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

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Abbreviations key:

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

ABSTRACT

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

INTRODUCTION

In the absence of a functional immune system, be it disease or treatment related, infection in children with cancer is typically heralded by fever alone. While the barriers and response to infection are a complex interplay between the innate and adaptive immune system, chemotherapy-induced neutropenia remains one of the most important risk factors for a severe, invasive bacterial infection.[1, 2] The duration and depth of neutropenia further influences risk, with as many as 80% of patients developing a severe infection after three weeks of profound neutropenia in the pre-antibiotic era.[2] Given the potential for severe infection and adverse outcome, much of the research has focused on the clinical syndrome of fever and neutropenia (FN), with very few studies addressing non-neutropenic fever (NNF) in this population.[3] A detailed understanding of the causes, outcomes and optimal treatment of NNF is increasingly important with the development of new generation cancer therapies that tend to cause less neutropenia but are still associated with a risk of infection.[4, 5]

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

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

METHODS

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

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

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

RESULTS

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

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

Seven different definitions of fever were used with the most common being a single temperature greater than or equal to 38.0 degrees Celsius (4 studies).[18, 19, 21, 22] Conversely only three different definitions of non-neutropenia were used with the most common being an ANC equal to or greater than 500 cells/μL (13 studies).[7, 10-21] A definition of bacteraemia was reported in eight studies [12, 13, 15-17, 19, 21, 22] with only four studies requiring common commensals to be cultured more than once.[13, 15, 16, 21]

Frequency of NNF

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

Cause of fever

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

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

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

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

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

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

Outcome

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

Empiric antibiotic treatment and location

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

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

one study [13] and there were no admissions to the intensive care unit or deaths with this approach across both.[7, 13]

Risk factors for bacteraemia

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

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

DISCUSSION

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

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

Although the true incidence of NNF is unknown, this review suggests it accounts for up to 50% of febrile presentations in children with cancer. Results of a US-based data linkage study indicate that NNF may actually be more common than this, accounting for over half of febrile presentations to the emergency department.[6] However, despite the frequency with which NNF appears to occur, no published guidelines for the investigation and management of NNF were identified. An international paediatric FN evidence-based guideline is available, although does not specifically address recommendations for patients with an ANC greater than 500cells/μL.[26, 27]. The paucity of studies in this area, as well as the absence of dedicated guidelines, likely explains the considerable variation in approach to the evaluation and treatment of NNF among a large group (n=316) of American Society of Pediatric Hematology/Oncology (ASPHO) members.[23] In this survey of practice, a number of different empiric antibiotic combinations were used and the presence of a CVC, or known source of 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 tunnelled-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 *Pseudonomas* spp was
225 reported, empiric NNF treatment strategies should cover for this pathogen in patients with severe
226 sepsis or clinical instability.

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

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

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

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

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

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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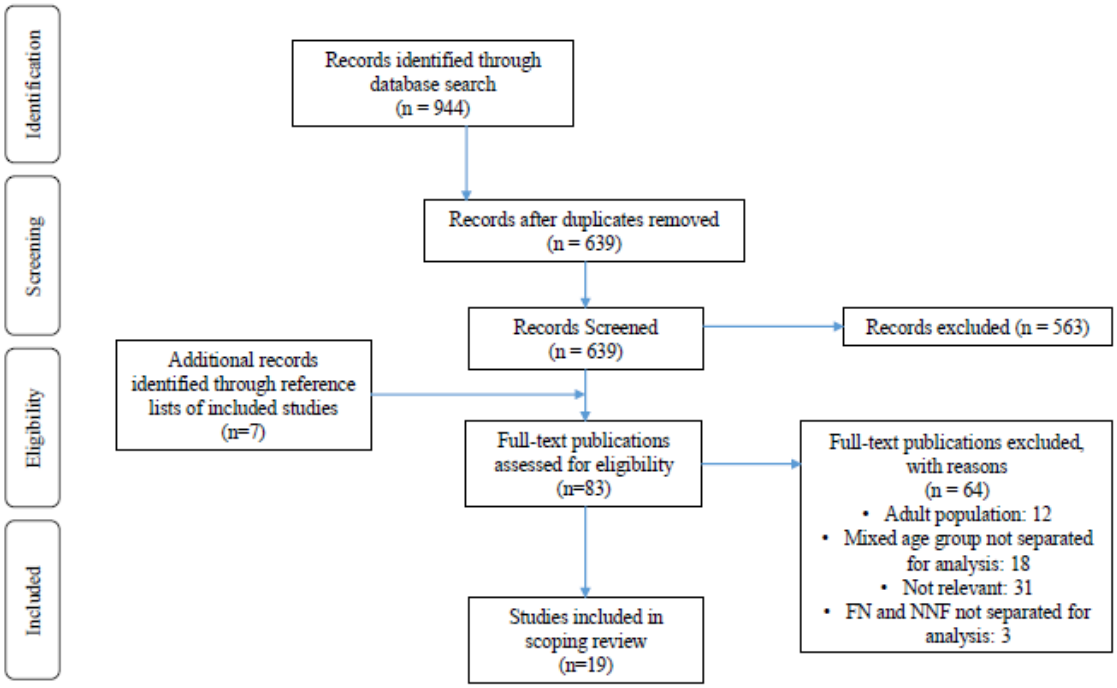

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360 FIGURE 1 Flow diagram of the NNF scoping review process

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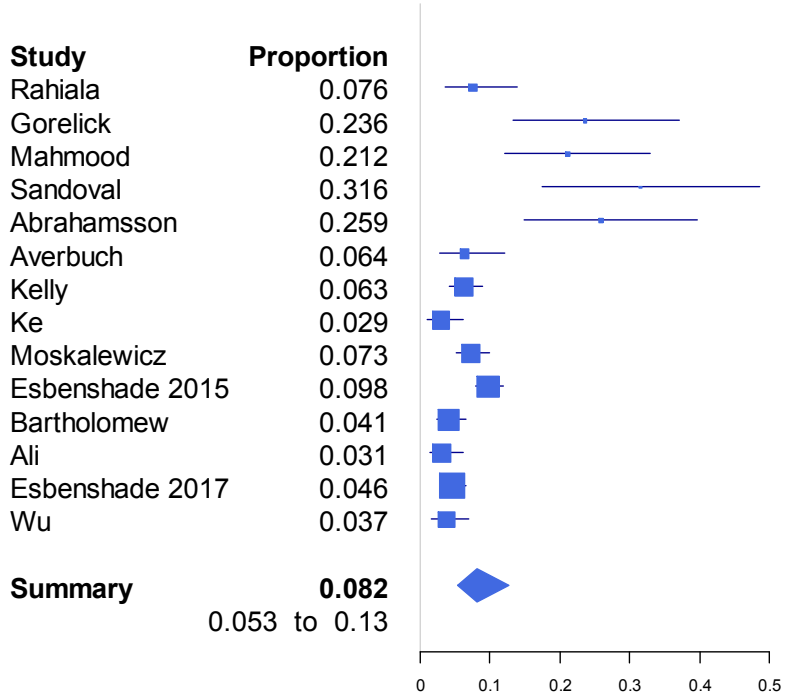

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363 FIGURE 2 Individual and pooled rate of bacteraemia

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

Author (study location)	*Study type* (time period)*	*Inclusion criteria*	*Definitions*	*NNF episodes (patients)*	*Med (r*
Wu, N. 2018 (USA) (abstract)	Prospective cohort (Duration NR)	Cancer dx, on active treatment, well-appearing OP with NNF	Fever: NR Non-neutropenia: ANC≥500cells/μL Bacteraemia: NR	242 (NR)	NR
**Esbenshade, AJ. 2017 (USA)	Multisite, retrospective cohort (2009-15)	Age <23y, cancer dx, NNF, CVC *in situ*	Fever: Temp ≥38.3°C or persistent temp ≥38.0°C for 1h Non-neutropenia: ANC≥500cells/μL Bacteraemia: ≥1 positive BC with recognised pathogen (common commensals ≥2 positive BC)	630 (NR)	6 to
Moskalewicz, RL. 2017 (USA)	Retrospective cohort (2002-14)	Age <22y, cancer dx, NNF, CVC *in situ*	Fever: Temp ≥38.0°C Non-neutropenia: ANC >500cells/μL Bacteraemia: ≥1 positive BC with recognised pathogen (common commensals ≥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 *in situ*	Fever: Single temp ≥38.3°C, or persistent temp ≥38.0°C for >0.5h Non-neutropenia: ANC≥500cells/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 *in situ*, BC	Fever: Single temp ≥38.5°C, or 2 temp ≥38.0°C over 24 hrs Non-neutropenia ANC ≥500cells/μL Bacteraemia: ≥1 positive BC with recognised pathogen (common commensals ≥ 2 positive BC)	392 (138)	7y (N

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

(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 *in situ*, BC taken	Fever: Temp ≥38.0°C Non-neutropenia: ANC ≥500cells/μL Bacteraemia: ≥1 positive BC	459 (167)	6.8y (0-25
Averbuch, D. 2008 (Israel)	Retrospective (1 year) and prospective (1 year) (Years NR)	Hematooncologic diseases, NNF, CVC *in situ* (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°C Non-neutropenia: ANC >1000cells/μL 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≥750cells/μL Bacteraemia: NR	38 (25)	NR
Abrahamsson, J. 1997 (Sweden)	Prospective case control (Duration NR)	Cancer dx, fever	Fever: Temp ≥38.5°C or ≥38.0°C twice within 3h Non-neutropenia: ANC >500cells/μL Bacteraemia: NR	54 (NR) (BC taken in 42)	8.3y 17.8
Mahmood, S. 1996 (UAE)	Retrospective cohort (1992-94)	Cancer dx, fever, CVC *in situ*	Fever: PA single temp ≥38.5°, absence of obvious non-infectious causes (such as blood products or cytotoxic agents) Non-neutropenia: ANC >500cells/μL	66 (NR)	NR

			Bacteraemia: NR		
Gorelick, MH. 1991 (USA)	Retrospective cohort (1989)	Cancer dx, OP onset fever, CVC *in situ*	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)

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

*All single centre unless otherwise specified.

**Study includes data from studies by Bartholomew et al, Ali et al and Kelly et al as well as three 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)

Author (study location)	*Indications for antibiotic treatment*	*Empiric antibiotics (dose)*	*Location of treatment*	*Duration*
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 ≥ 50µg/ml, toxic appearance or focal signs of bacterial infection	Ceftazidime or imipenem ± vancomycin IV	NR	NR
Gorelick, MH. 1991 (USA)	All patients with cancer, CVC and NNF	Vancomycin and cefotaxime IV	IP	NR

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

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

Author (study location)	*Bacteraemia, n (%)*	*Univariate analysis*	*Multivariate analysis*
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

			bacteremia than in those without bacteremia, 39.4°C vs 38.7°C; *p*=0.003) For every 1°C increase in temp > 38°C, OR increased by 5.0 (95% CI 1.6-16.1) A cutoff of 39°C had Se, Sp and PPV of 87.5%, 66.9% and 98.9%, respectively
Esbenshade, AJ. 2015 (USA)	24 (6.1)	Increased risk of bacteraemia (p<0.05): 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 Decreased risk of bacteraemia (p<0.001): 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 Bacteraemia not associated with age, sex, location (IP versus OP),	Independent predictors of bacteraemia (p<0.05): 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) Independent predictors of a reduced probability of bacteraemia (p<0.05) 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

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

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