Cost-effectiveness of ceftriaxone in the treatment of community-acquired pneumonia in adult hospital patients

A pharmaco-economic study based on a meta-analysis

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Objectives. A retrospective analysis was conducted to assess the cost-effectiveness of four intravenous antibiotic treatment regimens in the treatment of severe community-acquired pneumonia (CAP) in adults in a private hospital setting. The study compared some third-generation cephalosporin regimens with a second-generation cephalosporin and an amoxicillin/clavulanic acid (co-amoxiclav) regimen to investigate published South African treatment guidelines from a pharmaco-economic point of view.

Method. A pharmaco-economic model of local costs, from a payer perspective, was based on the results of a meta-analysis of clinical papers from peer-reviewed journals. The study compared intravenous (IV) ceftriaxone (2 g once daily), cefotaxime (IV 2 g 3 times a day), cefuroxime (IV 750 mg 3 times a day, followed by 500 mg orally 3 times a day) and amoxicillin/clavulanic acid (IV 750 mg 3 times a day, followed by 625 mg orally 3 times a day).

Results. An analysis of the odds ratios (ORs) of all two-way comparisons indicated that ceftriaxone ensured significantly higher probabilities of successful outcomes than the other antibiotic treatment regimens (ORs in the order of two were indicated). The pharmaco-economic results suggested that the ceftriaxone treatment regimen was the most cost-effective in the hospital treatment of CAP in adult patients. These results proved to be robust across sensitivity analyses for success rates and treatment days. A sensitivity analysis testing the assumption that patients could be discharged once the

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oral treatment was initiated indicated that the amoxicillin/clavulanic acid and cefuroxime treatment arms were more cost-effective. The clinical validity of such an assumption is questionable.

Conclusion. **Despite the conservative approach followed in terms of ceftriaxone data, both the clinical results and cost-effectiveness supported the use of ceftriaxone in the treatment of CAP in adults in the hospital setting.**

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Community-acquired pneumonia (CAP) is a world-wide problem with high mortality and morbidity rates.[1] In a country such as the USA, the mortality rate for CAP ranges from 10% to 25%.[2] CAP is the only infective disease consistently among the top 10 causes of death in both the First World and the developing countries. Pneumonia accounted for approximately 5% of all deaths in patients older than 65 years in South Africa during 1984.[3,4] It is therefore clear that this condition not only impacts upon personal health but, because of the high morbidity and mortality rates, also adversely affects community life and productivity. Mortality is, however, improved by the early initiation of treatment with antibiotics to which the causative organism is susceptible, and adversely affected by delayed or inappropriate initial therapy.[4]

A major cost in the treatment of patients with CAP is the antibiotic regimen. In an effort to promote the cost-effective treatment of the disease, the Pulmonology Society of South Africa has laid out guidelines for the management of CAP.[4] The aim of this study was to evaluate the economic implications of introducing third-generation cephalosporins into the treatment of CAP, using the guidelines as a benchmark or treatment reference scenario. The focus was explicitly defined as adult patients with CAP treated in private hospitals. The study was therefore limited to severe cases of CAP requiring hospitalisation and intravenous antibiotics.

Methodology

Study design

A meta-analysis of published data on CAP was conducted according to a pre-determined protocol following the recommendations of Mulrow.[5] Four treatment arms were planned for the study, reflecting the above guidelines and introducing third-generation cephalosporins for comparative purposes.

These arms consisted of: (*i*) intravenous (IV) amoxicillin/clavulanic acid (co-amoxiclav) (sequential treatment consisting of 750 mg 3 times a day and 625 mg orally 3 times a day), plus an oral macrolide; (*ii*) cefuroxime (IV 750 mg 3 times a day followed by 500 mg orally 3 times a day); (*iii*) cefotaxime (IV 2 g 3 times a day); and (*iv*) ceftriaxone (IV 2 g once daily). These doses are generally reported in the literature, and are therefore considered to be comparable. Severity has been considered to be comparable if patients were treated with an intravenous antibiotic regimen in a hospital setting.

In view of the unavailability of published data on the combination therapy, the first treatment arm was changed to only amoxicillin/clavulanic acid. This was not considered a serious loss in terms of representativeness and usefulness of the study results, because it still reflects clinical practice of the hospital treatment of pneumonia in many cases. The meta-analysis formed the clinical basis for the study and was followed by a costing exercise, quantifying the clinical results in terms of South African prices. This added an economic perspective and local content to the study.

Methods and assumptions

Literature search

A MEDLINE search for published papers was conducted and supplemented by Internet database searches. The key words used included 'community-acquired pneumonia', 'CAP,' 'adults', 'hospital', and the different drug names. Mostly English papers were assessed, although one German paper was considered but was judged inappropriate.

Inclusion criteria

Predetermined inclusion criteria for published papers, used to establish their suitability for the study, were established and included the following:

1. Papers that reported randomised, controlled trials. Blinding was not included as a selection criterion. This was considered impractical, as some treatment arms included oral agents while others contained only IV administered drugs.
2. Studies stating a clear diagnosis and including clinical success rates, defined as *clinical cure or improvement*. Papers reporting on lower respiratory tract infections were scrutinised and those actually reporting pneumonia or containing subgroups of CAP patients were included, with CAP-specific data being extracted. Severity was considered as one of the criteria determining the combinability of the data.
3. Clinical trials reporting results of treatment with the specified dosages and formulations of the study drugs.
4. For inclusion of a treatment arm into the study, more than one clinical trial was required. This requirement was lifted in the case of amoxicillin/clavulanic acid because the sample size (256 patients in each arm) reported by Brambilla *et al*.[6] was considered sufficient to justify inclusion.

Unfortunately, no threshold sample size or proportion of patients diagnosed with CAP could be imposed on the inclusion criteria. The number of papers available did not allow the inclusion criteria to be so conservative. Treatment days were also not included as an inclusion criterion, but a treatment arm could not be included in the study design if no data on length of treatment were available.

Exclusion criteria

Similarly, exclusion criteria were established and included:

1. Any trial not stating the specific diagnosis of CAP. Some pharmaco-economic studies failed in this respect and were excluded because they could potentially introduce bias.
2. Studies dealing with nosocomial pneumonia, bronchitis, immunosuppressed patients, only paediatric patients, and ambulatory treatment settings. Given the focus

of this current study, treatment in intensive care facilities was not considered valid for inclusion.

Statistical methods

Apart from the above qualitative criteria, statistical methods were employed to test the homogeneity of the data. A chi-square test with *a priori* significance level (alpha) of 5% was performed on the data from all appropriate trials for each drug. Only once it was proved in this way that the results were not trial-dependent and could therefore be combined were they included in the meta-analysis and aggregated. The success rates and treatment days for each treatment arm were calculated to be the weighted average of those reported in the relevant trials.

The aggregated data were described and analysed by reporting the odds ratio (OR) for every two-way comparison of drugs. The OR reports the relative odds of observing a specific outcome in a particular treatment scenario. This study sought to determine the relative odds of observing a satisfactory outcome (clinical cure or improvement) in one experimental drug compared with another. An OR greater than unity implies that it is more likely to observe a satisfactory outcome in the experimental drug than in the control drug. ORs less than unity refer to satisfactory outcome less likely to occur in the experimental group and unity implies no significant difference between the two treatment groups. Ninety-five per cent confidence intervals (CIs) for the ORs were calculated. If a 95% CI for the OR includes unity, it will indicate that there is no significant difference between the two comparators, tested at the 5% level of significance.

Pharmaco-economic analysis

The perspective of the pharmaco-economic analysis is that of the consumer/payer of health care services. The comparison was done by costing out the scenarios reported in the clinical trials, making use of South African private sector hospital prices and Representative Association of Medical Schemes Scale of Benefits rates where applicable. The charges taken into consideration were drug prices, administration costs and ward costs. The consumables used in IV drug administration included the peripheral line (Jelco cannula, intravenous line, buretrol and IV fluids, where applicable, and assumed to be replaced every 3rd day) and drug reconstitution (two syringes, one needle and two webcols). Ward costs have been calculated to the nearest half day. The clinical success rates calculated in the meta-analysis were used to determine the cost per successfully treated patient. Discounting was not taken into consideration because of the short duration of therapy and the fact that adverse reactions were not included in the study. Sensitivity analyses were performed on success rates, treatment days and ward costs, recalculating the results by making use of best-case scenarios as sourced from the literature. Assumptions about ceftriaxone were not varied in the sensitivity analyses and as a result, all scenarios were tested against the same reference value. For the sensitivity analysis on ward cost, it was assumed that the oral phases of treatment of cefuroxime (axetil) and amoxicillin/clavulanic acid would not require hospitalisation. This assumption was tested across the number of hospital days.

Results

Statistical and meta-analysis

Applying the inclusion and exclusion criteria reported above, 21 papers were identified from the literature as being relevant to the study.[1,2,6-24] From these papers, data from five clinical trials contained results that passed the homogeneity test and were therefore used for the meta-analysis. The results are reported in Table I. The data obtained from the meta-analysis were used to calculate the ORs for all the two-way comparisons. These results are illustrated in Fig. 1.

Table I. Statistics from individual clinical trials

	Satisfactory outcomes	Failures	Total	Success rate	Treatment days
Ceftriaxone*					
Baumgartner and Glauser[10]	46	3	49	93.9%	Not reported
Barradas *et al.*[11]	19	2	21	90.5%	4.20
Aggregate	65	5	70	92.9%	4.20
Cefotaxime**					
Barradas *et al.*[11]	14	5	19	73.7%	5.90
Vogel and Lode[20]	34	3	37	91.9%	Not reported
Aggregate	48	8	56	85.7%	5.90
Cefuroxime***					
Brambilla *et al.*[6]	223	33	256	87.1%	2.5 and 5.0
Siegel *et al.*[23]	18	2	20	90.0%	2.0 and 8.0
Aggregate	241	35	276	87.3%	2.46 and 5.22
Amoxicillin/clavulanic acid					
Brambilla *et al.*[6]	220	36	256	85.9%	2 - 3 and 5.0

* χ^2 0.26; *P* 0.6126; NS.
** χ^2 3.43; *P* 0.1799; NS.
*** χ^2 0.14; *P* 0.7083; NS.

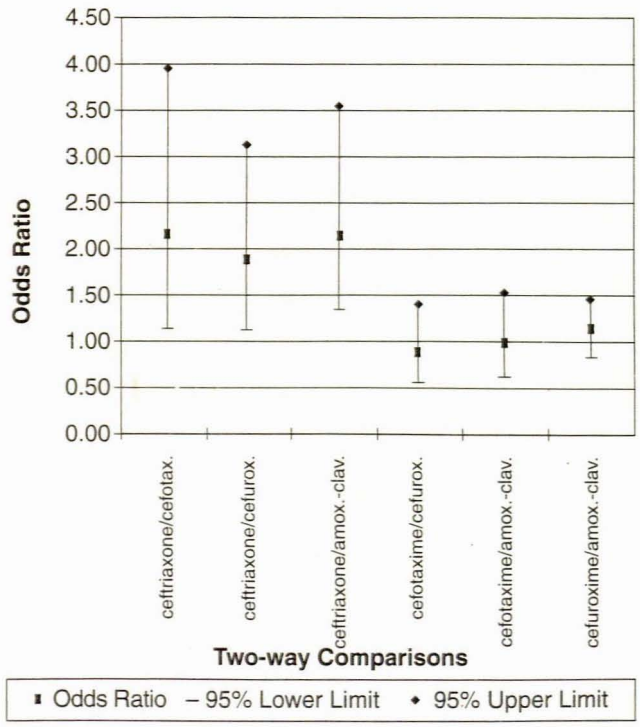

Fig. 1. Odds ratios.

As is clear from this figure, the CIs of the ORs of all comparisons involving ceftriaxone do not include unity, thus indicating statistically significant differences. The ORs for these comparisons are all in the order of 2, suggesting that it is twice as likely to obtain a favourable outcome using a 2 g once-a-day IV ceftriaxone treatment regimen as in any of the other comparator regimens considered.

Pharmaco-economic analysis

The fact that the statistical analysis suggested significant differences between ceftriaxone and the other comparators justified a cost-effectiveness analysis. If this had not been indicated, the cheapest regimen would also have been the most favourable pharmo-economic option. The results of the pharmaco-economic analysis are reported in Table II. As is evident from these results, amoxicillin/clavulanic acid treatment represents the cheapest regimen in terms of drug costs. This trend is continued when administration costs are included to given total drug delivery costs. However, when ward costs are calculated and added to the drug delivery costs, ceftriaxone treatment becomes the more suitable option. The cost-effectiveness analysis, calculated as the cost per satisfactory outcome (the ratio of total treatment costs and success rate), clearly indicates that the ceftriaxone regimen is the most cost-effective of the treatment arms considered. The most significant difference is observed between the two third-generation cephalosporins, ceftriaxone and cefotaxime. The difference between the other two treatment regimens does not appear to be economically significant.

Table II. Cost comparison between the four treatment arms

Cost analysis	Ceftriaxone	Cefotaxime	Cefuroxime	Amoxicillin/ clavulanic acid
Drug - IV	R252.27	R416.97	R118.09	R125.51
Drug - oral			R35.71	R30.28
Treatment days - IV	4.20	5.90	2.46	2.50
Treatment days - oral	-	-	5.22	5.00
Total drug (D)	R1 059.54	R2 460.10	R476.93	R465.18
Admin - IV (A)	R165.19	R189.19	R94.60	R94.60
Total drug delivery costs (D + A)	**R1 224.72**	**R2 649.30**	**R571.53**	**R559.77**
Ward charges (W)	R2 065.95	R2 754.60	R3 672.80	R3 443.25
Total (D + A + W)	**R3 290.67**	**R5 403.90**	**R4 244.33**	**R4 003.02**
Success rate	92.86%	85.70%	87.30%	85.94%
Cost per successfully treated patient	**R3 543.80**	**R6 305.60**	**R4 861.78**	**R4 658.06**

Sensitivity analyses

The results obtained from the pharmaco-economic analysis were tested for robustness across the assumptions made. To this effect, sensitivity analyses were performed for the success rates, treatment days and ward costs. The results are presented in Table III. In the analysis that tested success rates, the best success rates reported in the literature for cefotaxime, cefuroxime and amoxicillin/clavulanic acid were compared with the meta-analysis results for ceftriaxone. The results proved robust across these success rates, with the most favourable outcome still being associated with the ceftriaxone treatment arm. The difference between the cefotaxime and the cefuroxime and amoxicillin/clavulanic acid treatment arms became smaller in magnitude. When the most favourable treatment periods for cefuroxime and amoxicillin/clavulanic acid were used, the pharmaco-economic results were again robust and no significant changes were effected.

Table III. Sensitivity analyses for success rates, treatment days and ward costs

	Ceftriaxone	Cefotaxime	Cefuroxime	Amoxicillin/ clavulanic acid
Success rate				
Meta-analysis*	92.86%	-	-	-
Best-case†	-	91.90%	90.00%	85.94%
Cost‡	R 3 543.80	R 5 880.10	R 4 715.92	R 4.657.93
Treatment days				
Meta-analysis	4.2	5.90	-	-
Best-case	-	-	2.50	2.00
Cost	R 3 543.80	R 6 304.86	R 4 594.19	R 4 311.35
Hospital days				
Meta-analysis	4.20	5.90	-	-
Best-case	-	-	2.46	2.50
Cost	R 3.543.80	R 6 304.86	R 1 968.94	R 1 986.88

* Results obtained from the meta-analysis of the published literature.
† Best-case scenarios published in the literature.
‡ Cost per successfully treated patient.

The sensitivity analysis on ward costs involved the assumption that switching a patient from parenteral to oral treatment implied that the patient would also be discharged from hospital. This sensitivity analysis effected the only significant change in the results and suggested an advantage to parenteral/oral treatment regimens over those involving only parenteral treatment. The analysis showed a significant difference between the third-generation cephalosporins and the other two treatment arms. Cefotaxime was still almost twice as costly as ceftriaxone, but the latter was more than 75% more costly than cefuroxime or amoxicillin/clavulanic acid. It must be noted, however, that the success rates for the cefuroxime and amoxicillin/clavulanic acid arms reported in the literature referred to patients hospitalised for the full duration of treatment. The success rates for patients discharged once they were put on oral therapy may be lower than those reported, because of factors such as compliance and quality of care. To explore the sensitivity of the analysis to ward costs further, the number of hospital days were varied across the range from 2 to 10 days. Fig. 2 indicates that at a total of between 5 and 6 treatment days, the cefuroxime and amoxicillin/clavulanic acid treatment arms are equivalent to the ceftriaxone treatment in terms of cost-effectiveness. Considering the severity of illness in the patients investigated, this length of hospital treatment seems to represent a likely scenario from a clinical perspective. The findings from this sensitivity analysis strengthen the case for outpatient parenteral antibiotic treatment.

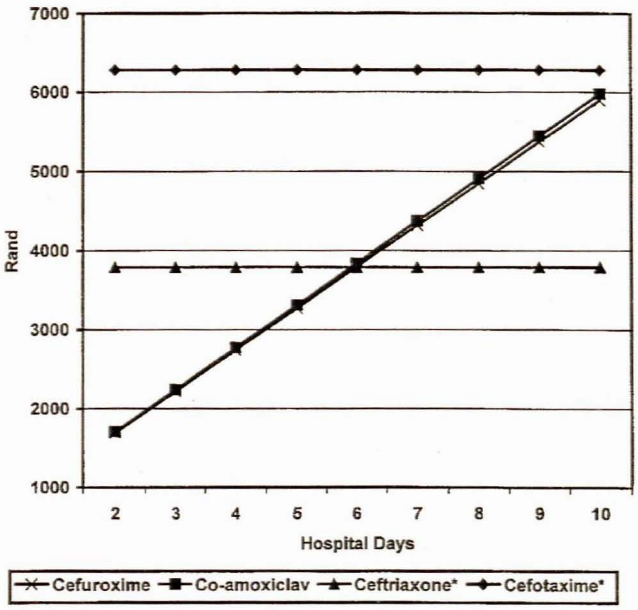

Fig. 2. Sensitivity analysis for hospital days (*at meta-analysis hospital treatment period).

Conclusion

The demands on health care systems in South Africa have increased dramatically in the last few years and have precipitated increasing concern by decision-makers to achieve value for money in many areas of health care. This has led to appreciation of the need for the evaluation of the true resource implications of many practices, including the use of antibiotics in the management of CAP. The pharmaco-economic analysis presented above and based on published data indicated a distinct advantage for ceftriaxone over the other antibiotic regimens for this disease. These findings were reasonably robust across most assumptions, the only exception being the impact of ward costs. If one is to assume that patients who are switched to oral treatment can be discharged immediately, the more traditional treatment regimens were identified as more cost-effective. However, this is probably not the case in most practical settings. This assumption will have to be tested to validate the representativeness of the scenario created in this way.

The pharmaco-economic analysis only considered drug prices, administration charges limited to consumable products, and ward charges. The actual time of preparing and administering the intravenous agents was not investigated and has therefore not been costed out. This is considered to be a limitation of the study. The cost of treatment failure has also not been considered in the analysis because no data on this aspect of the treatment of CAP have been published. As is the case for nursing administration time, a prospective trial will have to be launched to collect data on the cost of treatment failure.

In this study the results of the meta-analysis indicated that ceftriaxone resulted in a significantly higher likelihood of successful outcome in the parenteral treatment of hospitalised patients with CAP. Some concern about the applicability of the data to South African conditions was raised with clinicians. In a personal communication with Professor Keith Klugman of the South African Institute of Medical Research, he indicated that generally the same pathogens would be involved in the cases of CAP diagnosed in South Africa as in the papers used for the meta-analysis, justifying the use of published data as clinical basis for the study. However, the implications of this study in making comparisons between various antibiotic regimens for the treatment of CAP are sound and it is important to be aware of all hidden costs when making prescribing decisions about antibiotics of similar efficacy and tolerability.

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