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ORIGINAL ARTICLE

Systematic review of reduced therapy regimens for children with low risk febrile neutropenia

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Abstract
Purpose Reduced intensity therapy for children with low-risk febrile neutropenia may provide benefits to both patients and the health service. We have explored the safety of these regimens and the effect of timing of discharge.
Methods Multiple electronic databases, conference abstracts and reference lists were searched. Randomised controlled trials (RCT) and prospective observational cohorts examining the location of therapy and/or the route of administration of antibiotics in people younger than 18 years who developed low-risk febrile neutropenia following treatment for cancer were included. Meta-analysis using a random effects model was conducted. I^2 assessed statistical heterogeneity not due to chance. Registration: PROSPERO (CRD42014005817).
Results Thirty-seven studies involving 3205 episodes of febrile neutropenia were included; 13 RCTs and 24 prospective observational cohorts. Four safety events (two deaths, two intensive care admissions) occurred.

In the RCTs, the odds ratio for treatment failure (persistence, worsening or recurrence of fever/infecting organisms, antibiotic modification, new infections, re-admission, admission to critical care or death) with outpatient treatment was 0.98 (95% confidence interval (95%CI) 0.44–2.19, $I^2 = 0$ %) and with oral treatment was 1.05 (95%CI 0.74–1.48, $I^2 = 0$ %). The estimated risk of failure using outpatient therapy from all prospective data pooled was 11.2 % (95%CI 9.7–12.8 %, $I^2 = 77.2$ %) and using oral antibiotics was 10.5 % (95%CI 8.9–12.3 %, $I^2 = 78.3$ %). The risk of failure was higher when reduced intensity therapies were used immediately after assessment, with lower rates when these were introduced after 48 hours.
Conclusions Reduced intensity therapy for specified groups is safe with low rates of treatment failure. Services should consider how these can be acceptably implemented.

Keywords Paediatric · Febrile neutropenia · Systematic review · Outpatient · Oral antibiotics

Background

Febrile neutropenia is the commonest life-threatening complication of treatment of children with cancer [1]. It occurs in around a third of episodes of neutropenia, at a rate of 0.75 episodes per 30 days of neutropenia and 0.15 per month of chemotherapy exposure time [2, 3]. Febrile neutropenia describes a spectrum of conditions: a small number of patients suffer serious complications including organ failure and death, but most episodes have no significant sequelae. Current research into febrile neutropenia has focussed in two areas—risk stratification to define a 'low-risk' population (LRFN) and reduced therapy for such groups [4].

Reduced therapy regimens may provide benefits to both patients (including increased quality of life and reductions in hospital acquired infections) and the health service (including

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cost savings and reduced bed pressures) [5–8]. However, they should be explored rigorously in terms of both safety and efficacy, before changes are implemented. We therefore performed a systematic review to establish the safety and efficacy of these regimes and to identify how the timing of reductions in therapy might change these features.

We anticipated, given previous reviews, that the number of randomised controlled trials (RCTs) comparing the location and route of administration of antibiotics would be small [9, 10]. We also considered it important to estimate absolute numbers of patients experiencing failures, and therefore planned to use information from both prospective observational cohorts and the separate arms of RCTs to estimate failure rates.

For the purpose of this review, the three primary outcomes were treatment failure, safety and adequacy. These outcomes are likely to provide the information that patients and clinicians combine when making decisions about choice of care; thus, they are the most clinically relevant outcomes for those involved in planning and delivering paediatric haematology and oncology services. Multinational guidelines have recommended that the primary outcome of studies into febrile neutropenia should be a composite measure, hence our use of treatment failure (persistence, worsening or recurrence of fever/infecting organisms, antibiotic modification, new infections, re-admission, admission to critical care or death) as an outcome [11]. Meanwhile, knowledge about the safety of a strategy is essential to be able to consider its use at all, whilst information about adequacy would allow services to plan appropriately for potential re-admissions or changes in treatment associated with changing to a new low-risk strategy.

Finally, we understood that there may be concern regarding reduction of therapy from patients, their parents and the healthcare professionals caring for them. Therefore, we collected data on the rates of declined consent, where reported, as a way of gaining insight to the potential acceptability of these approaches.

Methods

We carried out a systematic review of reduced therapy regimens for children with low-risk febrile neutropenia. The protocol was prospectively registered (PROSPERO: CRD 42014005817) and published [12]. Electronic searches of MEDLINE, MEDLINE in-Process & Other non-Indexed Citations, EMBASE, CDSR, CENTRAL (via the Cochrane Library), LILACS, HTA and DARE were performed. The search strategy focused on febrile neutropenia and the interventions of antibiotics and early discharge, with a paediatric filter. No date or language filters were applied. The full database search strategy is provided in Online Resource 1. The conference proceedings of the RCPCH (Royal College of Paediatrics and Child Health), SIOP (International Society of Paediatric Oncology), ASPHO (American Society of Paediatric Haematology/Oncology), ASCO (American Society of Clinical Oncology) and ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy) meetings were searched. Reference lists of included articles and relevant systematic reviews were also reviewed. Authors of relevant studies and prominent clinicians within the field were contacted seeking further studies.

One reviewer (JM) screened the title and abstract of all studies for inclusion. A second reviewer (JC) independently screened a sample of 1000 of the titles and abstracts. The kappa statistic for agreement showed good agreement between reviewers ($k = 0.69$, 95 % confidence interval 0.59–0.79). Full text was obtained for all potential articles of interest. All full texts were assessed for eligibility (see Box 1) by two reviewers (JM and JC). Disagreements were resolved by consensus, or referred to a third reviewer (RP, five studies referred).

Box 1: Inclusion criteria

Study design: Randomised controlled trials, quasi-randomised controlled trials and prospective observational cohorts

Population: Aged <18 years with low-risk fever and neutropenia secondary to treatment for cancer, or results available for this subgroup

Interventions: One or more of

- Location of treatment—inpatient, outpatient or initial inpatient with early discharge to outpatient
- Route of antibiotic administration—intravenous, oral or intravenous with switch to oral (IVOST)

Outcomes: One or more of

- Treatment failure at 30 days—persistence, worsening or recurrence of fever/infecting organisms, modification of antibiotics, new infections, re-admission, admission to critical care services or death during treatment
- Safety—medical complications, defined as admission to critical care services or death
- Adequacy—resolution of the episode without change in antibiotic or location of the patient

Data were extracted by one researcher and independently checked by a second. The risk of bias was assessed using the Cochrane risk of bias tool for controlled trials and the NICE prognostic studies tool for observational cohorts [13, 14].

For the purpose of this review, the timing of discharge was grouped into outpatient (admission of less than 8 h), <24 h, 24–48 h, >48 h and entirely inpatient treatment. Early discharge is used to refer to all categories except entirely inpatient treatment, unless otherwise specified.

For each outcome, study level data were combined with a random-effects model using the DerSimonian and Laird estimator. Heterogeneity was examined using χ^2 test, the I^2 and tau^2 statistic and by visual inspection of forest plots. I^2 represents a quantitative assessment of the degree of statistical

heterogeneity beyond that expected by chance. Meanwhile, tau^2 provides an estimate of the between-study variance.

Subgroup and sensitivity analyses were performed as planned [12]. For the purpose of sensitivity analyses, as the studies used a variety of methods of risk stratification, the risk tools were grouped into more or less stringent tools. The more stringent tools generally required a period of observation after presentation, excluded very young patients, patients following BMT or with leukaemia (except ALL on maintenance), those with a neutrophil count $<0.1 \times 10^9$/L and patients with respiratory symptoms. Less stringent rules all had only two or three exclusion criteria which were not restrictive. For example, a less stringent rule might exclude patients with signs of sepsis and those with social concerns such as no reliable caregiver but allow the inclusion of all other patients, regardless of age, underlying diagnosis and neutrophil count. The risk of publication bias was explored using contour-enhanced funnel plots and the Harbord and Peters tests.

Results

Two thousand three hundred seventy titles and abstracts were assessed and 112 full text articles retrieved (see Fig. 1). The 80 full-text articles excluded are detailed in Online Resource 2. Five further studies were identified from the review of conference proceedings and reference searches.

Of the 37 included studies, 12 are RCTs [15–26]. One further RCT was identified but was not included in the RCT analyses as it compared early discharge on oral antibiotics with early discharge on an oral placebo [27]. However, the individual arms of this trial have been included in the analyses of the observational cohorts. No quasi-randomised trials were identified by the searches. Twenty-four observational cohorts are included, describing 26 separate treatment cohorts [7, 28–50] (Online Resources 3 and 4).

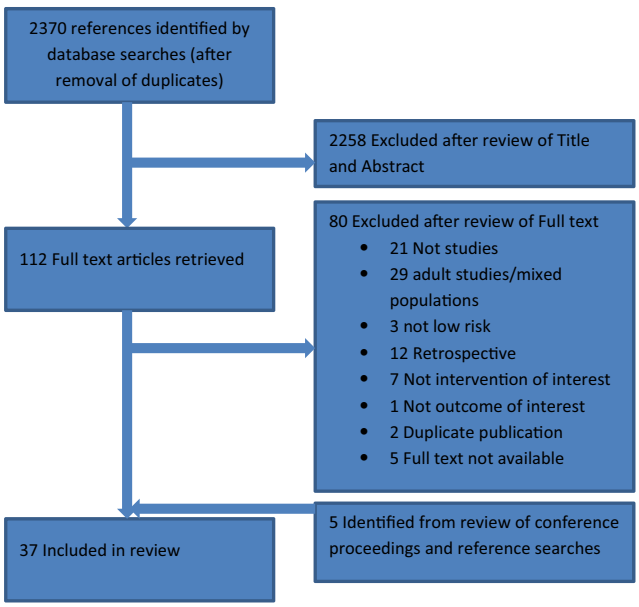

Fig. 1 Flow diagram for study selection

Multiple different risk stratification tools were used by the included studies; the majority of which were unnamed and unvalidated. The tools were grouped as described within "Methods". Twenty-five studies used more stringent tools and eight used less stringent tools. Four studies did not describe their risk stratification tool in enough detail to allow classification of the tool.

Risk of bias

All but one of the RCTs showed a moderate risk of bias as participants and outcome assessors were not blinded to the intervention received. Some outcomes are unlikely to be affected by this lack of blinding, including admission to critical care services or death. Other outcomes, particularly treatment failure, which are more susceptible to bias, have been specifically selected as pragmatic reflections of standard clinical practices such that the outcomes of unblinded studies are informative. Other than the issue of blinding, the RCTs were generally at low risk of bias, as were the prospective observational cohorts (see Table 1).

Adequacy

No studies explored the concept of adequacy outwith the definition of treatment failure. The timing of the final aspect of risk stratification universally matched the timing of discharge, and, hence, planned subgroup analyses of the timing of risk stratification were not performed.

Safety

There were two deaths within the data from the RCTs (12 studies, 1291 episodes) [15–27]. One child died of an adenovirus infection on day 10 of treatment. The second died of a *Pseudomonas aeruginosa* infection after an acute deterioration on day 3 (notably, this child was well until day 3 and had negative blood cultures on admission). Both patients were treated entirely with intravenous inpatient therapy. Further two safety events were identified in the observational cohorts (total 2663 episodes, 42 arms) [7, 15–34, 36–44, 46–50]. These two patients were admitted to intensive care; one with pneumonia and one with diarrhoea causing hypotension. Neither patient died. Both had been treated with oral therapy as outpatients from presentation. Therefore, the proportion of low risk episodes which resulted in intensive care or death is 0.1 % (95% confidence interval (95%CI) 0.03–0.3 %).

Table 1 Risk of bias tables

Randomised controlled trials

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Brack et al. [15]	−	−	+	+	−	−
Cagol et al. [16]	−	−	+	+	?	?
Gupta et al. [17]	−	?	+	+	−	−
Klaassen et al. [27]	−	?	−	−	−	−
Mullen et al. [18]	−	−	+	+	−	−
Orme et al. [19]	−	?	+	+	−	−
Paganini et al. [20]	−	−	+	+	−	−
Paganini et al. [21]	−	−	+	+	−	−
Paganini et al. [22]	−	−	+	+	−	−
Petrilli et al. [23]	?	?	+	+	−	−
Santolaya et al. [24]	?	?	+	+	−	−
Shenep et al. [25]	−	?	+	+	−	−
Varan et al. [26]	?	?	+	+	−	−

Prospective observational cohorts

	Population of interest	Loss to follow-up	Prognostic factor	Outcome of interest	Potential confounders	Statistical analysis
Abbas et al. [28]	−	−	−	−	−	−
Aquino et al. [29]	−	−	−	−	−	−
Bash et al. [30]	−	−	−	−	−	−
Dommett et al. [31]	−	−	−	−	−	?
Doyle et al. [32]	−	−	−	−	−	−
Fernandez et al. [33]	−	−	−	−	−	−
Kaplinsky et al. [34]	−	?	−	−	−	−
Karthaus et al. [35]	−	−	−	−	−	−
Lau et al. [36]	−	−	−	−	?	−
Malik [37]	−	−	−	−	−	−
Miedema et al. [38]	−	?	−	?	−	−
Mustafa et al. [7]	−	−	−	−	−	−
Paganini et al. [39]	−	?	−	−	−	−
Paganini [40]		−	−	−	−	−
Paganini [41]	−	−	−	−	−	−
Park et al. [42]	?	−	−	−	−	−
Petrilli et al. [43]	−	−	−	?	−	−
Phillips et al. [44]	?	−	−	−	−	−
Preis et al. [45]	?	−	−	?	−	−
Quezada et al. [46]	−	−	?	?	?	−
Sari et al. [47]	−	−	−	?	−	−
Shrestha et al. [48]	−	?	−	−	−	−
Tordecilla et al. [49]	−	?	?	?	−	−
Wiernikowski et al. [50]	?	−	−	−	−	−

Key: − low risk of bias, *?* unclear risk of bias, + high risk of bias

Treatment failure

Three RCTs compared the risk of treatment failure between inpatient and outpatient treatment, including discharge up to 48 h after admission [15, 19, 24]. The odds ratio for failure with outpatient treatment was 0.98 (95%CI 0.44–2.19, $I^2 = 0$ %, $\text{tau}^2 = 0$). There were insufficient trials for subgroup analyses, providing no clear evidence of a difference in failure rates between these treatment settings.

Eight RCTs compared the risk of treatment failure between intravenous and oral therapies, including change to oral medications up to 48 h after presentation [15–18, 20, 22, 23, 25].

The odds ratio for failure with oral treatment was 1.05 (95%CI 0.74–1.48 $I^2=0$ %, $tau^2=0$), providing evidence of no clear difference between the two approaches.

Treatment failure rates were then further explored using data derived from the observational cohorts combined with the individual arms of the RCTs. Within these data, 42 prospective arms in which patients were treated on any outpatient or early discharge regimen were included [7, 15, 17–24, 26–43, 46, 49, 50]. The estimated rate of failure using these approaches was 11.2 % (95%CI 9.7–12.8 %, $I^2=77.2$ %) and included patients treated on any outpatient or early discharge regimen.

Given the significant clinical and statistical heterogeneity in this group, this combined estimate suggests there are features of an early discharge strategy which will alter the risk of treatment failure. We therefore proceeded to analyse these as subgroups split by timing of discharge. For studies including patients treated entirely as outpatients, the treatment failure rate was 14 % (95%CI 9.7–19 %, $I^2=81.93$ %, Fig. 2a). The rate of failure for the seven studies of patients receiving early discharge after 48 h was 2.2 % (95%CI 1.2–4.1 %, $I^2=0$ %, Fig. 2b).

Thirty-four cohorts (from observational cohort studies and the individual arms of the RCTs) were included in the assessment of treatment failures following any oral therapy regimen

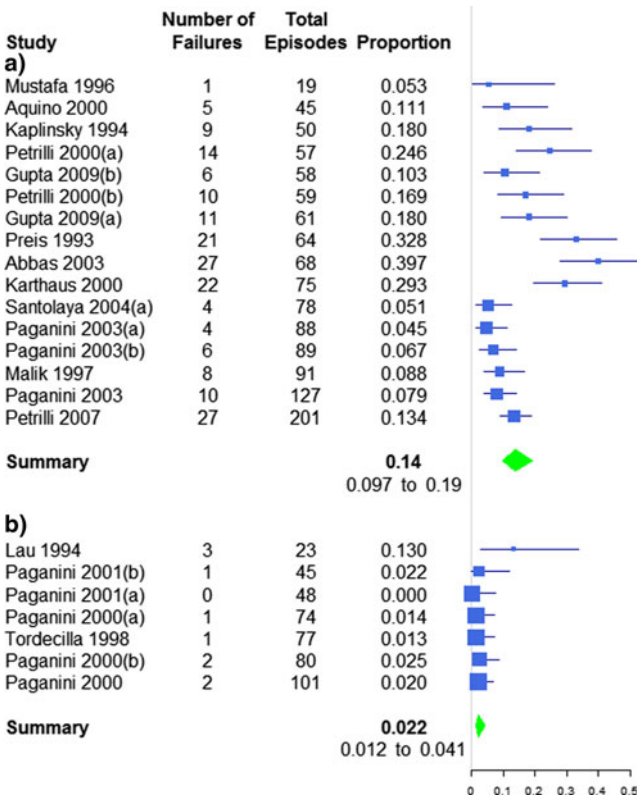

Fig. 2 Forest plots of rates of treatment failure in **a** studies treating patients entirely as outpatients and **b** studies discharging patients early after at least 48 h of inpatient care

[15–27, 29–33, 36, 37, 39–43, 46–49]. The estimated rate of failure using this approach was 10.5 % (95%CI 8.9–12.3 %, $I^2=78.3$ %) Due to high heterogeneity in this composite analysis, we again proceeded to subgroup analysis based on timing of change to oral antibiotics. The rate of failure for those receiving oral antibiotics after 48 h of intravenous administration was 3.4 % (95%CI 2–5.7 %, $I^2=11.21$ %), and for patients treated entirely with oral antibiotics, the rates of treatment failure were 17 % (95%CI 12–25 %, $I^2=74.45$ %).

Sensitivity analyses

The rates of the outcome measures were unaffected by the use of full-text articles alone, fixed effect meta-analysis or location of the study. There is a suggestion that using a more stringent risk stratification tool reduces the rates of treatment failure, as might be expected given the features used in risk tools. When considering the location of treatment, studies using the most stringent risk tools report failure rates of 7 % (95%CI 4.7–10.3 %, $I^2=82.31$ %) compared with failure rates of 19.1 % (95%CI 11.7–29.6 %, $I^2=77.15$ %) in studies with the least stringent risk tools. Similarly, regarding the route of administration of antibiotics, studies using the most stringent risk tools reported failure rates of 7.8 % (95%CI 5.2–11.6 %, $I^2=85.33$ %). There were only two studies exploring the route of administration of antibiotics and using less stringent tool. These found a failure rate between 8.8 and 51 %.

Publication bias

As the meta-analyses which provided the estimates of rates of treatment failure included the largest numbers of studies, we assessed publication bias primarily using these studies. When examining the studies which reported patients receiving early discharge or outpatient care, the Peters test did not reveal evidence of heterogeneity ($p=0.21$) whilst the Harbord test suggested that publication bias might be present ($p<0.001$). Examination of the contour-enhanced funnel plot (Fig. 3a) reveals that there is a widespread of the proportion of failures in studies with small standard error, but that in studies with a larger standard error, few evidenced high levels of treatment failure. This pattern does not differ between RCTs and observational cohorts. In the arms relating to oral antibiotic regimens, both the Harbord and Peters tests suggest publication bias ($p=0.06$ and 0.004, respectively), whilst the funnel plot (Fig. 3b) presents a similar picture to that of location.

Refusal to consent

Ten studies provided data on refusals to participate (Table 2) [15, 18, 19, 24, 25, 32, 36, 42, 46, 50]. The data provided were very heterogeneous and thus not amenable to meta-analysis. However, the data can be conceptually grouped into the issues

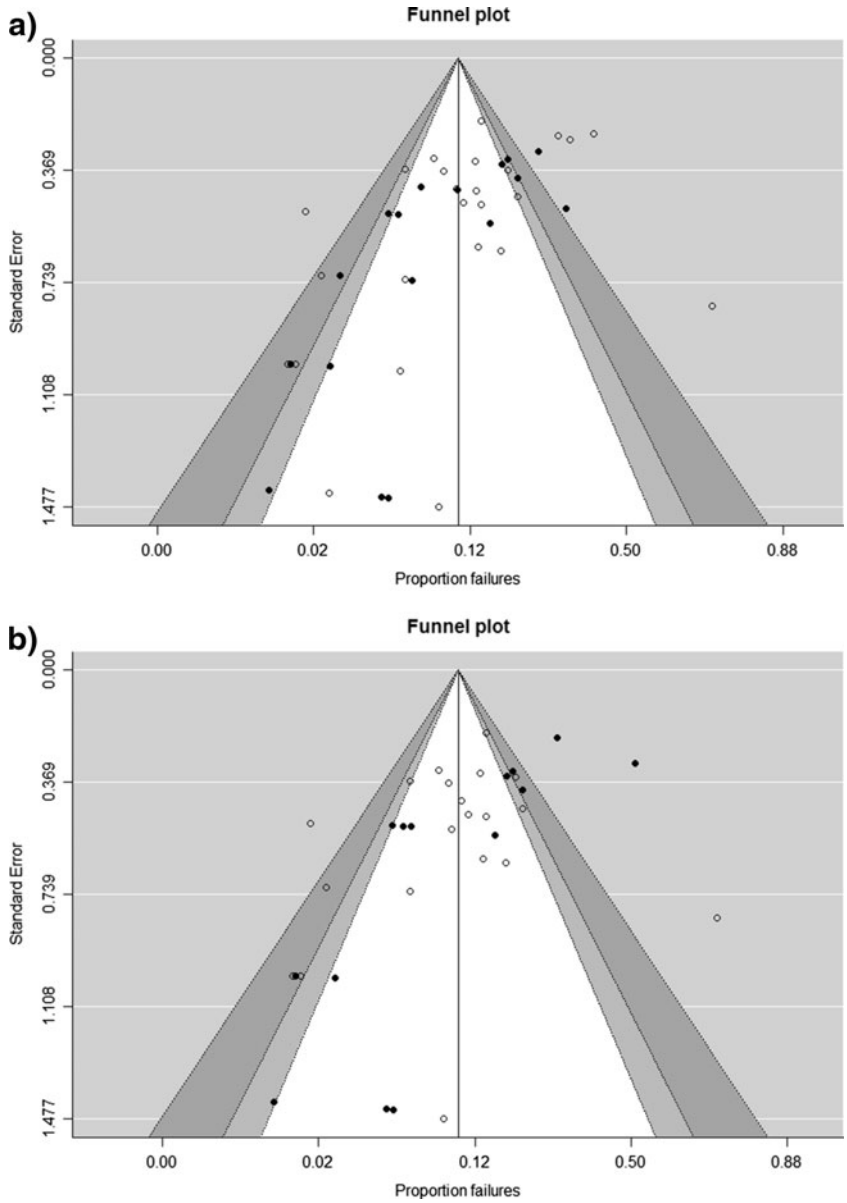

Fig. 3 Contour-enhanced funnel plots for treatment failure in **a** early discharge or entirely outpatient treatment and **b** IVOST or oral antibiotic regimens

of refusal to enrol in a study and refusal to confirm consent following enrolment (in study designs when enrolment takes place prior to episodes of febrile neutropenia and then further consent is sought at the time of presentation with an episode).

Eight studies looked at failure to consent to enrolment in the study. They found 147 of 782 patients (18.8 %, range 1.3–30.1 %) who were eligible for enrolment refused to participate. Two of these studies also included data on episodes that were not enrolled as the physician was uninterested or not willing for the patient to take part. These found that in 19.6–26.5 % of otherwise eligible episodes, the treating physician chose not to enrol the patient in the study.

Three studies provided data on confirmation of consent following enrolment. One looked at physicians' attitudes and found that in 7 (14 %) of 50 otherwise eligible episodes, the oncologist decided not to include the patient in the study. Meanwhile, two studies examined parental confirmation and found refusals of 8.3 and 12 % of eligible episodes. Finally, one study did not separate parental and physician refusal to confirm consent, but found that 8 of 67 episodes in enrolled patients were not included due to the preference of the physician or family.

Discussion

Outpatient therapy and oral antibiotics are safe treatment options for paediatric low-risk febrile neutropenia. The episodes included in this review had a very low risk of death or

Table 2 Refusal to consent data

Study	Concept described	Refusal by parents	Refusal by physicians	Total number of episodes	Notes
Brack et al. [15]	Enrolment	25	NA	93	
Doyle et al. [32]	Enrolment	5	NA	84	
Lau et al. [36]	Enrolment	5	NA	29	
Mullen et al. [18]	Enrolment	12	13	66	
Park et al. [42]	Enrolment	9	NA	39	Includes inability to take oral antibiotics
Quezada et al. [46]	Enrolment	3	9	34	First year of study only
Santolaya et al. [24]	Enrolment	2	NA	151	
Shenep et al. [25]	Enrolment	86	NA	286	
Orme et al. [19]	Confirmation following enrolment	6	7	50	
Quezada et al. [46]	Confirmation following enrolment	8	Included with parental refusal	67	
Wiernikowski et al. [50]	Confirmation following enrolment	2	NA	24	

NA not applicable

admission to critical care services. Furthermore, for the few adverse events observed, there was no obvious association between the occurrence and route or location of treatment. Remaining as an inpatient receiving intravenous antibiotics did not prevent all deaths within this group. This should be clearly recognised: low risk-febrile neutropenia is not 'no risk febrile neutropenia'. The overall rates of treatment failure are also low.

We found that studies that moved patients from a more intensive regimen to a reduced regime at 24 or 48 h had lower rates of treatment failure than those who were treated entirely on reduced regimes. This is an indirect comparison of observational cohorts, which may also differ by factors other than treatment protocol, making it inappropriate to draw firm conclusions. However, the finding is clinically plausible. Given this difference, a combined estimate of treatment failure rates is not meaningful and it would be seem prudent to use rates for each group separately to inform the design of future services.

For some studies, the reasons for re-admission, and therefore treatment failure, were clearly reported. In others, they were unclear or not documented. Where provided, the indications were variable (such that failure rate recorded within studies is driven by the components of the definition of treatment failure). For example, in some studies, a single repeated fever after reduction in therapy would be defined and counted as a treatment failure. This does not necessarily describe an unwell child and may not be of concern to either parents or clinicians. Additionally, where a child is on a reduced regime, there may be a tendency for physicians to increase therapy more rapidly than for children where standard, more familiar, treatment is already ongoing. Thus, the estimates of treatment failures within this review may be higher than the rates of clinically meaningful deterioration for children on reduced therapy regimens.

In the exploration of treatment failure in relation to the timing of discharge, we also note that a substantial proportion of data is from one group (Paganini et al.). Most data about discharge after at least 48 h of inpatient care are provided by this group. Along with this, the studies examining patients treated entirely as outpatients seem to be grouped within the forest plot into two distinct areas. Studies with smaller numbers of episodes have more variable failure rates compared to those with more episodes. Interestingly, the treatment failure rates in larger studies seem to be lower than for smaller studies, however, again the Paganini group provide much of these data. Therefore, it is unclear whether these differences are due to variations in treatment failure at the various time points or whether they are instead due to the impact of this group's definitions and approaches.

Within the literature, two previous systematic reviews have considered the role of both outpatient therapy and oral antibiotics and have generally found that these approaches are safe and efficacious. However, both reviews had areas for improvement. The Cochrane review focused mainly on adult patients, included only eight RCTs and examined the impact

of oral antibiotics alone, without consideration of the role of location of treatment [10]. Meanwhile, Manji et al. focused only on the broad concepts of outpatient and oral therapy and combined data from very different groups, resulting in the loss of some of the nuanced information from the original trials [9]. Furthermore, neither review included non-English studies despite the presence of very active research groups from South America.

Our review had more focused aims and objectives, a more extensive search strategy and considered the large volume of prospective observational cohort data that exists in this area. It provides more depth and clarity to the prior works.

When considered alongside the results of the two previous reviews by the Cochrane group and Manji et al., our work reinforces the conclusion that reduced therapy can be safely achieved in children with low-risk febrile neutropenia [9, 10]. However, our treatment failure rates contrast with those of Manji et al. [9]. The previous review had found that treatment failure was more likely in patients treated as inpatients than those who received outpatient care. Our review has found that the rate of treatment failure was higher in the group who were treated as outpatients earlier in their course. This difference in results is likely to be due to the differences in inclusion criteria for the two reviews, resulting in the comparison of different inpatient regimens. The Cochrane review by Vidal et al. found similar rates of failure for intravenous and oral regimens as our review [10].

We found there are high rates of refusal to participate in trials of these regimens, which relate to both families and physicians. In many areas of research, a refusal to consent rate of up to 30 % may not be considered problematic. However, in the context of children's cancer where high recruitment rates are generally seen, this rate of refusal is noteworthy [51]. Refusal to consent to enrolment was generally greater than refusal to confirm consent following enrolment. In studies that examined the number of refusals by physicians, these were similar to or greater than the refusals by parents. This may reflect physician refusal as a proxy for parents, or alternatively may represent uncertainty amongst physicians about the safety or efficacy of reduced therapy. No studies provided data on why families and physicians refused to participate, but two discussed potential issues. They used anecdotal evidence to describe practical issues as a potential barrier to participation for families, whilst a perceived lack of safety may be an issue for both families and physicians considering reduced therapy options.

The main strength of our work is in the examination of a large amount of data. The RCTs are few, and although they suggest that reduced therapy regimens are safe, the additional consideration of observational cohort data provides further support for these strategies. The inclusion of a large number of episodes also allows the consideration of the issue of timing in early discharge so as to inform service development in this area.

The main weakness within this work is its inability to completely define the features of a low-risk strategy that result in the lowest rates of treatment failure. This is mostly due to the considerable heterogeneity within the literature, with regards to the inclusion criteria and interventions used. In particular, we were unable to fully explore the influence of various risk stratification tools, as a large number of tools were used by the studies and thus sensitivity analysis could only be performed using broad groups.

Future work should consider further defining the features of a reduced therapy regime that influence failure rates, including the risk stratification tool, the definitions of treatment failure and the timings of assessment, discharge and change to oral antibiotics. Researchers should also intend to explore the issues surrounding the acceptance of reduced therapy, specifically looking for potential barriers and facilitators, and the differences in perspectives between families and health care professionals.

Conclusions

Reduced therapy regimens for paediatric low-risk febrile neutropenia are safe and have low rates of treatment failure. The adverse events observed seem to occur regardless of the route or location of treatment. The risk of treatment failure seemed to be higher when reduced intensity therapies were used immediately after assessment, with lower rates observed when these were introduced after 48 h. High rates of refusal to participate in trials of these regimens, by both families and physicians, require further investigation.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no competing interests.

References

1. Basu SK, Fernandez ID, Fisher SG, Asselin BL, Lyman GH (2005) Length of stay and mortality associated with febrile neutropenia among children with cancer. J Clin Oncol 23(31):7958–7966
2. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F et al (2007) 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 45(10):1296–1304
3. Ammann RA, Teuffel O, Agyeman P, Amport N, Leibundgut K (2015) The influence of different fever definitions on the rate of fever in neutropenia diagnosed in children with cancer. PLoS One 10(2), e0117528
4. Phillips RS, Lehrnbecher T, Alexander S, Sung L (2012) Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. PLoS One 7(5), e38300
5. Teuffel O, Cheng S, Ethier MC, Diorio C, Martino J, Mayo C et al (2012) Health-related quality of life anticipated with different management strategies for febrile neutropenia in adult cancer patients. Support Care Cancer Off J Multinatl Assoc Support Care Cancer 20(11):2755–2764
6. Sung L, Aplenc R, Alonzo TA, Gerbing RB, Lehrnbecher T, Gamis AS (2013) Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group. Blood 121(18):3573–3577
7. Mustafa MM, Aquino VM, Pappo A, Tkaczewski I, Buchanan GR (1996) A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. J Pediatr 128(6): 847–849
8. Teuffel O, Amir E, Alibhai SMH, Beyene J, Sung L (2011) Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. Pediatrics 127(2):e279–e286
9. Manji A, Beyene J, Dupuis LL, Phillips R, Lehrnbecher T, Sung L (2012) Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children—a systematic review of prospective trials. Support Care Cancer 20(6):1135–1145
10. Vidal L, Ben Dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K et al (2013) Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst Rev 10, CD003992
11. Feld R, Paesmans M, Freifeld AG, Klastersky J, Pizzo PA, Rolston KVI et al (2002) Methodology for clinical trials involving patients with cancer who have febrile neutropenia: updated guidelines of the immunocompromised host society/multinational association for supportive care in cancer, with emphasis on outpatient studies. Clin Infect Dis 35(12):1463–1468
12. Morgan JE, Stewart L, Phillips RS (2014) Protocol for a systematic review of reductions in therapy for children with low-risk febrile neutropenia. Syst Rev 3(1):119
13. Higgins JPT, Green S, editors (2011) Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Verrsion 5.1.0. The Cochrane Collaboration. Available from: www.cochrane-handbook.org
14. National Institute for Health and Clinical Excellence. Appendix I: Methodology checklist: prognostic studies. From The guidelines manual [Internet]. London: National Institute for Health and Clinical Excellence; 2012 [cited 2014 Feb 14]. Available from: www.nice.org.uk/article/pmg6b/chapter/Appendix-I-Methodology-checklist-prognostic-studies
15. Brack E, Bodmer N, Simon A, Leibundgut K, Kuhne T, Niggli FK et al (2012) First-day step-down to oral outpatient treatment versus continued standard treatment in children with cancer and low-risk fever in neutropenia. A randomized controlled trial within the multicenter SPOG 2003 FN study. Pediatr Blood Cancer 59(3):423–430
16. Cagol AR, Castro Junior CG, Martins MC, Machado AL, Ribeiro RC, Gregianin LJ et al (2009) Oral vs. intravenous empirical antimicrobial therapy in febrile neutropenic patients receiving childhood cancer chemotherapy. J Pediatr (Rio J) 85(6):531–535
17. Gupta A, Swaroop C, Agarwala S, Pandey RM, Bakhshi S (2009) Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol 31(9):635–641
18. Mullen CA, Petropoulos D, Roberts WM, Rytting M, Zipf T, Chan KW et al (1999) Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. Cancer 86(1):126–134
19. Orme L, Babl F, Barnes C, Barnett P, Donath S, Ashley D (2014) Outpatient versus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: a randomised trial. Pediatr Blood Cancer 61:1427–1433
20. Paganini H, Gomez S, Ruvinsky S, Zubizarreta P, Latella A, Fraquelli L et al (2003) Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina. Cancer 97(7):1775–1780
21. Paganini H, Rodriguez-Brieshcke T, Zubizarreta P, Latella A, Firpo V, Casimir L et al (2001) Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. Cancer 91(8):1563–1567
22. Paganini HR, Sarkis CM, De Martino MG, Zubizarreta PA, Casimir L, Fernandez C et al (2000) Oral administration of cefixime to lower risk febrile neutropenic children with cancer. Cancer 88(12):2848–2852
23. Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A (2000) Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. Med Pediatr Oncol 34(2):87–91
24. Santolaya ME, Alvarez AM, Aviles CL, Becker A, Cofre J, Cumsille MA et al (2004) Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. J Clin Oncol 22(18):3784–3789
25. Shenep JL, Flynn PM, Baker DK, Hetherington SV, Hudson MM, Hughes WT et al (2001) Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer. Clin Infect Dis 32(1):36–43
26. Varan A, Koksal Y, Akyuz C, Ceyhan M, Kanra G, Buyukpamukcu M (2005) The outpatient management of febrile neutropenia in selected children with cancer: a preliminary report. Pediatr Blood Cancer 45(4):512
27. Klaassen RJ, Allen U, Doyle JJ (2000) Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. J Pediatr Hematol Oncol 22(5):405–411
28. Abbas AAH, Felimban SK, Cittana BA, Yousef AA, Fayea NY, Khattab TM et al (2003) Once daily ceftriaxone and amikacin for outpatient treatment of neutropenic fever in children with acute lymphoblastic leukaemia. Haema 6(4):501–506
29. Aquino VM, Herrera L, Sandler ES, Buchanan GR (2000) Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer. Cancer 88(7): 1710–1714
30. Bash RO, Katz JA, Cash JV, Buchanan GR (1994) Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. Cancer 74(1):189–196
31. Dommett R, Geary J, Freeman S, Hartley J, Sharland M, Davidson A et al (2009) Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. Eur J Cancer 45(16):2843–2849
32. Doyle JJ, King SM, Comay SA, Freedman MH (1996) Oral antibiotic therapy for "low risk" febrile neutropenic episodes (fne). Pediatr Res 39(S4):154
33. Fernandez CM, Saavedra-Lozano J, Huerta J, Garrido C, Belendez C, Cela E et al (2012) Risk-based therapy for febrile patients with

neutropenia: a role for early hospital discharge. Pediatr Blood Cancer 59(6):1113–1114
34. Kaplinsky C, Drucker M, Goshen J, Tamary H, Cohen IJ, Zaizov R (1994) Ambulatory treatment with ceftriaxone in febrile neutropenic children. Isr J Med Sci 30(8):649–651
35. Karthaus M, Egerer G, Jurgens H (2000) Outpatient treatment of cancer patients with fever and neutropenia. Antibiot Chemother 50: 47–58
36. Lau RC, Doyle JJ, Freedman MH, King SM, Richardson SE (1994) Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. Pediatr Hematol Oncol 11(4):417–421
37. Malik IA (1997) Out-patient management of febrile neutropenia in indigent paediatric patients. Ann Acad Med Singapore 26(6):742–746
38. Miedema K, Tissing W, Van Vliet M, De Vries W, Kamps W, Abbink F et al (2012) Risk-adapted approach for fever and neutropenia in pediatric cancer patients. Support Care Cancer 20:S155
39. Paganini HR, Rodriguez Brieshcke T, Zubizarreta P, Latella A, Firpo V, Fernandez C et al (2001) Criteria of low risk of mortality in children with neutropenia and fever during cancer chemotherapy. Medicina (Mex) 61(1):63–66
40. Paganini H (2003) Tratamiento ambulatorio secuencia parenteral-oral de niños con neutropenia y fiebre de riesgo de mortalidad Sequential oral-parenteral outpatient treatment on low-risk children with fever and neutropenia. Arch Argent Pediatr 101(1):31–36
41. Paganini H (2000) Tratamiento secuencial parenteral-oral con antibióticos en niños con patología onco-hematológica con bajo riesgo de bacteriemia Sequential antibiotic parenteral-oral therapy in onco-hematologic patients with low-risk for bacteriemia. Arch Argent Pediatr 98(5):291–295
42. Park JR, Coughlin J, Hawkins D, Friedman DL, Burns JL, Pendergrass T (2003) Ciprofloxacin and amoxicillin as continuation treatment of febrile neutropenia in pediatric cancer patients. Med Pediatr Oncol 40(2):93–98
43. Petrilli AS, Carlesse FA, Pereira CAP (2007) Oral gatifloxacin in the outpatient treatment of children with cancer fever and neutropenia. Pediatr Blood Cancer 49(5):682–686
44. Phillips R, Phelan L, Picton S (2006) An audit of the use of oral antibiotics and early discharge in the treatment of low risk febrile neutropenia in children. Arch Dis Child 91(Suppl 1):A80–A82
45. Preis S, Jurgens H, Friedland C, Oudekotte-David AA, Thomas L, Gobel U (1993) Ceftriaxone alone or in combination with teicoplanin in the management of febrile episodes in neutropenic children and adolescents with cancer on an outpatient base. Klin Padiatr 205(4):295–299
46. Quezada G, Sunderland T, Chan KW, Rolston K, Mullen CA (2007) Medical and non-medical barriers to outpatient treatment of fever and neutropenia in children with cancer. Pediatr Blood Cancer 48(3):273–277
47. Sari N, Aki A, Ocal R, Karaman N, Ilhan I (2007) Oral ciprofloxacin and amoxicillin/clavulanate treatment in pediatric cancer patients with low-risk febrile neutropenia. Pediatr Blood Cancer. 481
48. Shrestha PN, Sah KP, Rana R (2009) Emperical oral antibiotic therapy for children with low risk febrile neutropenia during cancer chemotherapy. J Nepal Paediatr Soc 29(1):22–25
49. Tordecilla CJ, Campbell Bull M, Joannon SP, Rizzardini LC, Soto AV (1998) Criterios de alta precoz en niños con cáncer y neutropenia febril criteria of early discharge in children with cancer and febrile neutropenia. Rev Chil Pediatr 69(6):247–251
50. Wiernikowski JT, Rothney M, Dawson S, Andrew M (1991) Evaluation of a home intravenous antibiotic program in pediatric oncology. Am J Pediatr Hematol Oncol 13(2):144–147
51. Ablett S, Pinkerton CR (2003) Recruiting children into cancer trials—role of the United Kingdom Children's Cancer Study Group (UKCCSG). Br J Cancer 88(11):1661–1665