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# Risk factors of infections associated with antibiotic resistant microorganisms in patients with high risk neutropenia in a French hematology center

Baptiste Moisdon-Delapierre

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UNIVERSITÉ de CAEN NORMANDIE

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**DU GRADE DE DOCTEUR EN MÉDECINE**

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**Neutropénie fébrile de haut risque en onco-  
hématologie : facteurs liés à la résistance  
bactérienne aux antibiotiques à l'Institut  
d'Hématologie de Basse Normandie entre 2015 et  
2019**

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## Abbreviations

AMR: antimicrobial resistance

Anti-GPC: antibiotic with specific activity against Gram positive microorganisms with resistance to  $\beta$ -lactams

BPAROH: bacteria with problematic antibiotic resistance in onco-hematology

BSAROH: bacteria with significant antibiotic resistance in onco-hematology

BSI: bloodstream infection

CoNS: coagulase negative *Staphylococcus*

CPE: carbapenemase producing *Enterobacterales*

ECIL: European Conference of Infections in Leukemia

ESBL-E: extended spectrum  $\beta$ -lactamase *Enterobacterales*

FUO: fever of unknown origin

GNB: Gram negative bacilli

HR: hazard ratio

ICU: intensive care unit

IDSA: Infectious Disease Society of America

MRSA: methicillin resistant *Staphylococcus aureus*

SCT: stem cell transplantation

VRE: vancomycin resistant *Enterococci*

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## Introduction

Hematologic malignancies are frequent diseases, representing 10% of cancer (1), for which chemotherapy remains the main treatment. Drug induced neutropenia is a well-known complication in hematologic malignancies clinical treatment, with a particular concern towards life threatening infection (2) and fever is often the only sign of infection. Neutropenia threshold for febrile neutropenia definition is  $< 0,5$  G/L (3,4). Patients in low risk group have an expected granulocyte count  $> 0,2$  G/L and an expected duration of neutropenia  $< 5$  days, they can be treated with oral antibiotic treatment at home when fever occurs (5–7). Patients in high risk neutropenia group have an expected neutropenia  $< 0,1$  G/L and an expected duration of neutropenia  $> 7$  days. In these cases, hospitalization for intravenous antibiotic treatment is await, and fungal exposition risk increase (3,8,9). Incidence of febrile neutropenia is  $> 85\%$  in high risk group. Infections are rapidly severe (10,11), with a septic shock incidence between 5 and 10% (12) and an early mortality incidence of 6% (3,13). Majority of episodes of febrile neutropenia are highlighted by fever of unknown origin (FUO) (3). Microbiological documentation is only obtained in 10 to 30% of episode, and mainly in blood cultures (3,14–16). Concerning microbiological epidemiology, *Escherichia coli* ranks first and coagulase negative *Staphylococci* (CoNS) second in a recent European report (15). Frequent microorganisms are *Enterobacterales*, non-fermenting Gram-negative bacilli (GNB) *Staphylococci*, *Streptococci* and *Enterococci*. *Pseudomonas aeruginosa* is a non-rare pathogen in this class of patients, associated with high early mortality rates, justifying a systematic coverage of *Pseudomonas aeruginosa* if an antibiotic treatment is needed (17).



Antibiotic treatment needs to be quickly prescribed (18) because a delay in antibiotic treatment or an inappropriate empirical treatment are associated with a longer duration of hospitalization, a higher intensive care unit (ICU) admission rate and a higher mortality (19). European Conference for Infection in Leukemia (ECIL) and Infectious Disease Society of America (IDSA) designed international recommendations for antibiotic treatment guidance. The first line antibiotic treatment recommended is a monotherapy using a  $\beta$ -lactam with activity against *Pseudomonas aeruginosa* such as ceftazidime, cefepime, piperacillin-tazobactam, meropenem or imipenem-cilastatin (3,4,20,21). Carbapenems prescription is not recommended in case of an alternative exists with another  $\beta$ -lactam in particular (20,21). Aminoglycosides and antibiotics with specific activity against resistant Gram positive bacteria (e.g. anti-GPC) should not be systematically associated (28). The choice of an empirical antibiotic treatment must take into account the factors associated with high probability of infection with resistant strains, in others words, an excellent knowledge of local epidemiology (3,4).

As in general population, antimicrobial resistance (AMR) in pathogen microorganisms in neutropenic patients is a huge medical concern, with an important increasement rate in Europe (15) although some centers in Northern Europe reported low AMR level and low mortality associated with bloodstream infection (BSI) (24). Extended Spectrum  $\beta$ -Lactamase producing *Enterobacterales* (ESBL-E) are a frequent problem in neutropenic patients, and are associated with high mortality (14,15,17,25–29). Infections associated with carbapenemase producing GNB or vancomycin resistant *Enterococci* (VRE) are still rare in France but emerge in Southern Europe and North America, and are also associated with very high mortality in the neutropenia setting (30–32,18,33). Infections with GNB

are more frequently treated with an inappropriate first line antibiotic treatment, this situation is associated with a higher mortality (26,27,34,35). Resistance associated with Gram positive microorganisms are of less concern because of antimicrobials alternatives available (23,33,36,37).

It is well known that certain factors are statistically associated with a higher risk of infection by a resistant microorganism such as enteric colonization with resistant strain, previous antibiotic exposure, relapsing or refractory underlying hematological malignancy, nosocomial infection, prolonged or repeated hospitalizations, older age, urinary tracts catheter and ICU admission. Interestingly, the large majority of the studies establishing these associations were made in Southern Europe and North America centers, where AMR levels are high and where the usage of antibiotic prophylaxis with fluoroquinolones is frequent (4,26,27,31,32,34,38–45). The validity of these factors is still unclear in centers with low antibiotic resistance level, and where no fluoroquinolone prophylaxis is used (24), such as Northern Europe centers.

The primary objective of this study was to identify risk factors associated with infection by a Bacteria with Significant Antibiotic Resistance in Onco-Hematology (BSAROH) (see also in Material and Methods part), in patients with high risk febrile neutropenia. Secondary objectives were to measure the frequency of infections by a Bacteria with Problematic Antibiotic Resistance in Onco-Hematology (BPAROH) (see also in Material and Methods part), to describe of microorganisms involved in microbiologically documented infections with a focus on their resistance phenotype and the evaluation of antibiotic treatment prescription.

## **Material and methods**

We conducted a retrospective descriptive cohort study in the onco-hematology center of the Caen university hospital, located in Normandy. The study period ran from December 2015 to June 2019.

### *Study population*

We included all adult patients (> 18 years old) with a hematological malignancy treated by chemotherapy in our center, with a first hospitalization for the management of high risk neutropenia during the study period and with at least one episode of febrile neutropenia during the whole therapeutic sequence. High risk neutropenia was defined by predicted granulocyte count < 0.1 G/L and duration > 7 days. Febrile neutropenia was defined by granulocyte counts < 0.5 G/L or expected to within 48h and a unique temperature > 38.3°C or > 38°C during at least one hour or chills or unexplained acute organ dysfunction. For each patient, all hospitalizations for a unique therapeutic sequence were recorded. Hospitalizations for transfusion or treatment lasting < 48h were not recorded.

We excluded patients in palliative state, with chronic neutropenia not induced by antineoplastic agent, with relapse or refractory hematological malignancy, and with previous infection with BSAROH. Patients with previous enteric colonization with BSAROH were not excluded.

### *Primary outcome*

Our primary outcome was infection by BSAROH, defined as a microorganism with a non-natural resistance to one of the  $\beta$ -lactams recommended in first line in

international guidelines (ceftazidime, cefepime, piperacillin-tazobactam, imipenem-cilastatin, meropenem) (3,4).

### *Data collection*

Demographic and clinical data were recorded on computerized medical file. We recorded information on:

- a) Socio-demographic characteristics of patients, type of hematological malignancy, type of treatment and comorbidities (defined as a medical condition with significant and chronic organ damage or requiring an immunosuppressive treatment or a recurrent antibiotic treatment);
- b) 3 months before each hospitalization: history of previous hospitalization and ICU stay, antibiotic treatments, colonization with BSAROH, travel in foreign country. Short hospitalization < 48h for transfusion or treatment were not recorded as previous hospitalization.
- c) For the current hospitalization: ICU stay, suspected origin of infection, microbiological documentation (considered as the association of a BSI or a positive distal pulmonary sample associated with a clinical presentation of pneumonia), type of germ, antibiogram, mechanism of resistance (including: ESLB-E, BSAROH, and BPAROH, defined as non-natural resistance to imipenem-cilastatin, or meropenem or glycopeptides), and stool colonization (with germ and antibiogram);
- d) Information on all emergency antibiotic treatments prescribed in case of febrile neutropenia, including class and molecule, duration, type of prescription (probabilistic or based on antibiogram). Antimicrobial treatment was prescribed according to ECIL and IDSA guidelines (3,4). Monotherapy

with an intravenous  $\beta$ -lactam with activity against *Pseudomonas aeruginosa* is the standard, with ceftazidime, piperacillin-tazobactam, cefepime or imipenem-cilastatin. A carbapenem was used in absence of  $\beta$ -lactam alternative. Neither aminoglycosides nor anti-GPC were prescribed systematically. In the absence of microbiological documentation, antibiotic treatment was pursued until granulocyte count reached 0, 5 G/L. No antibiotic prophylaxis by fluoroquinolones was given.

The number of febrile episodes in each hospitalization was not recorded because of the difficulty to define persistent fever, recurrent fever or novel episode of febrile neutropenia in patients with prolonged hospitalization and antibiotic treatment.

For each patient, we recorded the status at the end of each hospitalization. Early death represented death before hospital discharge. Cause of death was considered infectious when death occurred before hospitalization discharge and when the cause of death was certainly or possibly related to infection. In case of fatal infection and concomitant progression of the hematological malignancy, we considered that progression of hematological malignancy was the cause of death. Treatment failure was defined as fatal infectious early death, ICU admission for severe infection or microbiological documentation with BSAROH.

### *Samples collected and microbiological techniques*

In case of fever, blood samples were systematically collected before the administration of antibiotic treatment. Distal pulmonary sample were not collected systematically unless in case of ICU admission for pneumonia. In case of positive sample with a frequent contaminant (CoNS for example), two positive samples

were needed to determine a microbiological documentation. When only one blood culture bottle grew, it was defined as a contamination unless physician considered it as significant and specified it in medical file. Stool specimens were systematically collected twice weekly for detection of resistant microorganisms. Bacterial identification was accessed using a Matrix-Assisted-Laser-Desorption-Ionization Time-Of-Flight (MALDI-ToF) system (Microflex®, Bruker, Bremen, Germany). Antimicrobial susceptibility testing was performed using the disk diffusion method and when required, minimum inhibitory concentrations were determined using the broth microdilution method, as recommended by the French committee of antibiogram (CA-SFM/EUCAST) (46). Resistant microorganisms detected in stools were *Enterobacterales* with resistance to third generation cephalosporin, *Pseudomonas aeruginosa*, methicillin resistant *Staphylococcus aureus* (MRSA) and VRE. No nasal swab for methicillin sensitive *Staphylococcus aureus* or MRSA detection was performed. The origin of infection was recorded as notified in the patient's medical file. When no origin was specified, infection origin was considered as FUO.

### *Statistics*

Baseline characteristics were presented using medians and range (minimum – maximum) for continuous variables, and number and frequencies for categorical variables. The time to events (infections with BSAROH) was compared using univariate and multivariate Cox regression analysis, and Kaplan-Meier curves were generated. Variables with  $p < 0.20$  in univariate analysis were introduced in multivariate Cox models to compute adjusted hazard ratios. The unit of analysis was each hospitalization, and data were considered censored if the patients died

before the end of the therapeutic sequence. Because of the multilevel structure of the data (with a same patient for multiple hospitalizations), we modeled patient as a random effect.

As infections with BSAROH occurred frequently during first hospitalization and patients with multiple hospitalizations and no BSAROH infection were frequently exposed to antibiotics, we conducted a sensitivity analysis focused on the first hospitalization of each patient.

A value of  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using R software [version 3.5.2: R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>].

### *Ethic issues*

Authorization of local ethic committee was obtained, according to French legislation.

## Results

### *Patient's characteristics*

Three hundred and forty-eight consecutive patients (corresponding to 713 hospitalizations) were hospitalized during the inclusion period. Thirty-three patients (54 hospitalizations) were excluded and 315 patients (659 hospitalizations) were enrolled (Figure 1). Patient's characteristics are summarized in Table 1. Four hundred and fifty-four of 659 hospitalizations (68.9%) were accessed for management of neutropenia following chemotherapy, 128 (19.4%) for allogenic stem cell transplantation (SCT) and 77 (11.7%) for autogenic SCT. The majority of patients, (n=168; 53.2%), suffered from acute myeloid leukemia. One hundred and ninety-five patients (63.1%) had at least one comorbidity (see also Table S1).

### *Microbiology*

Febrile neutropenia were microbiologically documented in 191 (31.2%) of 612 hospitalizations with fever, with 87 (14.2%) BSAROH and 58 (9.5%) BPAROH. Repartition of documented infections based on bacterial species or genera is presented in Figure 2 and the complete list of microorganisms responsible of documented infection is presented in Table S2. *Enterobacterales* were the most frequent isolated microorganisms (118/239: 49.3%) since *Escherichia coli* was largely found (87/239: 36.4%). *Pseudomonas aeruginosa* represented 9.2% of documented infections (22/239). *Enterococcus faecium* (10/239, 4.2%), *CoNS* (26/239, 9.6%) and *Streptococcus mitis* (9/239, 3.8%) were the most frequent microorganisms found in Enterococci, Staphylococci and Streptococci group, respectively. The AMR level and the type of AMR for the most frequent microorganisms in onco-hematology are presented in Figure 3 and Figure 4.



Interestingly, only one *Streptococcus* was classified as a BSAROH (e.g. a *Streptococcus mitis* strain harboring penicillin and cephalosporin resistance). The complexity of the connection between species, type of resistance and the resistance to some class of antibiotics is presented in Figure 5 (complete data frame available in Table S3). A positive fecal sample with resistant strain was documented in 203 of 659 hospitalizations (30.8%) (see also Table S4 for specifications concerning enteric colonization). Only 18 of 203 patients (8.9%) with enteric colonization had a documented infection with the *a priori* same microorganism (same resistance phenotype in stool and blood culture). No colonization with MRSA was notified. Only 5 (0.8%) VRE were detected, none of these patients had infection with VRE. The main type of resistance in *Enterobacterales* was ESBL-E (75/129, 58.1%). No carbapenemase producing *Enterobacterales* (CPE) was noted. Mechanisms of resistance in *Pseudomonas aeruginosa* were balanced, including interestingly, three patients colonized with a *Pseudomonas aeruginosa* harboring *bla*<sub>VIM-2</sub> gene, conferring resistance to all carbapenems. None of these patients had infection with this highly resistant microorganism.

### Outcomes

Patient outcomes are presented in Table 2. The median clinical follow-up was 571 days with a median duration for each episode of hospitalization of 23 days. One hundred and sixty four (52.1%) of 315 patients were only hospitalized once. At least one febrile episode was noted in 612 (92.9%) of 659 hospitalizations. More than a half of febrile episodes (53.5%) were FUO. A microbiological documentation was obtained in 191 of 612 (31.2%) hospitalizations with fever. A

total of 239 positive samples were collected, 19 were pulmonary samples and 220 were blood cultures. Note that patients could have multiple positive samples. Infections with BSAROH and BPAROH were documented in 87 (14.2%) and 58 (9.5%) of 612 hospitalizations with fever, respectively. An ICU admission was necessary in 62 of 659 hospitalizations (9.4%), including 49 (7.4%) for infection. An early death was noted in 31/659 (9.8 %) patients including 21/31 (67.4%) for an infectious cause. One hundred and thirty-five (42.9%) of 315 patients had died during the study period. The main cause of death was the hematological malignancy progression (60/135, 44.4%). Infection was the second cause of death (39/135, 28.9%) (See also Table S5). A treatment failure was noted in 126 of 659 hospitalizations (19.1%).

*Primary objective: risk factor of infection with BSAROH*

Univariate and multivariate analysis of the risk factors of microbiologically documented infection by BSAROH for all episodes of hospitalization are presented in Table 3 and Table 4. In univariate analysis, age (hazard ratio (HR) for 5 years=1.10 [1.05-1.15],  $p=0.03$ ), prior hospitalization within 3 months (HR=1.72 [1.04-2.84],  $p=0.03$ ) and a travel in foreign country within the last 3 months (HR=3.69 [1.67-8.16],  $p=0.01$ ) were factors significantly associated with a documented infection with a BSAROH (Table 3). In multivariate analysis, only age (adjusted HR for 5 years=1.02 [1.00-1.04],  $p=0.02$ ) and travel in foreign country (adjusted HR=3.58 [1.59-8.04],  $p=0.002$ ) remained statistically associated with a BSAROH infection. Gender, the presence of comorbidity, autogenic SCT, allogenic SCT, ICU admission history, previous infection or colonization with a BSAROH, were not associated with the onset of a BSAROH infection (Table 4).

Kaplan Meier curves are presented in Table S6. Neither exposure to all antibiotics nor exposure to one particular class of antibiotic was at risk factor of infection with a BSAROH. Similar results were obtained concerning the sensibility analysis restricted to the first episode of hospitalization of each patient (Table S7 and Table S8).

### *Antibiotic treatment*

An antibiotic treatment was prescribed in 612 (100%) hospitalizations with fever, unfortunately, antibiotic class was unknown in 2 patients. The main antibiotic treatment strategy used in first line was monotherapy with piperacillin-tazobactam in 427 (69.8%) hospitalizations. A combination therapy was prescribed in 116 (19.0%) hospitalizations (see Table 5). Carbapenem prescription was associated in one hundred and eighty-eight (30.7%) hospitalizations with fever. The median time of carbapenem exposure was 10 days. The most prescribed class of antibiotic treatment was penicillin associated with  $\beta$ -lactam inhibitors (501/610, 81.6%), with a median duration of treatment of 8 days

## **Discussion**

This study is a recent overview of the epidemiology of bacterial infections in the setting of high risk neutropenia. This type of update is essential for regular reevaluation of antibiotic stewardship in each center. The extrapolation of these results must be limited to centers in France and Northern Europe, where resistance levels are low and where patients do not receive antibiotic prophylaxis with fluoroquinolones.

This study had some limitations. Firstly, the retrospective nature exposed to bias, mainly for clinical presentation and origin of infection. In particular, interrogation data concerning travels in foreign country could be incomplete. Biases were prevented for the majority of the criteria by objective data such as microbiological results, age, death or ICU admission. The second main limitation was the microbiological approach since only 31.4% of all episode of febrile neutropenia had a microbiological documentation. This data probably minimized the incidence of microorganisms with less virulent presentation and less bloodstream potential dissemination such as anaerobic bacteria or non-fermenting Gram-negative bacilli others than *Pseudomonas aeruginosa*. Recent reports focused on the increasement of AMR level and the medical need of very broad-spectrum antibiotic treatment. Our study exposes another view in a low AMR level center, as already described by *Kjellander et al.* (24).

The validity of known factors associated with resistant microorganisms is unclear because these factors have been established from studies in centers with significant antibiotic resistance level (4,26,27,31,32,34,38–45), mainly in North America or Southern Europe. In our study, despite a population > 300 patients, the number of factors associated with BSAROH infection was limited. No association was found between the use of antibiotic treatment, the history of infection with a BSAROH and the history of colonization with BSAROH. In particular, only 18 of 203 patients (8.9%) with enteric colonization had a documented infection with the same microorganism. This surprising absence of association is probably linked with the low prevalence of AMR; infection with a sensitive microorganism remains the most probable situation, even in case of previous use of antibiotic treatment or history of BSAROH. Of course, spectrum of empirical antibiotic treatment should

not be diminished because infection with BSAROH are still frequent (14%) and hardly predictable, but very large spectrum empirical antibiotic treatment such as carbapenems or anti-GPC adjunction should not be used too early.

The risk factor with the highest HR in our study was the travel in foreign country, mainly because of CPE and ESBL-E, which is in consistent with previous studies (47–49). This clinical data must be systematically evaluated before hospitalization for profound neutropenia and a broader spectrum empirical antibiotic treatment could be a reasonable option.

No association was found between allogenic SCT, autogenic SCT recurrent hospitalizations and infection with a BSAROH. In our center, usage of a unique antibiotic guideline for neutropenia following chemotherapy in first hospitalization, recurrent hospitalization, autogenic SCT and allogenic SCT seems reasonable.

During a first hospitalization, if fever occurs in the first week, patients are frequently treated by cefotaxime or ceftriaxone because of the supposed community-acquired origin and the supposed lower probability of infection with *Pseudomonas aeruginosa* and ESBL-E or CPE. This frequent usage has not been evaluated in a prospective trial, neither in adults nor in children. The majority of infections with BSAROH in our study were observed during the first hospitalization, despite an absence of previous antibiotic treatment. Cefotaxime and ceftriaxone must be used with caution in first hospitalization because it could be associated with a risk of treatment failure.

Despite the high frequency of infection with sensitive microorganism, infection with BSAROH remains a frequent problem (14.2%) and identification of patients at risk remains challenging. Furthermore, the association between species, type of resistance and phenotypic resistance is complex (Figure 5), and highlights the risk

of treatment failure and the importance of a systematic antibiotic reevaluation at 48-72h. Note that interestingly, sensitivity to aminoglycosides remained very high (> 90%) in GNB. This class of antibiotics could be the best option in situations where obtaining a very broad spectrum antibiotic spectrum is essential such as severe presentation or concomitant  $\beta$ -lactam treatment.

Resistance levels in our study were low in comparison with rates observed in US and Southern Europe reports (18), but 2 mechanisms of antibiotic resistance remain problematic, particularly in *Enterobacterales*. At first, nearly 10% of patients with a community status and 40% with nosocomial status are colonized with ESBL-E (54,55). Secondly, the incidence of *Escherichia coli* and *Klebsiella pneumoniae* with high level of class A  $\beta$ -lactamase secretion, was high and exhibiting resistance to piperacillin-tazobactam, > 20% and > 50% respectively. This data should lead to a reevaluation of local recommendations since monotherapy with piperacillin-tazobactam was the first line antibiotic choice in almost 70% of febrile episode.

## **Conclusion**

In centers with low AMR level and no fluoroquinolones prophylaxis, classical risk factors do not discriminate patients with high probability of documented infection with a BSAROH. Despite a majority of infection by sensitive microorganisms, infection with BSAROH remains frequent and hardly predictable. A broad spectrum antibiotic treatment is essential for high risk febrile neutropenia but antibiotic escalation should be limited.

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## Tables and figures

Table 1. Patients Characteristics

|  |   |                |
|--|---|----------------|
| Patients, (hospitalizations) n (n)         |   | 315 (659)      |
| Number of hospitalizations, median (range) |   | 1 (1-7)        |
| Age, years, median (range)                 |   | 60 (18-77)     |
| Gender, n (%)                              | Male                                    | 169/315 (53.7) |
|  | Female                                  | 146/315 (46.3) |
| Treatment, n (%)                           | Chemotherapy                            | 454/659 (68.9) |
|  | Allogenic SCT                           | 128/659 (19.4) |
|  | Autogenic SCT                           | 77/659 (11.7)  |
| Disease, n (%) <sup>*</sup>                | Acute myeloid leukemia                  | 168/315 (53.2) |
|  | Acute lymphoblastic leukemia            | 31/315 (9.8)   |
|  | Lymphoma                                | 47/315 (14.9)  |
|  | Myeloma                                 | 43/315 (13.6)  |
|  | Other myeloid hematological malignancy  | 18/315 (5.7)   |
|  | Other lymphoid hematological malignancy | 1/315 (0.3)    |
|  | Aplastic anemia                         | 5/315 (1.6)    |
| Comorbidity, n (%) <sup>£</sup>            | Yes                                     | 195/315 (63.1) |
|  | No                                      | 114/315 (36.9) |

SCT: stem cell transplantation

\*: missing data: 3/315 (0.9%)

£: list in Table S1

Table 1. Patients Characteristics (continued)

|  |                |
|--|----------------|
| Patients, (hospitalizations) n (n)               | 315 (659)      |
| Antibiotic treatment in last 3 months, n (%)     | 435/659 (66)   |
| Hospitalization in last 3 months, n (%)          | 437/659 (66.3) |
| Hospitalization in ICU in last 3 months, n (%)   | 42/659 (6.4)   |
| Colonization with BSAROH in last 3 months, n (%) | 123/659 (18.7) |
| Link with foreign country; n (%)                 | 42/659 (6.4)   |

ICU: Intensive care unit

BSAROH: Bacteria with significant resistant to antibiotics in onco-hematology

Table 2. Patients' outcome

|   |                                    |                             |
|---|------------------------------------|-----------------------------|
| Follow up, days, median (range)                                   |                                    | 577 (3-1751)                |
| Duration of one episode of hospitalizations, days, median (range) |                                    | 23 (4-148)                  |
| Total duration of hospitalization, days, median (range)           |                                    | 43 (4-172)                  |
| Hospitalization with febrile episode, n (%) <sup>*</sup>          |                                    | 612/659 (92.9)              |
| Origin of infection, n (%)  | FUO                                | 327/612 (53.4)              |
|   | Digestive                          | 61/612 (10.0)               |
|   | ENT / Grade 3-4 Mucitis            | 55/612 (9.0)                |
|   | Pulmonary                          | 60/612 (9.8)                |
|   | Skin and soft tissue               | 37/612 (6.0)                |
|   | Catheter                           | 50/612 (8.2)                |
|   | Urinary                            | 22/612 (3.6)                |
| Microbiological documentation, n, (%)                             |                                    | 191/612 (31.2)              |
|   | Pulmonary distal sample            | 19/239 <sup>£</sup> (7.9)   |
|   | Bloodstream infection <sup>§</sup> | 220/239 <sup>£</sup> (92.1) |
| Concomitant antibiotic treatment at documentation, n (%)          |                                    | 51/191 (26.7)               |
| Microbiological documentation with BSAROH, n (%)                  |                                    | 87/612 (14.2)               |
| Microbiological documentation with BPAROH, n (%)                  |                                    | 58/612 (9.5)                |

FUO: fever of unknown origin; ENT: Ear nose and throat; BSAROH: bacteria with significant antibiotic resistance in onco-hematology; BPAROH: bacteria with problematic antibiotic resistance in onco-hematology

\*: 47 patients remained afebrile during at least one hospitalization.

£: 239 positive samples, one patient with documentation could have multiple positive samples

§: monomicrobial: 202/220 (91.8%), polymicrobial: 18/220 (8.2%)



Table 2. Patients' outcome (continued)

|                                    |                          |                |
|------------------------------------|--------------------------|----------------|
| Treatment failure, n (%)           |                          | 126/659 (19.1) |
| ICU admission, n (%)               |                          | 62/659 (9.4)   |
| ICU admission for infection, n (%) |                          | 49/62 (79)     |
| Early death, n (%)                 |                          | 31/315 (9.8)   |
| Early death for infection, n (%)   |                          | 21/31 (61.8)   |
| Death, n (%)                       |                          | 135/315(42.9)  |
| Cause of death, n (%)              | Hematological malignancy | 60/135 (44.4)  |
|                                    | Infection                | 39/135 (28.9)  |
|                                    | Treatment toxicity       | 31/135 (23.0)  |
|                                    | Other*                   | 3/135 (2.2)    |

ICU: intensive care unit

\*: 2 (1.5%) missing data see Table S5

Table 3. Primary outcome univariate analysis for all hospitalizations  
Risk factors of documented infection with bacteria with significant antibiotic resistance in onco-hematology (BSAROH)

|   | Documented infection with BSAROH<br>n=87 | Infection without documentation or other germ<br>n=572 | Hazard ratio [95%CI]     | p           |
|---|--|--|--------------------------|-------------|
| Male sex, n (%)                                       | 54 (62.1)                                | 309 (54.0)   | 1.33 [0.85-2.06]         | 0.21        |
| Age, years, median (IQR)                              | 63 (53-69)                               | 59 (49-66)   | <b>1.10 [1.05-1.15]*</b> | <b>0.03</b> |
| Presence of at least one comorbidity, n (%)           | 55 (63.2)                                | 345 (60.3)   | 1.10 [0.71-1.73]         | 0.65        |
| Allogenic SCT, n (%)                                  | 17 (19.5)                                | 11 (19.4)  | 0.89 [0.52-1.52]         | 0.67        |
| Autogenic SCT, n (%)                                  | 5 (5.7)                                  | 72 (12.6)  | 0.43 [0.17-1.07]         | 0.07        |
| Prior hospitalization within 3 months, n (%)          | 67 (77.0)                                | 370 (64.7)   | <b>1.72 [1.04-2.84]</b>  | <b>0.03</b> |
| ICU during prior hospitalization for treatment, n (%) | 5 (5.7)                                  | 37 (6.5)   | 0.86 [0.35-2.15]         | 0.75        |
| Foreign travel within 3 months, n (%)                 | 7 (8.0)                                  | 11 (1.9)   | <b>3.69 [1.67-8.16]</b>  | <b>0.01</b> |
| History of infection with BSAROH, n (%)               | 12 (13.8)                                | 64 (11.2)  | 1.26 [0.69-2.32]         | 0.45        |
| History of colonization with BSAROH, n (%)            | 17 (19.5)                                | 106 (18.5)   | 1.06 [0.62-1.81]         | 0.84        |
| Previous antibiotics                                  |  |  |                          |             |
| All antibiotics                                       | 64 (73.6)                                | 371 (64.9)   | 1.45 [0.89-2.34]         | 0.13        |
| β-lactam + inhibitor                                  | 46 (52.9)                                | 306 (53.5)   | 0.96 [0.63-1.47]         | 0.85        |
| Cephalosporin   | 32 (36.8)                                | 154 (26.9)   | 1.56 [1.01-2.41]         | 0.05        |
| Ceftazidime   | 14 (16.1)                                | 65 (11.4)  | 1.47 [0.83-2.6]          | 0.18        |
| Cefotaxime / ceftriaxone                              | 18 (20.7)                                | 107 (18.7)   | 1.13 [0.67-1.91]         | 0.65        |
| Cefepime  | 2 (2.3)                                  | 4 (0.7)  | 3.15 [0.73-13.5]         | 0.12        |
| Aminoglycosides                                       | 13 (14.9)                                | 96 (16.8)  | 0.85 [0.47-1.54]         | 0.59        |
| Quinolones  | 7 (8.0)                                  | 52 (9.1)   | 0.89 [0.41-1.96]         | 0.78        |
| Carbapenems   | 18 (20.7)                                | 126 (22.0)   | 0.90 [0.53-1.52]         | 0.68        |
| Anti-GPC  | 24 (27.6)                                | 191 (33.4)   | 0.75 [0.47-1.21]         | 0.24        |
| Other   | 26 (28.9)                                | 162 (28.3)   | 1.08 [0.68-1.72]         | 0.76        |

SCT: stem cell transplantation; ICU: Intensive care unit; IQR: interquartile range; Anti-GPC: antibiotic against Gram positive cocci (e.g. vancomycin, linezolid, daptomycin).

Table 4. Primary outcome multivariate analysis for all hospitalizations  
Risk factors ( $p < 0.20$  in univariate analysis) of documented infection with bacteria with significant antibiotic resistance in onco-hematology (BSAROH)

|  | Documented infection with BSAROH<br>n=87 | Infection without documentation or other germ<br>n=572 | Adjusted Hazard ratio [95%CI] | p            |
|--|--|--|-------------------------------|--------------|
| Male sex, n (%)                              | 54 (62.1)                                | 309 (54.0)   | 1.26 [0.79-1.96]              | 0.34         |
| Age, years, median (IQR)                     | 63 (53-69)                               | 59 (49-66)   | <b>1.02 [1.00-1.04]</b>       | <b>0.02</b>  |
| Autogenic SCT, n (%)                         | 5 (5.7)                                  | 37 (6.5)   | 0.58 [0.22-1.49]              | 0.25         |
| Prior hospitalization within 3 months, n (%) | 67 (77.0)                                | 370 (64.7)   | 1.54 [0.92-2.59]              | 0.1          |
| Foreign travel within 3 months, n (%)        | 7 (8.0)                                  | 11 (1.9)   | <b>3.58 [1.59-8.04]</b>       | <b>0.002</b> |
| Previous antibiotics                         |  |  |                               |              |
| All antibiotics                              | 64 (73.6)                                | 371 (64.9)   | 1.08 [0.58-1.98]              | 0.81         |
| Cephalosporin                                | 32 (36.8)                                | 154 (26.9)   | 1.51 [0.94-2.42]              | 0.09         |
| Ceftazidime                                  | 14 (16.1)                                | 65 (11.4)  | 1.36 [0.75-2.46]              | 0.32         |
| Cefepime                                     | 2 (2.3)                                  | 4 (0.7)  | 1.09 [0.63-1.89]              | 0.75         |

SCT: stem cell transplantation; IQR: interquartile range.

Table 5. Antibiotic treatment

| <b>First line treatment, n (%)*</b>                     |                                     |   |
|---|-------------------------------------|---|
|   | monotherapy                         | 492/612 (80.4)                              |
|   | combination therapy                 | 116/612 (10.7)                              |
|   | piperacillin- tazobactam            | 427/612 (69.8)                              |
|   | ceftazidime                         | 63/612 (10.3)                               |
|   | cefepime                            | 1/612 (0.2)                                 |
|   | ceftriaxone / cefotaxime            | 57/612 (9.3)                                |
|   | carbapenem                          | 36/612 (5.9)                                |
|   | other <sup>#</sup>                  | 26/612 (4.2)                                |
| <b>Total administration</b>                             |                                     |   |
| Molecule  | Administration, n (%) <sup>\$</sup> | Duration of treatment, days, median (range) |
| Penicillin + $\beta$ -lactamase inhibitors <sup>£</sup> | 501 /612 (81.6)                     | 8 (1-49)                                    |
| Ceftazidime   | 121/612 (19.8)                      | 9 (1-42) <sup>µ</sup>                       |
| Cefepime  | 9/612 (1.5)                         |   |
| Carbapenem  | 188/612 (30.7)                      | 10 (1-46)                                   |
| Aminoglycoside <sup>§</sup>                             | 163/612 (26.7)                      | 1 (1-7)                                     |
| Fluoroquinolone   | 44/612 (7.2)                        | 6 (1-30)                                    |
| Vancomycin  | 237/612 (38.7)                      |   |
| Linezolid   | 121/612 (19.7)                      | 13 (1-34) <sup>+</sup>                      |
| Daptomycin  | 19/612 (3.1)                        |   |

\*: 610 class of first line antibiotic treatment recorded, for 612 febrile episodes with antibiotic treatment. Two missing data. Total < 100%

<sup>#</sup>: aztreonam, amoxicillin-clavulanic acid, amoxicillin, fluoroquinolone, pristnamycin, linezolid, rovamycin

<sup>\$</sup>: total > 100%, patients could receive more than one antibiotic treatment

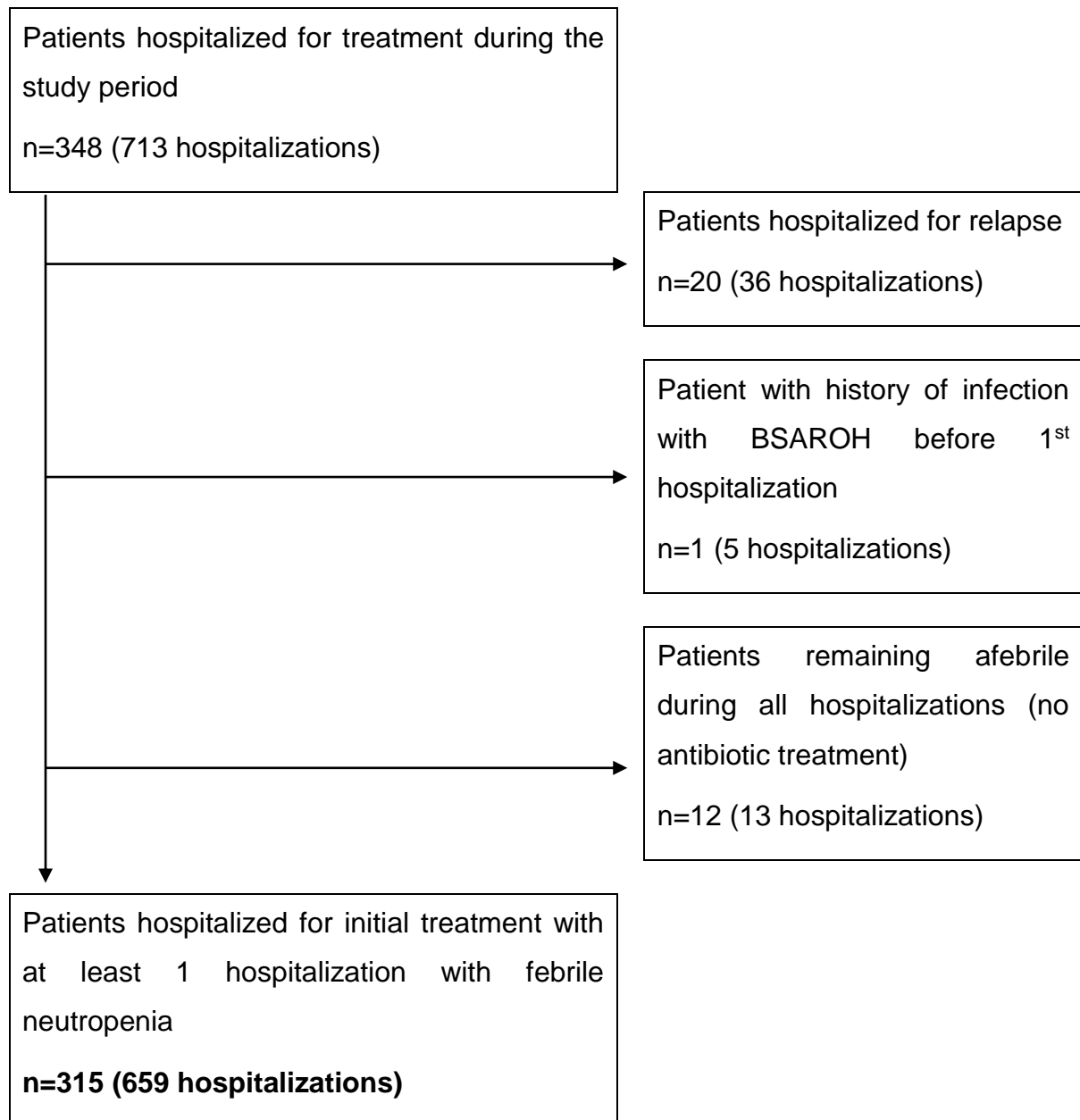
<sup>£</sup>: piperacillin-tazobactam: 454, amoxicillin-clavulanic acid: 42, ticarcillin-clavulanic acid: 5

<sup>µ</sup>: duration for all cephalosporins

<sup>§</sup>: amikacin: 146, gentamicin: 17

<sup>+</sup>: duration for all specific anti resistant Gram positive cocci

Figure 1. Study flow chart



BSAROH: bacteria with significant antibiotic resistance in onco-hematology

Figure 2. Microbiology of documented infections: 220 blood cultures and 19 distal pulmonary samples. A) Main microorganisms repartition B) Microorganisms subgroups repartition. Complete list in Table S2.

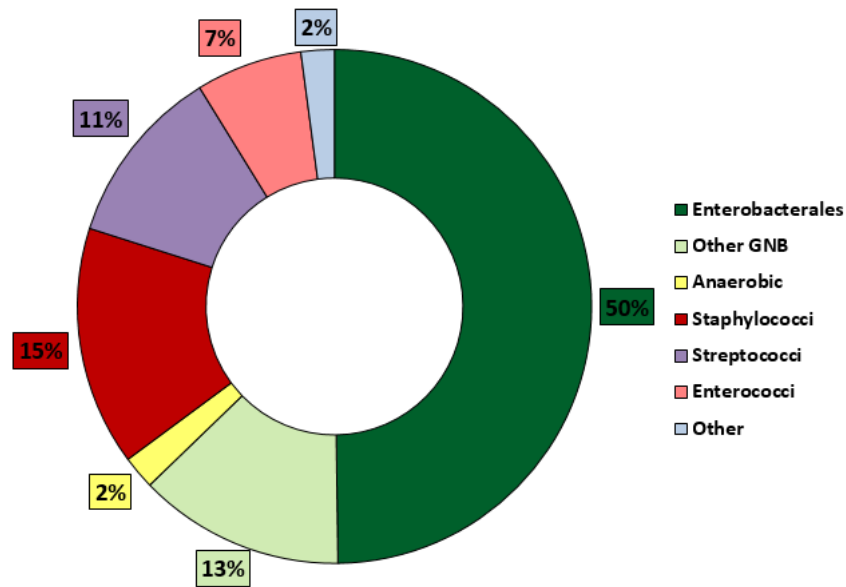


Figure 2A. GNB: Gram negative bacilli

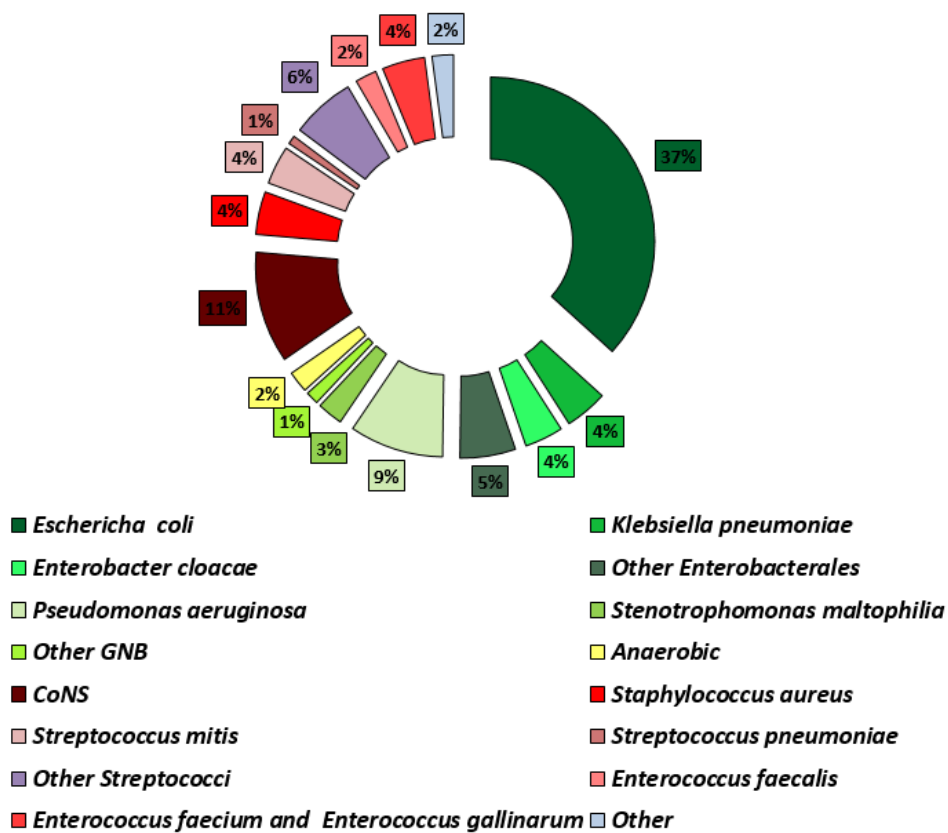


Figure 2B. GNB: Gram negative bacilli, CoNS: coagulase negative *Staphylococci*

Figure 3. Antimicrobial resistance types and rates in Gram-negative microorganisms. A) *Escherichia coli*, *Klebsiella pneumoniae*, other *Enterobacteriales*. B) *Pseudomonas aeruginosa*.

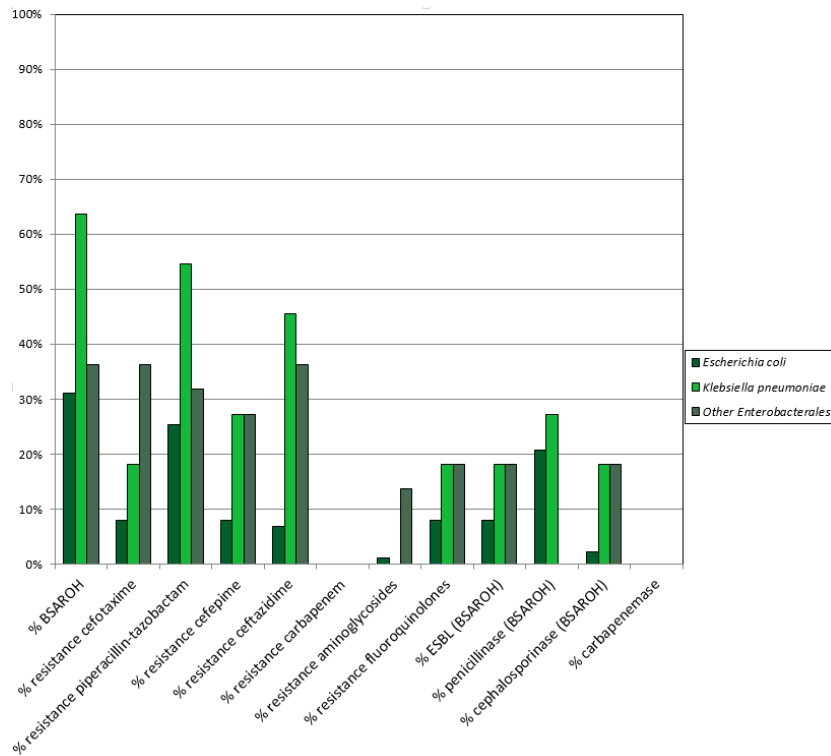


Figure 3A.

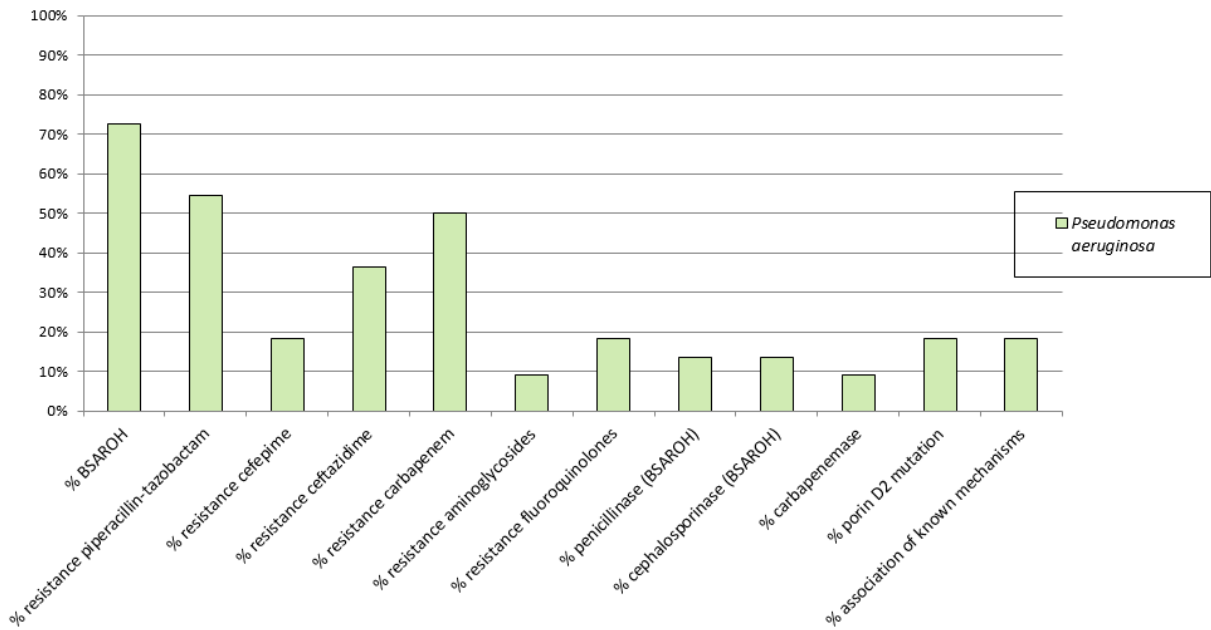


Figure 3B.

Figure 4. Antimicrobial resistance types and rates in Gram-positive microorganisms. A) *Staphylococcus aureus* and coagulase negative *Staphylococci* (CoNS). B) *Enterococcus faecalis* and *Enterococcus faecium*. C) *Streptococcus* sp. group.

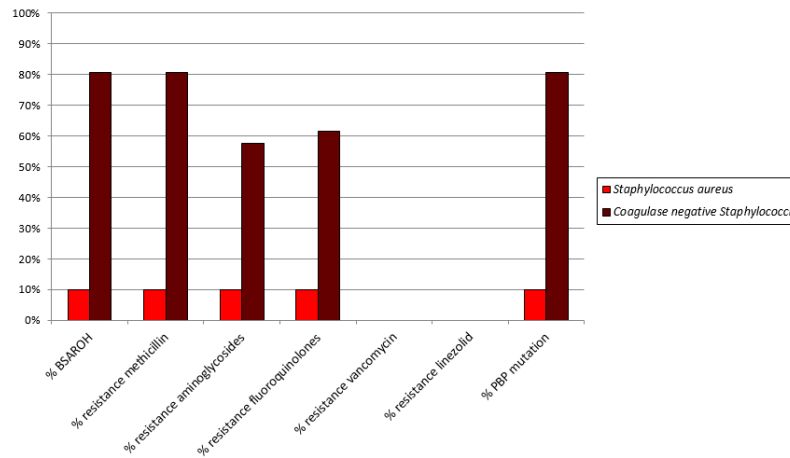


Figure 4A.

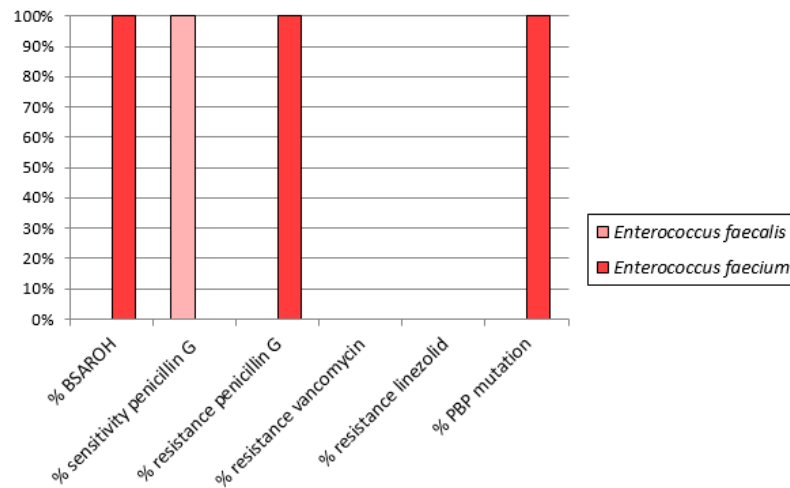


Figure 4B.

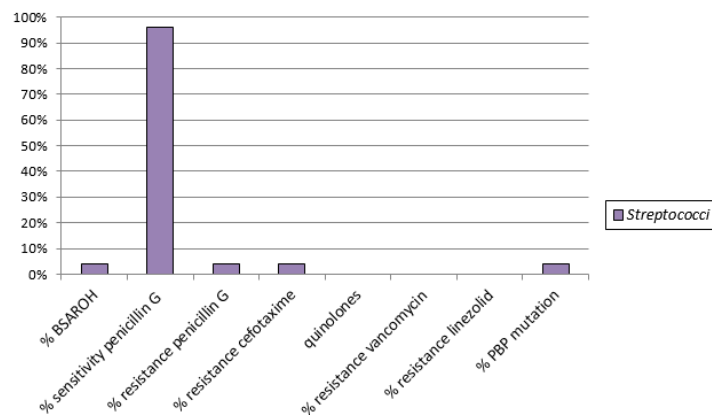
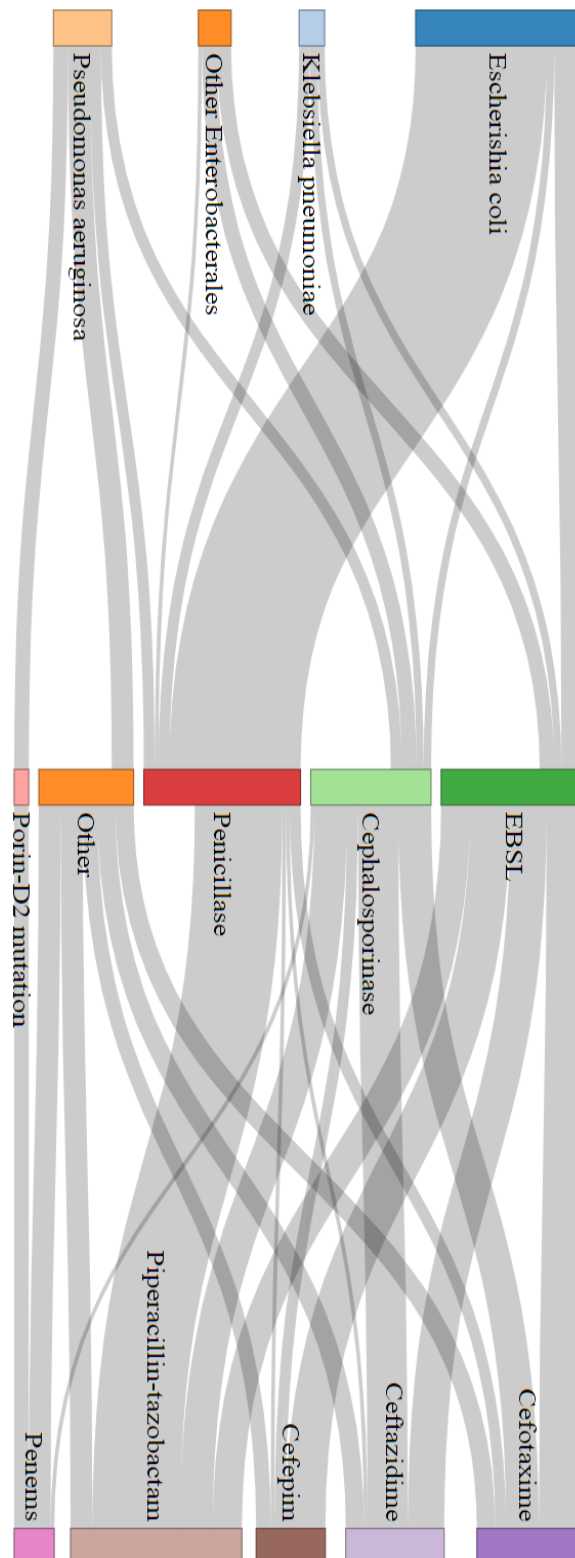


Figure 4C.



Figure 5. Sankey chart: link between resistance type and resistance level in documented infection.



ESBL: extended spectrum  $\beta$ -lactamase  
Complete data frame in Table S3.

## Supplementary data

Table S1. Patients' comorbidities

| Comorbidity                     | n  | Comorbidity                           | n  | Comorbidity                                | n  |
|---------------------------------|----|---------------------------------------|----|--|----|
| Hypertension                    | 68 | Chronic obstructive pulmonary disease | 14 | Pulmonary embolism                         | 6  |
| Stroke                          | 3  | Fungal infection                      | 1  | Asbestosis and/or pulmonary fibrosis       | 10 |
| Breast abscess                  | 1  | Atrial fibrillation                   | 9  | Heart failure                              | 4  |
| Aortitis                        | 1  | Asthma                                | 5  | Renal insufficiency                        | 2  |
| Inflammatory rheumatism         | 1  | Pulmonary cancer                      | 2  | Uterus cervix cancer                       | 1  |
| Colon or rectum cancer          | 2  | Prostate cancer                       | 4  | Pancreas cancer                            | 1  |
| Breast cancer                   | 10 | Thyroid cancer                        | 6  | Uterus cancer                              | 2  |
| Skin carcinoma                  | 6  | Urothelial cancer                     | 1  | Ischemic heart disease                     | 9  |
| Valvular heart disease          | 4  | Cholecystitis                         | 1  | Cirrhosis                                  | 2  |
| Colitis                         | 1  | diabetes                              | 13 | Pulmonary embolism                         | 5  |
| Barrett's esophagus             | 2  | Hepatitis                             | 9  | Horton's disease or polymyalgia rheumatica | 5  |
| Prostate hypertrophy            | 1  | Melanoma                              | 3  | Chronic lymphocytic leukemia               | 1  |
| Lymphoma                        | 3  | Myeloma                               | 1  | Pericarditis or Myocarditis                | 2  |
| Acoustic neuroma                | 2  | Neurofibromatosis                     | 1  | Obesity                                    | 10 |
| Digestive obstruction           | 1  | Chronic alcoholism                    | 4  | Orchitis or Epididymitis                   | 1  |
| Osteoporosis with bone fracture | 1  | Pancreatitis                          | 3  | Parkinson's disease                        | 1  |
| Deep vein thrombosis            | 11 | Recurrent pyelonephritis              | 4  | Ulcerative colitis or Crohn's disease      | 2  |
| Sarcoidosis                     | 2  | Ewing sarcoma                         | 1  | Schizophrenia                              | 2  |
| Splenectomy                     | 1  | Chronic tabagism                      | 16 | Cardiac conduction disorder                | 1  |
| Uveitis                         | 1  | Cornea abscess                        | 1  | Congenital cardiopathy                     | 1  |
| Arteriopathy                    | 5  | Indeterminate digestive cancer        | 1  |  |    |

Table S1. Patients' comorbidities (continued)

| <b>Comorbidity</b>                         | <b>n</b> | <b>Comorbidity</b>   | <b>n</b> | <b>Comorbidity</b>         | <b>n</b> |
|--|----------|----------------------|----------|----------------------------|----------|
| Cryoglobulin                               | 2        | Dyslipidemia         | 1        | Face skin infection        | 1        |
| Gastritis (acute or chronic)               | 3        | Cerebral hemorrhage  | 3        | Ocular herpes              | 1        |
| Pulmonary arterial hypertension            | 1        | Peritonitis          | 1        | Pneumothorax               | 1        |
| Arthropatic psoriasis                      | 1        | Thalassemia          | 1        | Intravenous drug addiction | 1        |
| Endocarditis                               | 1        | Hemochromatosis      | 1        | Recurrent pneumoniae       | 1        |
| Vertebralitis                              | 1        | Prostate hypertrophy | 1        | Recurrent yeast infection  | 1        |
| Septic shock after pneumococcus bacteremia | 1        | Tuberculosis         | 1        | Typhoid fever              | 1        |

Table S2. Microbiology of documented infection

| Total                    |                                     | n (%)          |
|--------------------------|-------------------------------------|----------------|
|                          | Blood culture                       | 220/239 (92.1) |
|                          | Distal pulmonary sample             | 19/239 (7.9)   |
| <i>Enterobacteriales</i> | <i>Escherichia coli</i>             | 87/239 (36.4)  |
|                          | <i>Klebsiella pneumoniae</i>        | 10/239 (4.2)   |
|                          | <i>Campylobacter fetus</i>          | 1/239 (0.4)    |
|                          | <i>Campylobacter freundii</i>       | 1/239 (0.4)    |
|                          | <i>Citrobacter koseri</i>           | 1/239 (0.4)    |
|                          | <i>Enterobacter cloacae</i>         | 9/239 (3.8)    |
|                          | <i>Hafnia alvei</i>                 | 2/239 (0.8)    |
|                          | <i>Klebsiella aerogenes</i>         | 3/239 (1.3)    |
|                          | <i>Klebsiella oxytoca</i>           | 2/239 (0.8)    |
|                          | <i>Klebsiella variicola</i>         | 1/239 (0.4)    |
|                          | <i>Morganella morganii</i>          | 1/239 (0.4)    |
|                          | <i>Proteus mirabilis</i>            | 1/239 (0.4)    |
| Other GNB                | <i>Pseudomonas aeruginosa</i>       | 22/239 (9.2)   |
|                          | <i>Capnocytophaga sputigena</i>     | 3/239 (1.3)    |
|                          | <i>Moraxella spp.</i>               | 1/239 (0.4)    |
|                          | <i>Stenotrophomonas maltophilia</i> | 6/239 (2.6)    |
| Anaerobic bacteria       | <i>Leptotrichia spp.</i>            | 2/239 (0.8)    |
|                          | <i>Bacteroides fragilis</i>         | 1/239 (0.4)    |
|                          | <i>Bacteroides vulgatus</i>         | 1/239 (0.4)    |
|                          | <i>Clostridium tertium</i>          | 1/239 (0.4)    |

GNB: Gram negative bacilli

Table S2. Microbiology of documented infection (continued)

|                      |                                   |               |
|----------------------|-----------------------------------|---------------|
| <i>Staphylococci</i> | CoNS*                             | 26/239 (10.9) |
|                      | <i>Staphylococcus aureus</i>      | 10/239 (4.2)  |
| <i>Streptococci</i>  | <i>Streptococcus mitis</i>        | 9/239 (3.8)   |
|                      | <i>Streptococcus pneumoniae</i>   | 2/239 (0.8)   |
|                      | <i>Streptococcus salivarius</i>   | 4/239 (1.8)   |
|                      | <i>Streptococcus agalactiae</i>   | 1/239 (0.4)   |
|                      | <i>Streptococcus dysgalactiae</i> | 1/239 (0.4)   |
|                      | <i>Streptococcus oralis</i>       | 1/239 (0.4)   |
|                      | <i>Streptococcus pyogenes</i>     | 3/239 (1.3)   |
|                      | <i>Streptococcus vestibularis</i> | 2/239 (0.8)   |
|                      | <i>Abiotrophia defectiva</i>      | 1/239 (0.4)   |
|                      | <i>Granulicatella adjacens</i>    | 2/239 (0.8)   |
| <i>Enterococci</i>   | <i>Enterococcus faecalis</i>      | 5/239 (2.2)   |
|                      | <i>Enterococcus faecium</i>       | 10/239 (4.2)  |
|                      | <i>Enterococcus gallinarum</i>    | 1/239 (0.4)   |
| Other                | <i>Actinomyces odontolyticus</i>  | 2/239 (0.8)   |
|                      | <i>Corynebacterium jeikeium</i>   | 1/239 (0.4)   |
|                      | <i>Lactobacillus rhamnosus</i>    | 1/239 (0.4)   |
|                      | <i>Micrococcus luteus</i>         | 1/239 (0.4)   |

\*: 26 coagulase negative *Staphylococci*, including 1 *Staphylococcus lugdunensis*

Table S3. Data frame of Figure 5. Link between resistance type and resistance level in documented infection

| Microorganism                   | Resistance type  | n, (%)    | Antibiotic resistance   | n  |
|---------------------------------|------------------|-----------|-------------------------|----|
| <i>Escherichia coli</i><br>N=86 | ESBL             | 7 (8.1)   | Cefotaxime              | 5  |
|                                 |                  |           | Ceftazidime             | 4  |
|                                 |                  |           | Cefepime                | 5  |
|                                 |                  |           | Piperacillin-tazobactam | 3  |
|                                 |                  |           | Carbapenem              | 0  |
|                                 | Cephalosporinase | 2 (2.3)   | Cefotaxime              | 2  |
|                                 |                  |           | Ceftazidime             | 2  |
|                                 |                  |           | Cefepime                | 0  |
|                                 |                  |           | Piperacillin-tazobactam | 1  |
|                                 |                  |           | Carbapenem              | 0  |
|                                 | Penicillinase    | 36 (41.9) | Cefotaxime              | 0  |
|                                 |                  |           | Ceftazidime             | 0  |
|                                 |                  |           | Cefepime                | 1  |
|                                 |                  |           | Piperacillin-tazobactam | 18 |
|                                 |                  |           | Carbapenem              | 0  |
|                                 | Other *          | 0         | Cefotaxime              | 0  |
|                                 |                  |           | Ceftazidime             | 0  |
|                                 |                  |           | Cefepime                | 0  |
|                                 |                  |           | Piperacillin-tazobactam | 0  |
| Carbapenem                      |                  |           | 0                       |    |

ESBL: Extended spectrum  $\beta$ -lactamase, \*: Carbapenemase = 0

Table S3. Data frame Figure 5. Link between resistance type and resistance level in documented infection (continued)

| Microorganism                            | Resistance type  | n, (%)   | Antibiotic resistance   | n |
|--|------------------|----------|-------------------------|---|
| <i>Klebsiella<br/>Pneumoniae</i><br>N=10 | ESBL             | 2 (20.0) | Cefotaxime              | 2 |
|  |                  |          | Ceftazidime             | 2 |
|  |                  |          | Cefepime                | 2 |
|  |                  |          | Piperacillin-tazobactam | 1 |
|  |                  |          | Carbapenem              | 0 |
|  | Cephalosporinase | 2 (20.0) | Cefotaxime              | 0 |
|  |                  |          | Ceftazidime             | 2 |
|  |                  |          | Cefepime                | 1 |
|  |                  |          | Piperacillin-tazobactam | 2 |
|  |                  |          | Carbapenem              | 0 |
|  | Penicillinase    | 3 (30.0) | Cefotaxime              | 0 |
|  |                  |          | Ceftazidime             | 1 |
|  |                  |          | Cefepime                | 0 |
|  |                  |          | Piperacillin-tazobactam | 3 |
|  |                  |          | Carbapenem              | 0 |
|  | Other *          | 0        | Cefotaxime              | 0 |
|  |                  |          | Ceftazidime             | 0 |
|  |                  |          | Cefepime                | 0 |
| Piperacillin-tazobactam                  |                  |          | 0                       |   |
| Carbapenem                               |                  |          | 0                       |   |

ESBL: Extended spectrum  $\beta$ -lactamase, \*: Carbapenemase = 0

Table S3. Data frame Figure 5. Link between resistance type and resistance level in documented infection (continued)

| Microorganism                            | Resistance type  | n, (%)   | Antibiotic resistance   | n |
|--|------------------|----------|-------------------------|---|
| Other<br><i>Enterobacterales</i><br>N=22 | ESBL             | 4 (18.2) | Cefotaxime              | 4 |
|  |                  |          | Ceftazidime             | 4 |
|  |                  |          | Cefepime                | 4 |
|  |                  |          | Piperacillin-tazobactam | 4 |
|  |                  |          | Carbapenem              | 0 |
|  | Cephalosporinase | 4 (18.2) | Cefotaxime              | 4 |
|  |                  |          | Ceftazidime             | 4 |
|  |                  |          | Cefepime                | 2 |
|  |                  |          | Piperacillin-tazobactam | 3 |
|  |                  |          | Carbapenem              | 0 |
|  | Penicillinase    | 1 (4.5)  | Cefotaxime              | 0 |
|  |                  |          | Ceftazidime             | 0 |
|  |                  |          | Cefepime                | 0 |
|  |                  |          | Piperacillin-tazobactam | 0 |
|  |                  |          | Carbapenem              | 0 |
|  | Other*           | 0        | Cefotaxime              | 0 |
| Ceftazidime                              |                  |          | 0                       |   |
| Cefepime                                 |                  |          | 0                       |   |
| Piperacillin-tazobactam                  |                  |          | 0                       |   |
| Carbapenem                               |                  |          | 0                       |   |

ESBL: Extended spectrum  $\beta$ -lactamase, \* Carbapenemase = 0



Table S3. Data frame Figure 5. Link between resistance type and resistance level in documented infection (continued)

| Microorganism                         | Resistance type   | n, (%)   | Antibiotic resistance   | n |
|---------------------------------------|-------------------|----------|-------------------------|---|
| <i>Pseudomonas Aeruginosa</i><br>N=22 | Porin-D2 mutation | 4 (18.2) | Carbapenem              | 4 |
|                                       | Cephalosporinase  | 3 (13.6) | Cefotaxime <sup>£</sup> | 3 |
|                                       |                   |          | Ceftazidime             | 3 |
|                                       |                   |          | Cefepime                | 0 |
|                                       |                   |          | Piperacillin-tazobactam | 3 |
|                                       |                   |          | Carbapenem              | 1 |
|                                       | Penicillinase     | 3 (13.6) | Cefotaxime <sup>£</sup> | 3 |
|                                       |                   |          | Ceftazidime             | 0 |
|                                       |                   |          | Cefepime                | 0 |
|                                       |                   |          | Piperacillin-tazobactam | 3 |
|                                       |                   |          | Carbapenem              | 0 |
|                                       | Other*            | 6 (27.3) | Cefotaxime <sup>£</sup> | 5 |
|                                       |                   |          | Ceftazidime             | 5 |
| Cefepime                              |                   |          | 4                       |   |
| Piperacillin-tazobactam               |                   |          | 6                       |   |
| Carbapenem                            |                   |          | 6                       |   |

\*: Association of known mechanisms of resistance; Carbapenemase = 2;

£: natural resistance, chromosomal cephalosporinase

Table S4. Microbiology of enteric colonization

|   |                                 |               |
|---|---------------------------------|---------------|
| <i>Enterobacteriales</i> , n (%) §      | ESBL                            | 75/129 (58.1) |
|   | Cephalosporinase                | 46/129 (35.7) |
|   | Penicillinase                   | 1/129 (0.8)   |
|   | Carbapenemase                   | 0             |
|   | Other                           | 7/129 (5.4)   |
| <i>Pseudomonas aeruginosa</i> , n (%) * | Cephalosporinase                | 5/30 (16.7)   |
|   | Penicillinase                   | 7/30(23.3)    |
|   | Porin-D2 mutation               | 7/30 (23.3)   |
|   | Carbapenemase                   | 6/30 (20)     |
|   | Association of known mechanisms | 5/30 (16.7)   |
| <i>Enterococcus faecium</i> , n (%)     | PBP mutation <sup>£</sup>       | 5/5 (100)     |
|   | VRE <sup>£</sup>                | 4/5 (80)      |

§: *Escherichia coli* + *Klebsiella pneumoniae* + *Enterobacteriales* = 129

ESBL: extended spectrum  $\beta$ -lactamase

\*only bacteria with significant antibiotic resistance in onco-hematology (BSAROH), 45/75 of *Pseudomonas aeruginosa* were wild type

PBP: penicillin binding protein; VRE: vancomycin resistant *Enterococci*

£: association of the two mechanisms in 4/5, total > 100%

Table S5. Causes of death

| <b>Cause of death</b>                             |   | <b>n</b> |
|---|---|----------|
| Progressive or relapsing hematological malignancy |   | 60       |
| Infection   |   | 39       |
| Toxicity of treatment                             | Sinusoidal obstruction syndrome                   | 3        |
|   | Anthracycline-induced cardiopathy                 | 2        |
|   | Graft versus host disease (acute and chronic)     | 14       |
|   | Cerebral hemorrhage                               | 1        |
|   | Interstitial pneumonitis                          | 1        |
|   | Polyneuropathy                                    | 1        |
|   | Multiple organ failures with multifactorial cause | 2        |
|   | Other   | 7        |
| Other   | Unexplained sudden death                          | 1        |
|   | Cardiac arrest during chemotherapy                | 1        |
|   | Cardiac arrest during endoscopy                   | 1        |
| Missing data                                      |   | 2        |

Table S5. Causes of death, infection (continued)

| Cause   | n (total: 39) |
|---|---------------|
| <i>Staphylococcus aureus</i> WT BSI             | 1             |
| Septic shock, FUI                               | 12            |
| <i>Escherichia coli</i> WT BSI                  | 2             |
| <i>Pseudomonas aeruginosa</i> WT BSI            | 2             |
| COVID   | 1             |
| Endocarditis with <i>Enterococci</i> *          | 2             |
| Epiglottitis with <i>Streptococcus pyogenes</i> | 1             |
| PMLE  | 1             |
| CMV disease                                     | 1             |
| <i>Klebsiella pneumoniae</i> WT meningitis      | 1             |

WT: wild type = no non-natural resistance; BSI: bloodstream infection; FUI: fever of unknown origin; COVID: infection with SARS *Coronavirus* 19; PMLE: progressive multifocal leukoencephalopathy; CMV: *Cytomegalovirus*

\*: 1 *Enterococcus faecalis*, 1 *Enterococcus faecium*

Table S5. Cause of death, infection (continued)

| Cause                  | n (total: 39) |
|------------------------|---------------|
| Peritonitis*           | 3             |
| Pneumocystosis         | 1             |
| Pneumonia <sup>‡</sup> | 9             |
| Viral pneumonia        | 1             |
| Cerebral toxoplasmosis | 1             |

\*: including 1 with *Pseudomonas aeruginosa* WT

<sup>‡</sup>: including 1 with *Pseudomonas aeruginosa* MDR, 2 with *Pseudomonas aeruginosa* WT, 1 with *Escherichia coli* WT, 1 with *Stenotrophomonas maltophilia* MDR

WT: wild type = no non-natural resistance; MDR: multi drug resistant

Table S6. Kaplan Meier curves of survival without bacteria with significant antibiotic resistance in onco-hematology (BSAROH) infection by A) age and B) history of travel in foreign country during the last 3 months

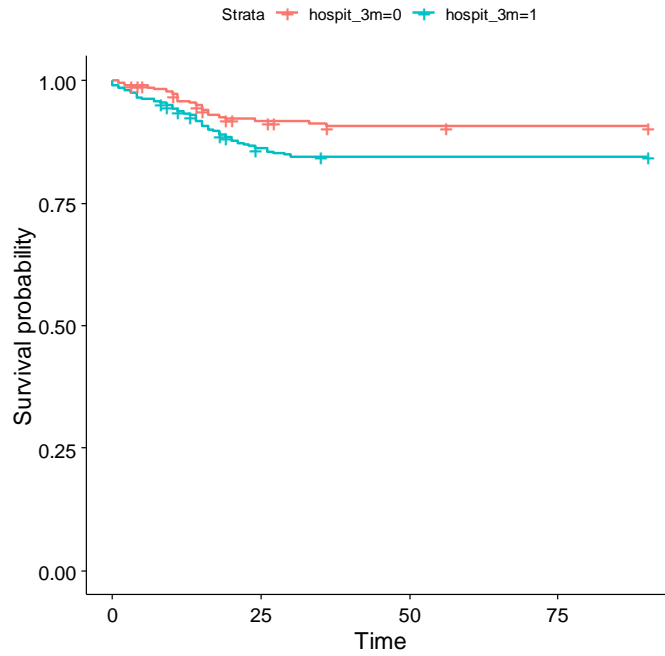


Table S6A.

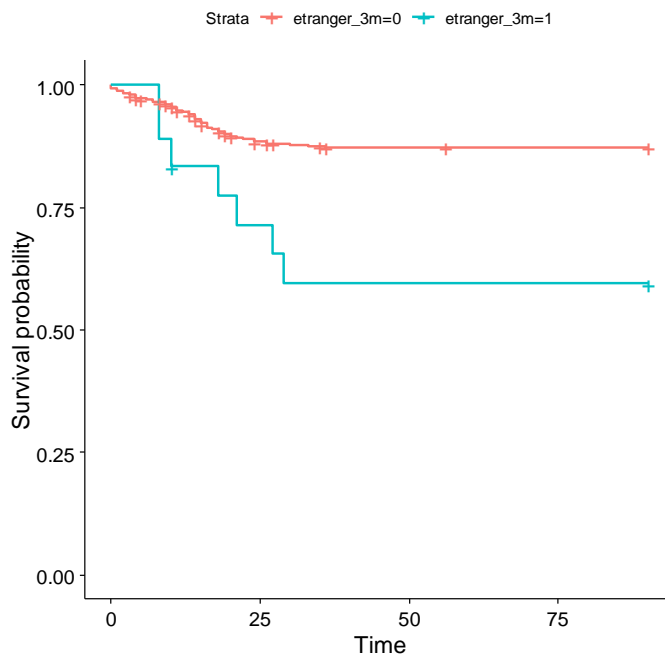


Table S6B.

Table S7. Primary outcome univariate analysis for first hospitalization. Risk factors of documented infection with bacteria with significant antibiotic resistance in onco-hematology (BSAROH)

|   | Documented infection with BSAROH<br>n=46 | Infection without documentation or other germ<br>n=269 | Hazard ratio [95%CI]    | p                          |
|---|--|--|-------------------------|----------------------------|
| Male sex, n (%)   | 32 (69.6)                                | 137 (50.9)   | <b>2.02 [1.08-3.79]</b> | <b>0.03</b>                |
| Age, years, median (IQR)                                    | 62 (53-70)                               | 60 (50-67)   | 1.10 [1.05-1.15]*       | 0.05                       |
| Presence of at least one comorbidity, n (%)                 | 31 (67.4)                                | 164 (61.0)   | 1.33 [0.72-2.46]        | 0.37                       |
| Prior hospitalization within 3 months, n (%)                | 27 (58.7)                                | 73 (27.1)  | <b>3.19 [1.77-5.74]</b> | <b>&lt;10<sup>-3</sup></b> |
| ICU during prior hospitalization for treatment, n (%)       | 0 (0)                                    | 1 (0.4)  | -                       | -                          |
| Foreign travel within 3 months, n (%)                       | 7 (15.2)                                 | 11 (4.1)   | <b>3.56 [1.59-7.97]</b> | <b>0.002</b>               |
| History of colonization with BSAROH during treatment, n (%) | 0 (0)                                    | 2 (0.7)  | -                       | -                          |
| Previous antibiotics  |  |  |                         |                            |
| All antibiotics   | 26 (56.5)                                | 84 (31.2)  | <b>2.54 [1.42-4.55]</b> | <b>0.002</b>               |
| β-lactam + inhibitor  | 13 (28.3)                                | 34 (12.6)  | <b>2.27 [1.19-4.30]</b> | <b>0.01</b>                |
| Cephalosporin   | 9 (19.6)                                 | 18 (6.7)   | <b>2.83 [1.37-5.87]</b> | <b>0.005</b>               |
| Ceftazidime   | 2 (4.3)                                  | 3 (1.1)  | 3.54 [0.86-14.6]        | 0.08                       |
| Cefotaxime / ceftriaxone                                    | 7 (15.2)                                 | 15 (5.6)   | <b>2.52 [1.13-5.64]</b> | <b>0.02</b>                |
| Cefepime  | 0 (0)                                    | 0 (0)  | -                       | -                          |
| Aminoglycosides   | 2 (4.3)                                  | 2 (0.7)  | 3.39 [0.82-14.00]       | 0.09                       |
| Quinolones  | 2 (4.3)                                  | 12 (4.5)   | 1.02 [0.25-4.23]        | 0.97                       |
| Carbapenems   | 1 (2.2)                                  | 0 (0)  | -                       | -                          |
| Anti-GPC  | 1 (2.2)                                  | 2 (0.7)  | 2.13 [0.29-15.48]       | 0.45                       |
| Other   | 11 (23.9)                                | 39 (14.5)  | 1.78 [0.90-3.5]         | 0.10                       |

IQR: interquartile range; ICU: Intensive care unit; Anti-GPC: antibiotic against Gram positive cocci (e.g vancomycin, linezolid, daptomycin).

Table S8. Primary outcome multivariate analysis for first hospitalization. Risk factors ( $p < 0.20$  in univariate analysis) of documented infection with bacteria with significant antibiotic resistance in onco-hematology (BSAROH)

|   | Documented<br>infection with<br>BSAROH<br>n=46 | Infection without<br>documentation<br>or other germ<br>n=269 | Adjusted Hazard<br>ratio [95%CI] | p            |
|---|--|--|----------------------------------|--------------|
| Male sex, n (%)                                       | 32 (69.6)                                      | 137 (50.9)   | 1.80 [0.94-3.41]                 | 0.08         |
| Age, years,<br>median (IQR)                           | 62 (53-70)                                     | 60 (50-67)   | <b>1.02 [1.00-1.05]</b>          | <b>0.05</b>  |
| Prior<br>hospitalization<br>within 3 months, n<br>(%) | 27 (58.7)                                      | 73 (27.1)  | <b>2.61 [1.43-4.76]</b>          | <b>0.02</b>  |
| Foreign travel<br>within 3 months, n<br>(%)           | 7 (15.2)                                       | 11 (4.1)   | <b>2.43 [1.05-5.64]</b>          | <b>0.038</b> |
| Previous<br>antibiotics                               |  |  |                                  |              |
| All antibiotics                                       | 26 (56.5)                                      | 84 (31.2)  | 1.64 [0.85-3.18]                 | 0.14         |
| BLI   | 13 (28.3)                                      | 34 (12.6)  | 1.40 [0.70-2.81]                 | 0.34         |
| Cephalosporin   | 9 (19.6)                                       | 18 (6.7)   | 1.74 [0.80-3.80]                 | 0.17         |
| Ceftazidime   | 2 (4.3)  | 3 (1.1)  | 2.12 [0.49-9.08]                 | 0.31         |
| Cefotaxime /<br>ceftriaxone                           | 7 (15.2)                                       | 15 (5.6)   | 1.54 [0.66-3.59]                 | 0.32         |
| Aminoglycosides                                       | 2 (4.3)  | 2 (0.7)  | 2.45 [0.55-10.7]                 | 0.24         |
| Other   | 11 (23.9)                                      | 39 (14.5)  | 1.28 [0.63-2.61]                 | 0.50         |

IQR: interquartile range; BLI:  $\beta$ -lactam + inhibitor.



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Le Doyen

ANNEE DE SOUTENANCE : 2020

NOM ET PRENOM DE L'AUTEUR : MOISDON (DELAPIERRE) Baptiste

TITRE DE LA THESE EN FRANCAIS : **Neutropénie fébrile de haut risque en onc-hématologie : facteurs liés à la résistance bactérienne aux antibiotiques à l'Institut d'Hématologie de Basse Normandie entre 2015 et 2019.**

RESUME DE LA THESE EN FRANÇAIS :

Chez les patients avec neutropénie de haut risque induite par une chimiothérapie, les facteurs de risque d'infections à germes résistants aux antibiotiques fréquemment utilisés en hématologie (BSAROH) sont mal connus dans les centres avec faible niveau de résistance aux antibiotiques et sans prophylaxie par fluoroquinolones. Nous avons inclus les patients hospitalisés à l'IHBN de Décembre 2015 à Juin 2019 pour une neutropénie > 7 jours et < 0.1G/L. Trois cent quinze patients ont été inclus, soit un total de 659 hospitalisations, la moitié d'entre eux (165/315, 53.2%) étaient atteints de leucémie aiguë myéloïde. Une documentation microbiologique a été obtenue dans 191 (31.2%) des 612 hospitalisations avec fièvre, dont 187 (14.2%) avec une BSAROH. Trois cent vingt-sept (53.4%) des épisodes fébriles étaient d'origine indéterminée. Après analyse multivariée et multiniveau, seuls l'âge (Hazard ratio (HR) pour 5 ans=1.02 [1.00-1.04], p=0.02) et l'antécédent de voyage dans les 3 derniers mois à l'étranger (HR=3.58 [1.59-8.04], p=0.002) sont des facteurs associés à la survenue d'une infection à BSAROH. L'exposition aux antibiotiques, les antécédents d'infection ou de colonisation à BSAROH, les hospitalisations et admission en réanimation au cours des trois derniers mois n'étaient pas significativement associés à la survenue d'une BSAROH. Dans les centres à faible niveau de résistance bactérienne, les facteurs de risque classique d'infections à BSAROH ne sont pas discriminants.

MOTS CLES: Neutropénie fébrile, Facteur de risque, Résistance aux antibiotiques

TITRE DE LA THESE EN ANGLAIS: **Risk factors of infections associated with antibiotic resistant microorganisms in patients with high risk neutropenia in a French hematology center.**

RESUME DE LA THESE EN ANGLAIS :

Risk factors of documented infection with bacteria with significant antibiotic resistance in onc-hematology (BSAROH) in high risk febrile neutropenia following chemotherapy are unclear in center with low antibiotic resistance level and no prophylaxis by fluoroquinolones. We included patients hospitalized for neutropenia > 7days and < 0.1G/L from December 2015 to June 2019 in a French hematology center. Three hundred and fifteen patients were included, for a total of 659 hospitalizations, half of them suffered from acute myeloid leukemia (165/315, 53.2%). A microbiological documentation was obtained in 191 (31.2%) of 612 hospitalizations with fever, including 187 (14.2%) with a BSAROH. Three hundred and twenty seven (53.4%) of febrile episode were fever of unknown origin. In multivariate hierarchic analysis, only age (Hazard ratio (HR) for 5 years=1.02 [1.00-1.04], p=0.02) and travel in foreign country within last 3 months (HR=3.58 [1.59-8.04], p=0.002) were associated with BSAROH. Antibiotic exposure, colonization with BSAROH, history of colonization with BSAROH, prior hospitalization and prior intensive care unit admission within 3 months were not significantly associated with a BSAROH onset. In center with low antibiotic resistance level, classical risk factors of BSAROH are not discriminant.

KEY WORDS: Febrile neutropenia, Risk factor, Antibiotic resistance