Systematic review of reductions in therapy for children with low risk febrile neutropenia

Jessica Morgan, Jemma Cleminson, Bob Phillips, Karl Atkin, Lesley Stewart

Citation

Review question(s)
In children with low-risk Febrile Neutropenia, are oral antibiotics (compared with IV antibiotics) safe?

In children with low-risk Febrile Neutropenia, are oral antibiotics (compared with IV antibiotics) efficacious?

In children with low-risk Febrile Neutropenia, is early discharge (compared with remaining in hospital) safe?

In children with low-risk Febrile Neutropenia, is early discharge (compared with remaining in hospital) efficacious?

In children with low-risk Febrile Neutropenia, is there a time of discharge where the safety and efficacy change?

Searches
Relevant electronic sources will be searched, including MEDLINE, MEDLINE in-Process & Other non-Indexed Citations, EMBASE, CDSR, Cochrane Central Registry of Controlled Trials (CENTRAL) (via the Cochrane Library), LILACS, CINAHL, HTA, and DARE. 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) and ASCO (American Society of Clinical Oncology) meetings will be hand searched for relevant abstracts. Reference lists of relevant systematic reviews and included articles will also be reviewed. Authors of relevant studies and prominent clinicians within the field will be contacted as time allows to seek further studies, as this is likely to be a poorly indexed area of biomedical research. Published and unpublished studies will be sought and no language restrictions will be applied. Non-English language studies will be translated if this is possible within three months of running the searches.

Types of study to be included
We will include randomised controlled trials and prospective single arm studies. Quasi-randomised trials will be eligible for inclusion provided the methods of allocation to treatment groups are clearly described.

Exclusion criteria: Retrospective studies. Participants enrolled more than 24 hours after initial empiric treatment.

Condition or domain being studied
Febrile neutropenia.

Participants/ population
Children or young adults (aged less than 18 years) who attend paediatric services with fever and neutropenia and are assessed to be at low risk of medical complications.

Intervention(s), exposure(s)
Any of:

(i) Location of treatment:

We will include studies that compare outpatient with inpatient (less than 8 hours in hospital) care. The location of
treatment may change at any point during the episode of febrile neutropenia but the time of change must be clearly reported.

(ii) Route of antibiotic administration:

We will include studies that compare oral with intravenous (IV) antibiotics. The route of administration may change at any point during the episode of febrile neutropenia but the time of change must be clearly reported.

Comparator(s)/ control
Any of the above interventions.

Context
Not applicable.

Outcome(s)
Primary outcomes
There will be three primary outcomes for this review. These are:

1. Treatment failure at 30 days. This will include persistence, worsening or recurrence of fever/infecting organisms, new infections, readmission, admission to critical care services or death during treatment. For the primary outcome modification of antibiotics will also indicate treatment failure.

2. Safety – this is the number of medical complications, defined as admissions to critical care services or death.

3. Efficacy – this is the ability of a treatment protocol to result in resolution of the episode of febrile neutropenia, without change in antibiotic or location of the patient.

See above.

Secondary outcomes
Treatment failure with modification of antibiotics excluded, time spent in hospital, adverse events leading to antibiotic discontinuation, 30 day overall mortality and infection-related mortality and the individual components of the primary composite outcome.

Data extraction, (selection and coding)
One reviewer will screen the title and abstract of all studies for inclusion. A second reviewer will independently screen 1000 papers or 10% of those identified through the search, whichever is greater. The kappa statistic for agreement will be calculated and if this shows significant disagreement (K< 0.4), all other studies will be screened by a second reviewer. Where it is not possible to identify whether a study should be included from the title and abstract, then full text of the paper will be sought and then assessed using the study eligibility form. Disagreements regarding which studies to include will be resolved by consensus, or if this proves impossible, by recourse to an independent adjudicator. Data will be extracted by one researcher using a standardised data extraction form and independently checked by a second.

Risk of bias (quality) assessment
The risk of bias in each study will be assessed by using an appropriate tool, dependent on the design of the original study. Assessment of randomised controlled trials will be based on the tool recommended in “Systematic reviews: CRD's guidance for undertaking reviews in health care”. Single arm studies will be assessed using the tool written by Hayden and used by NICE for prognostic studies.

Strategy for data synthesis
The study characteristics and quality assessments will be described narratively and represented in tabular form. A full list of anticipated statistical analyses will be published prior to commencing the review. Any post-hoc analyses performed out-with those defined in the protocol will be clearly identified as such in the presentation of results.

The interventions will be analysed separately by location of treatment and by route of antibiotic administration. The
outcomes of treatment failure, safety and efficacy for oral antibiotics and for outpatient treatment will be analysed using non-comparative data initially.

We will then explore differences between treatment strategies using the comparative data available. Findings for comparative categorical data will be expressed in both absolute terms and using the Odds Ratios (OR). Meanwhile, findings for continuous data will be reported as the weighted mean difference (with its standard deviation). Data regarding declining consent to randomisation will be presented using non-comparative methods.

It is anticipated that quantitative synthesis will be appropriate for most outcomes, given that this was possible in the previous systematic review. This synthesis will be performed at study-level rather than individual participant-level, given the time constraints of this systematic review, and the challenges in obtaining individual patient data. The data will be combined using a random effects model throughout, given the significant amount of clinical heterogeneity which is anticipated.

Heterogeneity and risk of publication bias will be assessed using standard systematic review techniques (described in full protocol).

**Analysis of subgroups or subsets**
The time of early discharge, defined as before 24 hours, 24–48 hours, and after 48 hours will be analysed as subgroups in order to assess whether the benefits and risks of early discharge are affected by different time periods.

We will use subgroup analysis to examine the effect of the specific risk stratification tool used in the study.

**Dissemination plans**
The results of this review will be submitted for publication in a scholarly journal following the PRISMA reporting guidelines as closely as possible. Lay and professional summaries of the project will be available from the authors. Areas of uncertainty and suggestions for further research will be outlined within the final report.

**Contact details for further information**
Jessica Morgan
jem539@york.ac.uk

**Organisational affiliation of the review**
Centre for Reviews and Dissemination, University of York

**Review team**
Dr Jessica Morgan, Centre for Reviews and Dissemination, University of York
Dr Jemma Cleminson, Centre for Reviews and Dissemination, University of York
Dr Bob Phillips, Centre for Reviews and Dissemination, University of York
Professor Karl Atkin, Department of Health Sciences, University of York
Professor Lesley Stewart, Centre for Reviews and Dissemination, University of York

**Collaborators**
Ms Kate Lewis-Light, Centre for Reviews and Dissemination, University of York

**Anticipated or actual start date**
07 April 2014

**Anticipated completion date**
01 September 2014

**Funding sources/sponsors**
Jessica Morgan is funded by Candlelighters, a children’s cancer charity, for her work on this study.
Conflicts of interest
None known

Language
English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Child; Child, Preschool; Fever; Humans; Infant; Neutropenia

Any other information
Submission of full protocol for publication is planned.

Reference and/or URL for protocol
http://www.crd.york.ac.uk/PROSPERFILES/5817_PROTOCOL_20140705.pdf

Stage of review
Ongoing

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09 April 2014

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22 July 2015

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Stage of review at time of this submission

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