

This is a repository copy of *Systematic review of reduced therapy regimens for children with low risk febrile neutropenia*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/93792/>

Version: Accepted Version

Article:

Morgan, Jessica E., Cleminson, Jemma, Atkin, Karl orcid.org/0000-0003-1070-8670 et al. (2 more authors) (2016) Systematic review of reduced therapy regimens for children with low risk febrile neutropenia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2651–2660. ISSN: 1433-7339

<https://doi.org/10.1007/s00520-016-3074-9>

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

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

Jessica Morgan^{1,2}, Jemma Cleminson¹, Karl Atkin³, Lesley A Stewart¹, Robert S Phillips^{1,2}

Affiliations: ¹ Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK; ² Department of Paediatric Haematology and Oncology, Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds, LS1 3EX, UK; ³Department of Health Sciences, University of York, Heslington, York, YO10 5DD, UK.

Address for correspondence: Dr Jessica Morgan, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK, jem539@york.ac.uk, Tel: +44 (0)1904 321082, Fax: +44 (0)1904 321041

Keywords: paediatric, febrile neutropenia, systematic review, outpatient, oral antibiotics

Main paper word count: 3087

Abstract word count: 249

Number of Figures: 3

• Captions:

- Figure 1: Flow diagram for study selection
- Figure 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 hours of inpatient care
- Figure 3: Contour-enhanced funnel plots for treatment failure in a) early discharge or entirely outpatient treatment and b) IVOST or oral antibiotic regimens

Number of Table

s: ~~2~~4

• Caption:

- ~~Table 1: Risk of bias tables~~
- Table ~~2~~4: Refusal to consent data (NA – not applicable)

Number of Online Resources: ~~4~~5

- Online Resource 1: Database search strategies
- Online Resource 2: Reasons for study exclusions
- Online Resource 3: Demographics of included studies
- Online Resource 4: Study interventions and definitions
- ~~Online Resource 5: Risk of bias tables~~

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

37 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.

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 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 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. 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, 5 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. 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 hours), <24 hours, 24-48hrs, >48 hours 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 & Laird estimator. Heterogeneity was examined using χ^2 test, the I^2 and τ^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 τ^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 Harbord and Peters tests.

Results

2370 titles and abstracts were assessed and 112 full text articles retrieved (see Figure 1). The 80 full text articles excluded are detailed in Online Resource 2. Five further studies were identified from review of conference proceedings and reference searches.

Of the 37 included studies, 12 are RCTs. (15–17, 19–27) 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.(18) 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.)

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 the 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 12).

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. A 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%).

Treatment failure

Three RCTs compared the risk of treatment failure between inpatient and outpatient treatment, including discharge up to 48 hours after admission. (15,20,25) The odds ratio for failure with outpatient treatment was 0.98 (95% CI 0.44–2.19, $I^2=0\%$, $\tau^2=0$). 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 hours after presentation. (15–17,19,21,23,24,26) 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. (7,15,17–25,27–43,46,49,50) 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%, $I^2=81.93\%$, Figure 2a). The rate of failure for the seven studies of patients receiving early discharge after 48 hours was 2.2% (95%CI 1.2–4.1%, $I^2=0\%$, Figure 2b).

34 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. (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 hours 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 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, Peters test did not reveal evidence of heterogeneity ($p=0.21$) whilst Harbord's test suggested that publication bias might be present ($p<0.001$). Examination of the contour enhanced funnel plot (Figure 3a) reveals that there is a wide spread of 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 Harbord and Peters tests suggest publication bias ($p=0.06$ and 0.004 respectively), whilst the funnel plot (Figure 3b) presents a similar picture to that of location.

Refusal to consent

10 studies provided data on refusals to participate (Table 2+). (15,19,20,25,26,32,36,42,46,50) The data provided were very heterogeneous and thus not amenable to meta-analysis. However the data can be conceptually grouped into the issues 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 admission to critical care services. Furthermore, for the few adverse events observed, there was no obvious association between 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 hours 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 hours 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 hours. High rates of refusal to participate in trials of these regimens, by both families and physicians, require further investigation.

Acknowledgements: We would like to acknowledge Kate Lewis-Light for her work on the searching for this review.

Funding: JM is funded by Candlelighters children's charity (Registered Charity No: 1045077) for the PhD of which this systematic review is a part.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Basu SK, Fernandez ID, Fisher SG, Asselin BL, Lyman GH. Length of Stay and Mortality Associated With Febrile Neutropenia Among Children With Cancer. *J Clin Oncol*. 2005 Nov 1;23(31):7958–66.
2. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F, et al. A Prospective Study on the Epidemiology of Febrile Episodes during Chemotherapy-Induced Neutropenia in Children with Cancer or after Hemopoietic Stem Cell Transplantation. *Clin Infect Dis*. 2007 Nov 15;45(10):1296–304.
3. Ammann RA, Teuffel O, Agyeman P, Amport N, Leibundgut K. The influence of different fever definitions on the rate of fever in neutropenia diagnosed in children with cancer. *PLoS One*. 2015;10(2):e0117528.
4. Phillips RS, Lehrnbecher T, Alexander S, Sung L. Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. *PLoS One*. 2012;7(5):e38300.
5. Teuffel O, Cheng S, Ethier MC, Diorio C, Martino J, Mayo C, et al. 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*. 2012 Nov;20(11):2755–64.
6. Sung L, Aplenc R, Alonzo TA, Gerbing RB, Lehrnbecher T, Gamis AS. Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group. *Blood*. 2013 May 2;121(18):3573–7.
7. Mustafa MM, Aquino VM, Pappo A, Tkaczewski I, Buchanan GR. A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. *J Pediatr*. 1996 Jun;128(6):847–9.
8. Teuffel O, Amir E, Alibhai SMH, Beyene J, Sung L. Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. *Pediatrics*. 2011 Feb;127(2):e279–86.
9. Manji A, Beyene J, Dupuis LL, Phillips R, Lehrnbecher T, Sung L. Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children - A systematic review of prospective trials. *Support Care Cancer*. 2012;20(6):1135–45.
10. Vidal L, Ben Dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, et al. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database Syst Rev*. 2013;10:CD003992.
11. Feld R, Paesmans M, Freifeld AG, Klastersky J, Pizzo PA, Rolston KVI, et al. 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*. 2002 Dec 15;35(12):1463–8.
12. Morgan JE, Stewart L, Phillips RS. Protocol for a systematic review of reductions in therapy for children with low-risk febrile neutropenia. *Syst Rev*. 2014 Oct 21;3(1):119.

13. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Version 5.1.0. The Cochrane Collaboration; 2011. 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. 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*. 2012;59(3):423–30.
16. Cagol AR, Castro Junior CG, Martins MC, Machado AL, Ribeiro RC, Gregianin LJ, et al. Oral vs. intravenous empirical antimicrobial therapy in febrile neutropenic patients receiving childhood cancer chemotherapy. *J Pediatr (Rio J)*. 2009;85(6):531–5.
17. Gupta A, Swaroop C, Agarwala S, Pandey RM, Bakhshi S. 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*. 2009;31(9):635–41.
18. Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. *J Pediatr Hematol Oncol*. 2000;22(5):405–11.
19. Mullen CA, Petropoulos D, Roberts WM, Rytting M, Zipf T, Chan KW, et al. Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer*. 1999;86(1):126–34.
20. Orme L, Babl F, Barnes C, Barnett P, Donath S, Ashley D. Outpatient Versus Inpatient IV antibiotic Management for Pediatric Oncology Patients with Low Risk Febrile Neutropenia: A Randomised Trial. *Pediatr Blood Cancer*. 2014;61:1427–33.
21. Paganini H, Gomez S, Ruvinsky S, Zubizarreta P, Latella A, Fraquelli L, et al. 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*. 2003;97(7):1775–80.
22. Paganini H, Rodriguez-Brieschcke T, Zubizarreta P, Latella A, Firpo V, Casimir L, et al. Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. *Cancer*. 2001;91(8):1563–7.
23. Paganini HR, Sarkis CM, De Martino MG, Zubizarreta PA, Casimir L, Fernandez C, et al. Oral administration of cefixime to lower risk febrile neutropenic children with cancer. *Cancer*. 2000;88(12):2848–52.
24. Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A. 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*. 2000;34(2):87–91.

25. Santolaya ME, Alvarez AM, Aviles CL, Becker A, Cofre J, Cumsille MA, et al. 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*. 2004;22(18):3784–9.
26. Shenep JL, Flynn PM, Baker DK, Hetherington SV, Hudson MM, Hughes WT, et al. Oral cefixime is similar to continued intravenous antibiotics in the empirical treatment of febrile neutropenic children with cancer. *Clin Infect Dis*. 2001;32(1):36–43.
27. Varan A, Koksai Y, Akyuz C, Ceyhan M, Kanra G, Buyukpamukcu M. The Outpatient Management of Febrile Neutropenia in Selected Children with Cancer; A Preliminary Report. *Pediatr Blood Cancer*. 2005;45(4):512.
28. Abbas AAH, Felimban SK, Cittana BA, Yousef AA, Fayeaa NY, Khattab TM, et al. Once daily ceftriaxone and amikacin for outpatient treatment of neutropenic fever in children with acute lymphoblastic leukaemia. *Haema*. 2003;6(4):501–6.
29. Aquino VM, Herrera L, Sandler ES, Buchanan GR. Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer. *Cancer*. 2000;88(7):1710–4.
30. Bash RO, Katz JA, Cash JV, Buchanan GR. Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. *Cancer*. 1994;74(1):189–96.
31. Dommett R, Geary J, Freeman S, Hartley J, Sharland M, Davidson A, et al. 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*. 2009;45(16):2843–9.
32. Doyle JJ, King SM, Comay SA, Freedman MH. Oral Antibiotic Therapy for “low Risk” Febrile Neutropenic Episodes (fne). *Pediatr Res*. 1996 Apr;39(S4):154–154.
33. Fernandez CM, Saavedra-Lozano J, Huerta J, Garrido C, Belendez C, Cela E, et al. Risk-based therapy for febrile patients with neutropenia: A role for early hospital discharge. *Pediatr Blood Cancer*. 2012;59 (6):1113–4.
34. Kaplinsky C, Drucker M, Goshen J, Tamary H, Cohen IJ, Zaizov R. Ambulatory treatment with ceftriaxone in febrile neutropenic children. *Isr J Med Sci*. 1994;30(8):649–51.
35. Karthaus M, Egerer G, Jurgens H. Outpatient treatment of cancer patients with fever and neutropenia. *Antibiot Chemother*. 2000;50:47–58.
36. Lau RC, Doyle JJ, Freedman MH, King SM, Richardson SE. Early discharge of pediatric febrile neutropenic cancer patients by substitution of oral for intravenous antibiotics. *Pediatr Hematol Oncol*. 1994;11(4):417–21.
37. Malik IA. Out-patient management of febrile neutropenia in indigent paediatric patients. *Ann Acad Med Singapore*. 1997;26(6):742–6.
38. Miedema K, Tissing W, Van Vliet M, De Vries W, Kamps W, Abbink F, et al. Risk-adapted approach for fever and neutropenia in pediatric cancer patients. *Support Care Cancer*. 2012;20:S155.

39. Paganini HR, Rodriguez Brieschcke T, Zubizarreta P, Latella A, Firpo V, Fernandez C, et al. [Criteria of low risk of mortality in children with neutropenia and fever during cancer chemotherapy]. *Medicina (Mex)*. 2001;61(1):63–6.
40. Paganini H. 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*. 2003 02PY - 2003;101(1):31–6.
41. Paganini H. 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*. 2000 10PY - 2000;98(5):291–5.
42. Park JR, Coughlin J, Hawkins D, Friedman DL, Burns JL, Pendergrass T. Ciprofloxacin and amoxicillin as continuation treatment of febrile neutropenia in pediatric cancer patients. *Med Pediatr Oncol*. 2003;40(2):93–8.
43. Petrilli AS, Carlesse FA, Pereira CAP. Oral gatifloxacin in the outpatient treatment of children with cancer fever and neutropenia. *Pediatr Blood Cancer*. 2007;49(5):682–6.
44. Phillips R, Phelan L, Picton S. An audit of the use of oral antibiotics and early discharge in the treatment of low risk febrile neutropenia in children. *Arch Dis Child*. 2006 Apr 1;91 Suppl 1:A80–2.
45. Preis S, Jurgens H, Friedland C, Oudekotte-David AA, Thomas L, Gobel U. 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*. 1993;205(4):295–9.
46. Quezada G, Sunderland T, Chan KW, Rolston K, Mullen CA. Medical and non-medical barriers to outpatient treatment of fever and neutropenia in children with cancer. *Pediatr Blood Cancer*. 2007;48(3):273–7.
47. Sari N, Aki A, Ocal R, Karaman N, Ilhan I. Oral Ciprofloxacin and Amoxicillin/Clavulanate Treatment in Pediatric Cancer Patients with Low-Risk Febrile Neutropenia. *Pediatric Blood and Cancer*; 2007. p. 481.
48. Shrestha PN, Sah KP, Rana R. Empirical oral antibiotic therapy for children with low risk febrile neutropenia during cancer chemotherapy. *J Nepal Paediatr Soc*. 2009;29(1):22–5.
49. Tordecilla C J, Campbell Bull M, Joannon S P, Rizzardini L C, Soto A V. 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*. 1998 12PY - 1998;69(6):247–51.
50. Wiernikowski JT, Rothney M, Dawson S, Andrew M. Evaluation of a home intravenous antibiotic program in pediatric oncology. *Am J Pediatr Hematol Oncol*. 1991;13(2):144–7.
51. Ablett S, Pinkerton CR. Recruiting children into cancer trials—role of the United Kingdom Children’s Cancer Study Group (UKCCSG). *Br J Cancer*. 2003;88(11):1661–5.

SUPPORTIVE CARE IN CANCER **Authorship/Disclosure Form**



All necessary documentation must be submitted with the manuscript to avoid delays in publication. Manuscripts will not be accepted without the signed forms received.

MANUSCRIPT ID NUMBER IF AVAILABLE. Unknown

Article title (first few words) Systematic review of reduced therapy regimens for children with low risk febrile neutropenia

First/Corresponding Author: Jessica Morgan.....

E-mail: jem 539@york.ac.uk

1. AUTHORSHIP

I, the undersigned author(s), certify that:

- I have seen and approved the final version of the manuscript, and all subsequent versions.
- I have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
- I have drafted the article or revised it critically for important intellectual content.

I accept public responsibility for it, and believe it represents valid work. As an author of this article, I certify that none of the material in the manuscript has been previously published, nor is included in any other manuscript. I certify that this manuscript is not under consideration for publication elsewhere, nor has it been submitted or accepted in another publication in any form. The rights or interest in the manuscript have not been assigned to any third party.

Moreover, should the editors request the data upon which the manuscript is based, I shall produce it. I also certify that I have read and complied with the copyright information, as found on the *SUPPORTIVE CARE IN CANCER* home page website.

After submission of this agreement signed by all authors, changes of authorship or in the order of the authors listed will not be accepted.

2. FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

It is the policy of *SUPPORTIVE CARE IN CANCER* to ensure balance, independence, objectivity, and scientific rigor in the Journal. All authors are expected to disclose to the readers any real or apparent conflict(s) of interest that may have a direct bearing on the subject matter of the article.

This pertains to relationships with pharmaceutical companies, biomedical device manufacturers or other corporation whose products or services may be related to the subject matter of the article or who have sponsored the study.

The intent of the policy is not to prevent authors with a potential conflict of interest from publication. It is merely intended that any potential conflict should be identified openly so that the readers may form their own judgments about the article with the full disclosure of the facts.

Please ensure that all and any disclosures/conflicts, are listed below and included within the manuscript. If no conflicts exist, please state: "Disclosures: None". Disclosures should be added in a separate section before the Reference list.

By checking the box next to my signature, I certify that:

all financial support or benefits received by me, by any member of my immediate family, or any individual or entity with whom or with which I have a significant relationship from any commercial source related directly or indirectly to the scientific work reported in the article have been disclosed and have been included in the submitted manuscript.

neither I, nor any member of my immediate family, nor any individual or entity with whom or with which I have a significant relationship has a financial interest in the subject matter discussed in the manuscript, except as disclosed. (I understand an example of such a financial interest would be a stock interest in any business entity which is included in the subject matter of the manuscript or which sells a product relating to the subject matter of the manuscript.)

all funding sources supporting the work and all institutional or corporate affiliations are acknowledged in a footnote.

I have had full access to all the data in the study (if applicable) and thereby accept full responsibility for the integrity of the data and the accuracy of the data analysis.

MANUSCRIPT ID NUMBER Unknown – Title: Systematic review of reduced therapy regimens for children with low risk febrile neutropenia

Completed forms must be scanned and included as a PDF file as part of the online submission process.

Author 1 (printed name): Jessica Morgan

- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity: JM is funded by Candlelighters children's charity (Registered
☐ Charity No: 1045077) for the PhD of which this systematic review is a part.

Signature:  Date: 9/5/15

Author 2 (printed name): Jemma Cleminson None

- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity:

Signature:  Date: 14.5.2015


Author 3 (printed name): Karl Atkin None

- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity:

Signature:  Date: 13.05.2015

Author 4 (printed name): Lesley A Stewart None

- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity:

Signature:  Date: 12/5/15

Author 5 (printed name): Dr Robert S Phillips: NONE

- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity:

Signature:  Date: 7/May/2015

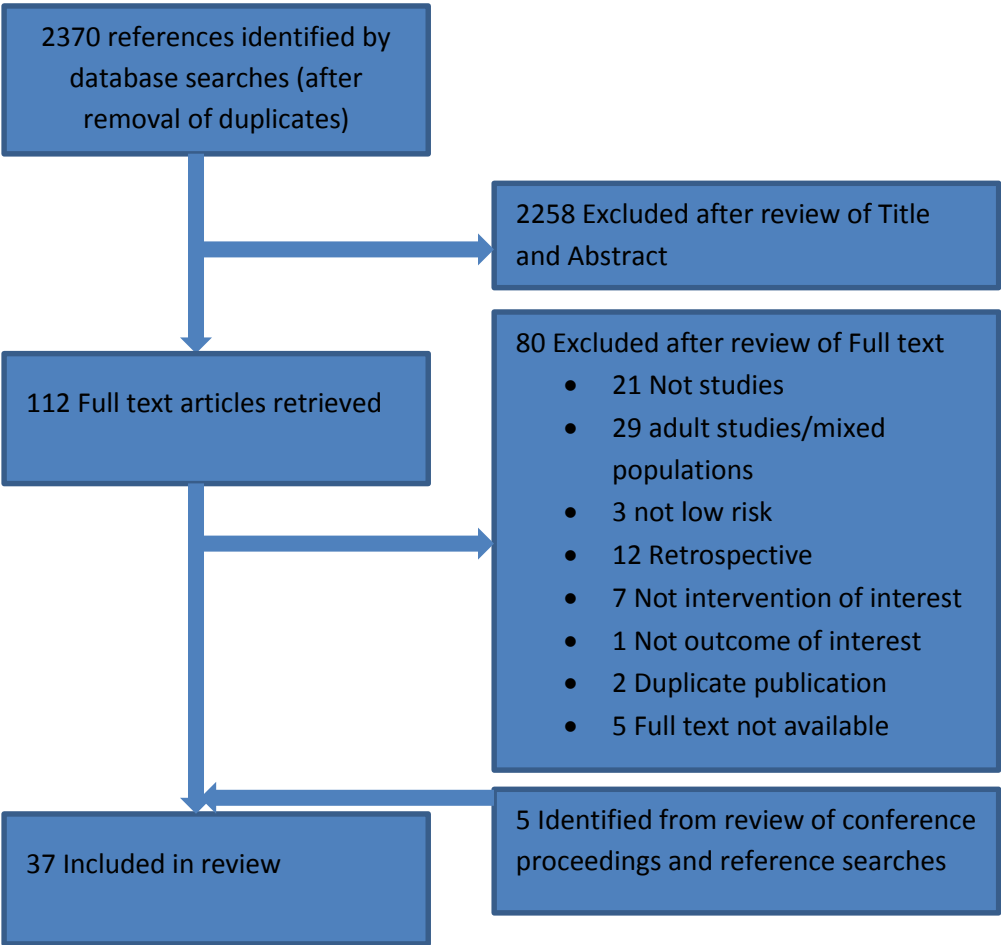
Author 6 (printed name):

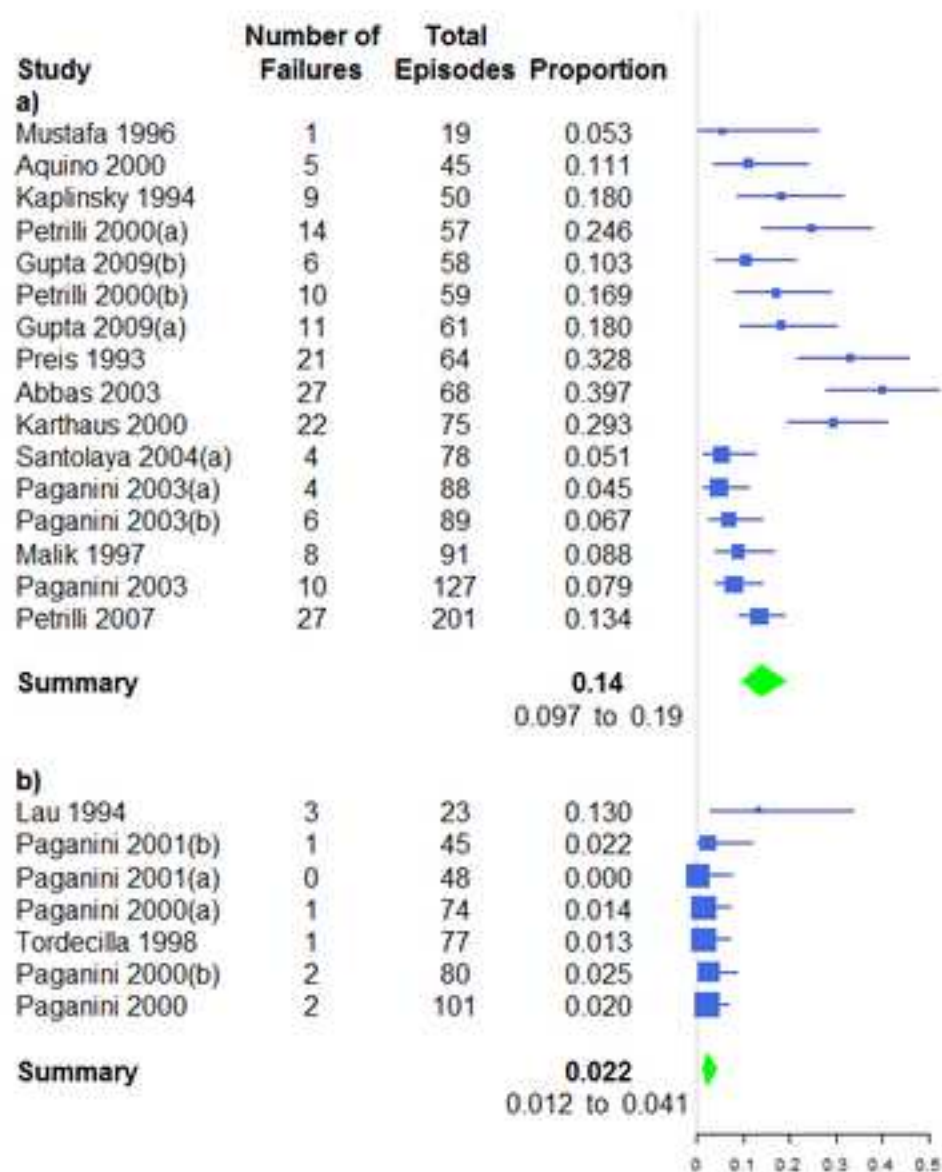
- ☐ Remuneration Entity:
☐ Consultant/advisory role: Entity:
☐ Stock ownership Entity:
☐ Funding Entity:

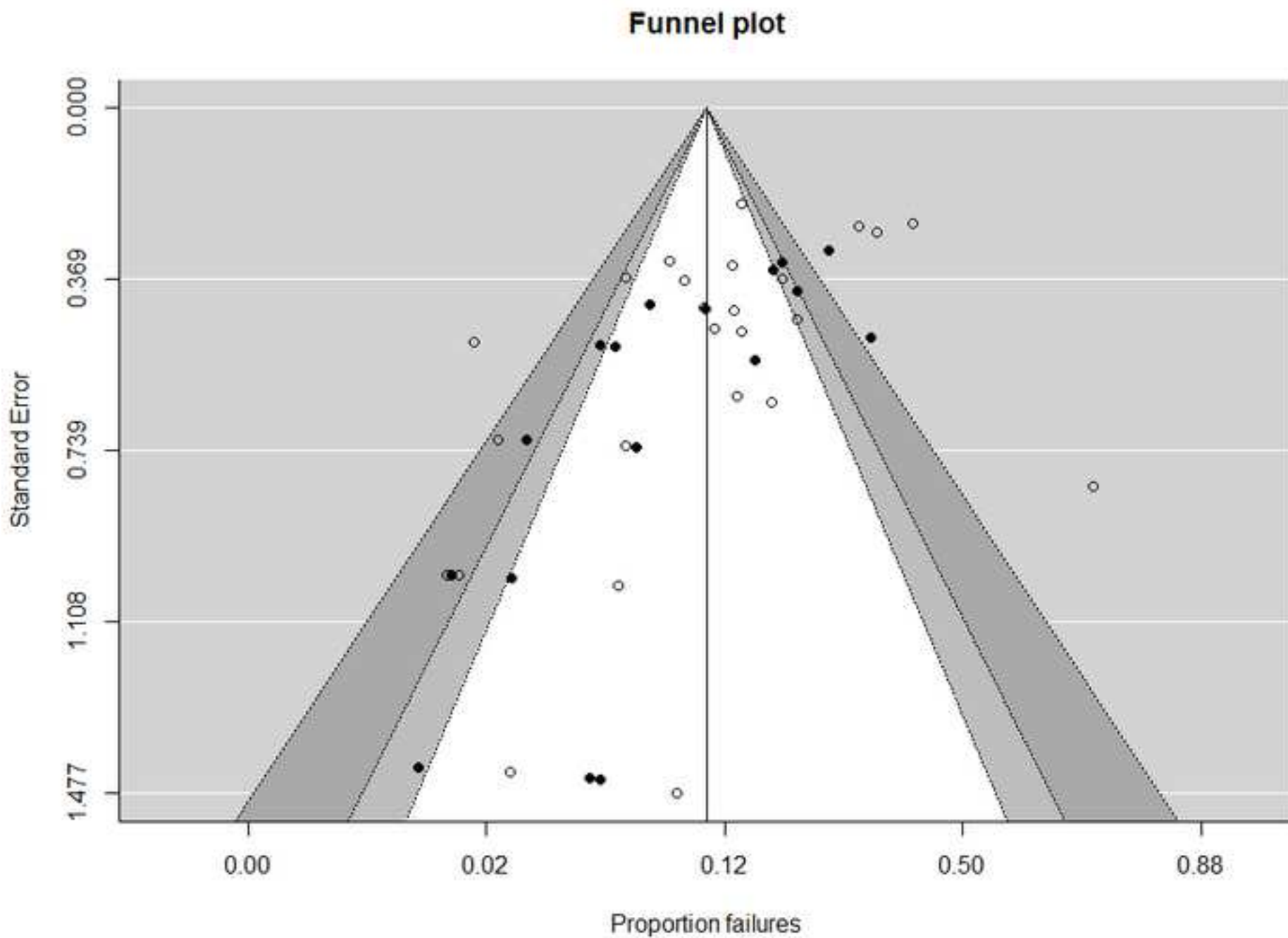
Signature: _____ Date: _____

Figure 1 Flow diagram for study selection

Figure 1 Flow diagram for study selection







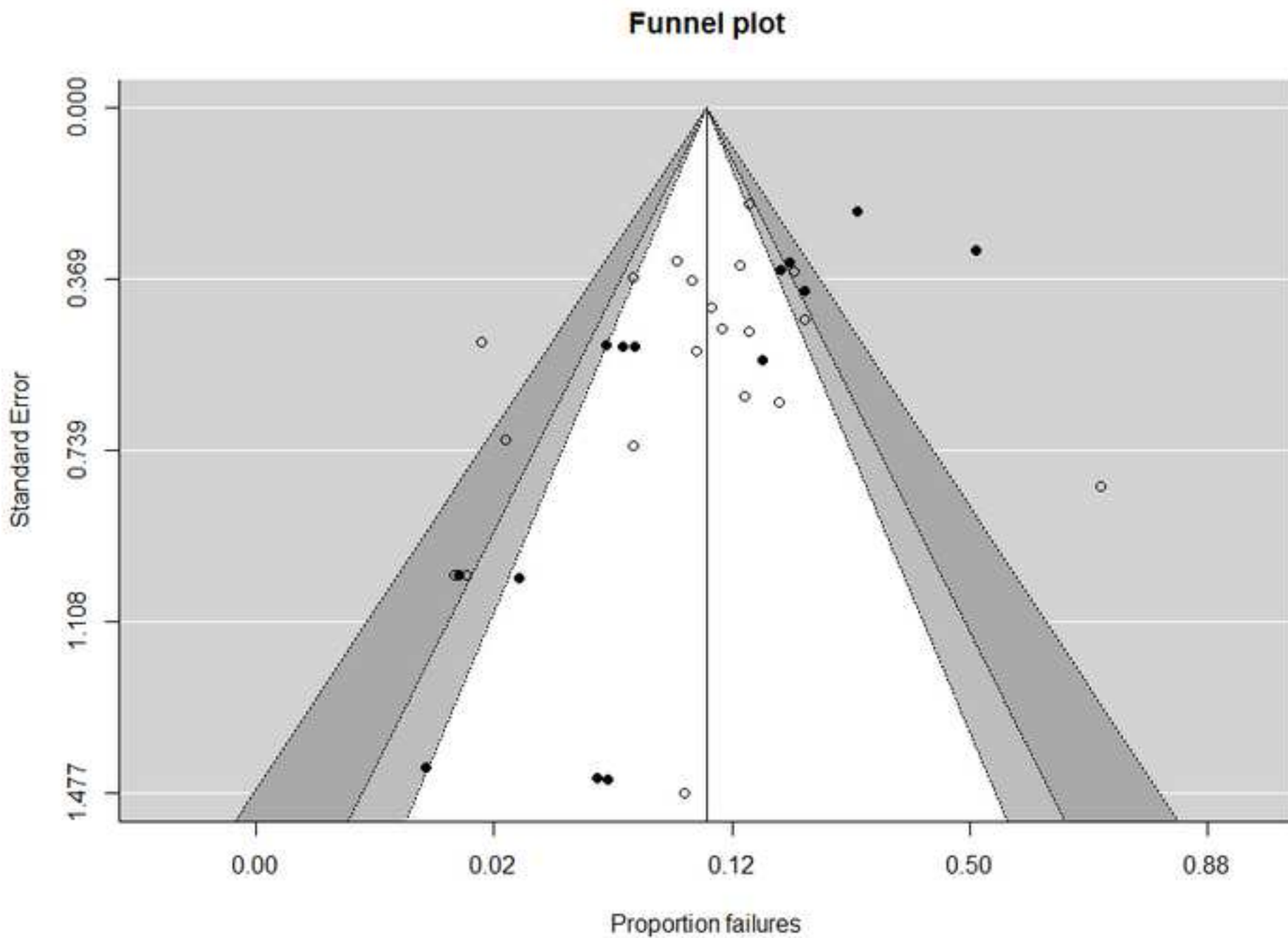


Table 1: Risk of bias tables**Randomised Controlled Trials**

	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, 2012	-	-	+	+	-	-
Cagol et al, 2009	-	-	+	+	?	?
Gupta et al, 2009	-	?	+	+	-	-
Klaassen et al 2000	-	?	-	-	-	-
Mullen et al, 1999	-	-	+	+	-	-
Orme et al, 2014	-	?	+	+	-	-
Paganini et al, 2003	-	-	+	+	-	-
Paganini et al, 2001	-	-	+	+	-	-
Paganini et al, 2000	-	-	+	+	-	-
Petrilli et al, 2000	?	?	+	+	-	-
Santolaya et al, 2004	?	?	+	+	-	-
Shenep et al, 2001	-	?	+	+	-	-
Varan et al, 2005	?	?	+	+	-	-

Key: - low risk of bias, ? unclear risk of bias, + high risk of bias

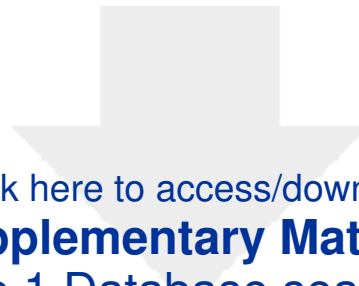
Prospective Observational cohorts

	Population of interest	Loss to follow-up	Prognostic factor	Outcome of interest	Potential confounders	Statistical analysis
Abbas et al, 2003	-	-	-	-	-	-
Aquino et al, 2000	-	-	-	-	-	-
Bash et al, 1994	-	-	-	-	-	-
Dommett et al, 2009	-	-	-	-	-	?
Doyle et al, 1996	-	-	-	-	-	-
Fernandez et al, 2012	-	-	-	-	-	-
Kaplinksky et al, 1994	-	?	-	-	-	-
Karthauss et al, 2000	-	-	-	-	-	-
Lau et al, 1994	-	-	-	-	?	-
Malik, 1997	-	-	-	-	-	-
Miedema et al, 2012	-	?	-	?	-	-
Mustafa et al, 1996	-	-	-	-	-	-
Paganini et al, 2001	-	?	-	-	-	-
Paganini, 2003	-	-	-	-	-	-
Paganini, 2000	-	-	-	-	-	-
Park et al, 2003	?	-	-	-	-	-
Petrilli et al, 2007	-	-	-	?	-	-
Phillips et al, 2006	?	-	-	-	-	-
Preis et al, 1993	?	-	-	?	-	-
Quezada et al, 2007	-	-	?	?	?	-
Sari et al, 2007	-	-	-	?	-	-
Shrestha et al, 2009	-	?	-	-	-	-
Tordecilla et al, 1998	-	?	?	?	-	-
Wiernikowski et al, 1991	?	-	-	-	-	-

Key: - low risk of bias, ? unclear risk of bias, + high risk of bias

Table 21 Refusal to consent data (NA – not applicable)

Study	Concept described	Refusal by parents	Refusal by physicians	Total <u>number of episodes</u>	Notes
Brack et al, 2012	Enrolment	25	NA	93	
Doyle et al, 1996	Enrolment	5	NA	84	
Lau et al, 1994	Enrolment	5	NA	29	
Mullen et al, 1999	Enrolment	12	13	66	
Park et al, 2003	Enrolment	9	NA	39	Includes inability to take oral antibiotics
Quezada et al, 2007	Enrolment	3	9	34	First year of study only
Santolaya et al, 2004	Enrolment	2	NA	151	
Shenep et al, 2001	Enrolment	86	NA	286	
Orme et al, 2014	Confirmation following enrolment	6	7	50	
Quezada et al, 2007	Confirmation following enrolment	8	Included with parental refusal	67	
Wiernikowski et al, 1991	Confirmation following enrolment	2	NA	24	



[Click here to access/download](#)

Supplementary Material

[Online Resource 1 Database search strategies.pdf](#)



Click here to access/download

Supplementary Material

Revised Online Resource 2 Reasons for study exclusion
14.7.15.pdf

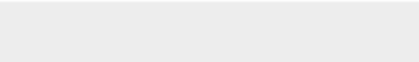
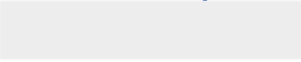





Click here to access/download

Supplementary Material

Online Resource 3 Demographics of included
studies.pdf





Click here to access/download

Supplementary Material

Online Resource 4 Study interventions and
definitions.pdf

