Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients

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
Amoxicillin-clavulanic acid was compared to cefotaxime for the treatment of suspected bacterial infections in patients with cirrhosis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with cirrhosis and suspected bacterial infection. The study sample comprised all cirrhotic patients hospitalised in the study site and with a bacterial infection. A bacterial infection was suspected if a patient had fever, encephalopathy, abdominal pain, urinary symptoms, and/or respiratory symptoms. The symptoms of an infection were pre-defined using criteria that were reported explicitly in the paper. The exclusion criteria for the study were: allergy to penicillin or cephalosporins; antibiotic treatment other than prophylactic norfloxacin during the two weeks prior to inclusion in the study; nosocomial pneumonia, that usually requires an antibiotic treatment with a broader antimicrobial spectrum; the isolation of gram-positive cocci in urine sediment, in which case the patient received amoxicillin-clavulanic aid; or mild urinary infections (defined as those without fever or encephalopathy, not requiring parenteral antibiotic treatment).

Setting
The study was set in secondary care in Spain.

Dates to which data relate
The dates for the effectiveness evidence, resources used and price year were not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Prospective costing was carried out on the same patient sample as that used in the effectiveness study.

Study sample
The authors reported that the required sample size was 29 patients in each group on the basis of a 62% infection
resolution rate for the cefotaxime group and 95% for the amoxicillin-clavulanic acid group, with 80% power to detect a statistically significant difference at the 5% level of significance. This calculation used previous microbiological data from patients infected while on prophylactic norfloxacin.

All cirrhotic patients hospitalised in the study site (n=96), with suspicion of bacterial infection, were randomised into two groups (48 in amoxicillin-clavulanic acid group and 48 in the cefotaxime group) and stratified for previous prophylaxis with norfloxacin and ascitic fluid infection. The recruitment rate was not reported. No evidence was reported to indicate whether the initial study sample was appropriate for the clinical study question.

**Study design**
This was a single-centre, randomised controlled trial. The method of randomisation was not reported. Patients were followed-up until the infection resolved. Infection was considered resolved when all clinical signs of infection had disappeared. In the amoxicillin-clavulanic acid group, ten patients were excluded from the analysis: infection was not demonstrated in nine patients and one patient required surgical treatment due to secondary peritonitis. In the cefotaxime group, six patients were excluded from the analysis: infection was not demonstrated in five patients and one because of secondary peritonitis. There was no blinding of the assessment of outcomes.

**Analysis of effectiveness**
The analysis of the clinical study was based on treatment completers only.

The primary health outcomes used in the analysis were infection resolution rate, number of complications and mortality.

The two groups were comparable in terms of demographic, clinical and laboratory data and the types of infection. Ten patients in the amoxicillin-clavulanic acid group and 12 from the cefotaxime group were on previous prophylaxis with norfloxacin.

**Effectiveness results**
The infection was resolved in 33 of the 38 patients (87%) treated with amoxicillin-clavulanic acid and in 37 of the 42 patients (88%) treated with cefotaxime (95% CI: -0.15 to 0.13, p>0.05).

Treatment failure was observed in five patients in the amoxicillin-clavulanic acid group (2 patients had bacterial resistance and one showed no response to treatment) and five patients in the cefotaxime group (one patient had bacterial resistance and two showed no response to treatment).

There was no significant difference in the number of complications (encephalopathy, renal dysfunction or gastrointestinal bleeding) between the amoxicillin-clavulanic acid group (47%) and the cefotaxime group (43%, p>0.05).

Four patients (11%) in the amoxicillin-clavulanic acid group and seven patients (17%) from the cefotaxime group died during hospitalisation, (p>0.05).

**Clinical conclusions**
The authors concluded that amoxicillin-clavulanic acid is as effective as cefotaxime in the treatment of bacterial infections in cirrhotic patients.

**Measure of benefits used in the economic analysis**
The authors reported that all the clinical outcomes were equivalent and no measure of benefits was reported in the study.
Direct costs
Direct costs for the hospital were included in the study. The study only included the cost of antibiotic treatment. The estimation of prices was taken from the in-hospital cost to the Pharmacy Department in the hospital. The estimation of quantities was taken from actual data. The study reported length of treatment (in days) separately to the cost of antibiotic treatment. The duration of antibiotic treatment was measured from the initiation of intravenous treatment to the resolution of the infection and cessation of treatment. The price year was not reported. Discounting was not carried out due to the short time frame of the study (less than one year).

Statistical analysis of costs
The average cost in each group was compared using the Student's t-test.

Indirect Costs
Indirect costs were not relevant to the chosen study perspective and were not reported.

Currency
Costs were reported in Euros. No currency conversion rate was reported.

Sensitivity analysis
No sensitivity analysis was reported.

Estimated benefits used in the economic analysis
The reader is referred to the effectiveness results reported previously.

Cost results
The cost of the antibiotics in the amoxicillin-clavulanic acid group was 50.2 euros (SD=23.8 euros).

The cost of the antibiotics in the cefotaxime group was 163.0 euros (SD=55.3 euros).

The cost of antibiotic treatment in the amoxicillin-clavulanic acid group was significantly lower than the cefotaxime group, (p<0.001).

Synthesis of costs and benefits
Not relevant.

Authors' conclusions
The authors concluded that amoxicillin-clavulanic acid is as effective but less expensive than cefotaxime in the treatment of bacterial infections in cirrhotic patients.

CRD COMMENTARY - Selection of comparators
The selection of comparators was justified in the paper and seemed to be appropriate for the setting of the study (Spain). You, as a user of this database should consider whether these two options reflect practice in your own clinical setting.

Validity of estimate of measure of effectiveness
The study used a randomised trial design. The measure of effectiveness seemed appropriate for the study question. The
A study had 80% power to detect a difference in resolution of infection. However, it is not clear that the study had sufficient power to determine whether the two antibiotics were equivalent. The authors reported that the groups were comparable at baseline. The analysis was based on treatment completers only; specifically, patients who did not have demonstrated infection were excluded from the analysis. This might not be appropriate if the study aim was to determine the effectiveness of the drugs when used as empirical treatment for suspected infection. A higher percentage of patients were excluded from the analysis in the amoxicillin-clavulanic acid group (20%) than in the control group (12%).

Validity of estimate of measure of benefit
The study did not include a measure of benefit because no statistically significant differences in clinical outcomes were found. The study therefore reported a cost-minimisation analysis. However, it is not clear that the study had sufficient power to determine whether the two antibiotics were equivalent.

Validity of estimate of costs
The study only included antibiotic costs from a narrow perspective, that of the hospital. The authors did not justify why they chose only to include antibiotic costs in the evaluation.

Other issues
The main limitation with this study was the omission of a sensitivity analysis with which to test the robustness of the study findings or assess the generalisability of the results to other health care settings.

Implications of the study
The authors suggest that amoxicillin-clavulanic acid is an effective alternative to cefotaxime for the empirical treatment of bacterial infections in cirrhosis. The authors proposed further studies to assess oral treatment with amoxicillin-clavulanic acid in non-complicated infections in cirrhotic patients.

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