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

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1 **Abstract**

2 **Objective:** To describe and analyze the differences between infections in children with febrile
3 neutropenia (FN) treated for solid tumor or blood cancer.

4 **Methods:** A prospective study included all episodes of FN in children from April 2007 to
5 April 2016 in 2-pediatric cancer centers in France. Medical history, clinical and laboratory
6 data available at admission and final microbiological data were collected. The proportion of
7 FN, severe infection, categories of microorganisms and outcomes were compared between the
8 two groups. The presumed gateway of the infection was *a posteriori* considered and
9 evaluated.

10 **Results:** We analysed 1197 FN episodes (mean age: 8 years). 66% of the FN episodes
11 occurred in children with blood cancer. Severe infections were identified in 23.4% of
12 episodes overall. The rate of severe infection (28.4% vs. 10.4%), types of microorganisms and
13 the need for a management in intensive care unit (2.6% vs. 0.5%) was significantly different
14 between children with blood cancer and solid tumor. Digestive or respiratory presumed
15 gateway of the infections was less frequent for patients with solid tumor.

16 **Conclusion:** Given these important microbiological and clinical differences, it may be
17 appropriate to consider differently the risk of severe infection in these two populations and
18 therefore the management of FN.

19

20 **Keys words:** *children; febrile neutropenia; cancer; risk of infection; prediction*

21

22 1. Introduction

23 Treatment protocols for childhood cancer have changed in last decades: intensified therapy,
24 combined with improved supportive care, have both contributed to the current 5-year survival
25 rate, which exceeds 70% for all cancers combined [1,2]. A first consequence of this
26 improvement is the increase in the number and duration of episodes of febrile neutropenia
27 (FN) and the increased risk of infectious complications [3]. Episodes of FN are thus among
28 the most frequent complications and causes of hospitalization in children treated with
29 chemotherapy [4]. At the same time, severe infections have been shown to be present in only
30 10-29% of FN cases [5-8], with mortality rates due to infectious complications of FN
31 episodes reduced to less than 0.25 to 0.75% in high-income countries [6,9].

32 For those reasons, a change has been proposed since 2012 by an international panel of
33 experts in FN management and updated in 2017 [10,11]. The idea was to propose a
34 management based on the risk of severe infection, in order to avoid a systematic intensive
35 management for all children with FN, which was a risk factor for in-hospital complications,
36 emergence of antimicrobial resistances [12,13], impairment of the quality of family life
37 [14,15], and increased medical costs [16,17]. The clinical decision rules proposed in these
38 guidelines to stratify the risk of severe infection, have however limited reproducibility in
39 external sets of patients [18,19]. These rules concern all patients regardless of the type of
40 cancer. We have shown previously that the type of cancer (i.e., blood cancer or solid tumor)
41 was a variable significantly associated with the risk of severe infection [20]: the infectious
42 complications were less frequent in children with solid tumors than in children with blood
43 cancers, probably because of differences in protocols of chemotherapy. Consequently, one
44 assumption to improve these rules could be to differentiate FN management based on the type
45 of cancer.

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

50

51 **2. Methods**

52 *2.1. Study design and patients*

53 Since April 2007 to April 2016, all consecutive episodes of FN were prospectively collected
54 in two centers in Lille, France (Pediatric hematology, Lille University Hospital and pediatric
55 oncology, Oscar Lambret Cancer Centre, Lille). These two centers maintained the same
56 recruitment over the study period and were the only reference centers for treatment of
57 children with cancer in the Northern France area, where one million children were living in
58 2012 [21]. Throughout the duration of the study these two centers followed the national
59 recommendations for the treatment of cancer from the French society against cancer in
60 children and teenagers (SFCE). Each patient aged less than 18 years who had a
61 chemotherapy-induced FN episode was included. Patients were not included if they were
62 being treated for an infection, received palliative care, or had undergone a stem cell
63 transplantation.

64 *2.2. Data collected*

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

69 *2.3. Definitions*

70 FN was defined by neutrophil count $<500/\text{mm}^3$ or a neutrophil count $<1000/\text{mm}^3$ that tends to
71 drop under $500/\text{mm}^3$ in the following 48 hours [5], and an adjusted axillary temperature
72 $\geq 38.5^\circ\text{C}$ once or $\geq 38.0^\circ\text{C}$ twice within 12 hours. High risk of deep and prolonged
73 chemotherapy-induced aplasia was defined by a neutropenia lasting for more than seven days
74 as previously defined [22,23]. Severe infection was defined by the occurrence of either (i) a
75 bacteremia, or (ii) bacterial infection, or (iii) focal infection at high risk of dissemination, or
76 (iv) an invasive fungal infection [20]. Bacteremia was defined by a positive blood culture,
77 except in cases of infection with coagulase-negative staphylococci or other contaminant
78 microorganisms, for which two positive blood cultures were required. Bacterial infection was
79 defined by positive bacterial culture from a normally sterile site. Focal infection at high risk
80 of dissemination was defined as any local infection with or without microbiological
81 documentation into a normally sterile site, with significant risk of loco-regional or systemic
82 spread (e.g. pelvic cellulitis, rapidly progressive cellulitis, appendicitis, pneumonia). Invasive
83 fungal infection is referred to a proven, probable, or possible fungal infection as defined by
84 the IFICG (Invasive Fungal Infections Cooperative Group) of the EORTC (European
85 Organization for Research and Treatment of Cancer) [24].

86 The management of FN episodes and the treatment of documented infections were
87 homogeneous between the two centers. It followed the guidelines established in the units by
88 the same team of pediatric infectious disease physicians in the Lille University Hospital,
89 adapted in 2013 on the basis of the 2012 pediatric guidelines published for the management of
90 fever and neutropenia [10]. Severe infections were divided into four microbiological
91 categories: gram-negative bacilli infection, gram-positive cocci infection, fungal infection,
92 and any other type of infection. The presumed gateway of the infection was determined *a*
93 *posteriori* with the type of clinical infection and microbiological documentation by two

94 pediatric infectious diseases experts and classified into six categories: oral, digestive,
95 cutaneous-catheter, respiratory, urinary or other gateway.

96 *2.4. Statistical analyses*

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

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

105

106 **3. Results**

107 From April 2007 to April 2016, 1197 episodes of FN were collected (mean age 8.0 years
108 (± 5.0), male/female ratio: 1.25). The inclusion rate by year according to the type of tumor and
109 the presence or not of severe infection was presented in Figure 1. The rate of severe infection
110 according to the tumor is presented Table I. The chemotherapy used was at high risk of deep
111 and prolonged neutropenia for 808 episodes of FN (68%), 69% in children treated for blood
112 cancer and 64% in children treated for solid tumor (Table II). The FN episode occurred in a
113 context of disease relapse in 148 cases (12%). A severe infection was diagnosed in 267 FN
114 episodes (22%, 95%CI: 20-25) statistically more frequently in patients with blood cancer (p
115 $< 10^{-5}$) (Table II). Twenty-three cases (2%, 95%CI: 1-3) were transferred in the intensive care
116 unit (ICU) with a rate significantly higher for FN episodes in patients with blood cancer. The
117 mortality rate was of 0.4% (95%CI: 0.2-1.0), with five FN-related death in patients treated for
118 blood cancer and none in patients treated for solid tumor ($p=0.13$).

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

127

128 **4. Discussion**

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

137 There were sparse data of these differences. Indeed, our study was one of the first to
138 analyze the differences in terms of infections between patient treated for solid tumor and
139 blood cancer with chemotherapy-induced FN. In 2002, some authors found no difference in
140 the amount of infection according to the type of cancer but bacteremia and pneumonia were
141 more frequent in patients treated for blood cancer, particularly for leukemia [25].

142 Contradictory results were described in adult patients with cancer. In 2013, a study found that
143 patients treated for blood cancer had more gram-negative bacilli bacteremia than patients with

144 solid tumor [26]. But another study found more infections in patients with solid tumor [27].
145 However the cancer types and treatments were too different between adults and children to
146 compare infectious events between the two populations [28].

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

160 Although the data were from only two centers, our series (n=1197 episodes of FN) is
161 one of the largest prospective cohorts of FN in children. Even if the distribution of
162 microorganisms was statistically different between the two groups, the number of patients
163 was not enough to show a difference by types of microorganisms involved, which is
164 suspected. Patients with blood cancer and solid tumor were treated in separate centers, but
165 these centers are not very far apart and work in close collaboration with similar strategies for
166 infectious diseases management decided by the same pediatric infectious disease unit. The
167 recruitment within these two centers was carried out in the same region of Northern France.
168 The prospective collection has ensured a high quality and homogeneity of these data. In our

169 study, the choice was made, like others [6,30,31] to predict severe infection rather than
170 bacteremia only, in order to consider all infectious events at risk of complication. This also
171 seemed more applicable in clinical practice. One patient may have been included several
172 times at each FN episode. This was not inconvenient since we showed in a previous work,
173 using a generalized mixed model, that the multiple inclusion of a single patient had no impact
174 [20]. It also seemed more logical to consider all episodes from a clinical practice perspective,
175 where the infectious risk is assessed at each FN episode and not only at the first.

176 The proportion of each type of cancer and identified microorganisms in patients with
177 severe infections were roughly similar to other studies on FN in children [30]. Some centers
178 had a higher proportion of gram-positive cocci [31] but with different proportion in the type
179 of tumor (less lymphoid leukemia). The predominance of gram-positive cocci in other studies
180 may be due to single CoNS positive blood cultures, considered as contaminants in this
181 research and in our clinical practice [29]. In 2013, Miedema et al. found also a majority of
182 gram-positive cocci in three centers. It could be explained by the use of prophylactic anti-
183 gram-negative antibiotics, particularly in one center, with the consequence of a higher
184 resistances rate [32].

185

186 **5. Conclusion**

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

194 would justify separating completely the patients treated for blood cancer and those treated for
195 a solid tumor to propose two decision rules predicting severe infection in children with FN.

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

208

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211 **Conflict of interests**

212 MD, RD, ML, FM, HD have no conflict of interest; AM has had appointments for lecture and
213 consultancy/advice (GSK vaccines, Pfizer), and invitations to ESPID meetings (GSK
214 vaccines, Pfizer); FD has been invited for a lecture without fees at the national pediatric
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365

366 **Fig 1.** Rate of inclusion by year between 2007 and 2016 with or without severe infection for
367 children treated for blood cancer or solid tumor

368 n, total of inclusion of febrile neutropenia cases each year; SI-, episodes of febrile neutropenia without severe
369 infection; SI+, episodes of febrile neutropenia with severe infection

370 Inclusion from April to December 2007*

371 Inclusion from January to April 2016**

372

373

374 **Table 1.** Rate of episodes of febrile neutropenia with severe infection in children according to
 375 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

376 FN: febrile neutropenia; CI: confidence interval; ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid
 377 Leukemia

378 Others: synovialosarcoma (n=9), melanotic neuroectodermic tumor (n=4), retinoblastoma (n=3); pleuroblastoma
 379 (n=3), carcinoma (n=3), hepatoblastoma (n=2), germinal tumor (n=2), desmoplastic tumor (n=1),
 380 myxofibrosarcoma (n=1), anaplastic tumor (n=1)

381

382

383 **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
<i>GNB (%)</i>	97(43)	15(36)	0.37
<i>GPC (%)</i>	57(24)	15(36)	0.16
<i>Fungi (%)</i>	21(10)	1(2)	0.12
<i>Others (%)</i>	50(23)	11(26)	
Presumed gateway of the infection ^a			< 10 ⁻⁵
<i>Oral (%)</i>	40(18)	1(2)	0.01
<i>Digestive (%)</i>	94(42)	16(38]	0.77
<i>Cutaneous or catheter (%)</i>	17(7)	15(36)	< 10 ⁻⁵
<i>Lower Respiratory tract (%)</i>	46(20)	3(7)	0.04
<i>Urinary tract (%)</i>	24(11)	6(15)	0.49
<i>Others (%)</i>	4(2)	1(2)	

384 FN, febrile neutropenia; SD, Standard deviation; GNB, gram negative bacilli; GPC, gram positive cocci; ICU,
385 Intensive care Unit
386 ^achi-2 or fisher exact test calculated with dichotomous variables. For example: GNB versus all others types of
387 microorganisms

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

<i>Microorganisms</i>	Blood	Cancer	Solid Tumor	<i>Blood</i>	<i>Urine</i>	<i>BAL</i>	<i>Stool</i>	<i>Others</i>
	n=173		n=34					
GPC (n=72)	57		15					
<i>Staphylococcus aureus</i>	6		2	7				1 (catheter)
CoNS	9		13	22				
<i>Streptococcus</i> †	36			35		1		
<i>Enterococcus</i>	4				3			1 (biopsy)
<i>Rothia musilaginosa</i>	2			2				
GNB (n=110)	95		15					
<i>Escherichia coli</i>	54		12	49*	19			1 (biopsy)
<i>Pseudomonas</i>	21		2	17**	5	1		
<i>Klebsiella</i> ‡	11			5	6			
<i>Enterobacter</i>	3		1	3				1 (peritoneal)
<i>Campylobacter</i>	2						2	
Others GNB	4			4				
Anaerobes (n=2)	2							
<i>Captocytophaga sputi</i> ‡‡	2			2				
Fungi (n=11)	10		1					
<i>Candida</i>	5		1	4		1		
<i>Mucor</i>	1					1		
<i>Fusarium</i>	1							1 (biopsy)
<i>Aspergillus</i>	3							3 (antigens)
Others (n=12)	9		3					
<i>Neisseria</i>	4			4				
<i>Lactococcus lactis</i>	1			1				
<i>Clostridium</i>	1		3				4	
<i>Mycobacterium tuberculosis</i>	1					1		
<i>Pneumocystis</i>	2					2		

390 BAL, Broncho alveolar lavage; FN, febrile neutropenia; GNB, gram negative bacilli; GPC, gram positive cocci;
 391 Ag, galactomannan; CoNS, coagulase negative Staphylococcus; other GNB, *Moraxella*, *Aeromonas hydrophila*
 392 * 3 patients with blood culture and urinary culture positive, and 3 patients with blood culture positive to another
 393 microorganism: 1 *Streptococcus*, 1 *Klebsiella*, 1 *Enterococcus*.
 394 ** 1 with also blood culture positive to *Acinetobacter*; † of which 1 *Streptococcus pneumoniae*;
 395 ‡ of which 5 *Klebsiella oxytoca*; ‡‡ anaerobes and Gram-negative bacilli

