Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital
Grant E M, Kuti J L, Nicolau D P, Nightingale C, Quintiliani R

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 piperacillin-tazobactam. Patients received an intermittent infusion every 6 hours (piperacillin 3 g-tazobactam 0.375 g) or every 8 hours (piperacillin 4 g-tazobactam 0.5 g). The patients were then dosed prospectively with a continuous infusion based on renal function, as calculated using the Cockroft-Gault method. The patients received the standard piperacillin 8 g-tazobactam 1 g continuous infusion regimen unless a nosocomial pathogen (e.g. Pseudomonas aeruginosa) was suspected, in which case a different regimen (piperacillin 12 g-tazobactam 1.5 g) was selected. A nosocomial infection was defined as any infection that developed 48 hours or longer after admission.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older who received a minimum of 3 full days of piperacillin-tazobactam therapy and whose clinical signs and symptoms were consistent with types of infection for which piperacillin-tazobactam would be deemed appropriate. Thus, they were eligible for conversion to continuous infusion. Patients with intraabdominal infection (community- or hospital-acquired) or hospital-acquired lung infection were eligible for inclusion, as were those with skin, soft tissue or bone infections, or various other infections (e.g. bacteraemia and urosepsis). Patients were excluded if they presented with an absolute neutrophil count below 1,000 cells/mm3, known hypersensitivity or allergy to beta-lactam antibiotics, infection with micro-organisms known to be resistant to piperacillin-tazobactam, or documented severe renal dysfunction. Pregnant or nursing patients were also excluded, as were patients who had received at least one day of intermittent infusion of piperacillin-tazobactam before conversion to continuous infusion.

Setting
The setting was tertiary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from March 1999 to October 2000. The price year was 2000.

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

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

**Study sample**
No power calculations to determine the sample size were reported and no specific sample size was planned. During the data collection period, 98 patients met the inclusion criteria and were evaluated. Of these, 47 patients were treated with continuous infusion and 51 received intermittent infusion. In the continuous-infusion regimen, 24 patients received piperacillin 8 g-tazobactam 1 g and 23 received piperacillin 12 g-tazobactam 1.5 g. In the intermittent-infusion regimen, 49 patients received piperacillin 4 g-tazobactam 0.5 g every 8 hours while 2 received piperacillin 3 g-tazobactam 0.375 g every 6 hours. In the continuous-infusion group, 28 patients (60%) were males and 19 (40%) were females, with a mean age of 66 (+/- 18) years. In the intermittent-infusion group, 33 patients (65%) were males and 18 (35%) were females, with a mean age of 65 (+/- 17) years.

**Study design**
The study was a prospective, open-label evaluation with a concurrent control, which was carried out in a large community teaching hospital (Hartford Hospital). The duration of follow-up was 7 to 14 days after the end of therapy. Follow-up consisted of a phone call or assessment of readmission to Hartford Hospital. All the patients in the continuous-infusion group were available for follow-up, as were 46 of the 51 patients in the intermittent-infusion group. Thus, the loss to follow-up for the intermittent-infusion group was 5 patients.

**Analysis of effectiveness**
All of the patients in the study were accounted for in the analysis. The primary health outcomes used were:

- the clinical response at the end of therapy,
- the microbiologic response,
- the test-of-cure response,
- the length of therapy,
- the rate of response,
- the number of patients receiving concomitant therapy, and
- adverse events.

Cure in this study was defined as the complete resolution of all acute signs and symptoms of infection. Patients who retained evidence of infection, but who demonstrated improved signs and symptoms were classified as improved. For the purpose of the statistical analysis, patients termed as cured and improved were combined and defined as clinical successes. Failure was the persistence or progression of signs and symptoms of infection, the development of new clinical findings consistent with active infection, or death from infection. If a patient improved during therapy but died from a non-infectious process, that patient was classified as improved. If death was related to infection, then that patient was classified as a failure.

At the end of therapy, each patient's microbiologic outcome was assigned one of the following categories:

- eradication (elimination of the pathogen from the site of isolation),
- presumed eradication (absence of appropriate fluid for culture coupled with clinical improvement after a pathogen was initially isolated),
- persistence (failure to eradicate the original pathogen from the site of isolation after completion of therapy, absence of appropriate fluid for culture coupled with lack of clinical improvement after a pathogen was initially isolated, and/or
development of resistance during therapy), or
unevaluable (patients without cultures or evident pathogens from the presumed site of infection).

The categories of eradication and presumed eradication were combined and defined as microbiologic success. Persistence was designated as microbiologic failure.

A statistical analysis demonstrated no significant demographic differences between the intermittent- and continuous-infusion groups in terms of their age, gender, and acute physiology and chronic health evaluation (APACHE) II score. No differences between the groups were generally demonstrated for the type of infection. The exception was a greater number of patients with urosepsis or bacteraemia in the continuous-infusion regimen (8) than the intermittent regimen (1), (p=0.010).

Effectiveness results
A successful clinical response, defined as cure or improvement, occurred in 44 patients (94%) in the continuous-infusion group and 42 (82%) in the intermittent-infusion group, (p=0.081). In terms of infection sub-groups, the number of patients in these sub-groups was too small for significant statistical analysis. However, successful responses tended to favour the continuous-infusion regimen.

Twenty-eight patients (60%) in the continuous-infusion group and 32 (63%) in the intermittent-infusion group were microbiologically evaluable. Microbiologic success occurred in 89% of the microbiologically evaluable patients in the continuous-infusion group and 73% of the microbiologically evaluable patients in the intermittent-infusion group, (p=0.092).

At follow-up, 4 patients (two from each group) who had been initially designated clinical successes were reclassified as failures.

The duration of therapy with piperacillin-tazobactam was similar between the groups, 7.3 (+/- 4.8) days for continuous infusion versus 8.7 (+/- 7.1) days for intermittent infusion, (p=0.26).

In the continuous-infusion group, 18 (38%) patients had a fever (temperature of above 101.0 degrees F, 38.3 degrees C) at the start of piperacillin-tazobactam. Of these, 17 (94%) defervesced. In the intermittent-infusion group, 14 (27%) were febrile when therapy began. Of these, 13 (93%) defervesced. The average number of days until temperature normalisation was significantly less for continuous infusion (1.2 +/- 0.8 days) than for intermittent infusion (2.4 +/- 1.5 days), (p=0.012).

Leukocytosis normalisation was not statistically significantly different between the two groups. The mean number of days to white blood cell count normalisation (white blood cell count of less than 11 x 10^3/mm3) exhibited a trend in favour of continuous infusion, but this difference did not achieve statistical significance.

Five patients (11%) in the continuous-infusion group and 9 (18%) in the intermittent-infusion group received concomitant antimicrobial therapy, (p=0.322). The clinical success rates for patients receiving concomitant therapy were 80% (4 out of 5 patients) for the continuous-infusion group and 67% (6 of 9) for the intermittent-infusion group. Statistical analyses were not performed for these patients due to the small sample size.

A few dosing and administrative mistakes occurred during the programme, none of which had adverse clinical outcomes. No other adverse events that could be directly associated with either continuous or intermittent infusion of piperacillin-tazobactam were apparent.

Clinical conclusions
The study demonstrated that continuous infusion provides clinical and microbiological outcomes resembling those of intermittent infusion.
Modelling
A decision tree was employed to compare the cost-effectiveness of intermittent versus continuous infusion in terms of the average level 1 costs (acquisition prices of drugs) and level 2 costs (all costs directly related to antibiotic use). The decision tree categorised each case as a treatment success or failure.

Measure of benefits used in the economic analysis
The measure of benefit used in the economic analysis was the success rate.

Direct costs
The resource quantities and the costs were not reported separately. The direct costs included in the analysis were those of the provider. These comprised level 1 costs (acquisition prices of drugs) and level 2 costs (all costs directly related to antibiotic use). Cost related to antibiotic use encompassed supplies, preparation, administration, treatment of adverse events, concomitant antibiotics and expenditures for treating failures. The drug costs were calculated on the basis of contract pricing given to Hartford Hospital for the year 2000 for piperacillin-tazobactam and all concomitant antimicrobials. The preparation and administration costs were extrapolated from a study undertaken by Hitt et al. (see Other Publications of Related Interest), which was conducted in the same institution. The study reported the average costs. The level 2 analysis excluded the daily hospital stay costs since they were common to both alternatives. Discounting was irrelevant, as the costs for each group were incurred during less than one year, and was thus not performed.

Statistical analysis of costs
The mean costs were reported with their standard deviations (+/- SD). Differences in the costs of treatment were compared using a Mann-Whitney U-test. Significance was defined as a p-value of less than 0.05.

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

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were performed to determine which study conditions or variables, if changed, would alter the economic outcomes. One and two-way sensitivity analyses (Data, version 3.5, TreeAge Software Inc.) were performed by varying each treatment arm's probability of success from 50 to 95%.

Estimated benefits used in the economic analysis
The success rate was 94% in the continuous-infusion group and 82% in the intermittent-infusion group, (p=0.092). This result approached statistical significance, thus it is possible that a larger trial may be necessary to prove these benefits statistically.

Cost results
The mean acquisition cost per patient for piperacillin-tazobactam was $291.22 (+/- 218.22) for continuous infusion and $371 (+/- 325.39) for intermittent infusion, (p=0.054).

The mean level 2 costs for continuous infusion ($399 +/- 407.22) were significantly lower than for intermittent infusion ($523.49 +/- 526.85), (p=0.028).
The mean level 2 costs for patients treated successfully were $322.64 (+/- 215.99) for continuous infusion and $526.88 (+/- 568.39) for intermittent infusion, (p=0.008).

The mean cost for patients who failed treatment was significantly higher for continuous infusion ($1,525.00 +/- 883.76) than for intermittent infusion ($507.64 +/- 280.63), (p=0.033).

Synthesis of costs and benefits
The costs and benefits were combined by calculating a cost-effectiveness ratio (mean level 2 cost/success rate). An incremental analysis was not performed. This ratio was $424.87 for each patient receiving continuous infusion and $638.40 for each patient receiving intermittent infusion. The results from the one-way sensitivity analysis showed that when the clinical success of intermittent infusion was kept constant at 82% and continuous infusion varied from 50 to 95%, the economic decision changed in favour of intermittent infusion at 83% efficacy for continuous infusion. However, when continuous infusion was kept constant and intermittent infusion was varied from 50 to 95%, the economic decision always favoured continuous infusion. This difference was due to the greater costs attributable to failures with continuous infusion in comparison with intermittent infusion. It is probably associated with the number of deaths occurring in the intermittent-infusion group (5 versus 0 in the continuous-infusion group).

Authors' conclusions
Continuous infusion of piperacillin-tazobactam is a cost-effective alternative to intermittent infusion for a wide variety of infections. Continuous infusion provides clinical and microbiological outcomes resembling those of intermittent infusion.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for choosing intermittent infusion of piperacillin-tazobactam as the comparator, it would appear to represent current practice in the authors’ setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis used a prospective, open-label controlled study. This was appropriate for the study question, as this study was part of an ongoing clinical programme in which patients who were started on intermittent infusion were converted onto continuous infusion. However, as the authors pointed out, caution must be used when interpreting the clinical efficacy results due to the non-randomised and unblinded design, although their results were in line with the results found with randomised controlled trials. Thus, it seems unlikely that bias or confounding affected the results. The study sample was representative of the study population, although the study sample appears to have been too small to detect statistically significant results. The patient groups were shown to be comparable at analysis. The analysis of effectiveness was handled credibly, with the methods and results of the study being clearly detailed throughout.

Validity of estimate of measure of benefit
The estimation of benefits (success rate) was obtained directly from the effectiveness analysis. However, the differences in success rates between the two groups were not statistically significant.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. Some relevant costs, such as daily hospital stay costs, were not included. However, this omission is unlikely to have affected the authors’ conclusions, as the authors did not expect these costs to reveal significant differences between continuous versus intermittent infusion. The costs and the quantities were not reported separately, thus hampering generalisability to other settings. Appropriate statistical techniques were performed to test for differences in costs between the two groups. Sensitivity analyses were also performed to take uncertainty into consideration, thus enhancing the generalisability to other settings. Since all costs were incurred in less than one year, discounting was unnecessary and was not performed. The
price year was reported, which will enhance any possible reflationary exercises.

**Other issues**
Although no large, multi-centre trials have compared continuous- versus intermittent-infusion regimens, numerous small studies have addressed this subject. The authors made appropriate comparisons of their findings with those from such studies and found similar results. The issue of generalisability to other settings was partly addressed through these comparisons and through the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of their analysis.

The authors reported some further limitations to their study, in that the limitations in their economic analysis call into question the accuracy of the sensitivity analysis. Principally, the number of patients who failed therapy in each treatment regimen was very small. Thus, it is impossible to determine whether data from this small number of failures accurately represents the costs associated with failing either treatment. In addition, more patients in the intermittent-infusion group died than in the continuous infusion group. This shortened antibiotic-related duration of treatment for the intermittent group, hence directly affecting the total cost of therapy. However, the authors performed a three-way sensitivity analysis by varying the probabilities for clinical success for both regimens, along with the cost of failing either regimen. They found that continuous infusion should remain the least costly method. Another limitation was that the definition of fever used in the study (> 101.0 degrees F) is higher than the standard breakpoint for fever (100.3 degrees F). This may therefore have influenced the time to defervescence, as patients may drop to a temperature below 101.0 degrees F quickly but not below 100.3 degrees F. In addition, the authors did not monitor the use of acetaminophen or non-steroidal anti-inflammatory agents in their analysis.

**Implications of the study**
Even though the authors found continuous infusion to be a cost-effective alternative to intermittent infusion of piperacillin-tazobactam, they highlighted the need for more randomised studies with larger populations to further substantiate the benefits of continuous infusion of piperacillin-tazobactam.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
11939682

**Other publications of related interest**


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Bacterial Infections /drug therapy /economics; Chi-Square Distribution; Drug Therapy, Combination /administration & dosage /adverse effects /economics; Female; Hospitals, Community /economics /statistics & numerical data; Hospitals, Teaching /economics /statistics & numerical data; Humans; Infusions, Intravenous; Male; Middle Aged; Penicillanic Acid /administration & dosage /adverse effects /analsogs & derivatives /economics; Piperacillin /administration & dosage /adverse effects /economics; Prospective Studies; Statistics, Nonparametric

AccessionNumber
22002000678

Date bibliographic record published
30/06/2004

Date abstract record published
30/06/2004