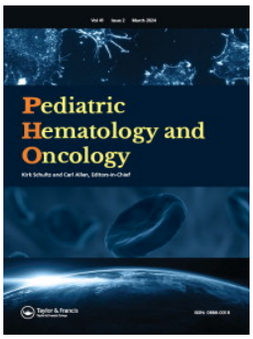

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BRIEF REPORT

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Consensus survey on the management of children with chemotherapy-induced febrile neutropenia and at low risk of severe infection

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ABSTRACT

Our aim was to identify national consensus criteria for the management of children with chemotherapy-induced febrile neutropenia (FN), for evidence-based step-down treatment approaches for patients classified at low risk of severe infection. In 2018, a five-section, 38-item survey was e-mailed to all pediatric hematology and oncology units in France ($n = 30$). The five sections contained statements on possible consensus criteria for the (i) definition of FN, (ii) initial management of children with FN, (iii) conditions required for initiating step-down therapy in low-risk patients, (iv) management strategy for low-risk patients, and (v) antibiotic treatment on discharge. Consensus was defined by respondents' combined answers (somewhat agree and strongly agree) at 75% or more. Sixty-five physicians (participation rate: 58%), all specialists in pediatric onco-hematology, from 18 centers completed the questionnaire. A consensus was reached on 22 of the 38 statements, including the definition of FN, the criteria for step-down therapy in low-risk children, and the initial care of these patients. There was no consensus on the type and duration of antibiotic therapy on discharge. In conclusion, a consensus has been reached on the criteria for initiating evidence-based step-down treatment of children with FN and a low risk of severe infection but not for the step-down antimicrobial regimen.

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Cancer; children; consensus; febrile neutropenia; risk management

Introduction

Each year, childhood cancer affects almost 300,000 children worldwide and between 1700 and 1800 children under the age of 15 in France.[1,2] Episodes of febrile neutropenia (FN) are common complications in children receiving chemotherapy; the frequency of

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occurrence depends on the type of chemotherapy and the treatment phase.[3,4] In high-resource countries, the systematic provision of rapid intravenous antibiotic therapy to patients with FN has generally reduced the infection-related mortality rate to below 1%;[5] however, this rate can be as high as 4% seven days after a bloodstream infection.[6] However, only 10–29% of FN episodes are associated with a severe infection.[7] Hence, some healthcare centers offer a lower-intensity care regimen to patients considered to have a low risk of severe infection. This strategy is sometimes subjective (i.e. based on local criteria or personal preferences) and differs from one center to another.[8,9]

In 2017, the International Pediatric Fever and Neutropenia Guideline Panel recommended that a clinical decision rule (CDR) should be used to determine whether or not a patient is at low risk of severe infection.[10] However, none of the rules published in international guidelines are sufficiently reproducible or effective.[11] A new, high-performance CDR for identifying patients at low risk of severe infection has been built and validated in a nationwide, multicenter study.[12] An ongoing impact analysis trial is assessing the CDR's impact on patient care (quality of life, length of hospital stay, and costs.) (NCT04938206). The successful implementation of this study required the development of harmonized definitions and practices at all the investigating centers.

The objective of the present nationwide survey in France was to identify points of consensus in the definitions and management of FN, so that the above-mentioned step-down therapeutic approach could be implemented in a standardized way.

Methods

Between August and September 2018, a survey questionnaire was e-mailed to all French pediatric oncology and hematology units ($n = 30$) including those that agreed to participate in the forthcoming CDR impact study ($n = 21$) (NCT04938206).

The questionnaire was divided into five sections (see Supplementary Table S1): (i) the definition of FN, (ii) the initial management of a child with FN, (iii) the conditions required for step-down therapy in patients classified as low-risk, (iv) the management strategy for low-risk patients, and (v) antibiotic treatment on discharge. The survey questionnaire's items were based on the most commonly used definitions and on the criteria for step-down treatment mentioned in the literature.[13–16] The questionnaire was reviewed and validated by local specialists. The response to each item was based on a four-point Likert scale, corresponding to "strongly agree", "somewhat agree", "somewhat disagree", and "strongly disagree". A "no opinion" answer was available. The questionnaire also contained a free text box for comments.

The questionnaire was sent out as an Excel® file (Microsoft Corporation, Portland, OR) on August 8, 2018. Two reminders were sent out over the following three weeks to get a maximum of answers, and data collection closed on September 15, 2018. All answers were anonymous, and the respondents e-mailed the completed Excel® file to the survey's initiators. A descriptive analysis of the answers was performed using Microsoft Excel®. Responses were expressed as a percentage, rounded to the nearest integer. As with Delphi-type studies, a consensus was defined as 75% or more of "strongly agree" and "somewhat agree" answers.[17] In line with the French legislation on studies of routine clinical practice, the study was approved by a committee (at the

French National Society for Pediatric Cancer (Paris, France)) with specific competency for research not requiring authorization by an institutional review board.

Results

Sixty-five specialist physicians (58%) from 18 different centers (two pediatric units dedicated to solid tumors, two pediatric units dedicated to blood cancers, and 14 pediatric onco-hematology units) replied to the survey.

A consensus was reached on 22 of the 38 suggested items (58%). The level of consensus was most notable for the definition of FN: a temperature ≥ 38.5 °C recorded at least once (98% agreement) or ≥ 38 °C recorded twice at least 1 h apart (85% agreement), and a threshold absolute neutrophil count < 500/mm^3 (98% agreement). The experts also agreed that the initial patient management must be initially managed in hospital for at least 48 h (95% agreement). They agreed that the initial antibiotic treatment is chosen locally, according to the department's procedure (86% agreement), the antibiotic monotherapy is possible in patients with no criteria for clinical severity (89% agreement) and the department must monitor microbial resistance closely and inform the clinicians on a regular basis (97% agreement). The underlying conditions required for step-down therapy for low-risk patients, and the parameters of the step-down treatment strategy (Table 1).

Table 1. Necessary underlying conditions to provide step-down therapy for patients classified at low risk of severe infection and criteria for outpatient management.

Proposals	Consensus
Necessary underlying conditions	
Risk stratification should reduce the intensity and/or duration of antimicrobial therapy	98%
The patient must be classified as low risk by the clinical decision rule	89%
The patient must be at least one year old	89%
The patient must not have adverse socio-economic factors that might compromise understanding, adherence or access to care	89%
The patient must not have any other medical conditions requiring hospital care	83%
The patient must not be undergoing chemotherapy	69%
The patient's clinical status must be good	98%
The patient must not have a severe infection that requires intravenous drug therapy in hospital (e.g. aspergillosis, severe pneumonia, a positive blood culture, etc.)	98%
Criteria for outpatient management	
A low-risk patient can be discharged from hospital after 48-72 h if:	
- the patient shows signs of exiting aplasia (neutrophil count ≥ 100/mm^3)	92%
- the patient has been afebrile for at least 48 h	98%
- the patient remains feverish but the body temperature is falling	17%
- follow-up every 48 h is scheduled*	94%
- initial tests reveal the presence of a respiratory tract virus	74%
- initial tests indicate low levels of inflammatory markers	83%
The parameters for treatment on discharge are:	
- the prescription of an oral or intravenous antibiotic for all low-risk patients	83%
- treatment for 5 to 7 days	54%
- treatment until the patient has been afebrile for 48 h	42%
- an undefined, shortened treatment regimen, the duration of which is left to the clinician's discretion	63%
Hospital readmission for adjustment of the patient's treatment is necessary if:	
- the patient's clinical status deteriorates	100%
- the patient experiences an adverse event with oral antibiotic treatment	74%
- a post-discharge blood culture is positive	97%

*Home hospitalization, day hospital, outpatient consultation, or phone follow-up.

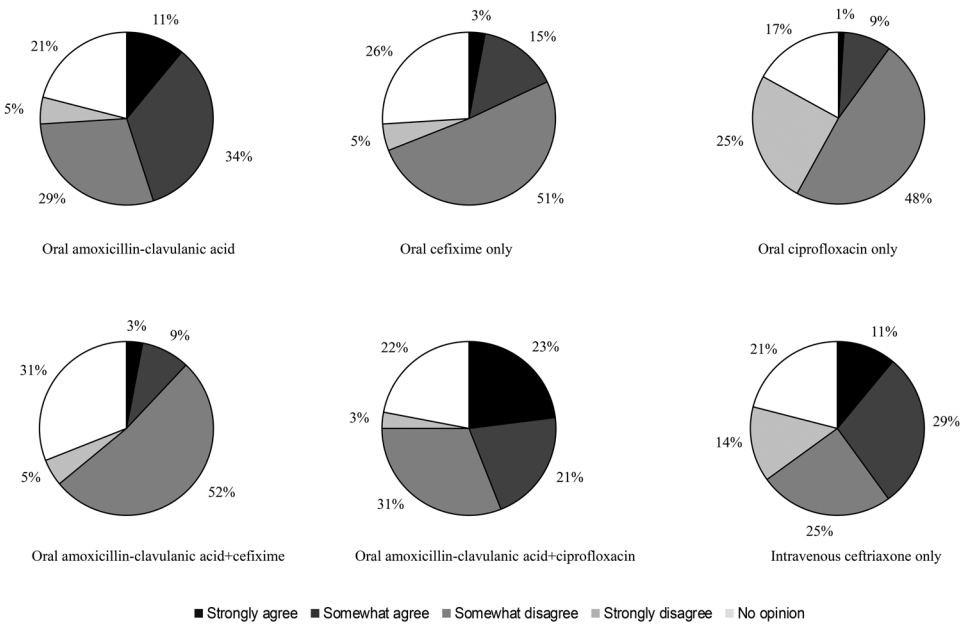

Figure 1. Outpatient antibiotic treatment in children with FN and a low risk of severe infection.

The implementation of algorithms for assessing the infectious risk (depending on the type of cancer, i.e. a hematologic cancer or a solid tumor, and the characteristics of the various subtypes),[3,10] was approved by 76% of the respondents overall and 100% of those working in a unit dedicated solely to hematologic cancer or to solid tumors.

With regard the parameters of outpatient treatments, our survey did not identify a consensus on a single type of post-discharge antibiotic regimen (Table 1); none of the regimens achieved the required consensus level of 75% (Figure 1). Depending on the antibiotic suggested for the post-discharge step-down regimen, between 17 and 31% of participants did not answer the item on step-down antibiotic treatment in patients at low risk of severe infection.

Discussion

The present survey highlighted a strong degree of consensus among study participants specialist in pediatric oncology and hematology in France with regard to the management of chemotherapy-induced FN in children. The definition of FN, which previously had varied from one center to another,[15] was now consensual and consistent with those found in the literature.[13,14] A consensus was also achieved on the criteria for initiating step-down therapy in children classified as being at a low risk of severe infection. However, the experts did not achieve a consensus on the type of antibiotic(s) to be used in the post-discharge step-down therapy.

We believe that the survey's results are important. Firstly, they illustrate the national-level convergence in practices, definitions and criteria for initiating a step-down therapeutic strategy. Secondly, the results showed that it was possible to implement

the CDR impact analysis trial in the investigating centers. The lack of a consensus on the antibiotic strategy is not a real limitation; it might reflect variations in bacterial profiles from one center to another and/or differences in knowledge of infectious diseases among oncologists. Despite the specialists' significant experience in the management of FN episodes in their units, a lower level of expertise in infectious diseases and antimicrobial treatments might explain the high proportion of "no opinion" answers for the corresponding survey questionnaire item (from 17 to 31%, depending on the antibiotic(s) suggested for the post-discharge step-down regimen).

The survey's results underlined differences not only between centers but also between members of the same medical team. These differences might have been due to a lack of standardization in the management of FN in children, which in turn resulted from the heterogeneity of the literature data on this subject. According to the international guidelines on the management of FN in children, a CDR should be used to determine the risk of infection in this context.[10] The lack of a validated CDR in high-resource countries until recently has led to variations in practice from one center to another.[9,15,18–20] The step-down therapy for patients considered to have a low risk of severe infection was therefore suggested and implemented in various ways and typically depended on the clinician's experience only.

The present study had a number of strengths, including its simple methodology and its focus on the concrete concerns of clinicians managing children with FN.[16] A reply was obtained from 86% of the centers having agreed to participate in the impact study. The participation rate was relatively high (58%), given the type of study (an e-mailed survey) and the short data collection period during the summer. This relatively high response rate probably reflects the level of interest in the evidence-based management of low-risk patients among specialists in pediatric onco-hematology. The use of a four-level Likert scale was a simple tool that allowed respondents to give their opinion on each item in a clear, flexible manner. The optional free text comments highlighted the issues with which onco-hematology specialists were not comfortable. In fact, comments were rare except with regard to the details of the step-down therapy. The "no opinion" answer was possible but rarely used, mainly for the choice of the antimicrobial step-down strategy. The lack of a "no antibiotic needed" proposition may have resulted in a "no opinion" answer. However, none of the participants suggested a no antibiotic strategy in the comments. We did not survey specialists in pediatric infectious diseases because, at the time of this survey, these physicians were not working on a routine basis in pediatric onco-hematology units. As mentioned above, the combination of a lack of expertise in infectious diseases, a low degree of microbiological documentation,[21] and a variety of local practices might account for the lack of consensus on a step-down therapy for low-risk patients. The lack of consensus probably also reflects the range of initial antimicrobial treatments administered to children admitted with FN.[15] A multicenter analysis of the microbiological data and the antimicrobial susceptibility of the identified pathogens might lead to a consensus if there are no major, center-specific differences in bacterial populations and antimicrobial resistance profiles.

This lack of consensus on a single type of post-discharge therapy also reflects the broad range of step-down approaches described in the literature.[12,22–27] One could therefore consider several types of step-down therapeutic approach, depending on the clinician's preference: discontinuing the antibiotic with inpatient monitoring; being discharged to home

with a course of daily intravenous antibiotics; or oral antibiotic monotherapy or combination therapy with scheduled outpatient follow-up. However, oral combination therapy is likely to be infrequent because monotherapy is recommended in the guidelines on the initial management of FN in children with no signs of sepsis.[10,28] Moreover, children classified as having a low risk of severe infection are, by definition, unlikely to experience an invasive infection by Enterobacteriaceae species such as *Pseudomonas aeruginosa*.

In conclusion, our survey enabled us to identify a number of prerequisites for harmonizing the definition of FN and the consensus criteria for initiating step-down therapeutic strategies in children with FN and a low risk of severe infection. The lack of consensus on the type of antibiotic(s) to be used in the post-discharge step-down regimen means that this treatment is left to the attending clinician's discretion.

Conflicts of interest

The authors have no conflicts of interest to declare with regard to this work.

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References

1. Wu Y, Deng Y, Wei B, et al. Global, regional, and national childhood cancer burden, 1990–2019: An analysis based on the Global Burden of Disease Study 2019. *J Adv Res*. 2022;40:233–247. doi:10.1016/j.jare.2022.06.001.
2. Poulalhon C, Vignon L, Idbrik L, et al. Data resource profile: The French childhood cancer observation platform (CCOP). *Int J Epidemiol*. 2020;49(5):1434–1435k. doi:10.1093/ije/dyaa048.
3. Castagnola E, Fontana V, Caviglia I, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin Infect Dis*. 2007;45(10):1296–1304. doi:10.1086/522533.
4. Delebarre M, Dessein R, Lagrée M, et al. Differential risk of severe infection in febrile neutropenia among children with blood cancer or solid tumor. *J Infect*. 2019;79(2):95–100. doi:10.1016/j.jinf.2019.06.008.
5. Long E, Babl FE, Phillips N, et al. Prevalence and predictors of poor outcome in children with febrile neutropaenia presenting to the emergency department. *Emerg Med Australas*. 2022;34(5):786–793. doi:10.1111/1742-6723.13978.
6. Garrido MM, Garrido RQ, Cunha TN, Ehrlich S, Martins IS. Comparison of epidemiological, clinical and microbiological characteristics of bloodstream infection in children with solid tumours and haematological malignancies. *Epidemiol Infect*. 2019;147:e298. doi:10.1017/S0950268819001845.
7. Barton CD, Waugh LK, Nielsen MJ, Paulus S. Febrile neutropenia in children treated for malignancy. *J Infect*. 2015;71(Suppl 1):S27–S35. doi:10.1016/j.jinf.2015.04.026.
8. Dommett R, Geary J, Freeman S, et al. Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropenia in a UK, multicentre, shared care setting. *Eur J Cancer*. 2009;45(16):2843–2849. doi:10.1016/j.ejca.2009.06.003.
9. Paolino J, Mariani J, Lucas A, et al. Outcomes of a clinical pathway for primary outpatient management of pediatric patients with low-risk febrile neutropenia. *Pediatr Blood Cancer*. 2019;66(7):e27679. doi:10.1002/pbc.27679.
10. Lehrnbecher T, Robinson P, Fisher B, et al. Guidelines for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients:2017 update. *J Clin Oncol*. 2017;35(18):2082–2094. doi:10.1200/JCO.2016.71.7017.

11. Macher E, Dubos F, Garnier N, et al. Predicting the risk of severe bacterial infection in children with chemotherapy-induced febrile neutropenia. *Pediatr Blood Cancer*. 2010;55(4):662–667. doi:10.1002/pbc.22586.
12. Delebarre M Gonzales F, Behal H, Tiphaine A, Sudour-Bonnange H, Lutun A, et al. Derivation and external validation of a new clinical decision rule (DISCERN-FN) to predict the risk of severe infection during febrile neutropenia in children treated for cancer. *Lancet Child Adolesc Health*. 2022;6(4):260–268. doi:10.1016/S2352-4642(21)00337-0.
13. Orme LM, Babl FE, Barnes C, Barnett P, Donath S, Ashley DM. Outpatient versus inpatient IV antibiotic management for pediatric oncology patient with low risk febrile neutropenia: a randomised trial. *Pediatr Blood Cancer*. 2014;61(8):1427–1433. doi:10.1002/pbc.25012.
14. Santolaya ME, Villarroel M, Avendaño LF, Cofré J. Discontinuation of antimicrobial therapy for febrile neutropenic children with cancer: a prospective study. *Clin Infect Dis*. 1997;25(1):92–97. doi:10.1086/514500.
15. Delebarre M, Tiphaine A, Martinot A, Dubos F. Risk-stratification management of febrile neutropenia in pediatric hematology-oncology patients: results of a French nationwide survey. *Pediatr Blood Cancer*. 2016;63(12):2167–2172. doi:10.1002/pbc.26121.
16. Gibson F, Chisholm J, Blandford E, et al. Developing a nation " low risk " febrile neutropenia framework for use in children and young people's cancer care. *Support Care Cancer*. 2013;21(5):1241–1251. doi:10.1007/s00520-012-1653-y.
17. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. 2014;67(4):401–409. doi:10.1016/j.jclinepi.2013.12.002.
18. Alvarez E, Chamberlain LJ, Aftandilian C, Saynina O, Wise P. Pediatric oncology discharges with febrile neutropenia: variation in location care. *J Pediatr Hematol Oncol*. 2017;39(1):e1–e7. doi:10.1097/MPH.0000000000000716.
19. Phillips RS, Sung L, Ammann RA, et al. Predicting microbiologically defined infection in febrile neutropenic episodes in children: global individual participant data multivariable meta-analysis. *Br J Cancer*. 2016;114(6):623–630. doi:10.1038/bjc.2016.28.
20. Gil-Veloz M, Pacheco-Rosas DO, Solórzano-Santos F, Villasís-Keever MA, Betanzos-Cabrera Y, Miranda-Novales G. Early discharge of pediatric patients with cancer, fever and neutropenia with low-risk of systemic infection. *Bol Med Hosp Infant Mex*. 2018;75(6):352–357. doi:10.24875/BMHIM.18000015.
21. Ojha RP, Asdahl PH, Steyerberg EW, Schroeder H. Predicting bacterial infections among pediatric cancer patient with febrile neutropenia: external validation of the PICCNICC model. *Pediatr Blood Cancer*. 2018;65(4):e26935. doi:10.1002/pbc.26935.
22. Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. *J Pediatr Hematol Oncol*. 2000;22(5):405–411. doi:10.1097/00043426-200009000-00004.
23. Villanueva MA, August KJ. Early discharge of neutropenic pediatric oncology patients admitted with fever. *Pediatr Blood Cancer*. 2016;63(10):1829–1833. doi:10.1002/pbc.26072.
24. Lehrnbecher T. Treatment of fever in neutropenia in pediatric oncology patients. *Curr Opin Pediatr*. 2019;31(1):35–40. doi:10.1097/MOP.0000000000000708.
25. Aquino VM, Buchanan GR, Tkaczewski I, Mustafa MM. Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. *Med Pediatr Oncol*. 1997;28(3):191–195. doi:10.1002/(sici)1096-911x(199703)28:3<191::aid-mpo7>3.0.co;2-e.
26. Aquino VM, Tkaczewski I, Buchanan GR. Early discharge of low-risk febrile neutropenic children and adolescents with cancer. *Clin Infect Dis*. 1997;25(1):74–78. doi:10.1086/514512.
27. Hodgson-Viden H, Grundy PE, Robinson JL. Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. *BMC Pediatr*. 2005;5(1):10. doi:10.1186/1471-2431-5-10.
28. Lehrnbecher T, Averbuch D, Castagnola E, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. 2021;22(6):e270–e280. doi:10.1016/S1470-2045(20)30725-7.