

Chemotherapy-induced febrile neutropenia in acute myeloblastic leukemia: A single-center study of adult patients

Neutropénie fébrile chimio-induite au cours de la leucémie aigüe myéloblastique : Une étude monocentrique de patients adultes

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ABSTRACT

Introduction: Management of febrile neutropenia (FN) depends on several elements. Despite their importance, tunisian data were poor.

Aim: To describe the clinical, microbiological and therapeutic profile of chemotherapy-induced FN during acute myeloblastic leukemia (AML).

Methods: This observational cohort study, conducted in hematology department of Aziza Othmana hospital, included all intensive chemotherapy-induced FN episodes observed in patients aged ≥ 18 years and diagnosed with AML in 2021. Data were retrospectively collected and descriptively analyzed.

Results: Among 33 patients, 121 FN episodes were studied. They were observed respectively during induction (52.1%), consolidation (38.8%) or salvage therapy (9.1%) cycles. Episodes were labeled as fever of unknown origin (29.8%), clinically documented infection (51.2%) and microbiologically documented infection (MDI) (19.0%). Clinical infectious sites were skin/soft tissue (44.6%), gastrointestinal tract (27.3%), respiratory tract (27.3%) and otorhinolaryngology tract (5.0%). Gram-positive cocci and Gram-negative bacilli were isolated respectively in 18 and 15 cases, with CoNS and Klebsiella pneumoniae being the commonest. Multidrug-resistant organisms were observed in nine episodes. Extended-spectrum-beta-lactamase was the most common resistance mechanism. An intensive care unit treatment was required in 13 episodes and noted in two episodes. Sepsis was observed in 28.1% of episodes. FN-related mortality was 7.4%, associated with sepsis, pneumonia and MDI.

Conclusion: Better supportive care strategies may improve infectious outcome in AML patients undergoing chemotherapy.

Keywords: Febrile neutropenia, Chemotherapy, Acute myeloid leukemia, Infections, Anti-microbial agents

RÉSUMÉ

Introduction : La prise en charge de la neutropénie fébrile (NF) dépend de plusieurs éléments. Malgré leur importance, les données tunisiennes sont pauvres.

Objectif : Décrire le profil clinique, microbiologique et thérapeutique de la NF chimio-induite au cours de la leucémie aiguë myéloblastique (LAM). **Méthodes :** Cette étude observationnelle, menée au service d'hématologie clinique de l'hôpital Aziza Othmana, a inclus tous les épisodes de NF chimio-induite, observés chez des patients âgés de ≥ 18 ans et diagnostiqués LAM en 2021. Les données étaient rétrospectivement collectées. Leur analyse était descriptive.

Résultats : Chez 33 patients, 121 épisodes de NF étaient observés. Ils étaient observés respectivement durant des cycles d'induction (52,1%), de consolidation (38,8%) ou de rattrapage (9,1%). Ils étaient classés comme fièvre d'origine indéterminée (29,8%), fièvre cliniquement documentée (51,2%), et fièvre microbiologiquement documentée (FMD) (19,0%). Les foyers cliniques étaient cutanéomuqueux (44,6%), digestif (27,3%), respiratoire (27,3%) et oto-rhino-laryngologique (5,0%). Dix-huit cocci Gram-positif et 15 bacilles Gram-négatif étaient isolés, les staphylocoques à coagulase négative et Klebsiella pneumoniae étant les plus fréquents. Les bactéries multirésistantes étaient observées dans 9 épisodes, la bêta-lactamase à spectre étendu était le mécanisme prédominant. Parmi 13 indications, un transfert en réanimation était noté dans 2 cas. Le sepsis était observé dans 28,1% des épisodes. La mortalité liée à la NF était de 7,4%, associée au sepsis, pneumopathie et FMD.

Conclusion : De meilleures stratégies thérapeutiques pourraient améliorer l'évolution de la NF chimio-induite durant la LAM.

Mots-clés : Neutropénie fébrile, Chimiothérapie, Leucémie aiguë myéloïde, Infections, Anti-infectieux

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INTRODUCTION

Febrile neutropenia (FN) is a major complication of chemotherapy (CT). It represents the first cause of mortality in acute myeloblastic leukemia (AML) (1). It is a diagnostic and therapeutic emergency that requires immediate management based on thorough evaluation and broad-spectrum antibiotic therapy (ATB) within the first hour, as each hour of delay increases mortality by 7.6% (2,3). Evaluating a patient with FN is challenging due to the poverty of clinical signs and microbiological investigations (4). Fever may be the only sign of infection, and approximately 60.0% of FN episodes have an unknown origin (5). The ATB is empirical and guided by several factors: the patient's individual data, clinical findings, possible colonization, microbiological results, and the local ecology (4). A better understanding of the clinical and microbiological documentation of FN episodes in leukemic patients would improve therapeutic management, reduce infection-related mortality, shorten hospital stays, and decrease associated costs. Literature on FN in AML from low-middle income countries like Tunisia is poor and presents several challenges. Given the poverty of such data and their practical importance, we decided to conduct this study.

We aimed to describe the clinical, microbiological, and therapeutic profiles of CT-induced FN during AML in the main hematology center in Tunisia.

METHODS

This was an observational cohort study. Data were retrospectively collected from a complete patient file used in the hospital. It included episodes of CT-induced FN diagnosed from January 2021 to September 2023 at the hematology department of Aziza Othmana hospital in Tunis, and observed in patients aged 18 years or older and treated by intensive CT for AML diagnosed in 2021. Episodes of FN during acute promyelocytic leukemia were not included.

FN was defined according to the infectious diseases society of America (IDSA) by a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ sustained over one hour period, associated with neutropenia < 0.5 G/L or an expected decrease of absolute neutrophil count less than 0.5 G/L during the next 48 hours (6). The end of an episode of FN was defined by the achievement of stable apyrexia for at least 72 hours. Any fever meeting the definition of FN and occurring after this period defined a new episode (7). The same patient may have been included several times in different episodes of FN, within the same CT cycle and/or during different cycles. Granulocyte-colony stimulating factor (G-CSF) were administered systematically, the day of their initiation depended on the CT cycle.

All patients were hospitalized in protective isolation rooms with laminar air flow. No prophylaxis nor digestive decontamination were performed. Patients were managed under a protected non-sterile regimen. For mucositis, only mouthwashes containing bicarbonate

and nystatin were used. Screening for multi-drug-resistant bacteria (MDR bacteria) was conducted only at the beginning of each CT cycle, using anal swabs.

Patient monitoring included daily clinical examinations and laboratory evaluations including at least a complete blood count, C-reactive protein, liver and renal function tests. At least one set of blood cultures was obtained from central venous catheters (CVC) and/or a peripheral vein site, during fever, hypothermia or chills. Chest X-ray and urine culture were routinely performed in case of fever. Additional microbiological tests and imaging were performed if clinically indicated. Aspergillus antigenemia was weekly performed.

First-line ATB were consistent with IDSA guidelines, based on an anti-pseudomonal β -lactam agent (6). In cases of fever without sepsis, piperacillin-tazobactam was used as first-line therapy. Ceftazidime was prescribed in case of allergy to penicillin. In sepsis with or without hypotension, dual therapy was initiated with either piperacillin-tazobactam plus amikacin or imipenem plus amikacin. Septic shock required triple therapy with imipenem, amikacin, and vancomycin. Amphotericin B was used as second line therapy in case of persistent isolated fever. ATB was then adjusted according to clinical and/or microbiological documentation. Glycopeptides were added only when Gram-positive cocci (GPC) were suspected.

We noted epidemiological data of patients, the cycle of CT inducing FN and the use of G-CSF. Then, we collected clinical, biological, microbiological, therapeutic and outcome features of each FN episode. The result of the microbiological investigation was noted: microbiologically documented infection (MDI) or non-microbiologically documented infection (NMDI). In cases of NMDI, we specified the category of fever according to the IDSA classification: clinically documented infection (CDI) or fever of unknown origin (FUO) (8). In cases of MDI, we mentioned the nature of infection (bacterial, viral and/or fungal), the responsible bacteria (Gram-negative bacilli (GNB) or GPC) and the presence of any potential MDR bacteria (6,9). We also noted the diagnosis of potential invasive pulmonary aspergillosis (10). Infection was considered catheter-related if at least two central blood cultures were positive for coagulase-negative staphylococci (CoNS) or other common commensals, if at least one central blood culture was positive for other organisms or if the catheter culture itself was positive.

Outcomes data consisted mainly of the occurrence of sepsis or septic shock according to the 2001 consensual definition, potential transfer to an intensive care unit (ICU) or death (11). Mortality was considered related to the FN when patients died due to an infection and/or one of its complications, with no other obvious cause of death.

All data were entered and analyzed using Microsoft Excel 2019 and IBM SPSS Statistics 25. A descriptive analysis was performed.

Quantitative variables were expressed as medians with interquartile range or means according to their distribution, while qualitative variables were expressed as frequencies and percentages. Comparisons of

percentages in independent samples were carried out using the chi-square test, and when it was not valid, Fisher's exact test was used. A statistically significant association was considered when $p < 0.05$.

This study was approved by the local ethics committee of Aziza Othmana hospital on December 20, 2023, under file N° 10/2023.

RESULTS

Among 33 patients, 121 FN episodes were studied. The mean age of patients was 42 ± 10 years [19- 62 years], with a sex ratio of 1.54. The mean number of episodes per patient was 4 ± 2 [1- 9 episodes]. FN occurred during induction cycles (cytarabine with anthracycline regimen) ($n=63$; 52.1%), salvage therapy (fludarabine with cytarabine and anthracycline regimen) ($n=11$; 9.1%), and consolidation cycles (high dose cytarabine regimen) ($n=47$; 38.8%). Their median timing relative to the onset of CT cycle was on day 12 (2.5- 15). G-CSF were prescribed during 70 episodes of FN (57.9%). The figure 1 shows the distribution of the 121 studied FN episodes according to the IDSA classification.

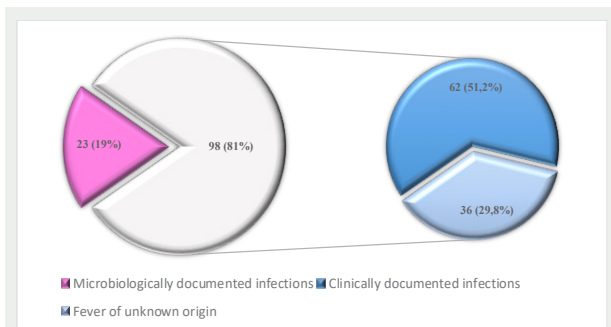


Figure 1. A pie chart showing the distribution of febrile neutropenia episodes according to the infectious diseases society of America classification

A clinical infectious site was identified in 81 episodes (66.9%), among which 19 episodes (15.7%) also had microbiological documentation. Among 40 episodes (33.1%) with no clinical infectious site, 4 episodes (3.3%) had additional microbiological documentation, while 36 episodes (29.8%) were classified fever of unknown origin. Different clinical infectious sites were shown in table 1. The predominant clinical site of infection was cutaneous-mucosal. An association of two or more clinical infectious sites in the same FN episode was observed in 35 cases (43.0%). The proportion of FN episodes associated with a respiratory tract infection was significantly higher during induction and salvage cycles ($32/60 = 53.0\%$) compared to the consolidation cycles ($3/21 = 14.0\%$) ($p = 0.002$). Table 2 shows main biological data of FN episodes.

In our cohort, four patients were colonized during 16 FN episodes with extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* ($n=6$), ESBL-producing *Klebsiella pneumoniae* ($n=3$), carbapenemase-producing *Pseudomonas aeruginosa* ($n=5$), and hyperproduced cephalosporinase-producing *Escherichia coli* ($n=2$). MDR screening identified colonization in two patients, while

the other two had a history of positive stool cultures despite negative screening. Polymicrobial infections were reported in six episodes. Bacterial infections were observed in 18 episodes, fungal infections in three, and SARS-CoV-2 infections in three episodes. One episode involved both bacterial and fungal infection. A catheter-related infection was noted in three cases. It should be noted that a CVC was placed in nine patients during 15 episodes. The predominant pathogens were CoNS and *Klebsiella pneumoniae*. CoNS co-occurred with *Staphylococcus aureus* in two episodes and with enterococcus in one. Both GPC and GNB were present in four episodes. Table 3 shows the distribution of isolated bacteria as well as their isolation sites.

Table 1. Clinical profile of febrile neutropenia

Clinical site of infection	Number of episodes (%)
Skin, soft tissue and mucous membranes	54 (44.6)
Mucositis	36 (29.8)
Phlebitis	18 (14.9)
Lesion of the anal margin	12 (9.9)
Cellulitis	4 (3.3)
Inflamed catheter insertion site	3 (2.5)
Oral candidiasis	2 (1.7)
Adenitis	2 (1.7)
Paronychia	1 (0.8)
Furuncle	1 (0.8)
Respiratory tract	33 (27.3)
Auscultatory abnormalities	21 (17.4)
Desaturation	18 (14.9)
Cough	12 (9.9)
Hemoptysis	2 (1.7)
Gastrointestinal tract	33 (27.3)
Diarrhea	31 (25.6)
Abdominal pain	9 (7.4)
Appendiceal pus in the Redon drain	1 (0.8)
Otorhinolaryngology site	6 (5.0)
Toothache	3 (2.5)
Rhinorrhea	2 (1.7)
Tonsillitis	2 (1.7)
Sinusitis	1 (0.8)
Dark nasal cavity	1 (0.8)
No definitive site identified	40 (33.0)

Table 2. Biological profile of febrile neutropenia

Biological parameter	Median value (IQR)
Neutrophils (G/L)	0.03 (0- 0.21)
Hemoglobin (g/dl)	6.9 (6- 7.9)
Platelets (G/L)	9 (4- 175)
Creatinine ($\mu\text{mol/l}$)	75 (57- 79.5)
Bilirubin ($\mu\text{mol/l}$)	16 (12- 22)
C-reactive protein (mg/l)	116 (69- 208.5)
Procalcitonin (ng/ml)	1.03 (0.44- 2.5)

Nine MDR bacteria were identified, ESBL production being the most common resistance mechanism ($n=5$), followed by methicillin-resistant *Staphylococcus aureus* (MRSA) ($n=2$) and carbapenemase-producing organisms ($n=2$). No vancomycin-resistant enterococcus (VRE) was identified. Among 23 MDI, invasive fungal infections

were documented in three episodes: *Candida albicans* candidemia, nasal fusariosis and both candidal and aspergillus sinusitis. Invasive aspergillosis was probable in two episodes with serum galactomannane ≥ 1 and possible in two others with only host and clinical criteria.

Table 3. Bacteriological profile of febrile neutropenia

Organisms	Episodes	Blood	Sputum	Pus	Catheter
Gram-positive cocci	15				
Coagulase-negative staphylococci	14	13	-	-	1
<i>Staphylococcus aureus</i>	2	1	-	1	-
<i>Enterococcus faecium</i>	1	1	-	-	-
<i>Enterococcus faecalis</i>	1	1	-	-	-
Gram-negative bacilli	15				
<i>Klebsiella pneumoniae</i>	6	6	-	-	-
<i>Escherichia coli</i>	4	2	2	-	-
<i>Pseudomonas aeruginosa</i>	3	1	-	1	1
<i>Rhizobium radiobacter</i>	1	-	-	-	1
<i>Stenotrophomonas maltophilia</i>	1	1	-	-	-

ATB was mainly empiric and adjusted by antibiogram results in 10 of 23 MDI episodes. Escalation to imipenem-cilastatine was prescribed for ESBL organisms (4/5), hyperproduced cephalosporinase GNB (1/2) and high-level penicillinase bacteria (n=1). Vancomycin and teicoplanin were respectively prescribed for MRSA (2/2) and beta-lactam-resistant *Enterococcus faecium* (n=1). Colistin was used in one carbapenemase-producing GNB (1/2). Antifungal therapy was initiated in 15 episodes, with amphotericin B for candidemia, fluconazole for mucositis (n=5) and voriconazole for nasal fusariosis and invasive aspergillosis cases.

ICU treatment was required in 13 episodes for septic shock (n=7) and acute respiratory distress (n=6). Among them, a transfer to the ICU was noted in two episodes. The median FN duration was four days [1-47]. Sepsis was noted in 34 episodes (28.1%), appearing at the fever onset in 12 episodes and later in 22 episodes with a median delay of two days [1-16]. Among sepsis episodes, seven (21.0%) progressed to septic shock within a median of two days [1-16]. Two of them were observed at the fever onset. Sepsis was significantly associated with CT cycles, occurring in 40.5% of episodes during induction and salvage therapy cycles vs. 8.5% during consolidation cycles ($p < 0.001$). Sepsis (56.5% vs 21.4%) and septic shock (17.4% vs 3.1%) were both significantly associated with MDI, $p=0.001$ and 0.024 respectively. FN-related mortality was 7.4% (9/121), significantly linked to MDI ($p=0.001$), respiratory tract infection ($p=0.003$) and sepsis ($p < 0.001$). Death occurred after a median of 13 days [6-30]. Figure 2 illustrates FN-related mortality risk factors.

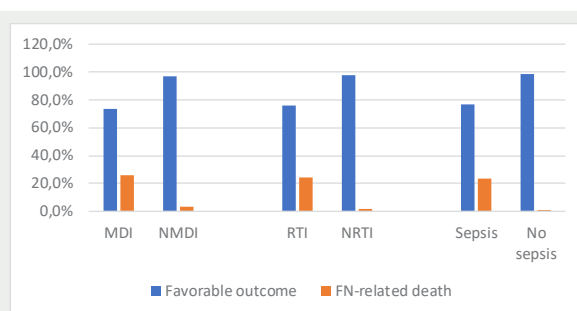


Figure 2. A histogram showing the association between febrile neutropenia-related mortality and the presence of a microbiological documentation, a respiratory tract infection and sepsis

MDI: Microbiologically documented infection, NMDI: Non microbiologically documented infection, RTI: Respiratory tract infection, NRTI: No respiratory tract infection, FN: Febrile neutropenia

DISCUSSION

This study was undertaken to describe the clinical profile, microbiological results, antibiotic sensitivity pattern, therapeutic data and outcome of treatment of FN in a single-center cohort of adult patients in Tunisia.

FN episodes were classified as CDI (51.2%), FUI (29.8%) and MDI (19.0%). CoNS was the most frequent identified organism. MDR bacteria were identified in nine episodes. Sepsis occurred in 28.1% of cases and FN-related mortality was 7.4%.

Our study had several limitations: its retrospective design, lack of systematic MDR screening, limited availability of microbiological investigations and restricted access to imaging. Additionally, limited access to ICU and several medications impacted optimal patient care.

Conversely, this study is relevant to daily clinical practice, focuses on a homogeneous population and concerns a multidisciplinary topic. It is original, as it represents the first tunisian study on CT-induced FN during AML. It allowed an appropriate statistical analysis due to the sample's size, and the results were encouraging.

Our study consists of an analysis of a case series without aiming for comparison. This type of study does not allow drawing generalizable conclusions to other cases.

The predominance of cutaneous-mucosal involvement in our study may be explained by the limited access to CVC and prophylactic mouthwashes, which increases the prevalence of mucositis and phlebitis. Digestive and pulmonary infections are more frequently reported as primary sites in the literature (1,12–15). These differences could be explained by the variability in care between services, particularly the frequency of CVC placement for patients treated by CT, the prevention of mucositis with effective mouthwashes not available in our country, food sterilization, digestive decontamination, and the difference in the *Aspergillus* spp. reservoir between countries.

Recent studies indicate that MDI is becoming more common than CDI and FUI, contrary to our results (12,13,15). Nunez et al and Chan et al reported MDI rates of 43.3% and 44.4%, respectively (12,16). This shift could be attributed to advancements in microbiological diagnostic techniques and raising awareness among healthcare staff about the importance of increasing the

number of cultures to determine the origin of the fever. However, MDI were less frequent (19.0%) in our study due to the limited access to infectious investigations and advanced microbiological testing.

A new classification of FN into MDI and NMDI should be proposed as it may be more appropriate than the traditional FUO, CDI, and MDI classification. Although clinical documentation is useful for adjusting empirical ATB, and even though certain clinical sites are associated with specific complications, knowing the identity of the pathogen responsible for the infection and its sensitivity to anti-infective agents is more beneficial for the management of fever. Despite MDI is the category of FN that helps target the implicated pathogens in the infection process, it progressed significantly more often than NMDI towards sepsis and death. The question arises: why does MDI still have the worst prognosis even when the pathogens responsible for the infection are known? Could this be due to a lack of therapeutic resources or the emergence of MDR organisms? This is an issue that requires further study.

In our study, the screening of MDR bacteria was insufficient. In fact, CT could alter the intestinal microbiota from the first cycle and the first episode of fever. This is why frequent and thorough screening for MDR bacteria in each patient is necessary to define a personalized therapeutic strategy (17). Ballo et al demonstrated that colonized patients had a longer fever duration, higher C-reactive protein levels, longer stays in ICU and lower survival rates compared to non-colonized patients (18). Our findings align with the literature regarding the increasing proportion of GPC over GNB and the predominance of staphylococci (12–15,19–21). These results could be explained by the prescription of empirical ATB primarily targeting GNB and the predominance of CT-induced mucositis, a major entry point for staphylococcal bacteremia. It could also be attributed to the frequent use of CVC and fluoroquinolone prophylaxis, which affects the intestinal flora composed of GNB.

In our study, nine MDR organisms were identified. Darakhshandeh et al reported high ESBL and carbapenemase rates in *Escherichia coli* and *Klebsiella pneumoniae*, with 65.0% of methicillin-resistant CoNS, and 67.0% of VRE (22). Globally, the emergence of MDR organisms represents a major public health issue. Inappropriate ATB and failure to comply with prescription guidelines are the primary causes of their emergence. A history of colonization or infection by MDR bacteria is also the main risk factor for MDR infections (23). Therefore, systematic MDR screening, assessment of risk factors for MDR infections in each patient, and a multidisciplinary approach are essential to combat these organisms and preserve new antibiotic classes. Our local hospital ecology appears to be improving, due the low prevalence of MDR organisms and non-fermenting GNB. However, fungal infection investigations remain limited due to restricted access to imaging and parasitological tests, which likely underestimates the number of invasive fungal infections. First-line antibiotic regimens followed international guidelines, but therapeutic escalation and empirical antifungal initiation were adjusted to local ecology and

individual patient data. The only case of candidemia in our study was not treated by caspofungin or liposomal amphotericin B as recommended due to their unavailability in our hospital. Challenges such as limited access to expensive drugs, recurrent stock shortages, inadequate ventilatory support, and restricted ICU access remain major barriers to effective management, particularly in cases involving MDR bacteria and severe septic conditions.

Our department's sepsis and septic shock diagnoses did not fully align with the 2016 consensus, potentially overestimating their frequency and contributing to poor outcomes. (24). Sequential organ failure assessment (SOFA) score, while useful for sepsis and mortality prediction, is not well-suited for hematology patients, prompting the development of a modified SOFAhem score excluding coagulation and neurological parameters (25,26).

The low mortality rate in our study (7.4%) is a strength. Consistent with the literature, it was significantly associated with sepsis, pneumonia, and MDI (1,20,24,27). Similar studies should be conducted to enhance understanding of FN. Prospective studies involving a homogeneous population would be particularly desirable to better describe the various characteristics of FN while improving access to radiological and microbiological investigations. More targeted research should also focus on the role of colonization screening, prophylaxis, and biological markers in FN management. Prospective testing of new therapeutic strategies integrating these elements would help translate findings into clinical practice. For assessing FN severity, a simpler, faster-to-calculate score, more adapted to hematology patients than SOFA and SOFAhem scores should be developed. Raising awareness among healthcare workers through training programs is essential to emphasize the importance of hygiene and asepsis measures, of increased microbiological investigations, and early FN management. Collaboration with anesthetists for the placement of CVC should be encouraged. Similarly, coordination between hematologists and resuscitators should aim to improve care for critically ill patients. The development of a hematology-ICU would represent a significant public health challenge for Tunisia to optimize the management of FN in severe cases.

Management of FN in patients undergoing CT in Tunisia remains challenging and requires better supportive care strategies. A multidimensional approach that combines research, training and healthcare system reorganization should be prioritized as key public health measure to ensure more effective and sustainable care of AML patients.

Abbreviations:

AML: Acute myeloblastic leukemia
ATB: Antibiotic therapy
CDI: Clinically documented infection
CoNS: Coagulase-negative staphylococci
CT: Chemotherapy
CVC: Central venous catheters
ESBL: Extended-spectrum beta-lactamase
FN: Febrile neutropenia
FUO: Fever of unknown origin
G-CSF: Granulocyte-colony stimulating factor
GNB: Gram-negative bacilli
GPC: Gram-positive cocci
ICU: Intensive care unit
IDSa: Infectious diseases society of America
MDI: Microbiologically documented infection
MDR: Multi-drug-resistant
MRSA: Methicillin-resistant *Staphylococcus aureus*
NMDI: Non-microbiologically documented infection
SOFA: Sequential organ failure assessment
VRE: Vancomycin-resistant enterococcus

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