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# Differential risk of severe infection in febrile neutropenia among children with blood cancer or solid tumor

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SUMMARY

*Objective:* To describe and analyze the differences between infections in children with febrile neutropenia (FN) treated for solid tumor or blood cancer.
*Methods:* A prospective study included all episodes of FN in children from April 2007 to April 2016 in 2-pediatric cancer centers in France. Medical history, clinical and laboratory data available at admission and final microbiological data were collected. The proportion of FN, severe infection, categories of microorganisms and outcomes were compared between the two groups. The presumed gateway of the infection was *a posteriori* considered and evaluated.
*Results:* We analyzed 1197 FN episodes (mean age: 8 years). 66% of the FN episodes occurred in children with blood cancer. Severe infections were identified in 23.4% of episodes overall. The rate of severe infection (28.4% vs. 10.4%), types of microorganisms and the need for a management in intensive care unit (2.6% vs. 0.5%) was significantly different between children with blood cancer and solid tumor. Digestive or respiratory presumed gateway of the infections was less frequent for patients with solid tumor.
*Conclusion:* Given these important microbiological and clinical differences, it may be appropriate to consider differently the risk of severe infection in these two populations and therefore the management of FN.



## Introduction

Treatment protocols for childhood cancer have changed in last decades: intensified therapy, combined with improved supportive care, have both contributed to the current 5-year survival rate, which exceeds 70% for all cancers combined.[1,2] A first consequence of this improvement is the increase in the number and duration of episodes of febrile neutropenia (FN) and the increased risk of infectious complications.[3] Episodes of FN are thus among the most frequent complications and causes of hospitalization in children treated with chemotherapy.[4] At the same time, severe infections have been shown to be present in only 10–29% of FN cases,[5–8] with mortality rates due to infectious complications of FN episodes reduced to less than 0.25% to 0.75% in high-income countries.[6,9]

For those reasons, a change has been proposed since 2012 by an international panel of experts in FN management and updated in 2017.[10,11] The idea was to propose a management based on the risk of severe infection, in order to avoid a systematic intensive management for all children with FN, which was a risk factor for in-hospital complications, emergence of antimicrobial resistances,[12,13] impairment of the quality of family life,[14,15] and increased medical costs.[16,17] The clinical decision rules proposed in these guidelines to stratify the risk of severe infection, have however limited reproducibility in external sets of patients.[18,19] These rules concern all patients regardless of the type of cancer. We have shown previously that the type of cancer (i.e., blood cancer or solid tumor) was a variable significantly associated with the risk of severe infection:[20] the infectious complications were less frequent in children with solid tumors than in children with blood cancers, probably because of differences in protocols of chemotherapy. Consequently, one assumption to improve these rules could be to differentiate FN management based on the type of cancer.

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The aim of this study was to determine whether differences in infections between patients treated for solid tumor and blood cancer appear to be sufficiently important to consider the type cancer as a discriminating variable that should be initially considered for the management of FN in children.

## Methods

### *Study design and patients*

Since April 2007 to April 2016, all consecutive episodes of FN were prospectively collected in two centers in Lille, France (Pediatric hematology, Lille University Hospital and pediatric oncology, Oscar Lambret Cancer Centre, Lille). These two centers maintained the same recruitment over the study period and were the only reference centers for treatment of children with cancer in the Northern France area, where one million children were living in 2012.[21] Throughout the duration of the study these two centers followed the national recommendations for the treatment of cancer from the French society against cancer in children and teenagers (SFCE). Each patient aged less than 18 years who had a chemotherapy-induced FN episode was included. Patients were not included if they were being treated for an infection, received palliative care, or had undergone a stem cell transplantation.

### *Data collected*

Data were collected using a standardized case report form completed at the time of each FN episode. Age, sex, type of cancer, high risk of deep and prolonged chemotherapy-induced aplasia, relapse of oncologic disease and all data needed for the diagnosis of infections, including the diagnosis of severe infections (see definitions) were collected.

### *Definitions*

FN was defined by neutrophil count $<500/mm^3$ or a neutrophil count $<1000/mm^3$ that tends to drop under $500/mm^3$ in the following 48 h,[5] and an adjusted axillary temperature $\geq$38.5 °C once or $\geq$38.0 °C twice within 12 h. High risk of deep and prolonged chemotherapy-induced aplasia was defined by a neutropenia lasting for more than seven days as previously defined.[22,23] Severe infection was defined by the occurrence of either (i) a bacteremia, or (ii) bacterial infection, or (iii) focal infection at high risk of dissemination, or (iv) an invasive fungal infection.[20] Bacteremia was defined by a positive blood culture, except in cases of infection with coagulase-negative staphylococci or other contaminant microorganisms, for which two positive blood cultures were required. Bacterial infection was defined by positive bacterial culture from a normally sterile site. Focal infection at high risk of dissemination was defined as any local infection with or without microbiological documentation into a normally sterile site, with significant risk of loco-regional or systemic spread (e.g. pelvic cellulitis, rapidly progressive cellulitis, appendicitis, pneumonia). Invasive fungal infection is referred to a proven, probable, or possible fungal infection as defined by the IFICG (Invasive Fungal Infections Cooperative Group) of the EORTC (European Organization for Research and Treatment of Cancer).[24]

The management of FN episodes and the treatment of documented infections were homogeneous between the two centers. It followed the guidelines established in the units by the same team of pediatric infectious disease physicians in the Lille University Hospital, adapted in 2013 on the basis of the 2012 pediatric guidelines published for the management of fever and neutropenia.[10] Severe infections were divided into four microbiological categories: gram-negative bacilli infection, gram-positive cocci infection, fungal infection, and any other type of infection. The presumed gateway of the infection was determined *a posteriori* with the type of clinical infection and microbiological documentation by two pediatric infectious diseases experts and classified into six categories: oral, digestive, cutaneous-catheter, respiratory, urinary or other gateway.

### *Statistical analyses*

The population of included patients was first described. Then, qualitative variables were compared using a chi-square test. Continuous variables were compared using a Student's *t*-test. A *p* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS package version 22 software.

This prospective, observational research was validated by the French ethic committee for observational studies: "comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé" and "commission nationale de l'informatique et des libertés", reference: DEC20081118-0010.

## Results

From April 2007 to April 2016, 1197 episodes of FN were collected (mean age 8.0 years (±5.0), male/female ratio: 1.25). The inclusion rate by year according to the type of tumor and the presence or not of severe infection was presented in Fig. 1. The rate of severe infection according to the tumor is presented Table 1. The chemotherapy used was at high risk of deep and prolonged neutropenia for 808 episodes of FN (68%), 69% in children treated for blood cancer and 64% in children treated for solid tumor (Table 2). The FN episode occurred in a context of disease relapse in 148 cases (12%). A severe infection was diagnosed in 267 FN episodes (22%, 95%CI: 20–25) statistically more frequently in patients with blood cancer ($p < 10^{-5}$) (Table 2). Twenty-three cases (2%, 95%CI: 1–3) were transferred in the intensive care unit (ICU) with a rate significantly higher for FN episodes in patients with blood cancer. The mortality rate was of 0.4% (95%CI: 0.2–1.0), with five FN-related death in patients treated for blood cancer and none in patients treated for solid tumor ($p = 0.13$).

A microbiological documentation was found in 207 FN (17% of FN episodes; 78% of FN with severe infection). The microorganisms identified are presented by category in Table 3. Globally, categories of microorganisms identified were statistically different between FN occurring in patients with solid tumor or blood cancer ($p < 10^{-5}$). The presumed gateway of the infection was statistically different between FN occurring in patients with solid tumor or blood cancer (Table 2). Severe infections without microbiological documentation ($n = 60$, including 52 with blood cancer) were: pneumonia ($n = 27$), cellulitis ($n = 11$), probable aspergillosis ($n = 11$), appendicitis ($n = 7$), septic shock ($n = 3$), acute colitis ($n = 1$).

## Discussion

Statistically significant differences in the rates and severity of infections were found between children with FN treated for solid tumor or blood cancer. Patients treated for blood cancer presented severe infections more frequently (28%) than those treated for solid tumor (10%) and had a higher ICU admission rate (2.6% vs. 0.2%). The presumed gateway of their infection was more often through the oral or lower respiratory tract. The presumed gateway of infection was more often cutaneous or catheter related for patients with a solid tumor. The distribution of types of microorganisms identified was globally statistically different between patients with blood cancer and solid tumor.

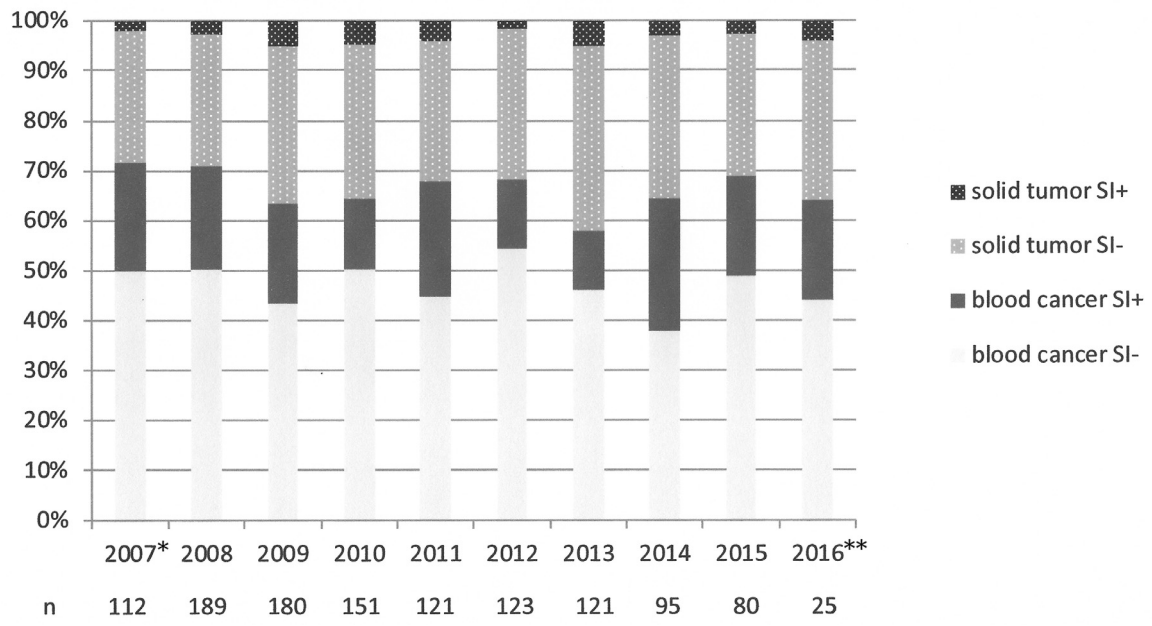


**Fig. 1.** Rate of inclusion by year between 2007 and 2016 with or without severe infection for children treated for blood cancer or solid tumor.
*n*, total of inclusion of febrile neutropenia cases each year; SI–, episodes of febrile neutropenia without severe infection; SI+, episodes of febrile neutropenia with severe infection.
Inclusion from April to December 2007*.
Inclusion from January to April 2016**.

**Table 1**
Rate of episodes of febrile neutropenia with severe infection in children according to the type of cancer (2007–2016).

| Type of cancer | Total ($n=1197$) | FN with severe infection ($n=267$) | | |
|---|---|---|---|---|
| | | *n* | % | 95%CI |
| ALL | 481 | 129 | 27 | 23–31 |
| AML | 163 | 62 | 38 | 31–46 |
| Lymphoma | 141 | 32 | 23 | 17–30 |
| Histiocytosis | 8 | 2 | 25 | 7–59 |
| Bone tumor | 169 | 18 | 11 | 7–16 |
| Neuroblastoma | 82 | 11 | 13 | 2–22 |
| Brain tumor | 46 | 3 | 6 | 2–17 |
| Rhabdomyosarcoma | 38 | 2 | 5 | 1–17 |
| Kidney tumor | 21 | 4 | 19 | 8–40 |
| Rhabdoid tumor | 19 | 4 | 21 | 9–43 |
| Others | 29 | 0 | 0 | 0–11 |

FN: febrile neutropenia; CI: confidence interval; ALL: Acute Lymploïd Leukemia; AML: Acute Myeloïd Leukemia.
Others: synovialosarcoma ($n=9$), melanotic neuroectodermic tumor ($n=4$), retinoblastoma ($n=3$); pleuroblastoma ($n=3$), carcinoma ($n=3$), hepatoblastoma ($n=2$), germinal tumor ($n=2$), desmoplastic tumor ($n=1$), myxofibrosarcoma ($n=1$), anaplastic tumor ($n=1$).

There were sparse data of these differences. Indeed, our study was one of the first to analyze the differences in terms of infections between patient treated for solid tumor and blood cancer with chemotherapy-induced FN. In 2002, some authors found no difference in the amount of infection according to the type of cancer but bacteremia and pneumonia were more frequent in patients treated for blood cancer, particularly for leukemia.[25] Contradictory results were described in adult patients with cancer. In 2013, a study found that patients treated for blood cancer had more gram-negative bacilli bacteremia than patients with solid tumor.[26] But another study found more infections in patients with solid tumor.[27] However, the cancer types and treatments were too different between adults and children to compare infectious events between the two populations.[28]

There may be multiple reasons for these differences. First, the type of cancer is probably not directly responsible for these differences, but more likely the chemotherapy drugs used.[29] At that time, some drugs were used quasi-exclusively for solid tumors and other drugs for blood cancers, with different targets. Chemotherapy drugs are usually more myeloablative with a more prolonged FN for blood cancer than for solid tumors. Second, when a similar treatment was used for both types of cancer, the doses and rates of administration were very different. The impact on the gut and thus on the risk of microbial translocation was therefore totally different. Third, the type of central venous access may have played a role. Catheter risks may vary depending on the type of central venous catheter or how it is managed. It was impossible to analyze this data in this study, because the population was nearly homogeneous: the patients treated for solid tumors had almost always an implantable catheter chamber, whereas patients treated for a blood cancer had almost always a tunneled central venous catheter (Broviac®).

Although the data were from only two centers, our series ($n=1197$ episodes of FN) is one of the largest prospective cohorts of FN in children. Even if the distribution of microorganisms was statistically different between the two groups, the number of patients was not enough to show a difference by types of microorganisms involved, which is suspected. Patients with blood cancer and solid tumor were treated in separate centers, but these centers are not very far apart and work in close collaboration with similar strategies for infectious diseases management decided by the same pediatric infectious disease unit. The recruitment within these two centers was carried out in the same region of Northern France. The prospective collection has ensured a high quality and homogeneity of these data. In our study, the choice was made, like others[6,30,31] to predict severe infection rather than bacteremia only, in order to consider all infectious events at risk of complication. This also seemed more applicable in clinical practice. One patient may have been included several times at each FN episode. This was not inconvenient since we showed in a previous work, using a gen-

**Table 2**
Infectious differences between children with blood cancer and solid tumor.

| Variables | Blood cancer ($n=793$) | Solid tumor ($n=404$) | $p$ |
|---|---|---|---|
| Mean age, in years (+/−SD) | 8.0 (+/−4.6) | 8.2 (+/−5.4) | 0.86 |
| Male/Female ratio | 1.37 | 1.05 | 0.03 |
| High risk of deep and prolonged neutropenia, *n* (%; 95%CI) | 549 | 259 | 0.07 |
| Bacteremia (%) | 126 | 24 | $<10^{-5}$ |
| Severe infections, *n* (%; 95%CI) | 225 | 42 | $<10^{-5}$ |
| Infection related ICU admission | 21 | 2 | 0.01 |
| Infection related death | 5 | 0 | 0.13 |
| Types of microorganisms[a] | | | $<10^{-5}$ |
| *GNB* (%) | *97(43)* | *15(36)* | *0.37* |
| *GPC* (%) | *57(24)* | *15(36)* | *0.16* |
| *Fungi* (%) | *21(10)* | *1(2)* | *0.12* |
| *Others* (%) | *50(23)* | *11(26)* | |
| Presumed gateway of the infection[a] | | | $<10^{-5}$ |
| *Oral* (%) | *40(18)* | *1(2)* | *0.01* |
| *Digestive* (%) | *94(42)* | *16(38]* | *0.77* |
| *Cutaneous or catheter* (%) | *17(7)* | *15(36)* | $<10^{-5}$ |
| *Lower respiratory tract* (%) | *46(20)* | *3(7)* | *0.04* |
| *Urinary tract* (%) | *24(11)* | *6(15)* | *0.49* |
| *Others* (%) | *4(2)* | *1(2)* | |

SD, Standard deviation; GNB, gram negative bacilli; GPC, gram positive cocci; ICU, Intensive care Unit.
[a] chi-2 or fisher exact test calculated with dichotomous variables. For example: GNB versus all others types of microrganisms.

**Table 3**
Microorganisms identified in severe infections of children with chemotherapy-induced febrile neutropenia and site of identification (2007–2016).

| *Microorganisms* | Blood cancer $n$ = 173 | Solid tumor $n$ = 34 | *Blood* | *Urine* | *BAL* | *Stool* | *Others* |
|---|---|---|---|---|---|---|---|
| **GPC (*n* = 72)** | **57** | **15** | | | | | |
| *Staphylococcus aureus* | 6 | 2 | *7* | | | | *1 (catheter)* |
| *CoNS* | 9 | 13 | *22* | | | | |
| *Streptococcus*[c] | 36 | | *35* | | *1* | | |
| *Enterococcus* | 4 | | | *3* | | | *1 (biopsy)* |
| *Rothia musilaginosa* | 2 | | *2* | | | | |
| **GNB (*n* = 110)** | **95** | **15** | | | | | |
| *Escherichia coli* | 54 | 12 | *49*[a] | *19* | | | *1 (biopsy)* |
| *Pseudomonas* | 21 | 2 | *17*[b] | *5* | *1* | | |
| *Klebsiella*[d] | 11 | | *5* | *6* | | | |
| *Enterobacter* | 3 | 1 | *3* | | | | *1 (peritoneal)* |
| *Campylobacter* | 2 | | | | | *2* | |
| *Others GNB* | 4 | | *4* | | | | |
| **Anaerobes (*n* = 2)** | **2** | | | | | | |
| *Captocytophaga sputi*[e] | 2 | | *2* | | | | |
| **Fungi (*n* = 11)** | **10** | **1** | | | | | |
| *Candida* | 5 | 1 | *4* | | *1* | | |
| *Mucor* | 1 | | | | *1* | | |
| *Fusarium* | 1 | | | | | | *1 (biopsy)* |
| *Aspergillus* | 3 | | | | | | *3 (antigens)* |
| **Others (*n* = 12)** | **9** | **3** | | | | | |
| *Neisseria* | 4 | | *4* | | | | |
| *Lactococcus lactis* | 1 | | *1* | | | | |
| *Clostridium* | 1 | 3 | | | | *4* | |
| *Mycobacterium* tuberculosis | 1 | | | | *1* | | |
| *Pneumocystis* | 2 | | | | *2* | | |

BAL, Broncho alveolar lavage; GNB, gram negative bacilli; GPC, gram positive cocci; Antigens, galactomannan; CoNS, coagulase negative Staphylococcus; other GNB, *Moraxella, Aeromonas hydophila*.
[a] 3 patients with blood culture and urinary culture positive, and 3 patients with blood culture positive to another microorganism: 1 *Streptococcus,* 1 *Klebsiella,* 1 *Entocococcus*.
[b] 1 with also blood culture positive to *Acinetobacter*.
[c] Of which 1 *Streptococcus pneumoniae;*.
[d] Of which 5 *Klebsialla oxytoca*.
[e] *Anaerobes and Gram-negative bacilli*.

eralized mixed model, that the multiple inclusion of a single patient had no impact.[20] It also seemed more logical to consider all episodes from a clinical practice perspective, where the infectious risk is assessed at each FN episode and not only at the first.

The proportion of each type of cancer and identified microorganisms in patients with severe infections were roughly similar to other studies on FN in children.[30] Some centers had a higher proportion of gram-positive cocci[31] but with different proportion in the type of tumor (less lymphoid leukemia). The predominance of gram-positive cocci in other studies may be due to single CoNS positive blood cultures, considered as contaminants in this research and in our clinical practice.[29] In 2013, Miedema et al. found also a majority of gram-positive cocci in three centers. It could be explained by the use of prophylactic anti-gram-negative antibi-

otics, particularly in one center, with the consequence of a higher resistances rate.[32]

## Conclusion

The physicians who manage those children with cancer are aware from experience that the risk of severe infection seems different. However, therapeutic protocols are usually not differentiated. Surprisingly, only a few clinical decision makers have identified the type of cancer as a differential risk of severe infection.[8,20,33,34] But the differences in terms of infections between patients with blood cancer and solid tumor have never been as widely analyzed as here. The strong differences shown here confirm the importance of the type of cancer as a useful variable for a differential management of children with FN. Our results would justify separating completely the patients treated for blood cancer and those treated for a solid tumor to propose two decision rules predicting severe infection in children with FN.

Currently, the management of FN is heterogeneous from one center to another, even within the same country.[35] Since the publication of the international guidelines for FN in children in 2012,[10] updated in 2017,[11] a work to propose standardized definitions and a relevant consensual core outcome has been launched.[36] However, the type of cancer is a variable considered in the risk assessment for severe infection in none of the six decision rules proposed in these guidelines. One possibility to take this variable into consideration could be to use a decision tree with a first division that could be the type of cancer. Given that the infection-related rate of mortality in children with solid tumor was zero in our large series and that the severity of infection during FN is rare (10%) in this population, an outpatient management of these patients could be probably rapidly proposed for low-risk patients. Other criteria are also needed to propose an alternative management of patients with blood cancer at low-risk of severe infection.

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## Conflict of interests

MD, RD, ML, FM, HD have no conflict of interest; AM has had appointments for lecture and consultancy/advice (GSK vaccines, Pfizer), and invitations to ESPID meetings (GSK vaccines, Pfizer); FD has been invited for a lecture without fees at the national pediatric primary-care meeting (AFPA) 2017 by GSK vaccines. He has received fees from Biocodex for two lectures in 2017 pediatric meetings.

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