(RESEARCH ARTICLE)

Bacterial ecology of sepsis in febrile neutropenics on hematology-oncology services

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Abstract

Introduction: Febrile neutropenia is a hematologic emergency that develops following treatment of hematologic malignancies. It exposes patients to the risk of sepsis, which is a major cause of morbidity and mortality. Currently, coagulase-negative staphylococci are the most common bloodborne isolates while enterobacteria are isolated less frequently. The objective of our study is to determine the epidemiological, bacteriological and antibiotic susceptibility profile of strains isolated from blood cultures collected from febrile neutropenic patients at Hassan II University Hospital, Fez.

Materials and methods: This is a prospective study, over a period of 4 years (January 2019 - December 2022) including 83 patients with bacteremia hospitalized in the department of hemato-oncology. Identification and detection of antibiotic resistance was performed according to conventional bacteriology methods and CA-SFM/EUCAST recommendations.

Results: Among 524 blood cultures received, we diagnosed 83 cases of bacteremia. The average age of the patients was 55 years. The average age of the patients was 55 years. The predominance of women was noted, with a sex ratio of 0.88. The majority of the episodes, 94.87%, occurred in patients followed for a neoplastic pathology. Hematological malignancies were the most responsible with a rate of 61.54% against 33.33% of solid tumors.

Gram-positive bacteria represent 56.6%, and 43.4% of Gram-negative bacteria. The proportions of the different bacterial classes (BGN / CG+) have remained stable over the last 4 years, Staphylococcus epidermidis was the most frequent isolated Gram-positive bacteria 24.1%(n=29) then Staphylococcus aureus 24.6% (n=18), followed by Gram-negative bacteria of enterobacteria type especially Escherichia coli which was the most frequently isolated pathogen (16.86%), followed by Klebsiella pneumoniae (10.84%) and non-fermenting Gram-negative bacteria such as Pseudomonas aeruginosa (8.4) and Acinetobacter baumanii (6%).

Bacteria of clinical interest have shown increasingly worrisome levels of beta-lactam resistance, with extended-spectrum beta-lactamase (ESBL)-producing strains of Klebsiella pneumoniae accounting for 4, 8% with only one case of carbapenemase, meticillin-resistant Staphylococcus aureus was 3.61% while no imipenem-resistant Pseudomonas aeruginosa or vancomycin-resistant enterococci were found. While Acinetobacter baumanii isolates (n=5) showed increased resistance to the majority of antibiotics tested, especially to imipenem which was 100%.

Discussion and conclusion: Gram-positive bacteremia of the genus coagulase-negative staphylococcus is the most common type of infection in febrile neutropenias showing an increasingly resistant profile to first-line antibiotics.

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However, Gram-negative infections have shown decreased susceptibility compared to previous years. A regular study of the bacterial ecology of blood culture isolates and a determination of antibiotic susceptibility are necessary to optimize the probabilistic antibiotic therapy of bacteremia.

Keyword: Bacteremia; Bacterial Ecology; Febrile Neutropenia; Hematology-Oncology Services.

1   Introduction

Febrile neutropenia is defined as a single oral temperature measurement of ≥38.3∘C or a sustained temperature ≥38∘C for 1 hour with a PNN of ≤500 cells/mm3 or a PNN that is ≤500 cells/mm3 over the following 48 hours [1].

Currently, coagulase-negative staphylococci are the most common blood isolates on hematology-oncology wards, whereas enterobacteria and non-fermenting gram-negative bacilli are isolated less frequently [2].

Antibiotic-resistant gram-negative bacterial species are causing an increasing number of infections in febrile neutropenic patients. In some centers, this has led to an epidemiological trend towards a predominance of gram-negative pathogens in the neutropenia population [3].In addition, resistant gram-positive pathogens, such as MRSA and VRE have become more common and frequent and are the most prevalent resistant isolates in some centers, accounting for 20% and 50% of episodes respectively [4].

Aggressive chemotherapies have improved the survival of patients with hematologic diseases. Unfortunately, however, they expose patients to the risk of bacteremia and sepsis, which is a major cause of morbidity and mortality [5, 6]. Febrile neutropenia is a hematological emergency that develops following treatment of hematological malignancies. The literature shows that life-threatening infection is observed in 48-60% of patients with febrile neutropenia [7].

The rapidity of the implementation of a probabilistic antibiotic treatment conditions the prognosis of the patient, the choice of which depends on several factors such as the result of the direct examination, the notion of colonization, the results of the previous bacteriological examinations and of course the bacterial ecology of the department. Among the germs responsible for these septicemias, we often find coagulase-negative Staphylococci, Staphylococcus aureus and Enterobacteriaceae. All these data as well as the frequency of multiresistance show the difficulty of choosing an empirical treatment taking into account the culture and sensitivity profile of all these microorganisms isolated in febrile neutropenia in this department.

Our study, carried out in the microbiology laboratory of the Hassan II hospital in Fez, aims to describe the bacterial ecology of sepsis in onco-hematology units and to draw up the antibiotic resistance profile of the germs most frequently encountered in febrile neutropenia, in order to guide the management of bacteremia and the prescription of an empirical antibiotic therapy for patients hospitalized in these units.

2   Material and methods

This is a prospective, descriptive study, spread over 4 years from January 1, 2019 to December 30, 2022, carried out in the microbiology laboratory of the CHU HASSAN II of Fez, focusing on the microbiological profile and antiobioresistance of bacteremia in febrile neutropenia in hemato-oncology services at the CHU Hassan II of Fez. On blood culture samples that are processed in the hospital laboratory. The data collected in this study were compared with the data collected in previous years, in order to analyze the evolution of the bacterial ecology of sepsis in febrile neutropenias as well as the sensitivity of the cultured germs to usual antibiotics.

All patients had fever ≥ 38.3°C, neutropenia (PNN< 500 cells/μl) and positive blood culture for bacteria hospitalized at the hemato-oncology department at Hassan II University Hospital.

Blood samples were collected for white blood cell count and absolute neutrophil count. In addition, blood cultures were performed in BACTEC Plus Aerobic and Anaerobic BD vials. All vials were incubated in the Bactec 9240 instrument (BD, USA) for five days. Blood culture positive vials were removed from the instrument. Gram staining was performed and a portion of the blood-broth mixture was subcultured onto solid plate medium based on the results of the Gram stain. Subsequent isolation and identification of bacteria was performed using conventional diagnostic methods such as catalase, oxidase, coagulase, optochin and biochemical tests. The susceptibility of all isolates to 14 different antibiotics was determined by disc diffusion. Antimicrobial susceptibility testing was performed on Mueller-Hinton agar medium using commercial antibiotic discs.

3   Results

During the study period, in 524 of received blood cultures we diagnosed 83 cases of bacteremia in febrile neutropenic patients hospitalized in the wards involved in the study (with a minimum length of stay > 48 h), moreover it was found that the highest rate of positive blood cultures was recorded in 2022 (n=32) and coagulase-negative staphylococcus was the most frequent incriminated agent.

These patients were mainly women, 44 women or 53% and 39 men or 46%. The sex ratio M/F was therefore 0.88. The average age of our patients was 55 years with extremes ranging from 1 to 77 years.
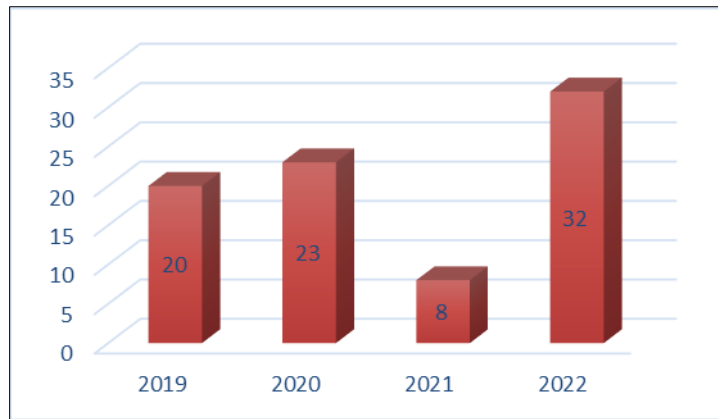

Figure 1 The distribution of sepsis cases by study year

In our series, out of the total number of episodes in which patients were followed for hematological malignancies, 27.30% (n=21) occurred in patients treated for ALL, 33.73% (n=28) for AML, and 18% (n=15) for lymphomas. Solid tumors were found in 2.4% of cases (n=2). Other pathologies, notably vasculitis, were found in 20% (n=17). Thus, in our sample, the recurrence of febrile neutropenia concerns both hematological malignancies and solid tumors.

In the majority of cases, it is a chemotherapy-induced febrile neutropenia. Only in 7 patients did neutropenia not occur as a result of cytotoxic treatment.

Table 1 Distribution of underlying pathologies

Underlying pathology	Workforce
AEG and organ failure	3
Multiple myeloma	3
AML	28
ALL	21
LYMPHOMA	15
Solid tumors	2
CML	2
AUTOIMMUNE DEASESES	9

During this period, the blood cultures taken came back sterile in 441 episodes, the positive blood cultures (n=83) revealed gram-negative bacilli (BGN) in 35 cases, gram-positive cocci (CGP) in 48 cases and no cases of candida were found.

The distribution of germs found on blood cultures by genus was characterized by a predominance of the genus Staphylococcus (n=47) followed by the family of Enterobacteriaceae where the genera Escherichia coli and Klebsiella were mostly represented (n=23) followed by Pseudomonas aeroginosa.

In our series, and from the results of all blood cultures performed, coagulase-negative Staphylococci isolated, including 3 species (hominis, haemolyticus and epidermidis) were predominantly represented (n=29). In addition, Staphylococcus epidermidis was the most frequent isolated Gram-positive bacterium (24.1%) then Staphylococcus aureus (n=18), followed by gram-negative bacteria like Enterobacteriaceae especially Escherichia coli was the most frequently isolated pathogen (16, 86%), followed by Klebsiella (10.84%) and non-fermenting gram-negative bacteria such as, Pseudomonas aeroginosa (8.4) and Acinetobacter baumanii species (6%).
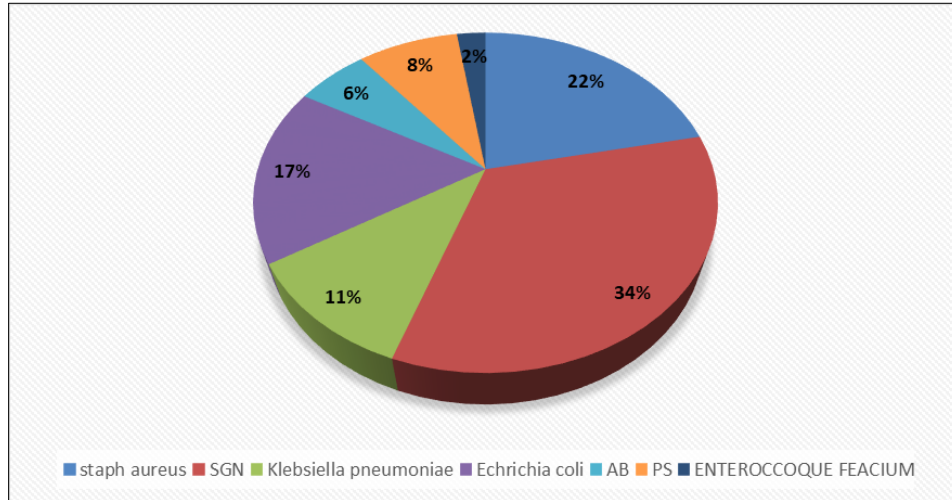

Figure 2 Distribution of microorganisms isolated from blood cultures

Gram-negative bacteria were sensitive to ciprofloxacin with a response range of 53.7% to 100%. The majority of E.coli isolates were susceptible to ceftazidime (87.8%) and were resistant to Co-trimoxazole (15.8%). Klebsiella isolates were 100% susceptible to imipenem.

The rate of extended-spectrum beta-lactamase (ESBL)-producing strains was 4.8%, with a predominance of Escherichia coli family Enterobacteriaceae 75% and meticillin resistance of S.aureus 3.61% while no imipenem-resistant P.aeruginosa strains were isolated (Table II).

Acinetobacter baumannii isolates (n=5) showed increased resistance to the majority of antibiotics tested. The rate of imipenem-resistant Acinetobacter baumannii was 100%. The most active antibiotic on these isolates was colistin. Indeed, MIC measurement by the microdilution method did not show resistance to colistin.

Of the 18 multidrug-resistant enterobacterial strains isolated, all strains were resistant to aminopenicillins and amoxicillin-clavulanic acid and also to ceftriaxone with only one case of carbapenemase. Our strains were mainly sensitive to amikacin (99% sensitivity) and colistin (100%). The ESBL plasmid was detected in 4 strains of enterobacteria.

No cases of ceftazidime or imipenem resistant Pseudomonas aeruginosa or vancomycin resistant enterococci were isolated in this series.

Cefoxitin-resistant strains of staphylococci were interpreted as resistant to all beta-lactams. In our series, three cases of staphylococcus aureus and eight cases of coagulase-negative staphylococcus (NGS) were resistant to cefoxitin.

Table 2 Antibiotic resistance rates (ATB) of isolated gram-positive bacilli

Germes /ATB	AMC	CTX	CAZ	IMP	FOX	VA	TEC	GN	AK	CIP	MY
STAPH AUREUS	-----	-----	-----	-----	3.61	0	0	0	-----	7.4	----
SGN	-----	-----	-----	-----	52	0	0	0	-----	6.3	----
ENTEROCCOQUE	----	0	----	-----	----	0	0	0	-----	-----	1

Data in the table are in percentages; AMC: Amoxicillin-Clavulanic acid; CTX: Ceftriaxone; CAZ: ceftazidime; FOX: Cefoxitime; IMP: Imipenem; CN: Gentamicin; AK: Amikacin; CT: Colistin; CIP: Ciprofloxacin; VA: Vancomycin. TEC: teicoplanin.

Table 3 Antibiotic resistance rates (ATB) of isolated gram-negative bacilli

Germes /ATB	AMC	CTX	CAZ	IMP	GN	AK	CT	CIP	SXT
K.P	85	30	25	1	30	10	0	7.1	11
E.COLI	65.2	35	12.2	25	25	25	0	25	15.8
A.BAUMANII	100	100	100	100	100	100	0	100	100
P.AERUGINOSA	------	-------	0	0	0	0	0	6.1	------

4   Discussion

In this prospective study positive blood cultures were obtained in 83 (15.83%) febrile neutropenia patients hospitalized at hemato-oncology wards, this result is compatible with that reported by Kuntegowdanahalli CL et al [8]. who found in their study on a comparable population from South India, an incidence of positive blood cultures reaching 19.44%, and Esa et al [9].who found a slightly higher rate of 28%.

During our study, among 83 cases of bacteremia diagnosed, we found 39 men and 44 women, so we note a female predominance with a sex ratio of 0.88. Our results are similar to those reported by several series [10,11]. On the other hand, several studies show a clear male predominance [12,13].

The mean age was 55 years. Our results are similar to those of several series: the series of Assiya El Kettani et al [13] whose mean age was 46 years, the national series of Azher Sabeeh Al-Zubaidy et al [12] where the mean age was 54 years.

Gram-negative organisms are always predominant in neutropenic patients. This result is in agreement with many other international studies that report that E. coli remains the most frequently isolated Gram-negative organism, which is also the case in these data [19,20]. The same finding was also objectified in studies reported from India, Turkey and Brazil [21,22] confirm the same conclusion.However, the current data show a significant decrease in Gram-negative infections, while Gram-positive microorganisms showed a large increase [15].

In our study, gram positive bacteria were the most predominant pathogens in 57.8% of cases, while gram negative bacteria were identified in only 42.1%. This result is comparable to that of Sharma A et al [15] who found gram positive microorganisms to be the most prevalent bacteria, but not to the results reported by Lakshmaih K.C et al [16] who found gram negative (63.64%) as the predominant type, despite the fact that both studies were performed on neutropenic fever in patients with hematological malignancy. Similarly, Nashwan AI et al [17] whose study was conducted at the medical department of Baghdad University Hospital on a comparable population showed that 75% of the isolated bacteria were gram negative, a discrepancy that may suggest a change in pathogens.

In one of the recent studies conducted in Iran, 67% of gram-negative bacteria and 29.8% of gram-positive infections were isolated from neutropenic patients. E. coli and coagulase-negative staphylococci being the most observed Gram-negative and Gram-positive microorganisms [17].This is consistent with our results.

Our study is the report on the microbial spectrum and antibiotic susceptibility profile of patients hospitalized in the hemato-oncology services at the Hassan II University Hospital Fez. The result of this study from blood cultures revealed that Gram-positive bacteria were the predominant pathogens of bacteremia in febrile neutropenias. This result is similar to reports prior to 1986 that Gram-negative bacteria were the most common cause of bacteremia [23] .Over the past few decades, the profile of bacterial infections in febrile neutropenic patients has changed considerably and Gram-positive strains have become predominant.

Staphylococcus aureus was the most common bacterium obtained from blood cultures in our series after coagulase-negative staphylococcus including staphylococcus epidermidis, followed by E. coli, klebsiella, Acinetobacter baumanii and Pseudomonas aeroginosa, these results are comparable to those reported by Blahová J et al [18], who found that the most common type of bacteria identified was staphylococcus followed by E.coli.

In general, the result obtained by our study is similar to the results of the study by Nejad et al [23], reported that 66% of the bacteria isolated from febrile neutropenic patients with cancer in Kerman, Iran were Gram-positive. The use of an intravenous catheter and fluoroquinolone prophylaxis for neutropenic cancer patients increased the rate of Gram-

positive bacteria. In the study of Meidani et al [24], conducted in Esfahan, the prevalence of Gram-positive strains (56.4%) in the blood culture of cancer patients was higher than Gram-negative bacteria. Compared with our study, this study was conducted on a small sample size with only 23 positive blood cultures.

In the present study, Escherichia coli was the most prevalent Gram-negative bacteria isolated (38.68%). In addition, many previous studies have reached a similar finding [25]. In several studies, the frequency of Klebsiella isolates (14.5%) was greater than the rate of Pseudomonas (6.60%). Pseudomonas aeruginosa was the second most common bacterium isolated in the majority of studies with an average frequency of 18.8% [25]. Gram-positive bacteria were isolated from 56.6% of the populations in our study, and Staphylococcus epidermidis was the most frequent isolate (51.7%). This finding is consistent with the results of other studies conducted in Iran that reported S. epidermidis as the most frequent gram-positive bacterium in febrile neutropenic cancer patients [23,24].

Determining the antibacterial susceptibility profile of bacterial pathogens in febrile neutropenic patients may be useful in selecting the best antibacterial agent [26]. E coli resistance to fluoroquinolones is a problem in many countries [27] and we have seen this phenomenon in our results. In this study, the majority of E.coli isolates were mainly susceptible to amikacin, gentamycin, colistin and cephalosporins especially ceftazidime (87.8%). Studies conducted between 2006 and 2013 reported that more than 95% of E.coli isolates were susceptible to carbapenems [25], but in the present study, 98% of E.coli isolates and 100% of Klebsiella were susceptible to carbapenems. This result is consistent with other studies that have reported sensitivity ranging from 90 to 100% for carbapenems [25]. For Acinetobacter baumannii isolates (n=5) showed increased resistance to the majority of antibiotics tested. The rate of Acinetobacter baumannii resistant to imipenem was 100%. The most active antibiotic on these isolates was colistin [24].

We found that none of the S.epidermidis isolates were susceptible to cefoxitin while almost all S. aureus isolates (83 %) showed susceptibility to it. This result is consistent with the study conducted in Iran by Meidani et al [24]. However, the sample size in their study was small; therefore, they might have underestimated the resistance rate. Consistent with several studies, all gram-positive isolates showed sensitivity to vancomycin. This is consistent with the study conducted by Taj M et al [14] and with our study which reported that gram-positive isolates were 100% susceptible to vancomycin.

In addition, regarding the sensitivity of gram positive organisms to antibiotics, in our study, imipenem was found to be the most effective, followed by tetracycline, tobramycin and clindamycin. This result was different from that found in a Kuntegwdanahalli CL et al study [8] which were highly sensitive to Amikacin, Vancomycin, Teicoplanin, and Levofloxacin.

As for gram-negative organisms, our study showed the highest sensitivity to Amikacin, Imipenem and Piperacillin/Tazobactam; a result similar to that of Kuntegwdanahalli CL et al [8]. Who found that gram negative bacteria were highly highly susceptible to Imipenem, Piperacillin/Tazobactam and moderate susceptibility to amikacin.

These observations suggested empirical antibiotic therapy in febrile neutropenia. In this study the first-line antibiotic therapy was also piperacillin/tazobactam and amikacin, which remains the preferred choice due to the double coverage of Gram-negative, also showing an appropriate sensitivity. This combination is able to cover on average 80% of Escherichia coli strains and has been preferred in the literature [12].

5   Conclusion

Febrile neutropenia is highly prevalent in institutes involved in the treatment of hematologic malignancies and is a major factor of morbidity and mortality, in the post-chemotherapy period. Gram-positive infection with coagulase-negative staphylococcus is the most common type of infection. Showing a considerable decrease in sensitivity to first line antibiotics, making this the most effective strategy; however, Gram-negative infections showed a significant decrease compared to the previous antibiogram. We also suggest continuous monitoring of the spectrum of locally prevalent pathogens and their susceptibility.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

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

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