Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis

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CRD summary
The review concluded that outpatient management of febrile neutropenia presented a safe and efficacious alternative to in-patient treatment. However, interpretation of the data may have been limited by variations between studies. The authors' conclusions reflected the evidence presented but variation between the included studies means that their conclusions should be interpreted with caution.

Authors' objectives
To evaluate the efficacy and safety of outpatient management of febrile neutropenia in cancer patients.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to the beginning of 2010. Search terms were reported in supplementary material. Web of Science and Scopus were used to search relevant references and conference proceedings from 2007 to 2010.

Study selection
Randomised controlled trials (RCTs) that compared any outpatient antibiotic treatment to any in-patient antibiotic treatment for management of febrile neutropenia in cancer patients were eligible for inclusion. RCTs that compared oral versus intravenous administration of antibiotics as part of outpatient management of febrile neutropenia in cancer patients were considered for inclusion. In-patient and outpatient administration were defined in the review. The primary outcome of interest was treatment failure at 30 days. Secondary outcomes included all-cause mortality at 30 days, adverse events and readmission to hospital.

Six studies compared outpatient versus in-patient treatment, eight compared oral versus intravenous administration of outpatient antibiotics. Half of the trials were conducted in children and half in adults. Time to discharge for participating outpatients ranged from immediate to more than 72 hours. Treatment duration in trials that compared in-patient versus outpatient regimens ranged from 6.3 to 10.4 days (in-patient) and from 6.0 to 9.4 days (outpatient). In trials that compared mode of administration, duration of intravenous treatment ranged from 4.8 to 8 days and duration of oral treatment ranged from 1.4 to 7 days.

One reviewer selected studies for further evaluation from titles and abstracts. Two reviewers selected studies for inclusion from full papers. Agreement between both reviewers was required for inclusion.

Assessment of study quality
All included papers were assessed for sequence generation, allocation concealment, blinding, incomplete outcome data and intention-to-treat analysis. Further details on the process of quality assessment were not reported.

Data extraction
Data were extracted to calculate relative risk (RR) and absolute risk reduction (ARR) of treatment failure, each with 95% confidence intervals (CIs). The number needed to treat (NNT) was calculated.

Two reviewers extracted data.

Methods of synthesis
Data were synthesised using a random-effects meta-analysis. The Cochrane Q test and $I^2$ statistic were used to assess heterogeneity between studies. Subgroup analyses were conducted by age. Sensitivity analyses were carried out to investigate the robustness of the conclusions. Assessment of publication bias through inspection of a funnel plot was considered.
Results of the review
Six RCTs compared outpatient versus in-patient treatment (738 participants, range 80 to 170) and eight compared oral versus intravenous administration of outpatient antibiotics (857 participants, 41 to 177). Six studies reported allocation generation and five reported allocation concealment. No studies reported blinding. Information on withdrawals was available from nine studies. Intention-to-treat analysis was reported in four studies.

There were no significant differences between in-patient and outpatient treatment regimens for treatment failure (RR 0.81, 95% CI 0.55 to 1.19; six studies). The were no significant differences between groups for absolute risk reduction. There were also no significant differences in treatment failure between oral compared with intravenous administration of antibiotics (RR 0.93, 95% CI 0.65 to 1.32; eight studies). There were no significant differences between groups for absolute risk reduction. Neither analysis contained substantial heterogeneity.

There were no significant differences between in-patient and outpatient management for all secondary outcomes (mortality, toxicity and readmission). No differences were observed between paediatric and adult studies. Sensitivity analyses that accounted for differences in study design did not change the direction or significance of the results. Publication bias was not assessed due to the small number of included trials.

Authors’ conclusions
Outpatient management of febrile neutropenia presents a safe and efficacious alternative to in-patient treatment. However, interpretation of the data may have been limited by variations between studies.

CRD commentary
The review question, inclusion criteria and search strategy were clear. Several relevant sources were searched. Potential for language and publication biases was unclear. The small number of studies precluded formal assessment of publication bias. Use of independent and duplicate processes for study selection and data extraction reduced risk of bias in these domains; whether the same processes were used for quality assessment was unclear.

The methods of synthesis were appropriate. Suitable measures were used to assess heterogeneity. Some aspects of quality assessment were briefly reported but it was not possible to determine the overall quality of the evidence. The authors highlighted variation between the studies for time to discharge, choice of antibiotic class and age and this might limit the interpretation of the evidence. The authors stated that the results may not be generalisable to settings other than dedicated experienced centres.

The authors’ conclusions reflected the evidence presented but variation between the included studies means that their conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state implications for practice.

Research: The authors suggested further research to investigate whether outpatient strategies were feasible in lower income countries and/or in rural areas. Patient preferences should be addressed in future research.

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