A randomized comparison of oral chloramphenicol versus ofloxacin in the treatment of uncomplicated typhoid fever in Laos

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
Two treatments for uncomplicated typhoid fever were examined. One was chloramphenicol, 50 mg/kg per day in four divided oral doses, for 14 days (CHLO). The other was ofloxacin, 15 mg/kg per day in two divided doses, for 3 days (OFLO).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised non-pregnant patients, aged older than 15 years and with suspected or blood culture-proven typhoid, who were not known to have contraindications to CHLO or OFLO and were not breastfeeding. The patients also had to be without signs of severe typhoid (reduced level of consciousness, pronounced jaundice, shock, gastrointestinal bleeding, signs of intestinal perforation) or intractable vomiting, and be able to take oral medication.

Setting
The setting was a hospital. The economic study was carried out in Laos.

Dates to which data relate
The effectiveness and resource use data were gathered from January 2001 to June 2003. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the clinical study.

Study sample
The study sample included eligible individuals who gave informed written consent to the study and were able to stay in hospital for the duration of the treatment. Of the 107 patients initially identified, Salmonella enterica serotype typhi (S. typhi) blood culture was positive in 50 patients. Twenty-three of these patients were included in the CHLO group and 27 in the OFLO group. The median age was 26 years (range: 16 - 50) in the CHLO group and 24 years (range: 16 - 35) in the OFLO group. There were 17 men in the CHLO group and 19 in the OFLO group. Formal power calculations
were not performed because of the lack of reliable clinical information on typhoid fever in Laos. However, it was planned to perform an interim analysis after recruiting 50 patients and to stop the trial if a significant difference was found in the main outcome measures.

**Study design**

This was a prospective, randomised controlled trial that was carried out at the Adult Infectious Disease Ward at Mahosot Hospital in Vientiane. An investigator, who was not involved in patient recruitment or assessment, randomised the patients in blocks of 10 from a random number table. Patients were withdrawn from the study, and treated at the discretion of the ward physicians, if the admission blood culture remained negative after 7 days of incubation. For patients randomised to CHLO, if a blood culture yielded S. typhi resistant to this antibiotic, treatment was changed to 3 days OFLO. Data for two patients were unavailable and were not used to derive some clinical outcomes. The patients were reviewed daily and were followed until hospital discharge. No blinding was performed.

**Analysis of effectiveness**

The analysis of the clinical study was conducted on an intention to treat basis. The outcome measures used were:

- treatment failure;
- fever clearance time (FCT)38 and FCT37.5;
- area under the fever-time curve (AUC)37.5; and
- hospital stay.

Treatment failure was defined as continuation of symptoms and tympanic temperature (>38.0 degrees C) for more than 10 days after the start of treatment, or continuation of symptoms and high tympanic temperature (>39.0 degrees C) at 7 days after the start of treatment, or the development of signs of severe disease. FCT38 and FCT37.5 were defined as time from the start of treatment to the first recording of a tympanic temperature that remained below 38.0 and 37.5 degrees C, respectively, for the subsequent 48 hours. The AUC37.5 was calculated as the area of the tympanic temperature-time curve above 37.5 degrees C for the duration of the patient's admission. The baseline comparability of the study groups was not discussed but the patient demographics were quite similar. However, the median number of days patients had been ill was significantly higher for those who had taken ampicillin before treatment (19.5; range: 14 - 24) than for those who had not (8; range: 2 - 30), (p=0.005). Clinical and laboratory features were similar between the groups.

**Effectiveness results**

There was one treatment failure in the CHLO group and none in the OFLO group, (p=0.05).

The FCT38 was 90 hours (range: 24 - 224) with CHLO and 54 hours (range: 6 - 93) with OFLO, (p=0.0009).

The FCT37.5 was 98 hours (range: 24 - 242) with CHLO and 60 hours (range: 18 - 100) with OFLO, (p=0.002).

AUC37.5 (hours x degrees C) was 52.8 (range: 10.2 - 137.6) with CHLO and 27.4 (range: 5.1 - 88.2) with OFLO, (p=0.008).

The hospital stay was 16 days (range: 7 - 20) with CHLO and 9 days (range: 5 - 14) with OFLO, (p<0.001).

**Clinical conclusions**

The effectiveness analysis showed that OFLO was associated with significantly better clinical outcomes than CHLO for patients with typhoid fever.
Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
The cost/resource boundary of the study was unclear, but the costs were relevant only to the patients. The health services included in the economic evaluation were the antibiotics under examination and hospital stay. The unit costs were presented separately from the quantities of resources used. Resource use was estimated using patient-level data that were derived from the sample of patients included in the clinical trial. The costs were estimated using manufacturers' prices, the two sources being prices of drugs compounded in Laos and drugs available in Vientiane from countries with good manufacturing practice (GMP) production. OFLO tablets were from Korea, while no GMP CHLO was available in Vientiane. Discounting was not relevant, owing to the short timeframe of the analysis, and was not carried out. The price year was 2003.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

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

Cost results
When only the bed charge and the least expensive antibiotic available were considered, the cost to the patient was $3.40 with OFLO for 3 days and $8.33 with CHLO for 14 days.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-consequences analysis was performed.

Authors' conclusions
Ofloxacin (OFLO) was the optimal treatment for typhoid in Laos, both in terms of clinical efficacy and costs.

CRD COMMENTARY - Selection of comparators
The authors provided a justification for the choice of the comparators. CHLO was the most commonly used treatment for typhoid, while OFLO represented a recently proposed alternative treatment. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The evidence came from a clinical trial, which was appropriate for the study question and limited the impact of confounding factors and selection bias. Further, an intention to treat basis was used for the assessment of the clinical outcomes. It was unclear whether the study groups were well matched at enrolment, although in general the patients were quite comparable. A formal justification for the choice of the sample size was not provided, owing to the lack of epidemiological data available for Laos. However, the authors stated that recruitment was stopped when statistically significant differences between the groups were observed in the main outcome measures. The sample of patients came from a specific area in Laos, which could not be representative of the population of individuals with typhoid because of wide variations in epidemiological data.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The authors did not state explicitly which perspective was adopted in the study. However, it was quite clear that only some categories of costs relevant to the patients were included in the analysis. Only hospital stay and antibiotic therapy were considered and the unit costs were reported. Drugs produced in other settings were considered in order to use the cheapest available antibiotic. The price year was reported, which aids reflation exercises in other settings. The costs were treated deterministically and no statistical analyses were carried out. Indirect costs and other non-medical direct costs were not considered in the analysis, but the authors stated that these costs were likely to be higher in the CHLO group.

Other issues
The authors reported the results of other published studies, and made limited comparisons with them. Slightly different patient populations were enrolled in some studies. The issue of the generalisability of the study results to other settings was not explicitly addressed and no sensitivity analyses were carried out. This limits the external validity of the study. The authors noted some problems associated with CHLO, such as the poor adherence and the development of CHLO resistance.

Implications of the study
The study results supported the use of OFLO for the treatment of typhoid. The authors pointed out that if fluoroquinolones become the treatment of choice for uncomplicated typhoid in Laos, adherence to a 3-day regimen should be encouraged.

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