Two doses of a lipid formulation of amphotericin B for the treatment of Mediterranean visceral leishmaniasis

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
The use of a short course of a lipid formulation of amphotericin B (L-AmB) to treat children suffering from Mediterranean visceral leishmaniasis (VL) (also known as Leishmania infantum). The short course comprised 2 doses of 10 mg/kg given on two consecutive days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children aged up to 14 years, with clinical characteristics consistent with Mediterranean VL (e.g. fever, anaemia, splenomegaly) and with visible parasites or amplified leishmania DNA detected on bone marrow aspirates. The exclusion criteria were concomitant diseases, allergy to study drugs, human immunodeficiency virus seropositivity or other immunosuppression, and prior treatment for leishmaniasis.

Setting
The clinical setting was a hospital. The economic study was performed in the Aghia Sophia Children's Hospital, Athens, Greece.

Dates to which data relate
The effectiveness evidence and resource use were gathered between January 1998 and December 2001 for the intervention group, and between January 1996 and December 1997 (5-day L-AmB) and between January 1993 and December 1996 (MA) for the control groups. Clinical evidence was also assessed up to 6 months of patient follow-up. The price year was not reported.

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

Link between effectiveness and cost data
The costing was performed on the same samples of patients as those used in the effectiveness study. It was carried out prospectively for the intervention group, retrospectively for the group receiving MA, and probably retrospectively for the group receiving 5-day L-AmB.
Study sample
Power calculations to determine the sample size do not appear to have been performed. The methods used to select the sample were not reported. A total of 45 children were included in the initial sample for the intervention group, of which 3 were excluded from the study and 1 refused to participate. Thus, the final intervention group comprised 41 children.
In the first control group (5-dose L-AmB), 33 patients were initially considered for the study, but 3 were excluded. The final sample comprised 30 children. In the second control group (MA), 59 children were initially included, but 7 were excluded. The final sample comprised 52 children.

The average age was 43.27 (+/- 5.16) months in the intervention group, 40.93 (+/- 7.01) months in the 5-day L-AmB group, and 50.49 (+/- 5.82) months in the MA group. There were 22 boys and 19 girls in the intervention group, 12 boys and 18 girls in the 5-day L-AmB group, and 29 boys and 23 girls in the MA group.

Study design
This was a cohort study with two historical comparison cohorts, which was performed in a single centre. Children in the intervention group (2-day L-AmB) received physical examinations and baseline routine tests at study entry, every 10 days for the first month after the therapy, and then monthly for 6 months. Body temperatures were measured 6 times/day during hospitalisation. Abdominal ultrasonography was performed at study entry and at 15, 30 and 90 days after therapy. The follow-up period was 6 months for the three groups. No loss to follow-up was reported.

Analysis of effectiveness
The effectiveness analysis was performed on all of the patients included in the final study samples. The main clinical outcomes were initial response, treatment failure, relapse of leishmaniasis, mean duration of fever and overall success. Initial response was defined as the absence of fever, a clinical improvement and a reduction of spleen size. Treatment failure was considered as the persistence of symptoms and the presence of parasites 2 weeks after therapy, and relapse of leishmaniasis as initial response followed by the reappearance of signs and symptoms of infection. In addition, laboratory parameters were compared at baseline, 15, 30 and 90 days. These included haemoglobin level, white blood cell count, platelet count, ratio of albumin to globulin, level of C-reactive protein and erythrocyte sedimentation rate. Finally, the rates of discontinuation of the therapies were compared (toxicity).

At baseline, the three groups were similar in all characteristics apart from spleen size and haemoglobin level. The spleen size of children receiving MA was significantly larger than that in the intervention group, (p=0.03). The haemoglobin level was significantly higher for children receiving 2 doses of L-AmB than for children receiving 5-day therapy, (p=0.01).

Effectiveness results
In the intervention group, 40 of the 41 children had a successful outcome at 6 months and only 1 child had a relapse at week 5.

In the 5-day L-AmB group, 27 participants had a successful outcome at 6 months, 2 had treatment failure and 1 had a relapse.

In the MA group, 47 children had a successful outcome after 6 months, 3 had treatment failure and 2 had a relapse of leishmaniasis.

There was no statistically significant difference in the response rate after 6 months among the three groups, (p=0.17 for intervention versus 5-day L-AmB; p=0.16 for intervention versus MA).

The mean duration of fever was significantly lower for the intervention group (1.9 +/-0.15 days) than for the 5-day L-AmB group (2.77 +/- 0.25 days), (p<0.01), or MA group (4.77 +/- 0.47 days), (p<0.01).

The average temperature at days 1 and 2 was significantly lower for the intervention group in comparison with the other two groups, (p<0.01).
In terms of laboratory variables, haemoglobin level, erythrocyte sedimentation rate and C-reactive protein level were correlated faster in the intervention group than in the 5-day L-AmB group. The reversal of albumin to globulin was correlated faster in the 2-day L-AmB group than in the MA group.

Three children discontinued the therapy in the MA group while none of the children discontinued the medication in the other two groups.

Clinical conclusions
The authors concluded that a therapy comprising 2 doses of L-AmB was at least as effective as the other two therapies compared and, in general, it showed a faster clinical response.

Measure of benefits used in the economic analysis
No summary benefit measure was used. A cost-consequences analysis was therefore carried out.

Direct costs
Discounting was not carried out because it was not relevant (short time-horizon). Some of the unit costs were reported separately from resource use. The quantity/cost boundary adopted appears to have been that of the Greek National Health Service. The cost categories included were administered drugs and hospital-related expenses. The resource use data were based on the patients’ charts, while the unit costs were obtained from marketed prices (for drugs) and National tariffs (hospital costs). Resource use was measured between January 1998 and December 2001 for the intervention group, and between January 1996 and December 1997 (5-day L-AmB) and between January 1993 and December 1996 (MA) for the control groups. The price year was not reported.

Statistical analysis of costs
Student t-tests were performed to estimate the statistical differences in average costs among the three groups.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Euros (Euro).

Sensitivity analysis
No sensitivity analyses were carried out.

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

Cost results
The estimated total cost per patient was Euro 1,664.25 (+/- 147.00) for the intervention group versus Euro 2,284 (+/- 168.00) for the L-AmB group and Euro 2,600.00 (+/- 126.60) for the MA group.

The cost per patient in the intervention group was significantly lower than the cost per patient in the other two groups, (p<0.01). This was mainly due to a significantly lower mean length of stay in the intervention group (6.24 +/- 0.80 days) than the other two groups (11.26 +/- 0.90 days and 28.52 +/- 0.90 days), (p<0.01).
Synthesis of costs and benefits
Not relevant because a cost-consequences analysis was performed.

Authors' conclusions
Therapy comprising two doses of a lipid formulation of amphotericin B (L-AmB) should be considered a cost-effective strategy because it was at least as effective as, and less costly than the alternatives considered.

CRD COMMENTARY - Selection of comparators
The authors compared a short course of L-AmB (2 doses of 10 mg/kg) with its standard dosage (5 doses of 4 mg/Kg) and with conventional therapy with MA. Therefore, the reason for the choice of the comparators appears clear. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis, although using a cohort study with historical controls, appears to have been robust given the comparability among the study groups and the numerous statistical analyses performed to assess this similarity. Many details of the patients’ characteristics were reported and several outcome measures were adopted. There were also details on the patients excluded and the reasons for their exclusion. The study sample was unselected and it appears to have been representative of the study population. However, the authors acknowledged that a prospective randomised trial would have been the most appropriate design. Power calculations were not reported and the sample size was small. These issues tend to limit the internal validity of the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the economic analysis. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs
All the categories of costs relevant to the perspective of the analysis appear to have been included, although the authors did not provide a breakdown of the costs considered. Statistical analyses to estimate the significance in the cost differences were conducted appropriately. The costs were specific to the study setting and sensitivity analyses were not conducted. Also, the issue of transferability of the cost results to other settings was not addressed. The sources and values of drug costs and the daily cost of hospitalisation were reported, but the unit costs (e.g. examinations, routine tests) were not listed in greater detail. The price year was not reported, thus making reflation exercises in other settings difficult. The authors stated that longer hospitalisations were the main cost driver, thus reductions in hospital stay could make MA more efficient.

Other issues
The authors briefly reported the main results from other studies, but the issue of generalisability was not explicitly addressed. Sensitivity analyses were not conducted and the overall external validity of the analysis was low. The authors, however, underlined that there are regional differences that have been observed in the response to treatments for leishmaniasis. Finally, the authors stated that an important development in the treatment of VL is the use of a new orally administered drug (miltefosine), although the effectiveness of this drug has still to be confirmed in different geographical areas.

Implications of the study
The results of this study suggested that a short course of L-AmB should be considered a cost-effective strategy for the treatment of Mediterranean VL. However, this conclusion needs to be confirmed in more precise trials.
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None stated.

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