Outcome of Febrile Neutropenic Patients Treated for Bacteriuria in Hematology

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Abstract

Introduction

Positive urine sample is a frequent finding in post-chemotherapy febrile neutropenia (FN) and can lead to prolonged antibiotic therapy. The aim of this study was to assess the outcome of bacteriuria episodes in FN patients receiving targeted antibiotic therapy.

Materials and methods

A multicentric retrospective study was conducted over a four-year period (2014-2019). All consecutive first bacteriuria episodes (≤2 bacteria with at least $\geq 10^3$ CFU/mL) during FN in hospitalized adult patients for hematological malignancies were included. Relapse and recurrence were defined by fever or urinary tract symptoms (UTS) with the same bacterial subspecies in urine occurring ≤ 7 days and ≤30 days, respectively, after antibiotic discontinuation. Mortality rate was determined at 30 days. Targeted antibiotic therapy ≤10 days for women and ≤14 for men was considered as short course.

Results

Among 97 patients, 105 episodes were analyzed; 67.6% occurred in women, 41.9% in AML patients, 17.1% were bacteremic, 14.2% presented with UTS, and 61.9% were treated with short-course antibiotic treatment. One death was reported. In men, no relapse/recurrence was noted, even in the short-course antibiotic group. In women, 2.8% of episodes treated with short-course antibiotic led to relapse or recurrence.

Conclusions

Relapse, recurrence, and mortality were uncommon events in FN patients experiencing bacteriuria episode, whatever the antibiotic duration. To distinguish asymptomatic bacteriuria from infection remained challenging in women. In men, the withdrawal of systematic urinalysis at onset of FN could lead to insufficient bacteriuria diagnosis and treatment.

Introduction

According to international guidelines, antibiotic therapy should be adapted in terms of spectrum and duration in the case of microbiologically documented infection during post-chemotherapy febrile neutropenia (FN) (1–3). There is no consensus on whether or not urine culture should be systematically sampled in asymptomatic patients. In their most recent guidelines, the Infectious Disease Society of America (IDSA) and the European Society for Medical Oncology (ESMO), recommended that only patients presenting a suspected focus of infection at this site should be sampled based on expert advice (1,4). Other regional guidelines recommended screening of every patient (5). In various centers, it is common practice to systematically take a urine sample at the onset of FN. Bacteriuria is thereby frequently found in patients with no clinical signs other than fever. Since guidelines and clinical practices are

heterogeneous, available studies have shown an extremely variable rate (2-48.9%) of bacteriuria at the onset of FN (6–10).

Furthermore, there is a lack of evidence regarding the treatment duration of urinary tract infections (UTI) during FN. In 2015, the Francophone Society of Infectious Diseases (SPILF) and the European Association of Urology (EAU) published guidelines on UTI treatment for the general population (11,12). These guidelines recommended UTI treatment of 7 to 14 days for women with risk factors for complications: and 14-28 days for men. FN patients were indistinctly regrouped with others under the “immunocompromised” term. In that case, it is recommended to discuss an extension of treatment duration; the physician could add 4-7 days to the 10-day duration for women and 7 days to the 14-day duration for men (12).

No guidelines pertain to management of bacteriuria without lower or upper urinary tract symptoms (UTS) during FN. Since leukocyturia is not interpretable, it is at the discretion of the physician to consider bacteriuria as responsible for UTI and to start a targeted antibiotic treatment. However, it is unclear whether the pathogen found in urine should be targeted. As a result, our aim was to determine the frequency of relapse/recurrence of febrile bacteriuria after discontinuation of antibiotic therapy. Influence of initial antibiotic duration on relapse/recurrence was analyzed.

Material And Methods

Study design and patients

This retrospective observational study was performed in the hematology departments of two 1200-bed regional referral University Hospitals (Poitiers and Tours, France) between January 1st, 2014, and March 1st, 2019.

As part of routine clinical examination, urine culture was performed for every episode of post-chemotherapy FN regardless of the presence of UTS. Adult patients ≥18 years old with post-chemotherapy FN for a hematological malignancy presenting with significant bacteriuria were included. Urine culture was considered as positive if the bacteriuria threshold was met as follows : in men, $\geq 10^3$ CFU/mL for all uropathogenic bacteria; in women $\geq 10^3$ CFU/mL for *Escherichia coli* and *Staphylococcus saprophyticus* and $\geq 10^4$ CFU/mL for all other uropathogenic bacteria (11). Leukocyturia was not considered since its threshold is not relevant in FN patients (11). Each febrile episode was defined by body temperature ≥ 38°C twice within a 1h-interval or ≥ 38.3°C once during the period of severe neutropenia <500/mm^3 from which positive urine culture was screened.

Were excluded: episodes in patients who did had undergone chemotherapy in the previous 30 days, patients already receiving antibiotic therapy 24h before urine culture, patients with urine culture growing ≥3 bacteria, patients with known uropathy (other than benign prostatic hypertrophy), patients with

urinary tract devices, patients treated for another microbiologically documented infection, patients with missing critical clinical data, and patients who died before the end of evaluated antibiotic course.

Ethics

The National Data Protection Authority (Commission Nationale Informatique et Libertés), which is responsible for the protection of individual data in France, approved the panel and its procedures. The protocol was registered as CHU86-R2019-03-01.

Data collection

Every positive urine culture performed in patients aged ≥18 years old hospitalized in the hematology departments was extracted from the hospital bacteriology database and matched with same-day leukocyte count. FN episodes were checked manually from the patient's medical file. For surveillance data at 30 days, patients admitted for their antineoplastic treatment are seen for a medical consultation within a month following their discharge by the hematologist or the referring practitioner. On this occasion, the presence of recent infections was systematically assessed.

Definitions

UTSs were defined as lower urinary tract symptoms, i.e., dysuria, increased daytime urinary frequency, and/or lumbar pain.

Since fever could have various origins during neutropenia, asymptomatic bacteriuria episodes were defined by positive urine culture associated with fever but without UTS, while UTI was defined by positive culture with UTS and fever.

Relapse was defined by another episode of fever and/or UTS associated with positive urine culture requiring antibiotic treatment ≤ 7 days after treatment discontinuation for the initial bacteriuria. Urine culture should retrieve the same bacterial subspecies with the same antibiotic susceptibility testing (AST) or an acquired resistance.

Recurrence was defined by fever and/or UTS, and positive urine culture retrieving the same bacterial subspecies with the same AST or with an acquired resistance between 7 and 30 days after treatment discontinuation for the initial bacteriuria. Occurrence of another bacteriuria after 30 days was considered as a distinct episode.

A short-duration antibiotic therapy was defined by treatment duration ≤10 days for women and ≤14 for men of appropriate antibiotic therapy tailored to the AST, as these were the minimum durations recommended by the French guidelines at the time of the study (12).

Complicated UTI risk factors were extracted from the SPILF guidelines: any functional or anatomical abnormality on the urinary tract, age >65 and 3 or more Fried criteria, age >75, or severe renal function impairment (clearance < 30mL/min) (12).

Statistical analysis

Continuous variables were expressed as mean or median, standard deviation and ranges, and categorical variables were expressed as absolute values and percentages. Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables, after checking for normality with the Shapiro-Wilk test, were appropriately used. Since a few patients had several episodes, a mixed-model logistic regression was used to confirm that the presence of different episodes in the same patient did not increased variability. As a result, a classic logistic model was used to search for differences in the outcomes of interest.

Results

Population and bacteriuria episodes

Between January 1st, 2014, and March 1st, 2019, positive urine culture with ≤ 2 bacteria was found in 193 episodes of post-chemotherapy FN, from which 88 (45.5%) episodes were excluded. The study flowchart is represented in Supplemental Figure 1. A total of 97 patients having 105 bacteriuria episodes, 71 (67.6%) occurring in 63 women and 34 (32.4%) in 34 men, were included. Demographic and clinical characteristics of episodes are described in Table 1. Median age was 58.9 years [19.8-79.9]. The main underlying hematological malignancies were acute myeloid leukemia (44 episodes, 41.9%), followed by non-Hodgkin lymphoma (25 episodes, 23.8%), and multiple myeloma (23 episodes, 21.9%). Bacteriuria occurred after hematopoietic stem cell transplantation in 50 (47.6%) episodes. Median duration of neutropenia at the onset of fever was 3 [1-6] days. Median duration of fever was 2 [1-4] days. Only one patient died within the 30 days after antibiotic discontinuation due to disease progression. There was no significant difference between men and women for the aforementioned characteristics.

Table 1
Demographic and clinical characteristics of 105 episodes of bacteriuria during febrile neutropenia in 97 patients, 63 men and 34 women, hospitalized for treatment of a hematological malignancy

Variables	Global cohort N=105	Male n=34	Female n=71
Age, median [IQR]	58.9 [48.5-65.3]	60.3 [52.9-65.4]	57.8 [48.2-65.2]
Neoplasia			
Acute Myeloid Leukemia	44 (41.9)	10 (29.4)	34 (47.9)
Multiple Myeloma	23 (21.9)	10 (29.4)	13 (18.3)
Non-Hodgkin Lymphoma	25 (23.8)	9 (26.5)	16 (22.5)
Hodgkin Lymphoma	4 (3.8)	2 (5.8)	2 (2.8)
Chronic MyeloMonocytic Leukemia	1 (0.9)	0	1 (1.4)
Acute Lymphoblastic Leukemia	5 (4.8)	0	5 (7.0)
Myeloproliferative Neoplasm	2 (1.9)	2 (5.8)	0
Burkitt Lymphoma	1 (0.9)	1 (2.9)	0
Line of treatment			
Induction	21 (20.0)	7 (20.6)	14 (19.7)
Consolidation	30 (28.6)	6 (17.7)	24 (33.8)
Autologous HSCT	38 (36.2)	18 (52.9)	20 (28.2)
Allogenic HSCT	12 (11.4)	3 (8.8)	9 (12.7)
Maintenance	4 (3.8)	0	4 (3.8)
Relapsing hematological disease	18 (17.1)	3 (8.8)	15 (21.1)
positive Fried criteria	6 (5.7)	2 (5.9)	4 (5.6)
Severe renal impairment	5 (4.8)	2 (5.9)	3 (4.2)
qSOFA ≥ 2	3 (2.9)	0	3 (4.23)

All variables are expressed as a number (percentage) otherwise indicated.

IQR: Interquartile range; HSCT: hematopoietic stem cell transplantation

Variables	Global cohort N=105	Male n=34	Female n=71
WHO classification of performance status:			
0	66 (62.9)	25 (73.5)	41 (57,8)
1	29 (27.6)	7 (20.6)	22 (30.9)
2	8 (7.6)	2 (5.9)	6 (8.5)
3	2 (1.9)	0	2 (1.9)
Days of admission, median [IQR]	21 [18-28]	20.5 [18-25]	22 [17-29]
Days of neutropenia, median [IQR]	3 [1-6]	1.5 [0.25-3]	3 [1-6]
Days under antibiotics, median [IQR]	11 [10-14]	14.5 [13-21]	10 [9-13]
Days of fever, median [IQR]	2 [1-4]	2 [2-3]	2 [1-4]
Mortality at day 30	1 (0.9)	0	1
All variables are expressed as a number (percentage) otherwise indicated.			
IQR: Interquartile range; HSCT: hematopoietic stem cell transplantation			

UTI characteristics and treatments

Fever apart, UTS were reported in 15 (14.2%) episodes, lower urinary tract symptoms in 10 (9.5%) episodes, and lumbar pain in 5 (4.7%) episodes. There were not significantly more symptomatic episodes in women than in men (8/71, 11.3% vs 2/34, 5.9%; p=0.49). *Escherichia coli* (n=70; 66,7%) was the most frequent pathogen found in urine, followed by *Enterococcus* spp. (n=18; 17.1%), and other Enterobacteriaceae (n=17; 16.2%). Among *E. coli*, 2.8% expressed an Extended-Spectrum Beta-Lactamase (ESBL) and 21.4% an Inhibitor Resistant TEM. Other Enterobacteriaceae expressed an ESBL in 29,4% of episodes (Supplemental Figure 2). Bacterial epidemiology was similar for men and women. Blood cultures were positive with the same bacteria in 18 (17.1%) episodes, 4 of them being symptomatic. Blood cultures were positive in 11/71 (15.4%) episodes in women and 7/34 (20.6%) episodes in men, with no significant difference (p=0.78).

Initial empirical antibiotic therapy for FN was appropriate for treatment of bacteria found in urine culture in 81 (77.1%) episodes. In the global cohort, 65 episodes (61.9%) were treated with a short antibiotic therapy. Among the 71 episodes that occurred in women, 47 (66.2%) episodes received a short antibiotic therapy. Among the 34 episodes in men, 18 (52.9%) received a short treatment. There were no statistical differences between the characteristics of episodes treated with short versus long antibiotic therapy in men and women (see Supplemental Table).

Relapses

None of the episodes occurring in male patients relapsed during the first 7 days following antibiotic discontinuation, whereas 2 (2.8%) episodes occurring in two different female patients did. In these two cases, neutropenia was prolonged >7 days. In both cases, relapse occurred 4 days after antibiotic discontinuation and once the neutrophil count was >500/mm^3. They had no complicated UTI risk factor except immunosuppression.

In the first episode, there was no symptom other than fever during the first episode of FN and at relapse. The pathogen found in urine and blood cultures was *E. faecalis* resistant to the initial empirical antibiotic regimen. Antibiotic therapy was adapted after three days, and then continued for seven more days.

In the second episode, there was no symptom other than fever during the first episode of FN and at relapse. The pathogen found was an Inhibitor Resistant TEM *E. coli*. This bacterium was susceptible to the empirical antibiotic therapy and was not present in the blood cultures. Antibiotic treatment lasted 10 days. In the relapse episode, *E. coli* had acquired an ESBL.

Recurrences

None of the male patients experienced recurrence in the 30 days following antibiotic discontinuation, whereas two women, who received a short duration antibiotic treatment, had a recurrence. The first episode occurred 10 days after antibiotic discontinuation, the other 27 days after. In one episode *E. coli* was resistant to the empirical antibiotic regimen, as it expressed a TEM Resistant Inhibitor. It acquired ESBL resistance after the first line of treatment. No blood culture was positive and no UTSs were present during the two septic episodes.

Discussion

Our study shows that relapse/recurrence of a symptomatic and/or febrile documented bacteriuria in hematology patients ongoing FN after chemotherapy is a rare event, regardless of antibiotic course duration, and is not associated with increased mortality.

Studying UTI during profound neutropenia is challenging. Due to the absence of leukocyturia in FN, there is no definite evidence of the urinary origin of sepsis. Klaasen and al. showed that a decrease of circulating neutrophils resulted in the absence of leucocyturia in the case of UTI (13). As a result, urinalysis is an unreliable marker of UTI in FN (9,14,15).

Neutrophils being central actors of the antibacterial response, urinary sepsis might occur without inducing any symptoms in FN patients. Steinrucken and al. considered the diagnosis of UTI only when UTSs were present (10). By contrast, our study supported the fact that an authentic urinary sepsis may occur even in the absence of UTS as 18 episodes of bacteriuria were bacteremic,;among these, only 4 (22.2%) were associated with UTS.

A study conducted by Grigg et al. included episodes of FN in hematological patients with urine culture available (9). Among 362 episodes, UTS were present in 39 out of the 345 episodes with negative or contaminated urine culture and in 9 out of the 17 episodes with positive urine culture. Having included patients with indwelling bladder catheter may have biased the presence of UTS. Stringent exclusion criteria eliminating indwelling bladder catheter were applied to our patients leading to the exclusion of 45.5% of the selected patients but reinforcing the clinical value of UTS.

In our population, 14.2% of the episodes presented UTS, which may correspond to true UTI according to the definition of UTI in the general population (16). Several studies in FN patients have shown that UTSs were a poor marker for bacteriuria insofar as they can be absent even in the case of significant bacteriuria (10,14,17). In light of our data and without further specific studies, hematology patients with FN urosepsis should still be considered, even in the absence of UTS.

Asymptomatic bacteriuria, also named urinary tract colonization (defined by the presence of $\geq 10^5$ CFU/mL bacteria in a urinary culture without signs or symptoms evoking a UTI in the general population), is frequent in women (1-16%) but anecdotal in men due to morphological and pathophysiological differences (16). Since UTS might be absent during UTI in FN patients, it remains impossible to differentiate UTI from asymptomatic bacteriuria. In a recent study, all bacteriuria in FN patient without UTS were defined as UTI (14). However, it seems important to emphasize that not all bacteriuria in FN patient are UTIs.

IL-6 and other neutrophilic activation markers to differentiate UTI and asymptomatic bacteriuria have been evaluated in elderly patients, but have yet to be tested in FN (18,19). Positron Emission Tomography, Computed Tomography and MRI, have proven to be useful tools in UTI diagnosis (20,21). Although it might be difficult to propose additional imaging to hematological patients with FN, who are frequently exposed to ionizing rays, these techniques might be interesting in differentiating asymptomatic bacteriuria and UTI.

Regarding treatment duration, there was no relapse or recurrence of bacteriuria in men treated with short duration antibiotic therapy $\leq$14 days, whereas two episodes of relapse occurred in women who had likewise received short treatment. Regarding women's UTI in unspecific conditions, several studies and a meta-analysis have shown the safety of antibiotic duration reduction to $\leq$7 days for UTI treatment (22,23). Evidence for men is scarcer. One randomized controlled study demonstrated that a 2-week treatment was not inferior to a 4-week treatment for prostatitis (24). In FN, there is no evidence suggesting that a longer treatment duration could be safer. Though the size of our cohort might be a bit small to formally conclude, no association between short treatment duration and relapse, recurrence, or mortality was detected. Nevertheless, our study showed that bacteriuria during FN still encouraged clinicians to prescribe a longer antibiotic therapy, given that 24/71 (33.8%) episodes in women and 16/34 (47.0%) episodes in men received long treatment despite quick resolution of fever. Since positive urine culture will potentially increase the duration and at times the spectrum of the adapted antibiotic therapy, the necessity for systematic screening in the onset of FN is questionable .

Systematic urinary testing in the absence of symptoms at the onset of FN was withdrawn from both the 2011 IDSA and the 2016 ESMO guidelines. The only scientific evidence nevertheless supporting this practice is the Grigg et al. study, which did not show a morbidity-mortality increase in patients whose urine was not screened (9). IDSA guidelines on asymptomatic bacteriuria in 2019 did not address this issue because of “lack of scientific evidence”(16). The two aforementioned studies showed that systematic urine culture at the onset of FN rarely altered the choice of antibiotic therapy, but a low number of bacteriuria episodes were studied, 12 for Steinrucken and al. and 17 for Grigg and al. (9,10). Moreover, they did not specify whether spectrum or duration modification was studied (9,10). Of note, the threshold of bacteriuria in these studies was $\geq 10^5$ UFC/mL corresponding to the usual threshold for asymptomatic bacteria. We nevertheless chose lower thresholds of bacteriuria, corresponding to the French guidelines for UTI, as we considered that every bacteriuria could potentially be an UTI in the FN setting (12).

ECIL-4 recommended that “empirical antibiotics can be discontinued after 72 h or more of intravenous administration in patients who have been hemodynamically stable since presentation and have been afebrile for 48 h or more, irrespective of their neutrophil count or expected duration of neutropenia” (25). In the case of true UTI, the length of antibiotic therapy should be adapted in order to provide sufficient treatment to avoid relapsing infection. This is especially true in men, for whom recommended antibiotic duration for a documented UTI far exceeds the treatment duration of a fever of unknown origin during FN.

Our study had some limitations due to its retrospective nature. However, the database was double-checked to reduce methodological bias. Concomitant blood stream infection could still be secondary to digestive translocation with urinary excretion of bacteria. In two of the four episodes in which relapse/recurrence occurred, bacteria had acquired a novel resistance phenotype suggesting the acquisition of resistance during first-line antibiotic treatment, even though it cannot be formally demonstrated in this setting. These drawbacks could be effectively ruled out using sequence typing to compare bacteria strains in further prospective studies. No imaging was performed to confirm the presence of an active UTI, whereas it could be implemented in further studies.

In conclusion, relapse, recurrence or death linked to urosepsis were rare events in FN affecting hematology patients. Shorter antibiotic courses did not seem to be associated with poorer outcome. To distinguish asymptomatic bacteriuria from infection remained challenging in women. In men, however, withdrawal of systematic urinalysis at onset of FN could lead to insufficient urosepsis diagnosis and treatment. Further randomized controlled studies are needed to confirm the safety of urinalysis withdrawal at the onset of post-chemotherapy FN to reassure clinicians and to remove a critical trigger for antibiotic consumption.

Declarations

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Conflicts of interest:

Blandine Rammaert has conflicts outside the submitted work: travel grants from Pfizer and MSD, speaker's fees from MSD, Gilead, Astellas, Iqone.

Emmanuel Gyan has conflicts outside the submitted work: research funding from Novartis and BMS, consulting fees from Novartis, Abbvie, Incyte, Jazz Pharmaceutical, support for travel from Gilead, Sanofi, speaker's fees from Novartis.

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not applicable

Code availability:

not applicable

Author's contributions:

TD, BR and JT conceived and designed the study, TD and PL collected the data, TD and JT contributed data analysis, TD, BR, JT, PG, PL, FR, MV performed the analysis, all authors contributed to manuscript preparation, reviewed the results and approved the final version of the manuscript.

Ethics:

The National Data Protection Authority (Commission Nationale Informatique et Libertés), which is responsible for the protection of individual data in France, approved the panel and its procedures. The protocol was registered as CHU86-R2019-03-01.

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