Outpatient management of febrile neutropenia: time to revise the present treatment strategy

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CRD summary
The authors concluded that outpatient management of adult cancer patients with low-risk febrile neutropenia was safe and effective, and comparable to standard hospital-based therapy. Limited evidence (such as small sample sizes, unclear quality and substantial heterogeneity) and limitations in the review process mean that the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the safety and efficacy of outpatient management compared with conventional inpatient therapy of low-risk febrile neutropenia in adults with cancer.

Searching
PubMed was searched for relevant articles. Search terms were reported, but search dates were not. In addition, reference lists of included articles were manually searched.

Study selection
Clinical trials that assessed the safety and efficacy of outpatient treatment (oral or intravenous antibiotics used alone or in combination) in adults diagnosed with solid tumors and low-risk, chemotherapy-induced febrile neutropenia (as defined in the review), were eligible for inclusion.

The outcomes of interest were the treatment response rate (the number of patients given a treatment regimen that resolved infection, fever and neutropenia without any severe medical complications), mortality, and hospital readmission rates.

Included studies were of patients with low-risk of mortality and complications, but some patients had various underlying malignancies (solid, haematological), expected durations of neutropenia, and documented foci of infection. Some patients were full outpatients (discharged within 24 hours of presenting with febrile neutropenia), while some were classed as early discharge (discharged after 24 hours of presentation). Studies compared outpatient versus inpatient febrile neutropenia management using the following antibiotics alone or in combination: amikacin, ampicillin/sulbactam, amoxicillin, ampicillin/clavulanate, aztreonam, ceftazidime, ciprofloxacin, clavulanate, clindamycin, gentamicin, gatifloxacin, mezlocillin, moxifloxacin, ofloxacin, piperacillin, vancomycin, and tazobactam. Just over half the studies had inclusion criteria specifying that patients should have no significant comorbidity or infection, that they should have a fever over 38.3°C; five studies also specified an absolute neutrophil count of over 1,000 cells/mm³.

The authors did not state how many reviewers screened studies for selection.

Assessment of study quality
The authors did not state that they performed a validity assessment.

Data extraction
The authors did not state how many reviewers extracted the data.

Methods of synthesis
Data were presented as a narrative synthesis and in tables. Studies were assessed to investigate the effect of route of antibiotic administration (oral versus intravenous, five studies), full outpatient (six studies) versus early discharge (three studies), and with documented infection versus without (six studies). A two-sided X² test was used to compare safety between full outpatients and patients discharged early as measured by readmission and death.

Results of the review
Ten studies (1,125 patients, range 30 to 191) were included in the review: six prospective randomised clinical studies.
There were no statistically significant differences in mortality rates between outpatients and patients receiving hospital-based management (10 studies) or treatment response rates, irrespective of the antibiotic administration route (10 studies). Oral administration of antibiotics did not result in associated mortality or permanent injury (10 studies), but there were eight episodes of antibiotic-related side effects, five of which were in patients receiving oral antibiotics.

Full outpatient studies (six studies) reported a statistically significantly higher admission rate compared with early discharge studies (three studies) \( (p<0.05) \), but there were no statistically significant differences in mortality.

Findings on missing treatment response related to microbiologically documented infection, severity of neutropenia and other factors, and readmission rates were also reported in the review.

**Cost information**

Three studies reported on resource consumption per episode using intravenous versus oral antibiotics: $7,336 (intravenous) versus $2,302 (oral); $1,585 (intravenous) versus $1,130 (oral); and £840 (intravenous) versus £470 (oral).

**Authors’ conclusions**

Outpatient management of adult cancer patients with low-risk febrile neutropenia was safe, effective, and comparable to standard hospital-based therapy.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. The literature search was limited to one electronic database and one other appropriate source and the search dates were not reported. The authors did not appear to make any specific attempts to locate unpublished data. Consequently, potentially relevant studies may have been missed. The authors did not report whether each stage of the review process was carried out in duplicate, which meant that there was the potential for reviewer error and bias.

The quality of the studies was not assessed, but the authors did acknowledge the limitations with the study designs. The authors also acknowledged the small sample sizes. A narrative synthesis was appropriate given the differences in patient characteristics and study methodologies.

A limited evidence base and limitations in the review process mean that the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further large, randomised trials are needed, and consensus must be reached on the definition of low-risk febrile neutropenia.

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