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Elina Eleftheria Pliakos, ScB, Nikolaos Andreatos, MD, Giannoula S. Tansarli, MD, Panayiotis D. Ziakas, MD, PhD, Eleftherios Mylonakis, MD, PhD

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The Cost-effectiveness of Corticosteroids for the treatment of Community-Acquired Pneumonia

Running title: Cost-effectiveness of Corticosteroids for CAP

Elina Eleftheria Pliakos, ScB[1] , Nikolaos Andreatos, MD[1] , Giannoula S. Tansarli, MD[1] , Panayiotis D. Ziakas, MD, PhD[1] , Eleftherios Mylonakis, MD, PhD[1]

[1]Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, Rhode Island, United States of America

Correspondence to: Eleftherios Mylonakis, M.D., Ph.D., FIDSA, Dean's Professor of Medical Science (Medicine, and Molecular Microbiology and Immunology), Chief, Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903

Email: emylonakis@lifespan.org

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Abbreviations List

CAP, Community-acquired pneumonia

ICER, Incremental cost-effectiveness ratio

PSI, Pneumonia Severity Index

ICU, Intensive care unit

IPDMA, Individual patient data meta-analysis

LOS, Length of Stay

Abstract

Background: The use of corticosteroids as adjunct treatment for community-acquired pneumonia (CAP) is associated with potential clinical benefits and the aim of this study was to evaluate the cost-effectiveness of this approach.

Methods: We constructed a decision-analytic model comparing the use of corticosteroids+antibiotics to that of placebo+antibiotics for the treatment of CAP. Cost-effectiveness was determined by calculating deaths averted and incremental cost-effectiveness ratios (ICER). Uncertainty was addressed by plotting cost-effectiveness planes and acceptability curves for various willingness-to-pay thresholds.

Results: In the base-case analysis, corticosteroids with antibiotics resulted in savings of $142,795 per death averted (ICER: $-142,795/death averted). In the probabilistic analysis, at a willingness-to-pay of $50,000, corticosteroids with antibiotics had a 86.4% chance of being cost-effective compared to placebo with antibiotics. In cost-effectiveness acceptability curves, the corticosteroids+antibiotics strategy was cost-effective in 87.6% to 94.3% of simulations compared to the placebo with antibiotics strategy for a willingness-to-pay ranging from $0 to $50,000. In patients with severe CAP (PSI classes IV/V) the corticosteroids+antibiotics strategy resulted in savings of $70,587 and had a 82.6% chance of being cost-effective compared to the placebo+antibiotics strategy.

Conclusions: The use of corticosteroids with antibiotics is a cost-effective strategy and results in considerable health care cost-savings, especially among patients with severe CAP (PSI classes IV/V).

Introduction

In the U.S., pneumonia results in 51,811 deaths[1] and 1 million adult hospitalizations[2] per year and the cost of a single community-acquired pneumonia (CAP) CAP hospitalization ranges from $11,148 to $51,219[3]. Efforts to improve the prognosis of CAP have focused on improving antimicrobial treatment[4-8] and on the use of immunomodulation to titrate the inflammatory response[9].

The adjunct use of corticosteroids for the treatment of CAP is an intervention that could potentially improve CAP outcomes, as studies suggest a possible clinical benefit[10-14]. Moreover, corticosteroids may also down-regulate inflammatory cytokine transcription[15], thus possibly accelerating the resolution of CAP[16] and decreasing morbidity and hospital length of stay (LOS). However, clinical benefits are inconsistent across different studies and the benefit based on CAP severity is not well-defined. In this context, the aim of this study is to evaluate the financial benefit from the use of corticosteroids in the treatment of CAP and provide a cost-effectiveness analysis that evaluates whether the use of corticosteroids adds sufficient healthcare value to the care of patients with CAP.

Methods

2.1 Model Structure

We constructed a decision model (e-Figure 1) assessing the cost-effectiveness of corticosteroids (oral or intravenous) as an adjunctive therapy in the treatment of CAP. The patient population of our study consisted of adult hospital inpatients with CAP. The use of corticosteroids was examined for all levels of CAP severity determined using the Pneumonia Severity Index (PSI). PSI stratifies patients in 5 classes based on the risk of death and other adverse outcomes[17]. PSI risk classes of I, II and III were considered as non-severe, while PSI classes IV and V were considered as severe[11].

Costs and outcomes were calculated for a time horizon of 2 months and the analysis was performed from a societal perspective. An impact inventory that lists the possible consequences of treatment outcomes, both within and outside the healthcare sector [18], that were considered in the analysis can be found in e-Table 1. Cost data were obtained from sources that reported values in US dollars. Mortality was defined as any death within 30 days after randomization, CAP-related readmission as the number of readmissions for CAP symptoms within 30 days after discharge, and intensive care unit (ICU) admission as secondary admissions to the ICU within 30 days after randomization. The model was developed using the software TreeAge Pro 2018 (TreeAge, Williamstown, MA). This study follows the recommendations made by the Consolidated Health Economic Evaluation Reporting Standards statement[19] and did not require IRB approval.

2.2 Model Inputs

To obtain studies that provide data on the effectiveness of corticosteroids in the treatment of CAP, we used the most recently published and relevant systematic reviews and meta-analyses[10-14]. Specifically, an individual patient data meta-analysis (IPDMA)[11] was used as the basis of our analysis as IPDMA is considered the 'gold-standard' of systematic reviews[20]. Specifically, after replicating the search strategy employed by two previous studies[11,21] for studies in English that were published up to January 2018, we did not identify any studies in addition to those reported by Briel *et al*[11]. Furthermore, all costs for this study were obtained from the literature and were adjusted to January 2018 US dollars using the consumer price index inflation calculator provided by the Bureau of Labor Statistics[22]. A detailed description for the assignment of probability and cost estimates can be found in e-Appendix 1. Of note is that, as detailed in the supplemental materials, the model incorporated the PSI as well as the side effects of hyperglycemia and neuropsychiatric complications.

2.3 Outcome & Data Analysis

In the base case analysis our primary outcome was the incremental cost-effectiveness ratio (ICER), defined as the ratio of the incremental cost between the two strategies (corticosteroid or placebo) over their incremental difference in effectiveness. The incremental cost was defined as the excess cost of adjunct corticosteroid therapy for the treatment of CAP compared to the cost of the baseline strategy. In turn, the incremental effectiveness was defined in terms of deaths averted.

The robustness of our model was evaluated with the use of deterministic (one-way sensitivity) and probabilistic sensitivity analysis (Monte Carlo). In the one-way sensitivity analysis[23], each parameter was tested across a range of multiple point estimates, while in the probabilistic analysis we varied all parameters of the model

111 simultaneously. The base-case estimates, ranges and distributions for all parameters
112 are presented in Table 1. Probabilities were modeled as uniform distributions
113 (conservative modeling option), while costs were modeled as gamma distributions, as
114 recommended by guidelines[24]. When a range was not available for a variable, we
115 approximated it by allowing the variable to vary between 50% and 200% of its base
116 case value[25]. If a standard deviation was not available, it was estimated by dividing
117 the range by 6, as suggested for data that do not follow the normal distribution
118 (approximation obtained with the use of Chebyshev's inequality)[26].

119 In the Monte Carlo analysis[27], the model was run 10,000 times[25] and each time
120 a value from the predetermined distributions (Table 2), was randomly selected for
121 each variable. The results of each simulation were plotted on an incremental cost-
122 effectiveness plane as points with coordinates (x,y), with x representing incremental
123 effectiveness and y representing incremental cost. Points located within the south-east
124 quadrant of the graph were considered to be cost-effective and dominant[28]. Finally,
125 cost-effectiveness acceptability curves were used to evaluate the cost-effectiveness for
126 various willingness-to-pay thresholds[29].

Results

When comparing the strategy corticosteroids+antibiotics to that of placebo+antibiotics for the treatment of CAP, the difference in cost between the strategies was $5,254.87. More specifically, the mean cost was $38,291.29 for the corticosteroid strategy and $43,546.16 for the placebo strategy. The exact calculations that were performed can be found in e-Appendix 2.

Importantly, the corticosteroid strategy is expected to prevent 1 death per 27 patients treated. This was derived from the difference in effectiveness, measured as the probability of survival, between the two strategies which was 0.0368[9,11,16,30-33] (0.9536 for the corticosteroid strategy and 0.9168 for the placebo strategy). In turn, the base case ICER value was $-142,795 per death averted (ICER: $-142,795/death averted). This ICER value suggests that the use of corticosteroids is a cost-effective strategy for the treatment of CAP that results in savings of $142,795 per death averted.

Interestingly, in the sensitivity analysis which evaluated the impact of fluctuations in each variable within the ranges specified in Table 1 on ICER, it was revealed that corticosteroids were no longer cost-effective if the LOS in the ICU for the group that received corticosteroids was longer than 7.1 days. No thresholds, within the ranges specified in Table 1, were identified with respect to any of the other variables. These findings of the one-way sensitivity analysis are summarized in the Tornado Diagram (Figure 1).

In the probabilistic analysis, the mean cost was $42,902.05 (CI: $42,711.66-$43,092.43) for the corticosteroid strategy and $48,770.36 (CI: $48,555.52-$48,985.19) for the placebo strategy. These values are in agreement with the average

cost values we obtained in the base case analysis, presented in Table 2, suggesting that our findings are robust. In addition, with respect to cost-effectiveness planes (e-Figure 2), the corticosteroid strategy was localized in the dominant and cost-effective quadrant in 86.4% of simulations. Lastly, in cost-effectiveness acceptability curves (Figure 2), the corticosteroids strategy was cost-effective in 87.6% to 94.3% of simulations for a willingness-to-pay ranging from $0 to $50,000.0

The difference in the probabilities of survival between severe CAP and non-severe CAP (Table 1) prompted us to perform an additional analysis with the currently available data in order to examine whether there is a cost-effectiveness difference between severe and non-severe CAP. We found that the corticosteroid strategy resulted in savings of $70,587 per death averted in severe CAP, while it resulted in additional costs of $483,016 per death averted in non-severe CAP. In the probabilistic analysis, the corticosteroid strategy was localized in the dominant and cost-effective quadrant in 82.6% of simulations for severe CAP and 29.9% simulations for non-severe CAP.

Furthermore, for completeness, we also performed the analysis without accounting for the adverse events[34,35]. We found that the mean cost was $38,035.79 for the corticosteroids+antibiotics strategy and $43,398.04 for antibiotics+placebo strategy. In this analysis, the corticosteroid strategy resulted in savings of $145,713 for CAP patients overall (ICER: $-145,713/death averted). In the probabilistic analysis, the corticosteroid strategy was localized in the dominant and cost-effective quadrant in 87.7% of simulations.

Discussion

Community-acquired pneumonia creates an economic burden of over $17 billion per year[36] and CAP hospitalizations cost $8 billion per year[36]. In this context, there is a high interest in identifying cost-effective interventions that both improve the outcomes of CAP and decrease its financial impact. In our study, the corticosteroids+antibiotics strategy had a 86.4% chance of being cost-effective, supporting the implementation of this strategy as a cost-saving strategy for the treatment of CAP (ICER: $-142,795/death averted). Moreover, our findings that corticosteroids have an 82.6% chance of being cost-effective for severe CAP and 29.9% for non-severe CAP suggest that patients with severe CAP, defined as patients who belong to PSI risk classes IV or V, benefit the most from the use of corticosteroids than patients with non-severe CAP.

The finding that corticosteroids are cost-effective for the treatment of CAP can be explained mainly from the cost savings associated with the shorter LOS of the corticosteroid group. This is particularly evident from the Tornado Diagram (Figure 1), as the majority of the most influential variables (top of graph) are LOS variables. Based on the data we have used in our study, corticosteroids reduce by 1 day the hospital LOS for severe CAP patients (10 *vs.* 9 days) as well as for non-severe CAP patients (7 *vs.* 6 days) and the ICU LOS for all CAP patients (5 *vs.* 4 days). This corresponds to LOS decreases of 10%, 14% and 20% respectively. Based on the high costs of general and ICU hospitalization[37,38], interventions that reduce the need for hospitalization are deemed cost-effective[39,40]. The use of corticosteroids can thus, alleviate the high hospitalization burden of pneumonia.

Another factor that seems important in determining the cost-effectiveness outputs is the mortality risk associated with each strategy. Specifically, in our study we pooled the data available in the IPDMA[11] with the aid of conventional meta-analysis, to determine the mortality probabilities that we used to construct our decision model. More specifically, the corticosteroid strategy resulted in a slightly lower probability of mortality, which resulted in a negative incremental effectiveness value and subsequently to cost-savings for this strategy. It should be noted, however, that there is controversy among research studies on whether there is an actual mortality benefit to using corticosteroids or not[10-14]. In fact, we used the IPDMA as the basis of our analysis as it provides a conservative figure. Other studies such as a Cochrane review[10] that was published almost concurrently with the IPDMA[11], and differed in methodology and data sets, found significantly reduced overall CAP mortality. Importantly, we have accounted for this concern through the sensitivity analysis. Specifically, the sensitivity analysis did not reveal any thresholds, within the ranges specified in Table 1, with respect to the mortality variables.

Other variables such as CAP-related readmission and the days of antibiotic treatment did not seem to have a large influence on our results. Specifically, for severe CAP the probability of CAP-related re-hospitalization was the same between the corticosteroid and placebo groups (0.02), while for non-severe CAP there was a very small difference in mortality (0.02 *vs.* 0.01)11. Similarly, the small difference in the days of antibiotic treatment between the corticosteroid and placebo groups [11] and the low cost of antibiotics resulted in this variable having a negligible influence. Importantly, the sensitivity analysis revealed that the cost of corticosteroids did not affect the cost-effectiveness findings. As can be seen from the Tornado diagram (Figure 1), even if the cost of corticosteroids was significantly higher the

corticosteroid strategy would still be cost-effective. In addition, the adverse events do not seem to play a major role in cost-effectiveness outcomes. To confirm this finding we performed an additional cost-effectiveness analysis without the adverse events and found that the savings were similar (ICER: $-142,795/death averted *vs.* ICER: $-145,713/death averted). This is the case as the incremental differences in cost are similar ($5,254.87 accounting for adverse events and $5,362.25 not accounting for adverse events).

Importantly, we found that the use of corticosteroids seems to be especially cost-effective for patients with severe CAP. This was the case for a variety of reasons including the low cost of corticosteroids[41], the high cost of additional hospitalization[37] and ICU stay[3], and the greater difference in mortality observed in this group[11]. Conversely, our findings suggest that the use of corticosteroids is not cost-effective for patients with non-severe CAP (PSI I, II, or III). This could be explained from the fact that mortality is almost zero in this group and that mild-to-moderate CAP in outpatients is characterized by high clinical response to common antibiotic treatment regimens, such as azithromycin, amoxicillin-clavulanate or levofloxacin[42-44]. Fernandez-Botran *et al.* reported that the major difference between severe and non-severe CAP is that the patients with severe CAP cannot mount an optimal local inflammatory response, while at the same time they exhibit a sustained systemic response[45]. It could be that corticosteroids help the severe group attenuate their exaggerated inflammatory response, while this attenuation is not needed in non-severe CAP. This can also be supported from findings that suggest a direct relationship between the intensity of the inflammatory response measured in the blood and episode severity[46]. Future studies should focus on the effects of corticosteroids among patient populations such as the elderly, that have high mortality even among mild/moderate

CAP as it is reasonable to assume that they would also benefit more from the use of corticosteroids in terms of cost-effectiveness as they have higher rates of hospitalization[47] and mortality[48].

As our study is a model based on the available literature there are several limitations that need to be noted. First, we were unable to model readmissions for complications that were not related to CAP. In addition, we did not distinguish based on the type of pathogen causing CAP. Studies focusing on well-defined risk subgroups may help to further inform the use of this strategy and special emphasis should also be placed on studying morbidity. Ideally, a large randomized trial assessing the exact costs, quality of life, LOS, and readmission associated with CAP with *a priori* stratification according to severity would appropriately settle the controversy with respect to the use of corticosteroids in CAP.

In conclusion, our study uses high quality data from an IPDMA and indicates that the use of corticosteroids in the treatment of CAP would be mostly cost-effective for patients with severe CAP. Even though the evidence on whether corticosteroids reduce mortality is inconclusive, the decreased hospital and ICU LOS with corticosteroids seem to confer financial benefits. Given the health and economic burden that CAP poses[1,36], as well as the controversy surrounding the use of corticosteroids in CAP[10-14], our analysis provides useful information for clinical decision makers [49] on the economic efficiency of employing this strategy for the treatment of CAP.

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Guarantors of the Article: Elina E. Pliakos, ScB and Eleftherios Mylonakis, MD, PhD.

Specific Author Contributions: EEP designed the study, performed the data collection and analysis, prepared tables and figures, participated in data interpretation, wrote and drafted the initial manuscript, and approved the final manuscript as submitted. Ms. Pliakos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. NA designed the study, participated in data collection, extraction and interpretation, wrote and drafted the manuscript, and approved the final manuscript as submitted. GST designed the study, participated in data collection, extraction and interpretation, revised the manuscript, and approved the final manuscript as submitted. PDZ designed the study, participated in data interpretation, reviewed and revised the manuscript, and approved the final manuscript as submitted. EM conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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444 # Tables

Table 1: Model Inputs and baseline estimates for Probabilities, LOS and costs		
	Base Case Value (Range and Distribution)	**Source**
Probabilities		
Probability of mortality for severe CAP and corticosteroids	0.08 (Range: 0.06-0.12) Uniform (0.06-0.12)	11
Probability of mortality for severe CAP and placebo	0.16 (Range: 0.12-0.21) Uniform (0.12-0.21)	11
Probability of mortality for non-severe CAP and corticosteroids	0.01 (Range: 0.00-0.03) Uniform (0.00-0.03)	11
Probability of mortality for non-severe CAP and placebo	0.00 (Range: 0.00-0.02) Uniform (0.00-0.02)	11
Proportion of patients with severe CAP	0.52 (Range: 0.26-1) Uniform (0.26-1)	11
Proportion of patients with non-severe CAP	0.48 (Range: 0.24-0.96) Uniform (0.24-0.96)	11
Probability of CAP-related readmission for severe CAP and corticosteroids	0.02 (Range: 0.01-0.04) Uniform (0.01-0.04)	11
Probability of CAP-related readmission for severe CAP and placebo	0.02 (Range: 0.01-0.03) Uniform (0.01-0.03)	11
Probability of CAP-related readmission for non-severe CAP and corticosteroids	0.02 (Range: 0.01-0.03) Uniform (0.01-0.03)	11
Probability of CAP-related readmission for non-severe CAP and placebo	0.01 (Range: 0.00-0.02) Uniform (0.00-0.02)	11
Probability of secondary intensive care unit admission for severe CAP	0.56 (Range: 0.28-1.00) Uniform (0.28-1.12)	50
Probability of secondary intensive care unit admission for non-severe CAP	0.44 (Range: 0.22-0.88) Uniform (0.22-0.88)	50
Probability of hyperglycemia requiring insulin in severe CAP and corticosteroids	0.13 (Range:0.12-0.17) Uniform (0.12-0.17)	11
Probability of hyperglycemia requiring insulin in severe CAP and placebo	0.08 (Range:0.06-0.10) Uniform (0.06-0.10)	11
Probability of hyperglycemia requiring insulin in non-severe CAP and corticosteroids	0.07 (Range:0.06-0.10) Uniform (0.06-0.10)	11
Probability of hyperglycemia requiring insulin in non-severe CAP and placebo	0.04 (Range:0.03-0.05) Uniform (0.03-0.05)	11
Probability of neuropsychiatric complications with corticosteroids in CAP patients	0.01 (Range:0.00-0.02) Uniform (0.00-0.02)	11
Probability of neuropsychiatric complications with placebo in CAP patients	0.00 (Range:0.00-0.01) Uniform (0.00-0.01)	11
Length of Stay or Treatment (in days)		
Hospital LOS for severe CAP and corticosteroids	9.0 (Range: 6.0-13.0) Gamma (9.0; SD: 1.2)	11
Hospital LOS for severe CAP and placebo	10.0 (Range: 7.0-15.0) Gamma (10.0; SD: 1.3)	11
Hospital LOS for non-severe CAP and corticosteroids	6.0 (Range: 4.0-8.0) Gamma (6.0; SD: 0.7)	11
Hospital LOS for non-severe CAP and placebo	7.0 (Range: 4.0-9.0) Gamma (7.0; SD: 0.8)	11
ICU LOS for corticosteroids	5.0 (Range: 3.0-8.0) Gamma (5.0; SD: 0.8)	33
ICU LOS for placebo	6.0 (Range: 4.0-8.0) Gamma (6.0; SD: 0.7)	33
Days of intravenous antibiotic treatment for corticosteroid	4.0 (Range: 3.0-6.0) Gamma (4.0; SD: 0.5)	11
Days of intravenous antibiotic treatment for	5.0 (Range: 3.0-7.0)	11

placebo	Gamma (5.0; SD: 0.7)	
Costs (US Dollars $)		
Cost of corticosteroid treatment (Prednisone 50mg oral for 7d)	2.9 (Range: 1.5-5.8) Gamma (2.9; SD: 0.7)	41
General hospitalization cost per day for Rhode Island	2,926.2 (Range: 1,463.1-5,924.3) Gamma (2,926.2; SD: 743.5)	37
Intensive care unit hospitalization cost per day	4,934.4 (Range: 2,467.2-9,868.8) Gamma (4,934.4; SD: 1233.6)	38
Cost of re-hospitalization	27,336.1 (Range: 13,668.1-54,672.2) Gamma (27,336.1; SD: 6834.0)	3
Cost of antibiotic treatment for CAP per day	91.12 (Range: 45.56-182.24) Gamma (91.12; SD: 22.78)	Supplemental Materials 2
Cost of hyperglycemia requiring insulin	2,436.3 (Range: 1218.2-4872.6) Gamma (2,436.3; SD: 609.1)	34
Cost of neuropsychiatric complications	894.9 (Range: 447.5-1789.8) Gamma (894.9; SD: 223.7)	35
Productivity Costs	2,604.4 (Range: 1,302.2-5,208.8) Gamma (2,604.4; SD: 651.1)	51

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Table 2: Base Case Analysis Results for Competing Strategies				
Base Case Estimates				
	Strategy	***Cost ($)***	***Effect (probability of survival)***	***ICER ($/death averted)***
CAP patients	Corticosteroids	38,291.29	0.9536	-142,795
	Placebo	43,546.16	0.9168	(baseline)

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Figures

Figure 1: Tornado Diagram. This graph is a summary of the one-way sensitivity analysis. From top to bottom it presents the variables that led to the greatest change in the incremental cost-effectiveness ratios.

Figure 2: Cost-effectiveness acceptability curves for various willingness-to-pay thresholds. These curves show the percent of the 10,000 simulations at which corticosteroids were cost-effective for the treatment of CAP.