Efficacy and cost of ampicillin-sulbactam and ticarcillin-clavulanate in the treatment of hospitalized patients with bacterial infections

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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
Ampicillin-sulbactam (1.5g or 3.0g every 6 hours) or ticarcillin-clavulanate (3.1g every 6 hours), as two beta-lactam-beta-lactamase-inhibitor combinations, in hospitalised patients with a variety of infections requiring parenteral antibiotic therapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study included hospitalised patients with a variety of infections (skin and soft tissue, intra-abdominal, gynaecologic, respiratory, urinary tract, or other infections (bacteremia, sepsis, bone, mixed)) requiring parenteral antibiotic therapy. Criteria for administration of a particular antibiotic regimen were infectious diagnosis based on physical examination, clinical evaluation of signs and symptoms, culture and sensitivity results, white blood cell count, and temperature. Patients receiving antibiotics for prophylaxis were not included.

Setting
Hospital. The economic analysis was carried out in the USA.

Dates to which data relate
No dates were provided.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. A total of 890 patients were treated; 357 patients with a mean (SD) age of 60.7 (21.1) years in the group receiving ampicillin-sulbactam (A-S) 1.5g, 307 patients with a mean (SD) age of 52.9 (21.2) years in the group receiving A-S 3.0g, and 226 patients with a mean (SD) age of 65.6 (17.6) years in the group receiving ticarcillin-clavulanate (T-C), (p<0.0001 for differences among treatment groups in terms of
age); each group was significantly different from every other group, (all p<0.01). The patients were classified into
groups according to infection site: skin and soft tissue (258 patients), intra-abdominal (257), respiratory (200), urinary
tract (67), gynaecologic (67), and other (41).

Study design
This was a multi-centre, retrospective, open-label cohort study, carried out in 54 centres across the USA. The duration
of the follow-up was not explicitly specified. Regarding loss to follow-up, the number of patients not evaluable for
analysis of the clinical response (because of relevant data not being available) was 37 for patients receiving A-S 1.5 g, 1
for patients receiving A-S 3 g, and 0 for patients receiving T-C. The corresponding values for the analysis of
bacteriologic response were 23, 90, and 52, respectively. Subjects were identified through the pharmacy order system
with approval of institutional review boards. Data for completing case report forms were collected by the pharmacist or
physician from patients' medical records.

Analysis of effectiveness
The principle used in the analysis of effectiveness appears to have been treatment completers only. The health outcomes
were clinical cure and bacteriologic cure rates. The satisfactory clinical response was the resolution of signs or
symptoms of infection with sufficient clinical improvement to allow discontinuation of antibiotic therapy or a switch to
oral anti-microbial therapy. Bacteriologic cure rates were determined when repeat cultures of appropriate samples were
available at the end of therapy. The results were also reported in terms of subgroups of infections. The treatment groups
were found to be comparable in terms of baseline demographic and clinical characteristics, except for age.

Effectiveness results
The effectiveness results were as follows:

Satisfactory clinical response was achieved in 85.9% of evaluable patients receiving A-S 1.5g, 82.5% receiving A-S 3g,
and 77.5% receiving T-C 3.1g, (p=0.044).

Infecting pathogens were eradicated in 63.2% of evaluable patients (A-S 1.5g), 65.2% (A-S 3g), and 62.6% T-C 3.1g),
(p=0.85).

Both agents were clinically and bacteriologically effective in patients infected with the most commonly identified
pathogens.

The only significant difference among groups was a higher bacteriologic eradication rate for T-C against Pseudomonas
sp, (p=0.013).

For skin and soft tissue infections, no statistically significant differences in clinical cure or bacteriologic eradication
rates were apparent among the three treatments.

The three regimens also had equivalent clinical efficacy in intra-abdominal infections, but A-S had significantly
superior bacteriologic efficacy to T-C in these patients (although this may be a function of the small number of patients
treated with T-C).

In gynaecologic infections, no statistically significant differences in clinical or bacteriologic efficacy were noted
between the two A-S doses and T-C (although the comparison was limited because only five women received T-C).

The results obtained for respiratory tract, urinary tract, and other infections generally were similar to those for skin and
soft tissue, intra-abdominal, and gynaecologic infections.

No statistically significant differences in clinical or bacteriologic cure rates were found.

Clinical conclusions
In this open, retrospective study, both 1.5g and 3.0g dosages of ampicillin-sulbactam had clinical and bacteriologic efficacy comparable with that of ticarcillin-clavulanate for the management of all except intra-abdominal infections.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported. The economic study appears to have been reduced to a cost-minimisation analysis based on the equivalent efficacy of the study regimens.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Some quantities were reported separately from the costs and cost items were reported separately. Cost analysis covered the costs of antibiotics (level 1) on a per-gram basis (acquisition cost multiplied by the total amount of drug administered) and materials required for preparation and administration (level 2) on a cost/dose basis. The perspective adopted in the cost analysis was not explicitly specified, but appears to have been that of the hospital. The sources of unit costs were each participating hospital. A cost:charge ratio of 0.6 was used to determine drug costs from charge data. The price year was not explicitly specified. Labour costs were assumed to be fixed and were therefore not included. Costs associated with adverse events and treatment failure and with hospitalisation were not collected.

**Statistical analysis of costs**
Cost of therapy was assessed by analyses of variance (ANOVA) and post hoc Newman-Keuls tests.

**Indirect Costs**
Indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The mean (SD) acquisition cost/patient (level 1) was $199.72 (281.77) in the group receiving A-S 1.5g, $335.42 (383.23) in the group receiving A-S 3.0g, and $374.35 (358.62) in the group receiving T-C; the level 1 cost of A-S 1.5g was significantly lower, (p<0.05) than that for either of the other two treatments.

The corresponding values for the preparation/administration (level 2) costs were AS 1.5g = $114.53 (133.32), A-S 3.0g = $86.79 (110.82), and T-C = $124.91 (151.88); the level 2 cost of T-C was significantly higher than that of A-S 3.0g, (p<0.05).

**Synthesis of costs and benefits**
Costs and benefits were not combined as it appears that the economic study was based on cost-minimisation analysis.
Authors' conclusions
In summary, in this trial ampicillin-sulbactam had efficacy comparable with that of ticarcillin-clavulanate in a variety of infections in hospitalised patients, at a potentially lower cost/course of treatment. Based on susceptibility of likely pathogens, ampicillin-sulbactam 1.5g provides adequate coverage, particularly in respiratory and urinary tract infections, and has the greatest potential for cost savings compared with either ampicillin-sulbactam 3.0g or ticarcillin-clavulanate.

CRD COMMENTARY - Selection of comparators
No specific health technology appears to have been regarded as the comparator. You, as a database user, should consider which one of these or other beta-lactam/beta-lactamase-inhibitor combinations are widely used in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results cannot be reasonably assured due to the open-label, retrospective, non-randomised nature of the study design, and the fact that no power calculations were performed to establish an appropriate sample size. However, the treatment groups were found to be comparable in terms of baseline demographic and clinical characteristics, except for age. The authors acknowledged that despite the similarity of the groups in terms of the above-mentioned baseline characteristics, the potential existed that A-S 1.5g was given preferentially to patients with less severe infections. The comparisons in terms of subgroups of infections may have further suffered from the shortage of patients in each subgroup; as acknowledged by the authors. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The analysis of benefits appears to have been based upon therapeutic equivalence of treatment alternatives. The economic analysis therefore included only costs.

Validity of estimate of costs
The following features enhanced the validity of the cost results: some quantities were reported separately from the costs; some details of methods of cost estimation were given; the perspective adopted in the cost analysis was apparent (although not explicitly reported); a cost-to-charge ratio was used to convert charges to costs; statistical analyses were performed on some resource use and cost data. However, in terms of limitations: the price year was not reported; the cost analysis was conducted retrospectively; and the direct cost analysis omitted some important cost items. As a consequence, the cost results may not be generalisable outside the study setting.

Other issues
The study results may need to be treated with some caution. The issue of generalisability to other settings or countries was not addressed, but appropriate comparisons were made with other studies. The issue of the degree to which the study sample was representative of the study population was not explicitly addressed.

Implications of the study
Since ampicillin-sulbactam has comparable activity against the pathogens responsible for most skin, gynaecologic, and intra-abdominal infections, it may be appropriate to reserve broader-spectrum agents such as ticarcillin-clavulanate for nosocomial infections, particularly those in which Pseudomonas sp are highly likely or documented. A controlled, randomised, clinical trial would be warranted to validate the study findings.

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