data on non-ICU patients are available in literature, mostly using a 10-day threshold to compare treatment length in enterobacteriaceae BSI.^{27,28} In 2014 a retrospective study conducted on immunocompetent patients obtained similar clinical and microbiological responses comparing 7-day antibiotic course to longer treatment.²⁹

Another RCT on neonatal BSI showed no significant difference in the efficacy of 7-day versus 14-day AT; however, sub-group analysis on *S. aureus* BSI showed a higher rate of treatment failure in the 7-day group, which is in accordance with guidelines recommending a 14-day treatment³⁰. In a study including 249 patients who received short-course AT for *P. aeruginosa* BSI, defined as 7–11 days of treatment (median 9 days), BSI relapse and mortality were similar to the long-course treatment group (median 16 days). In this cohort, 65% of the patients were immunocompromised.³¹ These findings are in accordance with the present study thresholds defining short and long courses of treatment for different bacteria.

Our study had several limitations, mainly due to its retrospective design. We did not report the potential adverse effects of AT, such as *C. difficile* infections or emergence of multi-drug resistant bacteria strains, of which the incidence would be interesting to compare between short- and long-course AT groups. The main outcome, BSI relapse within 30 days of antibiotic discontinuation, had very few occurrences. It underlined the global efficacy of AT, but was also responsible for a lack of power to highlight all risk factors related to BSI relapses. We chose a short follow-up of 30 days to be more selective when distinguishing relapses (involving the same strain as the index episode) from reinfections, as we did not perform sequencing analysis to prove it. We decided to not assess mortality as a primary outcome because death etiology is often hard to accurately indicate in AML patients, susceptible to die from infection, hemorrhage, chemotherapy toxicity, or refractory malignancy itself.²⁰ These events frequently overlap, assuming that patients suffering from R/R AML receive more cycles of chemotherapy, with higher risk of infection due to prolonged or repeated periods of neutropenia.

To conclude, short-course AT for treatment of BSI in AML patients with FN seemed as effective as prolonged treatment. BSI relapse rate and mortality rate at 30 days were low and unrelated to treatment duration. The only significant risk factor for relapsing BSI was long-duration neutropenia. There was a trend showing more R/R AML and more enterobacteriaceae among relapsing BSI episodes. Further prospective interventional studies including more patients are needed to assess the efficacy and safety of short AT in these patients.

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