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Original Article

Fever of Unknown Origin and Multidrug Resistant Organism Colonization in AML Patients

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Abstract. ***Background:*** **Colonization by multidrug-resistant organisms (MDRO) is a frequent complication in hematologic departments, which puts patients at risk of life-threatening bacterial sepsis. Fever of unknown origin (FUO) is a condition related to the delivery of chemotherapy in hematologic malignancies, in which the use of antibiotics is debated. The incidence, risk factors, and influence on the outcome of these conditions in patients with acute myeloid leukemia (AML) are not clearly defined.**
Methods**: We retrospectively analyzed 132 consecutive admissions of non-promyelocytic AML patients at the Hematology Unit of the University Tor Vergata in Rome between June 2019 and February 2022. MDRO swab-based screening was performed in all patients on the day of admission and once weekly after that. FUO was defined as fever with no evidence of infection.**
Results**: Of 132 consecutive hospitalizations (69 AML patients), MDRO colonization was observed in 35 cases (26%) and resulted independently related to a previous MDRO colonization (p=0.001) and length of hospitalization (p=0.03). The colonization persistence rate in subsequent admissions was 64%. MDRO-related bloodstream infection was observed in 8 patients (23%) and correlated with grade III/IV mucositis (p=0.008) and length of hospitalization (p=0.02). FUO occurred in 68 cases (51%) and correlated with an absolute neutrophilic count <500µ/L at admission (0.04).**
Conclusion**: In our experience, MDRO colonization is a frequent and difficult-to-eradicate condition that can arise at all stages of treatment. Prompt discharge of patients as soon as clinical conditions allow could limit the spread of MDRO. In addition, the appropriate use of antibiotics, especially in the case of FUO, and the contraction of hospitalization length, when feasible, are measures to tackle the further spread of MDRO.**

Keywords: Acute myeloid leukaemia; Multidrug-resistant organism; Colonization; Fever of unknown origin.

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Introduction. Acute myeloid leukemia (AML) is an aggressive hematologic malignancy of the myeloid lineage.

The choice of treatment requires a careful analysis of the biological characteristics of the disease[1] and a proper assessment of patients' fitness;[2] patients deemed eligible

for aggressive treatment are to receive anthracycline-based induction chemotherapy followed by cytarabine and/or hematopoietic stem cell transplantation (HSCT) as consolidation. Patients not eligible for this approach undergo less intensive therapies, such as hypomethylating agents (HMA) (± venetoclax) or other forms of low-intensity chemotherapy (i.e., low-dose cytarabine). Patients ineligible for active therapy are referred to palliative care.[1]

Immunosuppression caused by these treatments and prolonged hospitalizations expose AML patients to life-threatening infections, which can be sustained by multidrug-resistant organisms (MDROs), accounting for one of the major causes of mortality.[3]

Given the complex profile of antibiotic resistance and the rapid worldwide diffusion of MDROs, epidemiological surveillance of the microbiological colonization of patients has become a critical step. Actually, early detection of colonization prevents MDROs from spreading, through patients' isolation and delivery of targeted therapy, in case of fever.[4]

In the treatment of febrile neutropenia, the European Conference on Infections in Leukemia suggests a wise use of antibiotics to avoid further selection of resistance:[5–7] non-colonized patients should be treated with empirical therapy, not including carbapenems, while colonized patients should be treated with a "de-escalation" approach, choosing the antibiotics based on the MDRO antibiogram. Any modification of the therapeutic strategy at 72-96 hours should rely on the patient's clinical evaluation and the results of microbiologic culture tests.[7]

Fever, in the absence of non-infectious causes and clinical focus of infection and negativity of blood cultures or pathological microbiological findings related to a possible focus of infection, is defined as of unknown origin (FUO)[8]. The onset of FUO is frequently described in hematologic malignancies; the underlying mechanisms are poorly understood, and the use of antibiotics is a matter of debate.[7,8]

This retrospective study aims to analyze the incidence of Colonization by MDRO and FUO in a consecutive series of AML patients and assess these factors' effects on the outcome.

Material and Methods

Patients. We retrospectively analyzed 132 consecutive admissions for a total of 69 adult patients (≥18 years old) with non-promyelocytic AML seen at the Hematology Unit of the University Tor Vergata in Rome between June 2019 and March 2022. AML diagnosis and treatment schedules were defined according to the European LeukemiaNet guidelines.[1]

Baseline data were recorded for each patient at admission and included age, gender, ECOG, white blood cell count (WBCc), absolute neutrophil count (ANC), hemoglobin (Hb), lymphocytes count (Lyc), and lactate dehydrogenase (LDH). In addition, Patients on AML treatment regimens received antibiotic exposure in the previous six months before admissions to hematology departments. MDRO colonization at previous admissions, incidence and severity of neutropenia, grade III/IV mucositis according to WHO grading scale,[9] MDRO colonization, FUO occurrence, and outcome at 30 and 60 days from colonization were also recorded.

MDROs were defined as vancomycin-resistant enterococcus (VRE), methicillin-resistant Staphylococcus aureus (MRSA), Carbapenem-resistant Enterobacteriaceae (CRE), and Extended-spectrum beta-lactamases (ESBLs).

Nasal, oropharyngeal, anal, perianal, and urethral or vaginal MDRO screening culture swabs were performed in all patients on the same day of admission, and anal and perianal swabs once weekly thereafter. Colonized patients were isolated to contain the spread of the pathogen.

Bloodstream infection (BSI) was defined as the detection of a bacterium in one blood culture; two positive cultures were required for diagnosing coagulase-negative staphylococci or Corynebacterium spp. In addition, BSI was defined as related to MDRO (MDROrel BSI) in case of identification in blood culture of the same pathogen detected in screening culture swabs.

FUO was defined as fever (≥ 38.3°C once or ≥ 38.0°C lasting for at least 1 h or being measured twice within 12 h) in the absence of identified causes and negativity of blood cultures from both peripheral vein and central venous catheter (if present).

During neutropenia, no fluoroquinolone prophylaxis (FP) was used. In the case of febrile neutropenia, antibiotic therapy was started: in colonized patients, the choice of the antibiotic was driven by the sensitivity profile of MDRO, whereas non-colonized patients were treated empirically with a first-line β-lactam antibiotic piperacillin/tazobactam.

The study was approved by the Institutional Review Board and all patients provided informed consent to the processing of their sensitive data.

Statistical Analysis. Univariate and multivariate analyses were used to establish the connections between the variables. Chi-square or Fisher exact test was used for dichotomous variables; the independent test or Mann-Whitney test were used for continuous variables as appropriate. A p-value less than 0.05 was considered significant. All analyses were performed using the IBM SPSS Statistics 27 software.

Results. Characteristics of the study population are shown in **table 1**. One hundred thirty-two admissions were analyzed (for a total of 69 adult patients); intensive chemotherapy was administered in 74, non-intensive

Table 1. Characteristics of study population.

	All admissions	MDRO colonization		FUO	
Number of admissions (n, %)	132 (100)	35 (26)		68 (51)	
Age (median, range)	59 (24-90)	61 (26-80)	p= 0.6	59 (24-81)	p= 0.8
Male sex (n, %)	67 (51)	18 (51)	p= 1	31 (46)	p= 0.2
ECOG 0/1/2/3/4 (n, %)	66 (50) 24 (18) 28 (21) 10 (8) 4 (3)	17 (49) 10 (29) 3 (8) 5 (14) 0 (0)	p= 0.08	37 (55) 15 (22) 11 (16) 5 (7) 0 (0)	p= 0.1
Intensive chemotherapy/ Non intensive treatment/ Supportive care (n, %)	74 (56) 29 (22) 29 (22)	19 (54) 11 (32) 5 (14)	p= 0.2	43 (63) 18 (26) 8 (11)	**p= 0.02**
Induction phase*/ Consolidation phase/ Salvage phase/ Supportive care (n,%)	51 (39) 32 (24) 20 (15) 29 (22)	16 (46) 6 (17) 8 (23) 5 (14)	p= 0.1	33 (49) 14 (21) 12 (18) 9 (13)	**p= 0.02**
≥2 previous intensive chemotherapies (n, %)	40 (30)	15 (43)	p= 0.05	21 (31)	p= 0.8
Previous treatment with HMA (n, %)	16 (12)	1 (3)	p= 0.05	9 (13)	p= 0.6
Previous admissions to hematology departments (median, range)	1 (0-7)	1 (0-5)	p= 0.3	1 (0-7)	p= 0.9
Previous exposure to Piperacillin/Tazobactam (n, %)	72 (55)	17 (48)	p= 0.7	40 (59)	p= 0.3
Previous exposure to Vancomycin (n, %)	28 (21)	10 (35)	**p= 0.002**	17 (25)	p= 0.2
Previous exposure to Carbapenems (n, %)	45 (34)	14 (40)	**p= 0.03**	25 (37)	p= 0.5
Previous MDRO colonization (n, %)	25 (19)	15 (43)	**p< 0.001**	12 (18)	p= 0.6
Hb (median, range)**	9.2 (5.5-15.1)	7.9 (5.5-14.3)	p= 0.1	8.9 (6-15)	p= 0.6
ANC (median, range)**	1.955 (0-44.860)	1.190 (10-6950)	p= 0.1	1.725 (10-39.340)	p= 0.06
Ly (median, range)**	875 (30-18.390)	2.270 (0-6.950)	p= 0.09	1.135 (30-15.390)	p= 0.5
LDH (median, range)**	784 (86-9947)	875 (129-5720)	p= 0.6	291 (103-9947)	p= 0.9
ANC<500μ/L (n, %)	108 (82)	29 (83)	p= 0.7	62 (91)	**p= 0.002**
Days of ANC<500μ/L (median, range)	9 (0-60)	13 (0-44)	p= 0.3	15 (0-44)	**p= 0.001**
> 10 days of ANC<500μ/L (n, %)	76 (58)	21 (60)	p= 0.6	46 (68)	**p= 0.007**
ANC<100μ/L (n, %)	88 (67)	25 (71)	p= 0.3	51 (75)	**p= 0.02**
Days of ANC<100μ/L (median, range)	5 (0-35)	5 (0-33)	p= 0.1	8 (0-35)	**p=0.002**
Mucositis (n, %)	26 (20)	11 (31)	**p= 0.04**	17 (25)	p= 0.1
Days of hospitalization (median, range)	22 (3-145)	35 (7-145)	**p= 0.001**	29 (7-88)	**p= 0.001**

* In patients receiving HMAs, induction phase was considered below 6 cycles. ** at time of admission. **Abbreviations**: ANC, absolute neutrophils count; FUO, fever of unknown origin; Hb, hemoglobin; HMA, hypomethylating agents; LDH, lactate dehydrogenase; Ly, lymphocytes count; MDRO, multidrug-resistant organism.

treatment in 29, and supportive therapy in 29. **Table 2** summarizes the therapeutic regimens. MDRO colonization was detected in 35 admissions (26%) and correlated with previous exposure to Vancomycin (p=0.002) and Carbapenem (p=0.03), previous MDRO colonization (p<0.001), mucositis (p=0.04) and days of hospitalization (p=0.001). A near-significance correlation with FUO (p=0.1), ECOG (p=0.08), ≥2 previous intensive chemotherapies (p=0.05), and the absence of previous treatment with HMA (p=0.05) was also observed. In multivariate analysis, previous MDRO colonization (p=0.001) and days of hospitalization (p=0.03) remained independent factors significantly associated with MDRO colonization. Among these patients, the colonization persistence rate in subsequent admissions was 64%. CRE was the most frequently identified MDRO (in 29 cases, 22%); VRE was detected in 8 cases (6%), MRSA in 4 (3%), and ESBL in 2 (1.5%) (**Figure 1**). Two patients developed anal abscesses; CRE colonized both, presented mucositis, and had a long hospitalization (59 and 46 days).

BSI was observed in 33 patients (25%): 8 (24%) had MDROrelBSI (see below), 13 (39%) from GRAM + Vancomycin sensitive bacteria, 3 (9%) from E. Coli, 3 (9%) from K. Pneumoniae, 1 (3%) from P. Mirabilis, 1 (3%) from E. Faecium and 2 (6%) from MDRO not

Table 2. AML therapeutic regimens.

AML therapeutic regimens		
Intensive Chemotherapy		74 (%)
	Daunorubicin + Cytarabine (Including the association with Gentuzumab Ozogamicin and Midostaurine)	20 (27)
	CPX 3-5-1	9 (12)
	Fludarabine + Idarubicin + High dose Cytarabine	18 (24)
	High dose Cytarabine	27 (37)
Non intensive treatment		29 (%)
	Hypomethylating agents + Venetoclax	8 (28)
	Hypomethylating agents	14 (48)
	Others	7 (24)

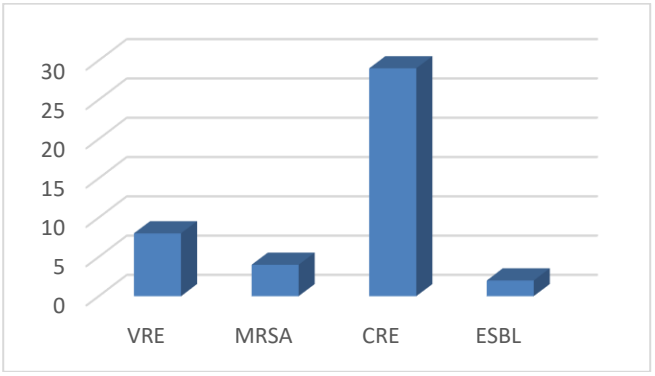

Figure 1. MDRO detected in the study population. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamases; MRSA, methicillin-resistant staphylococcus aureus; VRE, vancomycin-resistant enterococcus.

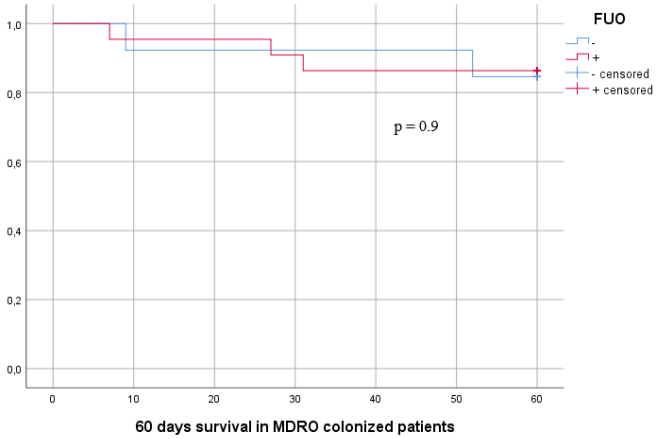

Figure 2. 60 days survival function in MDRO study population; comparison between patients who presented FUO and those who didn't.

detected in culture swabs: E. Faecium VRE and P. Aeruginosa CRE. Seven patients (21%) required oxygen therapy, 4 patients (12%) inotropic support; the median length of hospitalization was 34 days.

BSI was more frequent in colonized than non-colonized patients [12 (34%) vs. 21 (22%); p=0.1] and correlated with length of hospitalization (p=0.01).

Eight of 33 patients developed MDROrel BSI (23% of colonized patients; 6 K. Pneumoniae CRE; 2 E. Faecium VRE); 1 patient required oxygen therapy (12.5%), and 1 patient required inotropic support (12.5%); the median length of hospitalization was 48 days. MDROrel BSI correlated with mucositis (p=0.008) and length of hospitalization (p=0.02).

Patients presented FUO in 68 admissions (51%); 6 patients (9%) required oxygen therapy, 2 patients (3%) inotropic support; the median length of hospitalization was 29 days. We found a correlation with active treatment (p=0.02), neutropenia (ANC<500µ/L p=0.002, days of ANC<500µ/L p=0.001, >10 days of ANC <500µ/L p=0.007, ANC <100µ/L p=0.02) and days of hospitalization (p=0.001); FUO was also more common in colonized then non-colonized patients, even not reaching statistical significance [22 (63%) vs. 46 (47%); p=0.1]; in colonized patients, FUO was not reflected in a worse 60 days outcome (**Figure 2**). The relations between FUO, BSI and MDRO are shown in **figure 3**. In

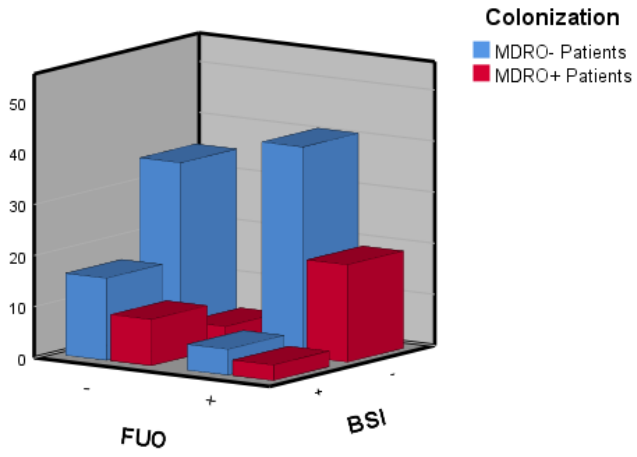

Figure 3. Correlations between FUO, BSI and MDRO colonization. The "+" sign refers to the occurrence of the FUO and/or BSI event; the "-" sign refers to the non-occurrence of the event. In some long admissions, both events occurred (Columns in front).

multivariate analysis, ANC<500µ/L remained an independent factor significantly associated with FUO (p=0.04).

The severity of the febrile event was higher in BSI than in FUO [in terms of requirement of oxygen therapy (21% vs. 9%, p= 0.1) and of the requirement of inotropic

support (12% vs. 3%, p=0.08)]. In comparison, we found no differences between BSI from bacteria not previously detected in culture swabs and MDROrel BSI [requirement of oxygen therapy 24% vs. 12.5%, p= 0.6; in terms of requirement of inotropic support 12% vs. 12.5%, p=1].

Mucositis correlated with MDRO colonization and MDROrel BSI (see above), LDH (p=0.02), Hb (p=0.03), days of ANC<500μ/L (p=0.003, >10 days of ANC <500μ/L p=0.01, days of ANC <100μ/L p=0.003, days of hospitalization (p<0.001), type of therapy [intensive chemotherapy 20 (27%); non-intensive treatment 4 (14%); support care 2 (7%); p=0.04); in multivariate analysis only days of hospitalization remained an independent variable significantly associated with mucositis (p=0.01).

We then carried out an outcome analysis: 11/69 patients (16%) died or were referred to end-of-life care at 30 days from admission, whereas 15/69 patients (22%) at 60 days. Nine patients died during the admission, 7 of whom from non-infectious causes (all at 30 days) and 2 because of infections (both at 60 days, from pneumonia). No patients died because of BSI.

Death or the referral to end-of-life cares, at 30 and 60 days, correlated with age (p=0.02 and p=0.006), ECOG (both p<0.001), BSI (p=0.006 and p=0.003), type of treatment (both p<0.001), LDH (p=0.02 and p=0.009).

In multivariate analysis, ECOG (p=0.02 and p=0.01) and BSI (p=0.01 and p=0.005) remained independent significantly associated factors.

Furthermore, patients who underwent intensive chemotherapy were categorized as those admitted to receiving induction (29 patients, 39%), consolidation (29 patients, 39%), or salvage (16 patients, 22%). We detected a lower incidence of mucositis among the consolidation group (45% vs. 7% vs. 31%, p=0.005) and, although not reaching the statistical significance, a higher incidence of sepsis in the salvage group (17% vs. 17% vs. 44%, p=0.08); a higher incidence of FUO was observed in the induction and salvage group (69% vs. 41% vs. 62%, p=0.09). There were no differences in MDRO colonization across the 3 groups (28% vs. 17% vs. 37%, p=0.3).

Discussion. Given the great impact of nosocomial infections in the management of AML, several studies[10,11] have focused on this topic, whereas only a few authors analyzed the features and role of MDRO colonization.[3,12–14] Ballo et al. studied a cohort of AML patients undergoing induction intensive chemotherapy in Frankfurt, Germany; the colonization rate was 41% with a high prevalence of VRE (74%), while CRE colonization correlated with an inferior outcome.[3] In the same institution, Scheich et al. found, in a cohort of AML patients undergoing HSCT, a colonization rate of 54%, mainly from VRE, and a lower 5-year overall survival in the MDRO-colonized population.[14] Jaiswal et al. observed, in a cohort of hematological patients in New Delhi, a high incidence of CRE colonization in those with AML (65%) and, among colonized patients, the diagnosis of AML resulted in being a risk factor for infection-related mortality.[13] A large multicentric Italian study considering a heterogeneous pool of hematological patients detected, in the AML subgroup, a colonization rate of 6%, with a large prevalence of CRE and ESBL and lower incidence of colonization at the onset of disease or during induction than in consolidation or salvage therapy.[12]

Our population shares similar characteristics with the previous two studies, with a high percentage of Colonization by CRE and a low by VRE (**Figure 1**). These data are in accordance with the epidemiological literature, which showed great variability between geographic areas, and, in recent years, a trend of increasing GRAM-MDRO and a higher prevalence of CRE in South-East vs. North-West Europe.[15,16] Furthermore, these differences may have been exacerbated by the heterogeneity of the category of patients examined: to the best of our knowledge, the present study is the first to focus on MDRO colonization in AML patients, receiving both intensive and non-intensive treatments and in phases different from induction.

These peculiarities allowed us to observe a high MDRO colonization persistence rate during hospitalizations (64%), which could explain a lower survival in the long term and after HSCT, as highlighted by Ballo et al. and Scheich et al.[3,14]

No impact on short-term outcomes was found; the reason is likely ascribed to the prompt use of targeted antibiotic therapy in case of fever in colonized patients. BSI, on the other hand, although not a direct cause of mortality, was found to correlate independently with an early dismal outcome. This was due to the delay in the resumption of antileukemic therapy due to the infectious episode and worsening of the patients' clinical condition.

The evaluation of the impact of MDRO colonization on mortality cannot be separated from an analysis of FP (carried out by Ballo et al.[3]). This topic is central to a long-lasting debate dealing with the risk of the expanding antibiotic resistance and decreased efficacy of subsequent antibiotic therapy.[17,18]

Recently, Castanon et al. published the results of a comparison of two cohorts of AML patients undergoing intensive chemotherapy. In cohort one, microbiological screening was not routinely performed, and FP was at the treating physician's discretion; in cohort two, both FP and microbiological screening were carried out. No differences were found in the incidence of infections during the induction phase between the 2 cohorts. However, during the consolidation phase, there was an increase in infections of GRAM- bacteria in cohort 1 and

of GRAM+ bacteria in the cohort 2.

Moreover, a significant decrease in deaths secondary to infections and overall mortality was observed in cohort 2. Of note, there were no differences in the incidence of FUO between the two cohorts.[19]

In this study, it is hard to distinguish the contribution made by bacteriologic screening, which allowed targeted antibiotic therapy to be instituted, and FP. In the era of microbiologic surveillance, FP cost-effectiveness, its impact on the incidence of MDRO colonization, and the occurrence of FP-associated resistance remain unsolved medical needs.

Although not reaching statistical significance in multivariate analysis, an association of MDRO colonization with oral mucositis emerged. This finding, along with the evidence of a link between alteration of the gastrointestinal microbiome and infectious complications,[20,21] suggests that mucositis could promote MDROrel BSI and MDRO colonization. Such an assumption appears even more realistic based on a recent meta-analysis showing the protective effect of anti-mucositis treatment on bacterial colonization in patients developing this complication after chemo-radiotherapy.[22]

Indeed, detecting anal abscesses in two patients colonized by CRE made us hypothesize that MDRO colonization is not only the consequence of an altered mucosal barrier but also the cause.

In our series, we found a correlation between mucositis and type of therapy [Intensive chemotherapy 20 (27%); non-intensive treatment 4 (14%); support care 2 (7%); p=0.04; in line with literature data, indicating a mucositis incidence of 20-40% in patients receiving standard chemotherapy and <5% receiving CPX-351[23–25]]. However, this is not reflected in the correlation between the type of therapy and MDRO colonization (p=0.2). Therefore, other factors, such as personal hygiene and previous dental conditions, probably play a role.

From our analysis, increased length of admission appears to be the common denominator of MDRO colonization and FUO (both variables independently correlated with days of hospitalization). In particular, the relationship between hospitalization and MDRO colonization may reflect a "chicken-or-the-egg" dilemma. Fever in colonized patients requires longer therapy and greater precautions than in non-colonized patients; on the other hand, a longer hospitalization places the patient at risk of Colonization by MDRO. Curiously, Ballo et al., in a cohort of AML patients undergoing induction chemotherapy, found no significant differences between the length of hospitalization in colonized and non-colonized patients.[3] This discrepancy may be due to the greater heterogeneity of the population examined in our study and the different strains of MDROs detected (higher prevalence of CRE in our population, correlated with a high risk of life-threatening infections).[3]

The incidence of FUO in AML patients ranges between 15 and 100% depending on the treatment phase and type of chemotherapy. Despite improvements in diagnostic techniques, there is no evidence of a downward trend over the years.[26–30] The etiology of this phenomenon may be traced back to the inflammatory state induced by the disease, the precise mechanisms of which are still partially unknown.[31] It is conceivable that FUO arises in a condition of bone marrow activation/inflammation sustained by the chemotherapeutic intervention, with the concomitancy of neutropenia. In this condition, bone marrow is the target of endogenous and/or exogenous stimuli that, acting similarly to granulocyte-colony stimulating factor, can cause fever.[32]

As we expected, the severity of the febrile event (in terms of the requirement of oxygen therapy and inotropic support) was higher in BSIs than in FUO cases; it is also likely that a proportion of the FUO cases, presumably the most severe ones, were misdiagnosed BSI. Furthermore, despite the more complex drug-resistance profile of bacteria, MDROrelBSIs presented a prognosis similar to the BSIs from a bacteria undetected by culture swabs; this is due to the prompt use of the correct antibiotic therapy through a de-escalation approach which, in a fragile population such as AML patients at high risk of infection (because of the Colonization by MDRO) is the best strategy. At the same time, no evidence exists for such an approach when no pathogen is identified.[7]

A useful biomarker in framing the febrile episode, unfortunately not available in our patients, is procalcitonin, which accurately identifies infections and correlates with the severity of BSI.[33–35] The positivity of this index without any finding on blood cultures could raise suspicion of a misdiagnosed infection; moreover, procalcitonin-guided management of febrile patients in intensive care units led to decreased antibiotic use and reduced mortality.[36,37] The only prospective trial of a procalcitonin-based decision-making approach carried out in hematologic patients did not bring the hoped-for effects, showing any significant differences in antibiotic use.[38] Of note, the population examined was small (60 patients, randomized 1:1) and included different types of hematologic malignancies.[38] Larger trials with more stringent selection criteria are needed to assess the efficacy and safety of this approach in clinical practice.

Conclusions. MDRO colonization is a frequent and difficult-to-eradicate complication in AML patients that can arise at all treatment stages, affecting long-term outcomes. Prompt discharge of patients as soon as clinical conditions allow may limit the spread of this phenomenon.

FUO needs to be a better-understood event, with

adequate management still waiting to identify the underlying causes. An in-depth elucidation of the contributors to FUO occurrence is critical to optimize antibiotic use and minimize hospitalization length. These achievements are necessary to tackle antibiotic resistance and limit health costs.[39]

The retrospective nature of this analysis, the small size of the population under investigation, and its heterogeneity are the study's main limitations. Larger studies are needed to confirm these data and put in place proper measures to reduce the risk of MDRO colonization.

Compliance with Ethical Standards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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