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ABSTRACT

Background: Adults admitted to hospital with community-acquired pneumonia (CAP) impose significant burden upon limited hospital resources. To achieve early response and possibly early discharge, thus reducing hospital expenditure, the choice of initial antibiotic therapy is pivotal.

Methods: A cost-consequences model was developed to evaluate ceftaroline fosamil (CFT) as an alternative to other antibiotic therapies (ceftriaxone, co-amoxiclav, moxifloxacin, levofloxacin) for the empiric treatment of hospitalized adults with moderate/severe CAP (PORT score III–IV) from the perspective of the Spanish National Health System (NHS).

Findings: Compared with ceftriaxone, the model predicted an increase in the number of CFT-treated patients discharged early (PDE) (30.6% vs. 26.1%) while decreasing initial antibiotic failures (3.8% vs. 7.6%). For patients with pneumococcal pneumonia, CFT was cost-saving vs. ceftriaxone (by 1.2%) and significantly increased PDE (32.1% vs. 24.6%). CFT resulted in cost-saving vs. levofloxacin, due lower initial antibiotic therapy costs and increased PDE (30.6% vs. 14.9%). Moxifloxacin and co-amoxiclav early response rate of 53.63% and 54.24% resulted in cost neutrality vs. CFT, with direct comparison hampered by the significantly different early response criteria utilized in the literature.

Conclusions: Despite a higher unit cost, CFT is a reasonable alternative to other agents for adults hospitalized with moderate/severe CAP, given the projected higher PDE achieved with similar or lower total costs.

Introduction

Community-acquired pneumonia (CAP) remains an acute infection with significant associated morbidity, mortality and economic burden[1–4], particularly prevalent in the elderly. Indeed, within an estimated European incidence of 0.2–242 per 1,000 adults/year, significantly higher rates are observed in the elderly population[3,4]. Accordingly, in the US, 1.3 million cases of CAP were estimated to have occurred in adults ≥65 years in 2012[5]. With the globally aging population, the incidence and burden of CAP is therefore set to increase even further[3,6,7]. One study in primary care showed an incidence of CAP in Spain that was in the range 4.63/1,000 people/year[4]. The incidence in people older than 65 years was higher in men, with a range of 7.06–36.93 compared to 5.43–19.62 in women.

Although mild disease can be managed in the community, a significant proportion of patients with comorbidities, such as metabolic or cardiovascular disease, or more severe CAP will require hospitalization[8]. The medical costs associated with each episode of inpatient care for CAP was estimated to exceed $18,000 in the US in 2012, which equated to an overall annual burden above $13 billion[5,6]. Similarly, in Europe, the estimated inpatient care direct costs amount to €5.7 billion per year with a further estimated €3.6 billion of indirect costs due to productivity loss[3]. Given that the main determinants of overall costs are in-patient treatment, hospital length of stay and the need for intensive care[3,9], effective treatment which can achieve rapid clinical cure and enable early discharge are therefore highly desirable. Furthermore, the rising concern of antibiotic resistance, which has been observed in all pathogens associated with CAP[3], also necessitates alternative effective treatments.

A series of well-established guidelines govern the treatment strategy, with the aim of reducing unnecessary hospitalization and readmissions, length of hospital stays, mortality and in turn cost[10–12]. Upon admission, most patients are treated empirically with antibiotics selected according to disease severity, local patterns of bacterial resistance and safety profiles[1]. As initial antibiotic treatment

failure has been shown to prolong hospital stay, increase antibiotic usage and add to hospital expenditure, this is a pivotal decision[13]. The most common antibiotic approach involves monotherapy with a respiratory fluoroquinolone or combination therapy with a macrolide plus a β-lactam[14,15].

Ceftaroline fosamil (CFT) is a fifth-generation cephalosporin with a broad spectrum of antibacterial activity. In an integrated analysis of the two pivotal, multicenter, phase III RCTs trials (FOCUS 1 and FOCUS 2), CFT treatment was non-inferior to ceftriaxone in adults with CAP (Pneumonia Outcomes Research Team (PORT) risk class III or IV)[16]. Specifically, CFT demonstrated numerically higher clinical cure rates than ceftriaxone in the clinically evaluable population both in the individual trials (FOCUS 1: 86.6% vs. 78.2%, FOCUS 2: 82.1% vs. 77.2%) and in the combined analysis (84.3% vs. 77.7%)[16]. Furthermore, when the trials data were analyzed focusing on the early response (Day 4, 72–96 h, CFT appeared to provide clinical benefit over ceftriaxone at Day 4, with Day 4 clinical response rates of 69.5% vs. 59.4%[17]. In addition, real-world studies have shown CFT to be effective, irrespective of whether it was used as monotherapy or concurrent therapy[18], first- or second-line therapy[18,19], in elderly patients[18,20] or in patients with significant comorbidities[20].

As newer agents, such as CFT, become available, the number of treatment options open to clinicians, will increase. However, given the rising concern of national health system expenditures, decisions need to be made based on economic value as well as clinical benefit. Focusing on Spain, between 2004 and 2013, the hospitalization rates for CAP in Spain increased significantly from 142.4 to 163.87 cases/100,000 inhabitants[21]. This study was therefore undertaken to evaluate intravenous (IV) CFT (600 mg q12hr) as an alternative to available IV antibiotic therapies for the empiric treatment of hospitalized patients with moderate/severe CAP from the perspective of the Spanish National Health System.

Methods

Model structure

A decision-tree model was developed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), to simulate the clinical pathway of a hypothetical cohort of adult patients admitted to hospital in Spain with moderate/severe CAP (PORT score III–IV) tracking the costs and consequences of treatments as shown in Figure 1. Upon admission, the initial decision was to either treat with CFT 600 mg every 12 h (q12hr) or an alternative antibiotic. The alternative antibiotics included in the analysis were ceftriaxone 1–2 g every 24 h (q24h), co-amoxiclav 1.2 g every 8 h (q8h), moxifloxacin 400 mg q24h or levofloxacin 0.5–1 g q24h, based on CAP guidelines and clinical expert consultation[10–12].

Patients initially receive intravenous (IV) antibiotic therapy for four days before clinical and microbiological assessment. After 4 days, responding patients[17] will either switch to a 5-day course of oral antibiotics and be discharged early, or remain in hospital due to conditions unrelated to pneumonia (e.g. unable to swallow), and continue to receive IV antibiotic therapy[22]. Non-responders after 4 days will either remain on IV therapy until clinical cure and discharge or switch to a second-line antibiotic (e.g. ceftriaxone) until clinical cure and discharge[23]. The non-responders switched to a second-line antibiotic could either be treated in the general ward or in an intensive care unit (ICU) and then switched to the general ward.
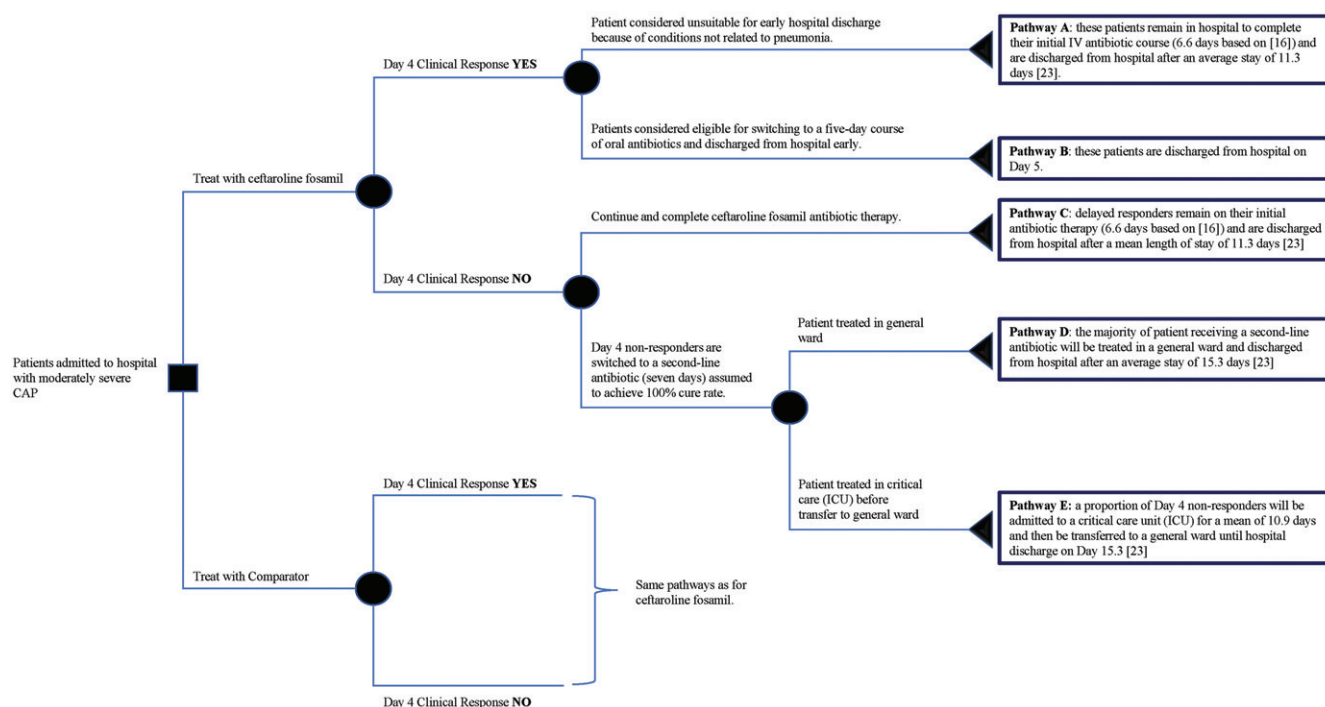

Figure 1. Schematic visualization of the decision-tree model. Over each branch, a brief description of the corresponding patient pathway has been summarized. Abbreviations. CAP, community-acquired pneumonia; ICU, intensive care unit; IV, intravenous.

Table 1. Clinical inputs for the cost-effectiveness analysis.

Description	Base-case	SE	Distribution	Source
Probability of clinical cure with CFT	0.843	0.0170	Beta	[16]
Probability of clinical cure with CFT in pneumococcal pneumonia	0.855	0.042	Beta	
Relative risk clinical cure CFT vs. ceftriaxone	1.10	0.028	LogNormal	[16]
Probability of clinical cure with ceftriaxone in pneumococcal pneumonia	0.686	0.052	Beta	[25]
Relative risk clinical cure CFT vs. co-amoxiclav	1.18	0.05	LogNormal	[25]
Relative risk clinical cure CFT vs. levofloxacin	1.05	0.05	LogNormal	[25]
Relative risk clinical cure CFT vs. moxifloxacin	1.08	0.04	LogNormal	[25]
Probability of Day 4 clinical response for CFT	0.695	0.0371	Beta	[17]
Probability of Day 4 clinical response for CFT in pneumococcal pneumonia	0.73	0.0516	Beta	[17]
Probability of Day 4 clinical response for ceftriaxone	0.594	0.0394	Beta	[17]
Probability of Day 4 clinical response for ceftriaxone in pneumococcal pneumonia	0.56	0.0567	Beta	[17]
Probability of Day 4 clinical response for co-amoxiclav	NA	NA	NA	
Probability of Day 4 clinical response for moxifloxacin	NA	NA	NA	
Probability of Day 4 clinical response for levofloxacin	0.34	0.046	Beta	[26]

Abbreviations. CFT, ceftaroline fosamil; NA, not applicable; SE, standard error.

This model structure was considered most appropriate since costs and clinical outcomes (resolution of signs and symptoms of the infection) occur over a relatively short period of time, typically <3 weeks from hospital admission to discharge[24].

Model inputs

Clinical efficacy inputs

The clinical inputs used in the cost-effectiveness analyses are summarized in Table 1. The clinical cure rate for CFT was obtained from an integrated analysis of phase III trials[16], and in the absence of head-to-head data, the clinical cure rates for the other antibiotics were estimated from a published network meta-analysis (NMA)[25]. Accordingly, the relative risk (RR) of CFT versus ceftriaxone, co-amoxiclav, levofloxacin and moxifloxacin were reported to be 1.10 (95% confidence intervals [CI] 1.04–1.16), 1.18 (95% CI 1.06–1.3), 1.05 (95% CI 0.96–1.15) and 1.08 (95% CI 0.99–1.16) respectively.

Day 4 clinical response was based on criteria set by the FDA and was defined as meeting criteria for both clinical stability and clinical improvement on Day 4:

- Clinical stability was defined according to the Infectious Diseases Society of America/American Thoracic Society guidelines as temperature <37.8 °C, heart rate <100 beats/min, respiratory rate <24 breaths/min, systolic blood pressure >90 mmHg, oxygen saturation >90% and confusion/disorientation (recorded as absent).
- Clinical improvement was defined as improvement of at least one of four symptoms present at baseline (i.e. cough, dyspnea, pleuritic chest pain, sputum production) with worsening of none.

Patients who did not meet both criteria were considered non-responders.

Day 4 clinical response rates, sourced from a post hoc analysis of the FOCUS trials in the CE population[17], were 69.5% for CFT and 59.4% for the ceftriaxone. Focusing on the pneumococcal pneumonia confirmed group, the clinical response rates at Day 4 were 73.0% in the CFT group and 56.0% in the ceftriaxone group. The values for the other comparators are summarized in Table 1 along with the corresponding references.

It is important to notice that the moxifloxacin early response criteria utilized in the literature were significantly different to those utilized for CFT, with early response defined as just body temperature <37.5 °C[27]. Similarly, early response criteria for co-amoxiclav were less stringent than the criteria used for CFT (improvement in two out of four CAP symptoms, clinical stability not required)[28]. Therefore, comparison against moxifloxacin and co-amoxiclav was hampered by the lack of comparable early response data in the literature. Nevertheless, threshold analysis was performed for both co-amoxiclav and moxifloxacin to assess the level of early response rate at which cost-neutrality could be achieved with respect to CFT.

Economic inputs

Health care resource use and costs are shown in Table 2. The average hospital length of stay (LOS) for patients both responding to and failing on initial antibiotic therapy, as well as the associated admission rates to and duration of stays in ICU for the latter patients was obtained from a large observational study of CAP management in hospitalized patients[23]. A prospective observational study of 200 patients with CAP admitted to hospital provided the proportion of treatment responders (44%) eligible for iv-to-oral switch and early hospital discharge[22]. The duration of first-line antibiotic treatment was assumed as 6.6 days for CFT and all comparators, consistent with the duration observed in the CFT trials[16]. Ceftriaxone monotherapy was selected as the second line antibiotic of choice for patients treated in general wards, following clinical experts' consultation, while a combination therapy (ceftriaxone + azithromycin) was deemed more suitable for ICU patients. The duration of second line antibiotic treatment was assumed to be 7 days, due to lack of reliable sources found in the literature but varied during the sensitivity analysis.

Ceftriaxone 1 g q24hr and levofloxacin 500 mg q24hr dosages were used for the base case as these were the doses used in the source clinical trials. However, higher doses are routinely needed in real life to achieve similar efficacy to that observed in clinical trials. Additional scenarios with

Table 2. Economic inputs for the cost-consequences analysis.

Health care resource use	Average value (SE)	Distribution	Reference
Mean hospital LOS (95% CI) initial antibiotic treatment success (days)	11.3 (0.24)	Normal	23
Mean hospital LOS (95% CI) initial antibiotic treatment failure (days)	15.3 (0.5)	Normal	23
Proportion of treatment failures admitted to ICU	19.8% (1.57%)	Beta	23
Duration of ICU stay (days)	10.9 (0.51)	Normal	23
Proportion of patients eligible for IV-to-oral therapy	44% (3.51%)	Beta	22
Duration of antibiotic treatment (days)	6.6	1	16
Duration of second-line antibiotic treatment (days)	7	1	Assumption

Unit costs	Value (€ 2017)	Reference	
Hospital day stay (per day)	553.90	Spanish National Price List[30]	
ICU stay (per day)	1,456.52		
Drug Acquisition Costs (per unit/per day)			
Ceftaroline 600 mg q12hr	60.00/120.00		
Ceftriaxone 1 g q24hr	3.89/3.89		
Co-amoxiclav 1.2 g q8hr	4.0/12.0		
Moxifloxacin 400 mg q24hr	31.2/31.2		
Levofloxacin 500 mg q24hr	12.15/12.15		
Oral Step-down Antibiotic (co-amoxiclav)	4.0/12.0		
Second-line antibiotic in general ward (ceftriaxone)	3.89/3.89		
Second-line antibiotic in ICU (ceftriaxone + azithromycin)	10.86/10.86		

Abbreviations. CI, confidence interval; ICU, intensive care unit; IV, intravenous; LOS, length of stay; q8hr, every eight hours; q12hr, every 12 hours; q24hr, every 24 hours; SE, standard error.

ceftriaxone 2 g q24hr and levofloxacin 1 g q24hr were simulated to reflect the doses most commonly used in clinical practice. Drug and hospital resource costs were sourced from the Spanish national price list 2017.

Model assumptions

When building the decision-tree model, multiple assumptions had to be made to simplify the clinical pathways and allow data from multiple sources to be integrated. Firstly, the early response rate across trials was assumed to be comparable. Secondly, the duration of IV treatment in patients remaining in hospital beyond 4 days was assumed to be the same for CFT and all the comparators considered, due to the lack of treatment specific data published in the literature[16]. Thirdly, as the costs of initial microbiological testing, and concomitant antibiotics providing coverage against atypical pathogens were assumed to be the same in both treatment arms, these were not considered in the model in the base case (consistent with the clinical trial protocols from which the efficacy inputs have been derived). Nevertheless, one additional scenario was tested adding concomitant macrolide therapy (azithromycin 500 mg q24h – first 3 days IV then oral formulation for a daily cost of €7.31) to each beta-lactam treatment (ceftaroline fosamil, ceftriaxone, co-amoxiclav) as recommended in the latest clinical guidelines and likely happening in clinical practice[14,15].

Model analyses

The model predicted health outcomes such as percentage of patients discharged at Day 4, percentage of patients experiencing antibiotic treatment failure, and percentage of patients treated in the ICU, as well as incremental costs of CFT versus each of the comparators were included in the analysis. Furthermore, sub-group analysis focusing on the

pneumococcal pneumonia confirmed group was performed for CFT versus ceftriaxone, given the high-mortality associated with this specific causative organism[3]. Due to lack of data a pneumococcal subgroup analysis was not possible for the other comparators.

Deterministic one-way sensitivity analysis was performed to identify the primary sources of uncertainty in the model's estimates of treatment costs and clinical outcomes. The model base-case inputs were varied within their 95% CIs, obtained from assigned statistical distributions as specified in Tables 1 and 2 (beta-distribution for probabilities, and log-normal distribution for relative risks) while the costs were varied by ±25%.

In additional, probabilistic sensitivity analysis (PSA) was undertaken to assess the impact of simultaneously varying clinical outcomes and health care resource use with respect to the model outcomes, using Monte Carlo simulation (1,000 simulations were performed).

Results

Compared to ceftriaxone-treated patients, a higher percentage of CFT-treated patients were predicted by the model to be eligible for early discharge (30.6% vs. 26.1%; Figure 2), and fewer were projected to experience initial antibiotic failure (3.8% vs. 7.6%) or require ICU treatment (0.9% vs. 1.9%) (see Table 3). The predicted total average costs of CFT were €286.10 per patient higher than ceftriaxone (1 g q24hr), resulting in a 5% increase (Table 4 and Figure 2). Specifically, CFT patients were projected to have higher initial antibiotic drug costs and oral step-down costs versus ceftriaxone. Similar results were obtained when ceftriaxone 2 g q24hr dosage was compared, but the marginal increase in total costs between CFT and ceftriaxone was reduced to 4.6%. Simulating the combination of CFT and ceftriaxone with a macrolide marginally increased the total costs per patient (€5,917.13 and €5,684.98 respectively) compared to the base
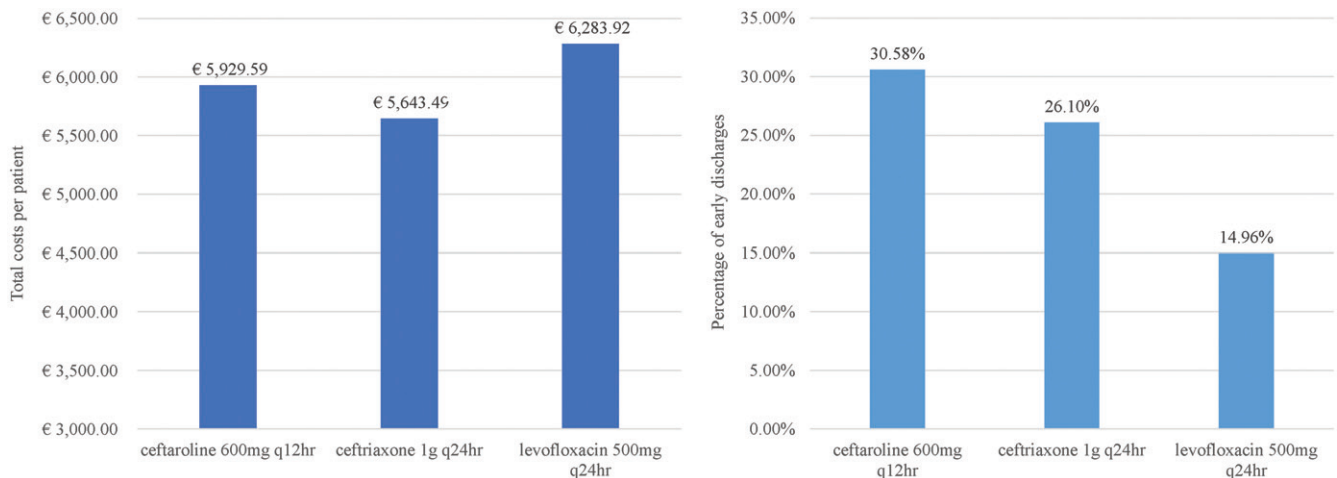
Figure 2. Comparison of total costs per patient (left side) and the percentage of patients discharged early (right side) for CFT, Ceftriaxone, and Levofloxacin. Abbreviations. CFT, ceftaroline fosamil; q12hr, every 12 hours; q24hr, every 24 hours

Table 3. Total and incremental percentage of patients, for each treatment pathway (according to Figure 1), predicted by the model.

	All pneumonias					Pneumococcal pneumonia		
	CFT	Ceftriaxone		Levofloxacin		CFT	Ceftriaxone	
	Total (%)	Total (%)	Incremental vs. CFT (%)	Total	Incremental vs. CFT	Total (%)	Total (%)	Incremental vs. CFT (%)
Initial antibiotic treatment success. Patient remains on initial antibiotic to complete IV course of therapy. (Pathway A + Pathway C)	64.63	64.38	0.25	72.03	7.4%	63.97	61.54	2.43
Initial antibiotic treatment success. Clinical response achieved at Day 4. Patients switched to oral antibiotic and discharged early (Pathway B)	30.58	26.14	4.44	14.96	15.62%	32.12	24.64	7.48
Initial antibiotic treatment failure. Patients switched to second-line antibiotic and managed in general ward (Pathway D)	3.84	7.61	−3.77	10.44	−6.6%	3.14	11.08	−7.94
Initial antibiotic treatment failure. Patients switched to second-line antibiotic and managed in ICU (Pathway E)	0.95	1.88	−0.93	2.58	−1.63	0.78	2.74	−1.96

Abbreviations. CFT, ceftaroline fosamil; ICU, intensive care unit; IV, intravenous.

Table 4. Total and incremental hospital costs per patient by antibiotic regimen and pneumonia type.

	All Pneumonias (€ 2017)					Pneumococcal pneumonia (€ 2017)		
	CFT	Ceftriaxone		Levofloxacin		CFT	Ceftriaxone	
	Total	Total	Incremental vs. CFT	Total	Incremental vs. CFT	Total	Total	Incremental vs. CFT
Total average hospital cost	€5,929.59	€5,643.49	€286.10	€6,283.92	€−354.33	€5,829.77	€5,884.40	€−54.63
Initial antibiotic therapy	€681.65	€22.07	€659.58	€71.36	€610.29	€679.57	€21.78	€657.79
Oral antibiotic step-down	€24.22	€20.70	€3.52	€11.85	€12.37	€25.44	€19.51	€5.92
Second-line antibiotic	€1.77	€3.50	€−1.73	€4.80	€−3.03	€1.44	€5.10	€−3.65
Hospital stay (general ward)	€5,071.43	€5,299.04	€−227.61	€5,786.91	€−715.48	€5,000.25	€5,403.71	€−403.46
Hospital stay (ICU)	€150.52	€298.18	€−147.65	€409.01	€−258.48	€123.07	€434.30	€−311.23

Abbreviations. CFT, ceftaroline fosamil; ICU, intensive care unit.

case results (see Table 4) without impacting the incremental total costs per patient (since the same macrolide treatment was added to both comparators).

When the analysis was restricted to patients with pneumococcal pneumonia, CFT was estimated to be cost-saving versus ceftriaxone (1 g q24hr), with a total cost reduction of €54.63 per patient (Table 4). Despite higher projected initial antibiotic and oral antibiotic step-down costs, those associated with hospitalization and second-line antibiotics were predicted to be lower with CFT. More patients achieved initial antibiotic treatment success with CFT than ceftriaxone (63.97% versus 61.54%), and more CFT patients would be early discharged than ceftriaxone (32.1% versus 24.6%). Considering a higher dosage of ceftriaxone (2 g q24hr) resulted in higher cost-savings of €74.62 per patient while adding macrolide concomitant therapy to CFT and ceftriaxone did not impact the per-patient costs savings.

CFT was also predicted to be cost-saving overall versus levofloxacin 500 mg q24hr (€354.33 per patient), mainly ascribable to the relatively high Day 4 response rate which resulted in reduced length of hospital stay (Table 4). Indeed, in comparison with levofloxacin, CFT increased the percentage of early discharges (30.6% vs. 14.96%) and decreased initial antibiotic failures (4.8% vs. 13%) and number of patients
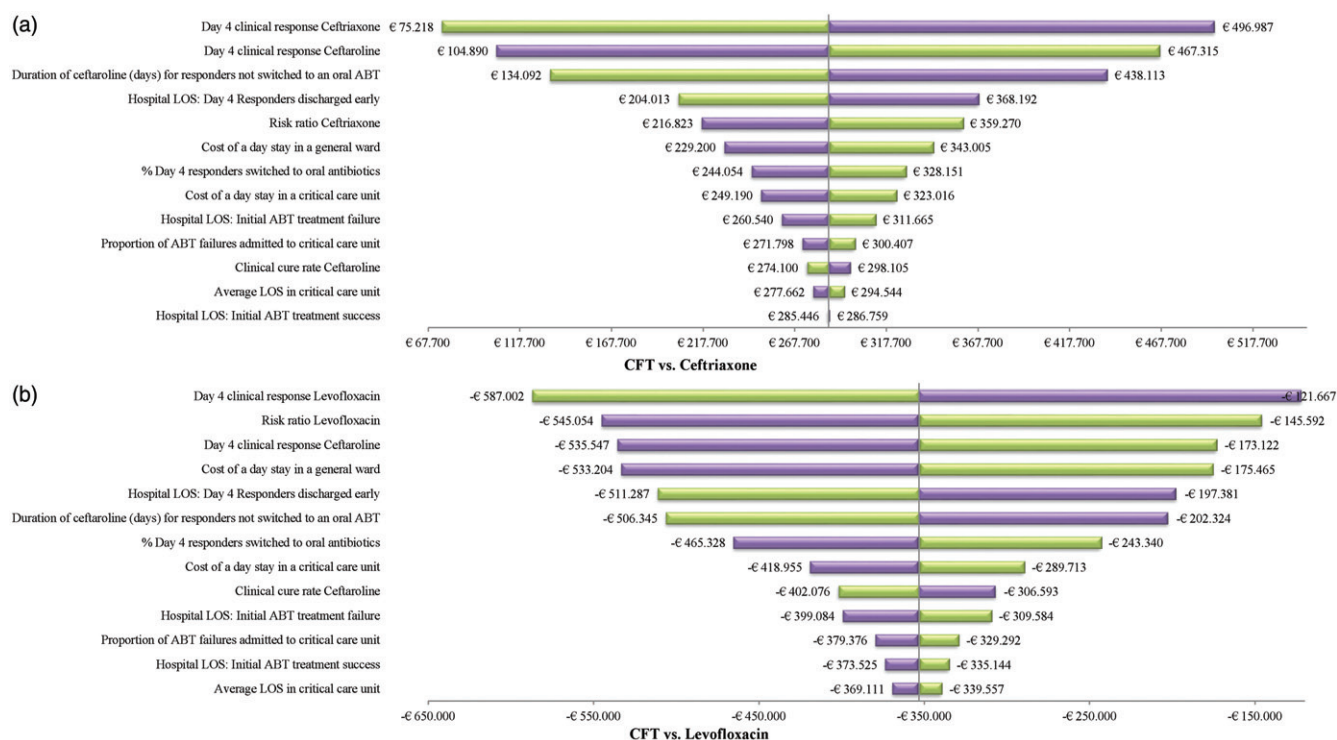
Figure 3. Deterministic sensitivity analysis results: CFT 600 mg q12hr versus Ceftriaxone 1 g q24hr (a); CFT 600 mg q12hr versus Levofloxacin 500 mg q24hr (b). Abbreviations. ABT, antibiotic therapy; CFT, ceftaroline fosamil; LOS, length of stay; q12hr, every 12 hours; q24hr, every 24 hours.

treated in ICU (0.9% vs. 2.6%) (see Table 3). Increasing levofloxacin dosage (1 g q24hr) increased total cost savings per patient, predicted by the model, to €425.68 while adding concomitant macrolide therapy to CFT reduced the cost savings per patient to €312.79.

Threshold analysis indicated that total cost neutrality with respect to CFT was achieved with an early response rate of 53.63% and 54.24% for moxifloxacin and co-amoxiclav respectively. Considering concomitant macrolide therapy with the beta-lactams (CFT and co-amoxiclav) marginally reduced moxifloxacin early response rate for achieving cost neutrality to 52.1% while had no impact on CFT/co-amoxiclav comparison.

Finally, consistently with the literature, the model demonstrated that antibiotic costs represent a small proportion of overall hospital costs (<11% of total costs), the main driver being hospital length of stay (>85% of total costs).

Sensitivity analyses

The deterministic sensitivity analyses, where each input parameter was varied separately as the lower and upper bound of the corresponding confidence interval (see Table 1), demonstrated that day 4 responses, clinical cure rates and antibiotic treatment duration were the key drivers of total costs, when comparing CFT with ceftriaxone (see Figure 3(a)). Similarly, the top-three parameters generating the most variation in total costs when comparing CFT with levofloxacin were day 4 responses and the risk ratio of clinical cure rates, as highlighted in Figure 3(b). The full list of per patient incremental cost obtained setting each model parameter to the

lower and upper bound of the confidence interval is presented in Figure 3(a) with respect to ceftriaxone and in Figure 3(b) with respect to levofloxacin.

Threshold analysis was repeated for moxifloxacin and co-amoxiclav using the lower and upper bounds of the risk ratio confidence intervals (see Table 1). Varying the moxifloxacin and co-amoxiclav risk ratios to the lower and upper bounds of the confidence interval resulted in an early response rate of 48–57.2% and 48.3–58.1%, respectively, for achieving cost-neutrality with respect to CFT.

The probabilistic sensitivity analysis, during which the cost and clinical inputs were simultaneously varied by random sampling from the input distributions (see Tables 1 and 2) demonstrated that CFT reduced the total cost in 90.9% of the cases compared with levofloxacin and in 3% of the cases compared with ceftriaxone.

Discussion

With an aging population, the incidence of CAP and in turn the associated economic burden will continue to rise in the coming years[3]. Given the rising amount of treatments available to clinicians and the fact that treatment decisions will be based upon both clinical and economic factors, this modelling study was undertaken to compare the cost and consequences of using CFT in hospitalized adults with moderate to severe CAP with respect to alternative antibiotics commonly used.

The greater early treatment success with CFT compared with ceftriaxone was associated with a reduction in costs for second line antibiotic and hospitalization. However, these

cost savings were insufficient to offset the higher CFT drug acquisition and infusion costs; resulting in a marginal ($<5\%$) increase in total costs versus ceftriaxone (1–2 g q24hr). Nevertheless, the model predicted that in responding patients more would be discharged early with CFT than ceftriaxone. Furthermore, in the pneumococcal pneumonia subgroup analysis, CFT treatment resulted cost-saving while significantly increasing the number of patients achieving initial antibiotic treatment success and early discharge. This would suggest that CFT may be preferred to ceftriaxone in hospitalized adults with suspected pneumococcal pneumonia, which is one of the main causative organisms of CAP[3].

When compared against levofloxacin, the model demonstrated that CFT would result in significant cost savings per patient, due to greater clinical efficacy resulting in decreased initial antibiotic treatment failures and increased percentage of early discharges.

The sensitivity analysis demonstrated that early response, treatment duration and length of hospitalization are the key drivers of total costs, which is consistent with what has been previously described in the literature[13]. Furthermore, the model demonstrates that antibiotic costs represent a small proportion of overall hospital costs, the main driver being hospital LOS[3,13]. This may be of benefit in focusing payers' attention away from pharmacy spend alone towards a review of the overall economic burden of managing patients with moderately severe CAP in their hospital.

The developed model has multiple limitations. Firstly, except for ceftriaxone, there are no head to head clinical trials comparing CFT with the other antibiotics; thus, the clinical inputs were based on available literature (see Table 1) and indirect comparison (NMA)[25] validated by clinical expert opinion. Furthermore, significantly different criteria used to measure early response data (Day 4) were observed in the literature, which hampered comparisons with moxifloxacin and co-amoxiclav (see Section 2.2.1). Secondly, the treatment length has been assumed equal between CFT and all the comparators (see Table 2), given the lack of evidence in literature. Given that this parameter is one of the key driver of total costs, especially when comparing CFT with ceftriaxone (see Figure 3(a)), further studies leveraging real-world evidence regarding average length of treatment for each of the considered comparators might be of interest. Thirdly, antibiotic dosage used in the clinical trials differs to the dosage used in clinical practice. Multiple scenarios with increased antibiotic dosage demonstrated a limited impact of the dosage variations with respect to the model outcomes and conclusions. However, the clinical efficacy was assumed to remain constant due to the lack of literature evidence. Fourthly, the unit costs used in the analysis (see Table 2) could change in the future due to the introduction of generics and do not take into considerations confidential discounts provided by the manufacturers. Therefore, these two aspects along with other considerations (e.g. changes in recommended dosages) will dictate modified cost-consequences results. Finally, susceptibility rates were not considered in the analysis, which might be a critical factor in countries with high levels of emerging antibiotic resistance[3,29]. Specifically,

different types of causative organisms for CAP would have different susceptibility patterns with respect to each of the antimicrobial agents commonly used[29], in turn affecting the clinical efficacy of each treatment. On one hand, this would require additional data regarding country-specific susceptibility patterns along with organism-specific clinical inputs for each comparator included in the analysis, thus significantly increasing the complexity of the analysis. On the other hand, this could be of significant interest for future analyses, given that the diverse nature of resistance across Europe highlights the need of developing national guidelines to provide optimal treatment[3].

Conclusion

In conclusion, despite a higher unit cost, ceftaroline fosamil is a reasonable alternative to other agents in the treatment of adults hospitalized with moderate/severe CAP, given the projected higher rate of patients discharged early achieved with similar or lower total costs than the alternative treatments considered.

portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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