

1 **Non-neutropenic fever in children with cancer: a scoping review of management and outcome.**

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Absolute Neutrophil Count	ANC
American Society of Pediatric Hematology/Oncology	ASPHO
Central Venous Catheter	CVC
Clinical Decision Rule	CDR
Febrile Neutropenia	FN
Non-Neutropenic Fever	NNF
Odds Ratio	OR

26

27 **ABSTRACT**

28 To date very few studies have addressed non-neutropenic fever (NNF) in children with cancer and
29 there are no consensus guidelines. This scoping review aims to describe the rate of bacteraemia, risk
30 factors for infection and management and outcomes of NNF in this population. Across 15 studies
31 (n=4106 episodes), the pooled-average bacteraemia rate was 8.2% and risk factors included tunnelled
32 external central venous catheter, clinical instability and higher temperature. In two studies, antibiotics
33 were successfully withheld in a subset of low-risk patients. Overall outcomes of NNF appear
34 favourable, however further research is required to determine its true clinical and economic impact.

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50 **INTRODUCTION**

51 In the absence of a functional immune system, be it disease or treatment related, infection in children
52 with cancer is typically heralded by fever alone. While the barriers and response to infection are a
53 complex interplay between the innate and adaptive immune system, chemotherapy-induced
54 neutropenia remains one of the most important risk factors for a severe, invasive bacterial infection.^{1,2}

55 The duration and depth of neutropenia further influences risk, with as many as 80% of patients
56 developing a severe infection after three weeks of profound neutropenia in the pre-antibiotic era.²

57 Given the potential for severe infection and adverse outcome, much of the research has focused on the
58 clinical syndrome of fever and neutropenia (FN), with very few studies addressing non-neutropenic
59 fever (NNF) in this population.³ A detailed understanding of the causes, outcomes and optimal
60 treatment of NNF is increasingly important with the development of new generation cancer therapies
61 that tend to cause less neutropenia but are still associated with a risk of infection.^{4,5}

62 The frequency of NNF during paediatric cancer treatment is largely unknown but likely varies
63 according to type of malignancy and treatment. In a national prospective study of FN in Australia,
64 over half of emergency department presentations in children with cancer and fever were due to
65 NNF.(Haeusler GM, personal communication, 04/10/2018) Results of a data linkage study from the
66 United States suggest similarly high rates of NNF presentations to the emergency department.⁶ This
67 burden of NNF has been previously unrecognised, as evidenced by the paucity of guidelines, care
68 pathways and dedicated research in this area.^{3,7} Furthermore, little is known about the cause of fever,
69 frequency of bacteraemia and outcomes of these patients.

70 The aim of this scoping review is to bring together all available studies that provide clinical details
71 about children with cancer and NNF. In particular, our objectives are to describe the rates of
72 bacteraemia, risk factors for infection, empiric antibiotic management and outcomes of NNF in this
73 population.

74 **METHODS**

75 A comprehensive electronic search strategy across multiple databases to identify all studies relevant to
76 the focussed clinical question was performed. As a scoping review, data was combined to describe the
77 nature of the existing research, strengths and limitations of the studies, and make conclusions
78 regarding clinical and research implications. Simple meta-analysis of proportions was undertaken
79 using the binomial model developed by Simmonds *et al*, with 95% confidence intervals estimated by
80 bootstrapping with replacement in 1000 samples.⁸

81 The search was developed using three primary research terms, including fever, cancer diagnosis and
82 non-neutropenia. This search was extended to include possible variations and synonyms of key search
83 terms. Electronic databases searched included MEDLINE (Ovid), EMBASE (Ovid) and PubMed. No
84 language or date filters were applied. Reference lists of relevant systematic reviews and included
85 articles were also reviewed.

86 Two reviewers independently screened the title and abstract of studies for inclusion. Disagreements
87 were resolved by consensus. The search occurred on 25 September 2018. Studies were included in
88 this review if they reported clinical details of paediatric patients (age <21) with cancer or
89 haematological malignancy and NNF. Non-neutropenia was defined as absolute neutrophil count
90 (ANC) greater than or equal to 500 cells per microliter. Fever was defined according to the original
91 study. For studies including episodes of FN and NNF, only those were included in the analysis if
92 results of NNF were reported separately.

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94 RESULTS

95 A total of 646 titles and abstracts were reviewed, of which 83 full text articles were retrieved. From
96 this, 16 relevant articles, describing 15 studies, were identified for inclusion in this review (Fig. 1).^{3, 6,}
97 ^{7, 9-24} No dedicated NNF treatment guidelines were identified in this search. One survey of practice
98 was found but not included as patient level data were not reported.²³

99 The inclusion criteria across the studies included in this review varied. Notably, nine (60%) studies
100 only included patients with a central venous catheter (CVC) *in situ*.^{11-17, 19, 21} The type of CVC also
101 varied across the studies with implanted Ports more common in six^{11, 13, 15, 16, 19, 21} while tunnelled
102 external CVC were more common in two, albeit older, studies^{12, 17} (type not reported in 7). Acute
103 lymphoblastic leukaemia was the most common underlying cancer diagnosis across all studies.<sup>11-17, 19-
104 22</sup>

105 Seven different definitions of fever were used with the most common being a single temperature
106 greater than or equal to 38.0 degrees Celsius (4 studies).^{18, 19, 21, 22} Conversely only three different
107 definitions of non-neutropenia were used with the most common being an ANC equal to or greater
108 than 500 cells/ μ L (13 studies).^{7, 10-21} A definition of bacteraemia was reported in eight studies<sup>12, 13, 15-
109 17, 19, 21, 22</sup> with only four studies requiring common commensals to be cultured more than once.<sup>13, 15, 16,
110 21</sup>

111 *Frequency of NNF*

112 In five studies, NNF episodes were reported as a subset of all febrile episodes (i.e. both FN and NNF
113 reported).^{10, 17, 18, 20, 22} Of these, NNF accounted for between 38 and 49% of all febrile episodes.

114 *Cause of fever*

115 Across the 15 studies, of the pooled average rate of bacteraemia was 8.2% (95% confidence interval
116 (CI) 5.4% to 12%) over 4106 NNF episodes (Fig. 2). Overall, eleven studies reported a bacteraemia
117 rate less than 10%.^{7, 11-16, 18, 19, 21, 22} In studies that excluded common commensals unless cultured more
118 than once, the bacteraemia rate ranged from 4 to 10%, pooled average 6.3% (95%CI 4.6% to 8.5%).^{12,}
119 ^{13, 15, 16, 21} In the remaining ten studies that either did not report the definition of bacteraemia^{7, 10, 11, 14, 18,}
120 ^{20, 24}, or included common commensals cultured once^{17, 19, 22}, the bacteraemia occurred between 3 and
121 32% of NNF episodes, pooled average 9.7% (95% CI 5.1% to 18.0%). Of the five studies that
122 included patients without a CVC, rates of bacteraemia were not analysed separately from patients with
123 a CVC in situ in the non-neutropenic population.^{7, 10, 18, 22, 24}

124 Notably, estimated mid-year of the data collection for each study was a significant predictor in meta-
125 regression, with more modern studies having a lower proportion of bacteraemia (OR of each year
126 from 1986 onwards 0.93; 95% CI 0.90 to 0.96).

127 In studies reporting the type of bacteraemia, including four that that excluded common commensals
128 cultured once, Gram positive bacteria were the most frequently identified^{11-15, 17, 19, 21} Overall,
129 coagulase negative staphylococci were the most common cause of bacteraemia, followed by
130 *Enterococcus* spp, *Staphylococcus aureus*, *Streptococcus pneumoniae* and oral viridans streptococci.
131 Among Gram negative bacteria, Enterobacteriaceae were the most common followed by
132 *Pseudomonas* spp and *Acinetobacter* spp. A total of seven fungal blood stream infections (*Candida*
133 *albicans* in 3; *Candida* species in 1; *Candida parapsilosis* in 2; *Trichosporin* spp in 1) were reported
134 across five of the nine studies that provided details on the type of organisms.^{11, 14, 15, 17, 21}

135 Limited antibiotic susceptibility details were provided in five studies.^{11, 12, 15, 19, 21} The proportion of
136 bacteraemia episodes with inherent or acquired resistance to third generation cephalosporins, namely

137 ceftriaxone, ranged from 46 to 75%. In one study, 12 out of 16 (75%) high risk bacteria (including
138 Enterobacteriaceae, *S. aureus*, oral viridans streptococci, *S. pneumoniae*) were susceptible to
139 ceftriaxone compared to three out of 17 (18%) low risk bacteria (including coagulase negative
140 staphylococci, *Enterococcus* spp, *Bacillus* spp).¹⁹

141 Five studies provided additional details on other infective causes of fever with upper respiratory tract
142 infections most frequent, occurring in between 14 and 63% of episodes.^{11, 18, 19, 21, 22}

143 **Outcome**

144 Overall the outcomes of NNF appear favourable (Table 1). Where reported, there were no deaths and
145 admission to the intensive care unit was infrequent.^{7, 10, 12-15, 18, 19} Five studies described a risk stratified
146 approach to treatment based on a combination of clinical and biochemical parameters, including C-
147 reactive protein $\geq 50\mu\text{g/mL}$, toxic or focal signs of bacterial infection, sepsis or chills.^{7, 10-13}
148 Importantly, there were no adverse outcomes described with this approach, which included reduced
149 intensity treatment for patients identified as low risk. Apart from C-reactive protein, no other studies
150 reported on the predictive ability of biomarkers including procalcitonin and lactate.

151 **Empiric antibiotic treatment and location**

152 Eight studies provided details on empiric NNF antibiotic treatment, with ceftriaxone the most
153 common agent used (Table 2).^{10-13, 15, 17, 19, 21} Across the four studies that reported duration of
154 treatment, no site routinely exceeded 48 to 72 hours.^{11, 12, 15, 19} The outpatient setting was most
155 frequently employed to monitor these patients and provide additional doses of antibiotics.

156 In two studies, antibiotics were only administered to patients with rigors or unwell appearance,
157 resulting in subset of patients on no antibiotics for the NNF episode.^{7, 13} Notably, only 7 of 24
158 episodes of NNF with bacteraemia that were not commenced on antibiotics required readmission in

159 one study¹³ and there were no admissions to the intensive care unit or deaths with this approach
160 across both.^{7, 13}

161 ***Risk factors for bacteraemia***

162 Five studies investigated clinical characteristics associated with bacteraemia in patients with NNF
163 (Table 3).^{11, 13, 15, 19, 21} Type of CVC was significantly associated with bacteraemia in four out of five
164 studies with an increased risk observed in patients with a tunnelled external CVC (OR 4.0 to 14) or
165 PICC (OR 4.0), compared to implantable ports.^{15, 19, 21, 24} Across three studies the presence of
166 hypotension, fluid bolus requirement or chills or rigors was also significantly associated with
167 bacteraemia.^{11, 15, 21} Other significant associations included height of temperature^{13, 15} and absence of
168 upper respiratory tract infection (URTI) symptoms.^{15, 21}

169 Only one clinical decision rule (CDR), designed to predict bacteraemia in children with cancer and
170 NNF, was identified. This rule (EsVan) was retrospectively derived in a single centre and has
171 undergone retrospective, multisite validation.^{15, 16} In the original derivation study factors not
172 associated with an increased risk of bacteraemia during NNF included absolute monocyte count,
173 inpatient versus outpatient presentation, mucositis, recent corticosteroid treatment, decreased oral
174 intake and exposure to sick contacts.¹⁵ The EsVan model incorporates 12 weighted clinical variables
175 and has moderate discrimination with a C-statistic of 0.898. In validation the C-statistic fell to 0.687
176 for the original model and 0.721 for a modified model (EsVan2) which excludes the variables
177 diagnosis and location of onset of fever. Of note, the EsVan2 model performed better for prediction of
178 bacteraemia with high-risk organisms (defined as Gram negative or *Staphylococcus aureus*) with a C-
179 statistic of 0.841.^{9, 16}

180 **DISCUSSION**

181 In contrast to the breadth of paediatric FN research, very few studies have explored the causes,
182 treatment and outcomes of NNF in children with cancer. Although only 15 studies were identified in
183 this review, the rate of bacteraemia appears to be less than 10% and very few adverse outcomes were
184 described. Treatment approaches also appear similar, with at least four sites routinely providing daily
185 antibiotics in the outpatient setting for 24 to 72 hours for patients who are clinically stable.

186 There is no consensus definition for NNF. While most studies included in this review defined
187 neutropenia as an ANC greater than or equal to 500 cells/ μ L, many different definitions for fever were
188 reported. This variation is not surprising given international consensus was unable to be achieved on a
189 definition of fever in paediatric cancer patients with FN.²⁵ While the impact of varying temperature
190 thresholds for fever is unknown, temperature height on presentation with NNF was an independent
191 predictor of bacteraemia in two studies^{13, 15}.

192 Although the true incidence of NNF is unknown, this review suggests it accounts for up to 50% of
193 febrile presentations in children with cancer. Results of a US-based data linkage study indicate that
194 NNF may actually be more common than this, accounting for over half of febrile presentations to the
195 emergency department.⁶ However, despite the frequency with which NNF appears to occur, no
196 published guidelines for the investigation and management of NNF were identified. An international
197 paediatric FN evidence-based guideline is available, although does not specifically address
198 recommendations for patients with an ANC greater than 500cells/ μ L.^{26, 27} The paucity of studies in
199 this area, as well as the absence of dedicated guidelines, likely explains the considerable variation in
200 approach to the evaluation and treatment of NNF among a large group (n=316) of American Society
201 of Pediatric Hematology/Oncology (ASPHO) members.²³ In this survey of practice, a number of
202 different empiric antibiotic combinations were used and the presence of a CVC, or known source of
203 infection had variable impact on decision to start antibiotics. An overview of the treatment approach

204 to NNF is available which emphasises adherence to local sepsis or possible CVC associated blood
205 stream infection protocols, where relevant.³

206 In most studies, bacteraemia was documented in less than 10% of NNF episodes. The three studies
207 that reported much higher rates (between 24 and 32%) included patients treated from 1989 to 1996
208 and improvements in supportive care and CVC maintenance may explain this reduction.^{10, 17, 24} The
209 type of CVC also appears to influence the risk of bacteraemia, with significantly higher rates seen in
210 patients with tunneled-external CVCs compared to implantable Ports across four out of the five
211 studies investigating this association.^{13, 15, 19, 21, 24} Given the high proportion of NNF episodes with a
212 CVC it is not surprising that Gram positive bacteria, frequently associated with CVC infections, were
213 the most common pathogens isolated.²⁸ Ongoing improvements in CVC care have the potential to
214 further reduce infections in this vulnerable population.²⁹ Bacteraemia with *Streptococcus pneumoniae*
215 was also documented in these patients, and while serotypes were not reported, this also highlights the
216 importance of vaccination during cancer treatment as part of the infection-prevention bundle.³⁰

217 In keeping with results of the ASPHO survey of practice, ceftriaxone was the most commonly used
218 empiric monotherapy for NNF.^{11, 14, 15, 19, 21, 23} This is presumably due to the ease of administration and
219 concern over the adverse effects of Gram negative sepsis in this population. Notably, although as
220 many as 75% of all bacteraemia episodes had inherent or acquired resistance to ceftriaxone, very few
221 adverse outcomes were reported. While these results suggest daily ceftriaxone may be safe to use,
222 consideration should be given to local susceptibility patterns. Furthermore, some studies described a
223 risk stratified approach to treatment with alternative ‘broad-spectrum’ empiric antibiotics used in
224 patients who were unwell, or had chills or rigors.¹¹⁻¹³ As bacteraemia with *Pseudomonas* spp was
225 reported, empiric NNF treatment strategies should cover for this pathogen in patients with severe
226 sepsis or clinical instability.

227 There was some commonality in the clinical features associated with bacteraemia, in particular type of
228 CVC, height of temperature and presence of chills or rigors. Bacteraemia also appears less likely in
229 patients with NNF and upper respiratory tract infection symptoms. As this was the most common
230 infective cause of NNF, treatment algorithms incorporating this clinical variable have the potential to
231 dramatically reduce antibiotic exposure in this population.

232 In contrast to the 27 CDRs that have been derived for prediction of infection or adverse outcome in
233 children with cancer and FN, only one NNF CDR has been developed.^{25, 31, 32} This rule, designed to
234 predict bacteraemia, incorporates up to 12 clinical variables routinely available to clinicians when
235 assessing these patients in the emergency department.¹⁵ In a multisite validation study, albeit
236 retrospective, the CDR retained its discriminatory ability for the prediction of high-risk bacteraemia,
237 arguably the most serious and potentially life-threatening causes of NNF.^{9, 16} Further research is
238 required to determine the clinical applicability and impact of this CDR to children outside the United
239 States. Based on available evidence, the latter is likely to be high as reduced intensity treatment,
240 including no antibiotics, appears safe in patients with NNF considered lower risk of infection.^{7, 11-13}

241 This is the first time that the common condition of NNF has been systematically reviewed. While
242 every effort was made to identify all relevant studies of children with cancer and NNF, the absence of
243 accepted terminology and a definition of this syndrome means some publications may have been
244 missed. Studies included in this review also comprised patients treated across three decades, where
245 changes in chemotherapy, supportive care and CVC choice and maintenance, limit direct comparisons
246 and conclusions that can be drawn.

247 The limited research investment into NNF, together with the apparent variations in practice and
248 paucity of guidelines, suggest that the frequency and impact of this syndrome has been largely
249 unappreciated. Reassuringly, outcomes appear favourable, intensive care admissions are infrequent,

250 adverse events are uncommon and patients have been managed successfully in the outpatient setting.
251 Further research is required to determine the most appropriate management strategies including the
252 role of novel biomarkers, antibiotic type and duration as well as the true clinical, economic and
253 quality of life impact of reduced intensity treatment of NNF. Existing risk factors of bacteraemia, as
254 well as the NNF CDR (EsVan) should undergo further prospective validation and local and
255 international guidelines developed to reduce unnecessary variations in practice. A collaborative,
256 international approach, similar to what has been achieved for FN, would enable large, multisite
257 datasets to more rapidly inform practice change and further improve the management of fever and
258 infection in children with cancer.^{26, 33, 34}

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260 **CONFLICTS OF INTEREST**

261 There are no conflicts of interest to declare.

262

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266 **REFERENCES**

- 267 1. Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S3-
268 23.
- 269 2. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating
270 leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64(2):328-40.
- 271 3. Morgan JE. Fifteen minute consultation: Fever in children being treated for cancer. *Arch Dis Child*
272 *Educ Pract Ed.* 2018.
- 273 4. Teh BW, Harrison SJ, Pellegrini M, Thursky KA, Worth LJ, Slavin MA. Changing treatment
274 paradigms for patients with plasma cell myeloma: impact upon immune determinants of infection.
275 *Blood Rev.* 2014;28(2):75-86.
- 276 5. Teh BW, Harrison SJ, Worth LJ, Thursky KA, Slavin MA. Infection risk with immunomodulatory
277 and proteasome inhibitor-based therapies across treatment phases for multiple myeloma: A systematic
278 review and meta-analysis. *Eur J Cancer.* 2016;67:21-37.
- 279 6. L. ME, Amber S, Achamyeleh G, Rajen M, Lillian S, L. MM. Why pediatric patients with cancer
280 visit the emergency department: United States, 2006–2010. *Pediatr Blood Cancer.* 2015;62(3):490-5.
- 281 7. Wu N, Muller W, Morgan E. Outcomes of observation without Empiric IV antibiotics in febrile,
282 non-neutropenic pediatric oncology patients. *Pediatr Blood Cancer.* 2018;65 (Supplement 1):S164-S5.
- 283 8. Simmonds MC, Higgins JP. A general framework for the use of logistic regression models in meta-
284 analysis. *Stat Methods Med Res.* 2016;25(6):2858-77.
- 285 9. Erratum. *Cancer.* 2018;124(8):1841-4.

- 286 10. Abrahamsson J, Pahlman M, Mellander L. Interleukin 6, but not tumour necrosis factor-alpha, is a
287 good predictor of severe infection in febrile neutropenic and non-neutropenic children with
288 malignancy. *Acta Paediatr.* 1997;86(10):1059-64.
- 289 11. Ali BA, Hirmas N, Tamim H, Merabi Z, Hanna-Wakim R, Muwakkit S, et al. Approach to Non-
290 Neutropenic Fever in Pediatric Oncology Patients-A Single Institution Study. *Pediatr Blood Cancer.*
291 2015;62(12):2167-71.
- 292 12. Averbuch D, Makhoul R, Rotshild V, Weintraub M, Engelhard D. Empiric treatment with once-
293 daily cefonicid and gentamicin for febrile non-neutropenic pediatric cancer patients with indwelling
294 central venous catheters. *J Pediatr Hematol Oncol.* 2008;30(7):527-32.
- 295 13. Bartholomew F, Aftandilian C, Andrews J, Gutierrez K, Luna-Fineman S, Jeng M. Evaluation of
296 febrile, nonneutropenic pediatric oncology patients with central venous catheters who are not given
297 empiric antibiotics. *J Pediatr.* 2015;166(1):157-62.
- 298 14. Beauchemin MM, Fernbach AE, Lopez I, Kelly KM, Sulis ML. Risk factors for bacteremia in
299 pediatric patients with cancer and non-neutropenic fever. *Pediatr Blood Cancer.* 2012;59 (6):1113.
- 300 15. Esbenshade AJ, Pentima MC, Zhao Z, Shintani A, Esbenshade JC, Simpson ME, et al.
301 Development and validation of a prediction model for diagnosing blood stream infections in febrile,
302 non-neutropenic children with cancer. *Pediatr Blood Cancer.* 2015;62(2):262-8.
- 303 16. Esbenshade AJ, Zhao Z, Aftandilian C, Saab R, Wattier RL, Beauchemin M, et al. Multisite
304 external validation of a risk prediction model for the diagnosis of blood stream infections in febrile
305 pediatric oncology patients without severe neutropenia. *Cancer.* 2017;123(19):3781-90.

- 306 17. Gorelick MH, Owen WC, Seibel NL, Reaman GH. Lack of association between neutropenia and
307 the incidence of bacteremia associated with indwelling central venous catheters in febrile pediatric
308 cancer patients. *Pediatr Infect Dis J.* 1991;10(7):506-10.
- 309 18. Ke ZY, Xu L, Zhang TT, Mo YL, Huang LB, Zhang XL, et al. A prospective study of febrile
310 episodes in inpatient children on chemotherapy. *Pediatr Infect Dis J.* 2010;29(10):968-70.
- 311 19. Kelly MJ, Vivier PM, Panken TM, Schwartz CL. Bacteremia in febrile nonneutropenic pediatric
312 oncology patients. *Pediatr Blood Cancer.* 2010;54(1):83-7.
- 313 20. Mahmood S, Revesz T, Mpofu C. Febrile episodes in children with cancer in the United Arab
314 Emirates. *Pediatr Hematol Oncol.* 1996;13(2):135-42.
- 315 21. Moskalewicz RL, Isenalumhe LL, Luu C, Wee CP, Nager AL. Bacteremia in nonneutropenic
316 pediatric oncology patients with central venous catheters in the ED. *Am J Emerg Med.* 2017;35(1):20-
317 4.
- 318 22. Rahiala J, Perkkio M, Riikonen P. Infections occurring during the courses of anticancer
319 chemotherapy in children with ALL: a retrospective analysis of 59 patients. *Pediatr Hematol Oncol.*
320 1998;15(2):165-74.
- 321 23. Salzer W, Steinberg SM, Liewehr DJ, Freifeld A, Balis FM, Widemann BC. Evaluation and
322 treatment of fever in the non-neutropenic child with cancer. *J Pediatr Hematol Oncol.* 2003;25(8):606-
323 12.
- 324 24. Sandoval C, Giamelli J, Visintainer P, Jayabose S, Ozkaynak MF, Tugal O, et al. #605
325 Management of febrile non-neutropenic episodes in pediatric oncology patients. *J Pediatr Hematol*
326 *Oncol.* 1998;20(4):374.

- 327 25. Haeusler GM, Thursky KA, Slavin MA, Mechinaud F, Babl FE, Bryant P, et al. External
328 Validation of Six Pediatric Fever and Neutropenia Clinical Decision Rules. *Pediatr Infect Dis J*.
329 2018;37(4):329-35.
- 330 26. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al.
331 Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic
332 Stem-Cell Transplantation Recipients: 2017 Update. *J Clin Oncol*. 2017;35(18):2082-94.
- 333 27. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, et al. Guideline for the
334 management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-
335 cell transplantation. *J Clin Oncol*. 2012;30(35):4427-38.
- 336 28. Simon A, Bode U, Beutel K. Diagnosis and treatment of catheter-related infections in paediatric
337 oncology: an update. *Clin Microbiol Infect*. 2006;12(7):606-20.
- 338 29. Bundy DG, Gaur AH, Billett AL, He B, Colantuoni EA, Miller MR. Preventing CLABSI among
339 pediatric hematology/oncology inpatients: national collaborative results. *Pediatrics*.
340 2014;134(6):e1678-85.
- 341 30. Crawford NW, Balloch A, Tikkanen L, Merchinaud F, Downie P, BATTERY JP. Pneumococcal
342 conjugate vaccine administration during therapy for pediatric leukemia. *Pediatr Infect Dis J*.
343 2015;34(1):e9-15.
- 344 31. Phillips B, Wade R, Stewart LA, Sutton AJ. Systematic review and meta-analysis of the
345 discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and
346 young people. *Eur J Cancer*. 2010;46(16):2950-64.

347 32. Phillips RS, Lehrnbecher T, Alexander S, Sung L. Updated Systematic Review and Meta-Analysis
348 of the Performance of Risk Prediction Rules in Children and Young People with Febrile Neutropenia.
349 PLoS One. 2012;7(5):e38300.

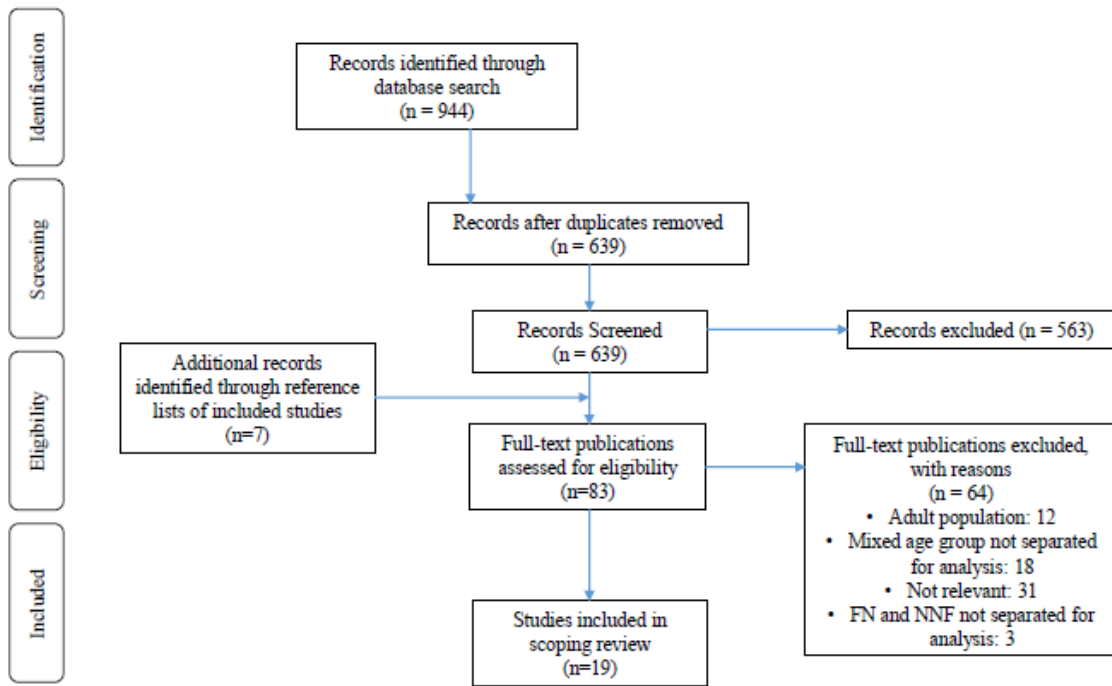
350 33. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, et al. Guideline for the
351 management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-
352 cell transplantation. J Clin Oncol. 2012;30(35):4427-38.

353 34. Phillips RS, Sung L, Ammann RA, Riley RD, Castagnola E, Haeusler GM, et al. Predicting
354 microbiologically defined infection in febrile neutropenic episodes in children: global individual
355 participant data multivariable meta-analysis. Br J Cancer. 2016;114(6):623-30.

356

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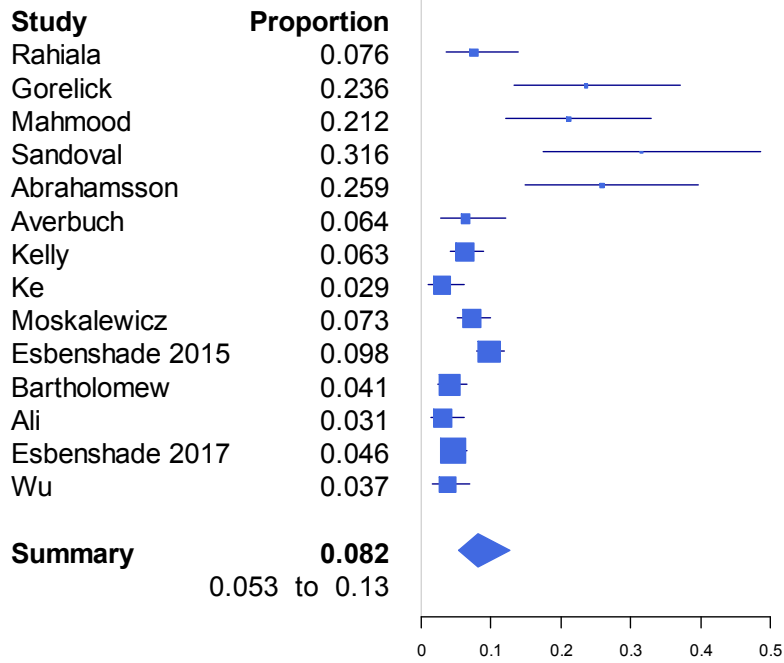


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360 FIGURE 1 Flow diagram of the NNF scoping review process

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363 FIGURE 2 Individual and pooled rate of bacteraemia

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366 TABLE 1 Studies describing rate of bacteraemia and outcomes in children with cancer and NNF

<i>Author (study location)</i>	<i>Study type* (time period)</i>	<i>Inclusion criteria</i>	<i>Definitions</i>	<i>NNF episodes (patients)</i>	<i>Med (ra</i>
Wu, N. 2018 (USA) (abstract)	Prospective cohort (Duration NR)	Cancer dx, on active treatment, well-appearing OP with NNF	Fever: NR Non-neutropenia: ANC \geq 500cells/ μ L Bacteraemia: NR	242 (NR)	NR
**Esbenshade, AJ. 2017 (USA)	Multisite, retrospective cohort (2009-15)	Age <23y, cancer dx, NNF, CVC <i>in situ</i>	Fever: Temp \geq 38.3°C or persistent temp \geq 38.0°C for 1h Non-neutropenia: ANC \geq 500cells/ μ L Bacteraemia: \geq 1 positive BC with recognised pathogen (common commensals \geq 2 positive BC)	630 (NR)	6 to
Moskalewicz, RL. 2017 (USA)	Retrospective cohort (2002-14)	Age <22y, cancer dx, NNF, CVC <i>in situ</i>	Fever: Temp \geq 38.0°C Non-neutropenia: ANC >500cells/ μ L Bacteraemia: \geq 1 positive BC with recognised pathogen (common commensals \geq 2 positive BC)	534 (246)	7y (4

Ali, BA. 2015 (Lebanon)	Retrospective cohort (2011-12)	Age<18y, cancer dx, on active treatment, OP onset NNF, CVC <i>in situ</i>	Fever: Single temp $\geq 38.3^{\circ}\text{C}$, or persistent temp $\geq 38.0^{\circ}\text{C}$ for >0.5h Non-neutropenia: ANC ≥ 500 cells/ μL Bacteraemia: NR	254 (83) HR: 62 (24) LR: 192 (76)	NR
Bartholomew, F. 2015 (USA)	Retrospective cohort (2008-12)	Cancer dx, on active treatment, NNF, CVC <i>in situ</i> , BC	Fever: Single temp $\geq 38.5^{\circ}\text{C}$, or 2 temp $\geq 38.0^{\circ}\text{C}$ over 24 hrs Non-neutropenia ANC ≥ 500 cells/ μL Bacteraemia: ≥ 1 positive BC with recognised pathogen (common commensals ≥ 2 positive BC)	392 (138)	7y (N)

<p>Esbenshade, AJ. 2015 (USA)</p>	<p>Retrospective cohort (2007-12)</p>	<p>Age <23y, cancer dx, NNF, CVC <i>in situ</i></p>	<p>Fever: Temp $\geq 38.3^{\circ}\text{C}$ or persistent temp $\geq 38.0^{\circ}\text{C}$ for 1h</p> <p>Non-neutropenia: ANC $\geq 500\text{cells}/\mu\text{L}$</p> <p>Bacteraemia: ≥ 1 positive CVC BC with recognised pathogen (common commensals ≥ 2 positive BC)</p>	<p>932 (463)</p> <p>750 (80) with OP onset NNF</p> <p>182 (20) with IP onset NNF</p>	<p>5y (1)</p>
<p>Beauchemin, M. 2012 (USA) (abstract)</p>	<p>Retrospective cohort (2009-11)</p>	<p>Cancer dx, OP onset fever, CVC <i>in situ</i></p>	<p>Fever: NR</p> <p>Non-neutropenia: ANC $> 500\text{cells}/\text{mm}^3$</p> <p>Bacteraemia: NR</p>	<p>164 (85)</p>	<p>7.8y (0.92)</p>
<p>Ke, ZY. 2010</p>	<p>Prospective</p>	<p>Cancer dx, IP onset fever ($>48\text{h}$)</p>	<p>Fever: Temp $>38.0^{\circ}\text{C}$</p>	<p>206 (NR)</p>	<p>6y (0)</p>

(China) (brief report)	cohort (2005 -09)	after admission)	Non-neutropenia: ANC >500cells/μL Bacteraemia: NR		15)
Kelly, MJ. 2010 (USA)	Retrospective cohort (2001-07)	Cancer dx, OP onset NNF, CVC <i>in situ</i> , BC taken	Fever: Temp ≥38.0°C Non-neutropenia: ANC ≥500cells/μL Bacteraemia: ≥1 positive BC	459 (167)	6.8y (0-2)
Averbuch, D. 2008 (Israel)	Retrospective (1 year) and prospective (1 year) (Years NR)	Hematooncologic diseases, NNF, CVC <i>in situ</i> (inc. 6 pts with non-cancer immune deficiency)	Fever: Single temp ≥38.5°C, or temp ≥38.0°C twice in 4h Non-neutropenia: ANC >500cells/μL & not expected to decrease Bacteraemia: Bacteraemia: ≥1 positive BC with recognised	125 (54)	5y (0-18y)

			pathogen (CoNS ≥ 2 positive BC)		
Rahiala, J. 1998 (Finland)	Multisite, retrospective cohort (1984-91)	ALL dx, on active treatment	Fever: Temp $>38.0^{\circ}\text{C}$ Non-neutropenia: ANC $>1000\text{cells}/\mu\text{L}$ Bacteraemia: ≥ 1 positive BC	119 (NR)	5.7y (1-16)
Sandoval, C. 1998 (USA) (abstract)	Retrospective cohort (1994-96)	Cancer dx, NNF	Fever: NR Non-neutropenia: ANC $\geq 750\text{cells}/\mu\text{L}$ Bacteraemia: NR	38 (25)	NR
Abrahamsson, J. 1997 (Sweden)	Prospective case control (Duration NR)	Cancer dx, fever	Fever: Temp $\geq 38.5^{\circ}\text{C}$ or $\geq 38.0^{\circ}\text{C}$ twice within 3h Non-neutropenia: ANC $>500\text{cells}/\mu\text{L}$ Bacteraemia: NR	54 (NR) (BC taken in 42)	8.3y 17.8y
Mahmood, S. 1996 (UAE)	Retrospective cohort (1992-94)	Cancer dx, fever, CVC <i>in situ</i>	Fever: PA single temp $\geq 38.5^{\circ}$, absence of obvious non-infectious causes (such as blood products or cytotoxic agents) Non-neutropenia: ANC $>500\text{cells}/\mu\text{L}$	66 (NR)	NR

			Bacteraemia: NR		
Gorelick, MH. 1991 (USA)	Retrospective cohort (1989)	Cancer dx, OP onset fever, CVC <i>in situ</i>	Fever: Single temp >38.5°C, or ≥3 temps >38.0°C within 24h Non-neutropenia: ANC ≥500/mm ³ Bacteraemia: positive CVC BC ± positive peripheral BC Exit site infection: erythema, induration, warmth or purulent drainage	55 (37)	3.3y (21)

367 **Abbreviations:** abs, antibiotics; AE, adverse event; AGC, Absolute Granulocyte Count; ALL, acute
368 lymphoblastic leukaemia; ANC, absolute neutrophil count; BC, blood culture; BSI, blood stream
369 infection; CAI, community acquired infection; CoNS, coagulase negative staphylococcus; CVC,
370 central venous catheter; c/w, compared with; dx, diagnosis; ED, emergency department; FN, febrile
371 neutropenia; HR, high risk; ICU, intensive care unit; IP, inpatient; IV, intravenous; LRTI, lower
372 respiratory tract infection; LR, low risk; neg, negative; NR, not reported; NNF, non-neutropenic fever;
373 OP, outpatient; PA, per axillary; PICC, peripherally inserted central catheter; PO, per oral; pos,
374 positive; temp, temperature; pt, patient; PTLN, post-transplant lymphoproliferative disorder; UTI,
375 urinary tract infection; URTI, upper respiratory tract infection; SSTI, skin and soft tissue infection;
376 TE, tunnelled external; y, years.

377 *All single centre unless otherwise specified.

378 **Study includes data from studies by Bartholomew et al, Ali et al and Kelly et al as well as three
379 new and unpublished datasets. Data presented in this table is from unpublished sites only.

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382 TABLE 2 Indications, empiric antibiotics and location of treatment of NNF (for NNF definition see
 383 TABLE 1)

<i>Author (study location)</i>	<i>Indications for antibiotic treatment</i>	<i>Empiric antibiotics (dose)</i>	<i>Location of treatment</i>	<i>Duration</i>
Wu, N. 2018 (USA) (abstract)	Patients presenting with cancer and fever who appear unwell to receive empiric antibiotics	NR	NR	NR
Moskalewicz, RL. 2017 (USA)	All patients with cancer, CVC and NNF receive empiric antibiotics	Ceftriaxone IV daily	NR	NR
Ali, BA. 2015 (Lebanon)	All patients with cancer, CVC and NNF receive empiric antibiotics. Antibiotic type and location tailored to risk status. High risk NNF (any of): clinically ill-appearing, other abnormal vital signs (persistent tachycardia despite fever control, tachypnoea, desaturation, and hypotension) or chills or lethargy	High-risk: “broad-spectrum” IV antibiotics Low-risk: ceftriaxone IV daily	High risk: IP Low risk: OP with daily follow up	High risk: as clinically indicated Low risk: minimum 48h (continued until resolution of fever or focus of infection)
Bartholomew, F. 2015 (USA)	Antibiotics not routinely given to all patients with cancer and NNF. Antibiotics only given to patients with chills/rigors or unwell appearance	Chills or unwell: IV antibiotics (type NR) Clinically well: no antibiotics	Chills or unwell: IP Clinically well: OP	Not applicable – antibiotics not routinely given

Esbenshade, AJ. 2015 (USA)	All patients with cancer and NNF	Ceftriaxone IV daily	OP	Single dose
Beauchemin, MM. 2012 (USA) (abstract)	All patients presenting with cancer and fever to outpatient setting	At least one dose of ceftriaxone and a follow-up visit 24 hours later	OP	NR
Kelly, MJ. 2010 (USA)	All patients with cancer, CVC and fever receive empiric antibiotics while awaiting FBE result.	Ceftriaxone (50mg/kg, max dose 2 g) IV daily	Unwell appearing: IP Well appearing: OP	Maximum of 48h pending BC results. Second dose ceftriaxone only given if remains febrile at 24h.
Averbuch, D. 2008 (Israel)	All patients with cancer, CVC and NNF receive empiric antibiotics	Clinically unwell or focal infection: NR Clinically well and no focal infection: cefonicid (50mg/kg) IV daily and gentamicin (5mg/kg) IV daily	Clinically unwell or focal infection: IP Clinically well and no focal infection: OP	48-72h pending BC results
Abrahamsson, J. 1997 (Sweden)	Antibiotics not routinely given to all patients with cancer and NNF. Antibiotics only given to patients with CRP \geq 50 μ g/ml, toxic appearance or focal signs of bacterial infection	Ceftazidime or imipenem \pm vancomycin IV	NR	NR
Gorelick, MH. 1991 (USA)	All patients with cancer, CVC and NNF	Vancomycin and cefotaxime IV	IP	NR

384 **Abbreviations:** BC, blood culture; CVC, central venous catheter; CRP, c-reactive protein; FBE, full
 385 blood examination; IP, inpatient; IV, intravenous; NNF, non-neutropenic fever; NR, not reported; OP,
 386 outpatient.

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389 TABLE 3 Studies exploring risk factors and predictors for bacteraemia in children with cancer and
 390 NNF

<i>Author (study location)</i>	<i>Bacteraemia, n (%)</i>	<i>Univariate analysis</i>	<i>Multivariate analysis</i>
Moskalewicz, RL. 2017 (USA)	39 (7.3)	Increased risk of bacteraemia (p<0.02): Absence of URTI symptoms Type of CVC (TE-CVC versus port) IV normal saline bolus >20 mL/kg in ED Neuroblastoma c/w ALL Other cancer dx (inc. Wilms tumour, retinoblastoma, hepatoblastoma, hepatocellular carcinoma, Langerhans cell histiocytosis, and peripheral nerve sheath tumour) c/w ALL	Independent predictors of bacteraemia (p<0.05): Absence of URTI symptoms (OR, 2.1, 95% CI 1.0-4.5) TE-CVC c/w Port (OR 4.5, 95% CI 1.7-11.4) IV normal saline bolus >20 mL/kg (OR, 2.4, 95% CI 1.2-4.9) Other cancer dx c/w ALL (OR, 4.79, 95% CI 1.8-12.7)
Ali, BA. 2015 (Lebanon)	8 (3.1)	Increased risk of bacteraemia (p=0.005): Unwell appearance (chills, hypotension, lethargy) (OR 9.7, p=0.005) Bacteraemia not associated with age, disease type (solid or haem) temperature or ANC.	NR
Bartholomew, F. 2015 (USA)	24 (6.1)	Bacteraemia not associated with age, sex, ANC or type of CVC	Independent predictors of bacteraemia: Fever >39.2°C (mean fever was higher in patients with

		<p>bacteremia than in those without bacteremia, 39.4°C vs 38.7°C; $p=0.003$)</p> <p>For every 1°C increase in temp > 38°C, OR increased by 5.0 (95% CI 1.6-16.1)</p> <p>A cutoff of 39°C had Se, Sp and PPV of 87.5%, 66.9% and 98.9%, respectively</p>
<p>Esbenshade, AJ. 2015 (USA)</p>	<p>24 (6.1)</p> <p>Increased risk of bacteraemia ($p<0.05$):</p> <ul style="list-style-type: none"> Type of CVC (TE-CVC & PICC versus Port-A-Cath) History of HSCT Hypotension Reported chills or observed rigors Absence of URTI symptoms Myalgia CVC exit site infection Temperature Increased line days for PICC and TE-CVC Increasing ANC in those with ANC>1000/μl <p>Decreased risk of bacteraemia ($p<0.001$):</p> <ul style="list-style-type: none"> ALL diagnosis versus another cancer type Exposure to cytarabine, anti-GD2 antibody therapy, or ATG Known source of fever other than URTI or SSTI at the line site <p>Bacteraemia not associated with age, sex, location (IP versus OP),</p>	<p>Independent predictors of bacteraemia ($p<0.05$):</p> <ul style="list-style-type: none"> Height of temperature (OR 2.4, 95% CI 1.7-3.3) PICC line versus Port-A-Cath (OR 4.0, 95% CI 1.5-10.2) TE-CVC versus Port-A-Cath (OR 13.8, 95% CI 6.6-28.9) Hypotension (OR 3.1, 95% CI 1.4-6.7) Increased ANC (OR 1.2, 95% CI 1.0-1.4) Reported chills or observed rigors (OR 2.1, 95% CI 1.1-4.1) <p>Independent predictors of a reduced probability of bacteraemia ($p<0.05$)</p> <ul style="list-style-type: none"> ALL diagnosis (OR 0.3, 95% CI 0.1-0.9) Increasing age (OR 0.7 95% CI 0.5-0.99) Outpatient location at presentation (OR 0.4, 95% CI 0.2, 0.9)

		sick contact exposure, corticosteroids or TPN, presence of GI symptoms, mucositis, decreased oral intake, reported decreased energy level and AMC.	AMC (OR 0.8, 95% CI 0.7-0.95) Exposure to cytarabine, anti-GD2 antibody therapy, or ATG (OR 0.1, 95% CI 0.03- 0.2)
Kelly, MJ. 2010 (USA)	29 (6.3)	Increased risk of bacteraemia (p<0.05): External CVC (16.2%) versus internal CVC (4.4%) No focus (6%) versus focus of infection (0%) on examination Higher median heart rate (143 versus 134 bpm) Bacteraemia not associated with age, sex, temperature, respiratory rate, blood pressure, cancer diagnosis, ANC, history of bacteraemia and location (IP versus OP)	Independent predictors of bacteraemia (p<0.05): External CVC c/w internal catheter (RR 4.0, 95% CI 1.8-9.0)
Averbuch, D. 2008 (Israel)	8 (6.4)	Increased risk of bacteraemia (p<0.05): Hickman/Broviac catheters ((9.3%) versus port-a-caths (0%)	NR
Sandoval, C. 1998 (USA) (abstract)	12 (31.6)	Increased risk of bacteraemia (p<0.05): External CVC (32%) versus Port (0%) Elevated WCC	Independent predictors of bacteraemia (p<0.005): Type of CVC

391 **Abbreviations:** AMC, absolute monocyte count; ANC, absolute neutrophil count; ALL, absolute
392 lymphocyte count; ATG, anti-thymocyte globulin; bpm, beats per minute; CI, confidence interval;
393 CVC, central venous catheter; c/w, compared with; dx, diagnosis; ED, emergency department; haem,
394 haematology; GI, gastrointestinal; HSCT, haematopoietic stem cell transplant; inc., including; IP,
395 inpatient; IV, intravenous; NR, not reported; OP, outpatient; OR, odds ratio; PICC, peripherally
396 inserted central catheter; PPV, positive predictive value; RR, respiratory rate; Se, sensitivity; Sp,

397 specificity; SSTI, skin and soft tissue infection; TE, tunnelled external; TPN, total parenteral
398 nutrition; URTI, upper respiratory tract infection; WCC, white cell count.

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