Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study

Innes H E, Smith D B, O'Reilly S M, Clark P I, Kelly V, Marshall E

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Oral antibiotic therapy plus early hospital discharge was compared with standard inpatient intravenous antibiotic treatment given until hospital discharge. The oral antibiotic regimen, which comprised ciprofloxacin (750 mg 12 hourly) plus amoxicillin-clavulanate (675 mg 8 hourly), was given for a total of 5 days. The standard inpatient intravenous antibiotic regimen comprised gentamicin (80 mg 8 hourly) and tazocin (4 g piperacillin and 500 mg tazobactam 8 hourly).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients undergoing cytotoxic chemotherapy for cancer, who were aged 18 years old or older, and who were at low-risk of neutropenic fever. The main inclusion criteria were:

- patients with neutropenia (defined according to standard criteria), but with an anticipated duration of neutropenia of no longer than 7 days;
- patients haemodynamically stable with no signs or symptoms that required intravenous fluid support;
- patients with adequate renal function and the ability to maintain satisfactory oral intake.

The main exclusion criteria were patients who had undergone autologous bone marrow or peripheral blood stem-cell transplantation, or who had received antibacterial medication within 7 days of enrolment. Further exclusion criteria were any coexisting medical condition that would require inpatient treatment or monitoring, and clinically documented infection likely to require targeted or prolonged duration of antibiotic therapy. Patients who were unable to tolerate oral medication, or had a known allergy to the study drugs were also excluded. All of the patients were also required to have a responsible adult prepared to act as a carer.

Setting
The setting was secondary care. The economic analysis was conducted at the Clatterbridge Centre for Oncology in Merseyside, UK.

Dates to which data relate
The effectiveness and cost data were gathered from a randomised controlled trial in which recruitment started in
February 1997 and ended in August 2000. The price year was not reported.

**Source of effectiveness data**
The effectiveness data were derived from a single prospective study.

**Link between effectiveness and cost data**
It is likely that the costing was undertaken prospectively on the same group as that used in the effectiveness study.

**Study sample**
Power calculations were based on the authors’ experience and published studies. These suggested that 63 episodes per group were required to ensure that the oral arm would not be 20% worse (p=0.05) with a power of 80%. A total of 111 patients, representing 135 episodes of fever associated with neutropenia, consented to participate. Of the 135 episodes evaluated, 9 episodes were excluded (7 in the intravenous arm and 2 in the oral arm) because they either failed to meet the inclusion criteria (8) or withdrew consent (1). In all, 126 episodes of low-risk neutropenia fever occurred in 102 patients. Sixty episodes were assigned to receive the intravenous regimen and 66 the oral regimen. The median age in the intravenous arm was 50 years (age range: 18 - 76) and 61.7% were women. The median age in the oral arm was 53 years (age range: 18 - 78) and 62.1% were women. There were 51 first episodes in the oral arm and 51 in the intravenous arm.

**Study design**
The study was a randomised controlled trial that was conducted in a single centre. The patients were reviewed 7 to 10 days after hospital discharge to ensure full recovery, and were supplied with a daily diary to record their temperature every 6 hours. The patients were also provided with 24-hour contact with the centre (through a telephone number) to report any symptom deterioration. No loss to follow-up was reported. Neither patients nor physicians were blinded to the treatment. Randomisation was carried out through consecutively drawn sealed envelopes.

**Analysis of effectiveness**
The analysis of the clinical study appears to have been conducted on an intention to treat basis. The primary health outcomes were success and safety of the antibiotic regimen. Success was defined as lysis of fever and the resolution of symptoms and signs with no modifications to the initial antibiotic regimen and with no recurrence within 7 days. Safety was assessed by the frequency of serious medical complications. The secondary end points were total duration of hospital admission, frequency of readmission and toxicity of treatment. Toxicity was assessed according to the Common Toxicity Criteria (CTC) of the National Cancer Institute. Symptom diaries for self-completion were used for patients in the oral arm who had been discharged before completion of the antibiotic regimen. The study groups were shown to be comparable at baseline in terms of their demographics and clinical characteristics.

**Effectiveness results**
The success rate for the initial regimen was similar in both groups, 90% in the intravenous arm versus 84.8% in the oral arm. The net difference was 5.2% (95% confidence interval, CI: -7 - 17.3; p=0.55).

The success rates in the 102 first episodes were very similar, 88.2% in the intravenous arm versus 84.3% in the oral arm, (p=0.77).

There was one death in the intravenous arm, but none in the oral arm. There were no severe other severe medical complications in the intravenous arm versus one (hypotension) in the oral arm. Five episodes required changes to the antibiotic regimen (because of persistent fever) in the intravenous arm versus 10 episodes in the oral arm (because of vomiting, development of severe oesophagitis and persistent fever).

Five patients in the oral arm, but none in the intravenous arm, required readmission to the hospital.
Both antibiotic regimens were very well tolerated. In the oral arm, there was one episode (0.8%) of severe toxicity (CTC grade 3), 14 patients had CTC grade 1-2 diarrhoea (21.2%) and 5 patients had CTC grade 1-2 nausea or vomiting (7.6%). In the intravenous arm, there were no episodes of toxicity of CTC grade higher than 1.

The median inpatient stay was 4 days (range: 2 - 8) in the intravenous arm versus 2 days (range: 1 - 16) in the oral arm, (p<0.0005). The oral antibiotic policy resulted in a reduction of 66 inpatient days (199 compared with 265).

Clinical conclusions
The study showed that the oral strategy was as safe and effective as the intravenous option for treating low-risk neutropenic fever.

Measure of benefits used in the economic analysis
The authors did not develop a summary benefit measure. In effect, a cost-consequences analysis was performed.

Direct costs
The perspective was unclear, but it was likely to have been that of the UK National Health Service (NHS). The direct costs were for hospitalisation, antibiotics and the nursing care required for episodes of neutropenia fever. The hospitalisation costs were calculated using a mean cost per routine inpatient day, as determined by prior studies. These included medical, nursing, paramedical services and supplies, and general services, but excluded pharmacy and pathology costs. The antibiotic costs were calculated according to standard NHS charges. Nursing resources were compared using "GRASP", to obtain an estimate of the nursing time required in "actual patient contact". The costs incurred by diagnostic tests and other therapeutic interventions were assumed to be equivalent in both arms, and were therefore excluded. Resource use was estimated on the basis of individualised data coming from the effectiveness trial. The quantities were derived directly from the study. The costs and the quantities were not reported separately. Discounting was unnecessary. The price year was not reported.

Statistical analysis of costs
No statistical analysis of the costs was performed.

Indirect Costs
No indirect costs were included.

Currency
UK pounds sterling (€).

Sensitivity analysis
No sensitivity analysis was performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The cost of hospitalisation and antibiotics was more than 19,000 less in the oral arm (total cost 31,110) than the intravenous arm (total cost 50,380). Each episode in the oral arm cost approximately 56% of an episode in the standard treatment arm. The mean cost per episode was 840 in the intravenous arm and 470 in the oral arm.
The authors stated "the estimated number of 'direct patient care hours' per episode in the oral arm was less than half of each episode in the intravenous arm (11 compared with 21)".

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
Oral antibiotics combined with early hospital discharge for patients who remain stable after a 24-hour period of inpatient monitoring offers a feasible and cost-effective alternative to the conventional treatment of low-risk neutropenic fever.

CRD COMMENTARY - Selection of comparators
The comparator was justified on the grounds that it represented the conventional inpatient intravenous antibiotic treatment. You should consider whether this is a widely used technology in your own setting. However, the authors noted that since the comparator already incorporated a policy of discharge, the savings would be greater if compared with more conventional treatment approaches.

Validity of estimate of measure of effectiveness
The estimate of effectiveness might have been internally valid given the use of a randomised, controlled trial. A justification was given for the end points used. However, the impact on quality of life would also have been appropriate for assessing the effectiveness of oral versus intravenous antibiotics. The authors acknowledged that, given the relative small size of the study, there was limited power to detect small but clinically important differences in safety. The two study groups were comparable at baseline. The study sample was selected on the basis of very strict inclusion and exclusion criteria. Thus, caution should be exercised when extrapolating the results of the study to the general population of patients eligible for early discharge, also because the study was carried out in a single centre. The authors discussed the use of a strict definition of "low risk patients" and the recent introduction of a risk index scoring system.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was, in effect, a cost-consequences analysis.

Validity of estimate of costs
The perspective was unclear, but it was likely to have been that of the UK NHS. The indirect costs were not included in the study. The costs and the quantities were not reported separately and only limited details were given of the unit costs and quantities. This will hinder the reproducibility of the results in other settings. Moreover, the price year was not reported and a statistical analysis of the costs and a sensitivity analysis were not performed. The cost estimates were specific to the study setting. The sources of the cost and resource use data were reported.

Other issues
The generalisability of the results was discussed and adequate comparisons were made with studies dealing with the same topic. The study considered patients with a low risk of neutropenic fever and this was reflected in the authors' conclusions. The authors highlighted the limitations of their study (see preceding commentaries) and do not appear to have reported their results selectively.

Implications of the study
The authors believed that the results of their study should provide a platform for larger trials to further evaluate the policy of oral antibiotics with early discharge in the multi-centre setting.
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None stated.

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Other publications of related interest

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