

Cost-Effectiveness and Antimicrobial Resistance in Community-Acquired Pneumonia

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COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) covers those infections of the lung parenchyma that are not acquired in hospital or a long-term care facility. CAP is a common infectious disease, with annual incidence rates of 1.6 per 1,000 adults in Spain and 11.6 per 1,000 adults in Finland [1, 2]. CAP is associated with significant morbidity and is the leading cause of death due to infection in developed countries [3, 4]. The economic burden of CAP is substantial: in the United States, CAP accounts each year for 10 million physician visits, and about 1 million hospitalizations at an estimated hospital cost of \$9 billion [5, 6].

ANTIMICROBIAL TREATMENT

Patients suffering from mild to moderate CAP are generally treated with oral antimicrobials in the community [7]. Hospitalisation may be required for elderly patients, patients who have underlying chronic illnesses or patients with more serious disease. In the majority of patients [4], antimicrobial treatment is empirical in that treatment is initiated in the absence of information about the causative pathogen involved in CAP and the antimicrobial susceptibility pattern of the isolated organism. The empirical approach is also the prevailing method of drug selection [8]. The treatment approach to CAP is challenging due to the expanding spectrum of causative pathogens, the rising prevalence of resistance to antimicrobial agents and the increasing pressure to reduce the length of hospitalization [9].

Various professional societies have published clinical guidelines to guide antimicrobial treatment of CAP [10, 11]. These guidelines recommend a beta-lactam-based therapy for CAP as first choice. Moxifloxacin monotherapy is a useful alternative for outpatients with comorbid conditions, outpatients in whom infection with atypical pathogens (in particular *Legionella spp.*) needs to be taken into consideration, inpatients who do not require intensive care unit care, patients recently treated with other antibiotics, and patients

with suspected 'high-level' drug-resistant *Streptococcus pneumoniae*.

ANTIMICROBIAL RESISTANCE

The guidelines of the European Respiratory Society also stated that the selection of antimicrobial needs to reflect local patterns of microbial resistance in addition to the severity of illness, the frequency of specific pathogens and drug safety profiles [10]. When antimicrobials first became available, changes in the susceptibility of pathogens were of little concern. However, inappropriate use of antimicrobials, (human-to-human) clonal spread of multi-drug resistant strains and the presence of co-morbidities have all contributed to the rise in antimicrobial resistance over the years. Antimicrobial resistance can have a substantial impact on outcomes and costs of treatment. For instance, there is evidence that CAP patients with pneumococcal resistance may be at greater risk of poor outcomes [12]. Also, if first-line treatment fails due to resistance, additional costs are incurred due to the need for second-line treatment or hospitalization, or both.

Fluoroquinolones are a class of antibiotics developed in the 1980s. Newer fluoroquinolones have increased activity against Gram-positive bacteria, including *Streptococcus pneumoniae*, and against atypical micro-organisms (*Mycoplasma*, *Chlamydia* and *Legionella*). Current resistance to fluoroquinolones is still low (< 1%) [13], but if fluoroquinolones become more widely used in the community for the treatment of CAP, resistance is expected to spread with the potential induction of cross-resistance even to the new fluoroquinolones. There is debate over the role of fluoroquinolones in treating CAP. On the one hand, as current resistance of *Streptococcus pneumoniae* to macrolides and tetracyclines is relatively high and rising over time in many countries [14], a case can be made for switching to anti-pneumococcal fluoroquinolones as an alternative to penicillins. On the other hand, it could be argued that the use of fluoroquinolones needs to be restricted in order to contain future resistance development and to safeguard the value of this class of antibiotics.

ECONOMIC EVALUATION

In a context of spiraling health care costs and limited resources, policy makers and health care payers are con-

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cerned about the costs of antimicrobial treatment in addition to its effectiveness. Pharmaco-economic evaluation is a technique that can be used to determine whether antimicrobial treatment of CAP adds sufficient value to justify its costs. An economic evaluation is defined as a comparative analysis of at least two health technologies in terms of both their costs and outcomes [15]. Evidence derived from economic evaluations is used to inform antimicrobial pricing/reimbursement decisions in many countries. Antibiotics that provide better value are rewarded by means of a more favourable price/reimbursement. The requirement for economic evaluation fits within an overall trend towards evidence-based decision making in healthcare [16].

AIMS

Recently, four economic evaluations have been published that investigated the value of antimicrobial treatment of CAP

in Belgium, Canada, France, Spain and the United States [17-20]. The aim of this Letter is to describe these studies because they present the opportunity to examine the possible relationship between cost-effectiveness and antimicrobial resistance of *Streptococcus pneumoniae* in CAP. Indeed, each economic evaluation explored the impact of varying the local estimates of resistance levels on the cost-effectiveness of antimicrobials by means of extensive sensitivity analyses.

COST-EFFECTIVENESS AND ANTIMICROBIAL RESISTANCE IN CAP

Study Design

The four economic evaluations employed decision-analytic models to evaluate the cost-effectiveness of empirical antimicrobial treatment of patients suffering from mild-to-moderate CAP [17-20]. Design characteristics of these studies are summarized in Table 1. Treatment strategies in-

Table 1. The Value of Antimicrobial Treatment of Community-Acquired Pneumonia

Studies	Martin (2007) (17)	Martin (2008) (18)	Moore (2008) (19)	Sabes-Figuera (2008) (20)
Country	France, Germany, USA	Belgium	Canada	Spain
Currency	Euro and US dollars (2006)	Euro (2006)	Canadian dollars (2006)	Euro (2004)
Analysis	Cost-consequence analysis	Cost-consequence analysis	Cost-consequence analysis	Cost-consequence analysis
Perspective	Third-party payer	Third-party payer	Third-party payer	Third-party payer
Sample	Patients with mild-to-moderate community-acquired pneumonia	Patients with mild-to-moderate community-acquired pneumonia	Patients with mild-to-moderate community-acquired pneumonia	Patients with community-acquired pneumonia
Study first-line treatment	Moxifloxacin	Moxifloxacin	Moxifloxacin	Moxifloxacin
Comparator first-line treatments	Clarithromycin, co-amoxiclav, azithromycin, doxycycline, roxithromycin, amoxicillin, cefuroxime acetyl	Clarithromycin, co-amoxiclav, cefuroxime acetyl	Azithromycin	Telithromycin, amoxicillin, clarithromycin
Study design	Model-based study	Model-based study	Model-based study	Model-based study
Source clinical data	Literature, expert opinion	Literature, expert opinion	Literature, expert opinion	Literature, expert opinion
Source economic data	Literature	Literature	Literature	Literature
Cost measures	Drugs, contacts with healthcare professionals, hospitalisation	Drugs, contacts with healthcare professionals, hospitalisation	Drugs, contacts with healthcare professionals, hospitalisation	Drugs, contacts with healthcare professionals, hospitalization
Effectiveness measures	First-line clinical failure avoided, second-line treatment avoided, hospitalization avoided	First-line clinical failure avoided, second-line treatment avoided, hospitalization avoided, deaths avoided	First-line clinical failure avoided, second-line failure avoided, hospitalization avoided	Number of patients without complications, number of patients hospitalized
Results	Moxifloxacin dominant for all outcomes	Moxifloxacin dominant for all outcomes	The incremental cost-effectiveness ratio of moxifloxacin treatment as compared with azithromycin was CAN\$ 96.04 per first-line clinical failure avoided, CAN\$ 118.71 per second-line failure avoided and CAN\$ 502.47 per hospitalisation avoided.	Moxifloxacin dominant for all outcomes
Sensitivity analysis	Deterministic and probabilistic sensitivity analysis	Deterministic and probabilistic sensitivity analysis	Deterministic and probabilistic sensitivity analysis	Deterministic sensitivity analysis
Incremental analysis	Dominance	Dominance	Yes	Dominance

volved oral antimicrobials, were recommended by clinical practice guidelines and reflected prevailing treatment pathways in the countries studied. First-line treatment was initiated in the community, with failure resulting in second-line treatment in the community or hospitalization. As these economic evaluations were carried out from the perspective of the third-party payer, the analyses considered health care costs only and did not include costs due to productivity loss.

The base case analysis calculated incremental cost-effectiveness ratios using the following equation:

$$ICER = (C_1 - C_0) / (E_1 - E_0)$$

where C_1 is the cost of the intervention; C_0 is the cost of the alternative with which the intervention is compared; E_1 and E_0 are the respective health outcomes of intervention and comparator.

The first-line intervention was moxifloxacin in each economic evaluation. The comparator strategies were beta-lactams (e.g. co-amoxiclav, cefuroxime), macrolides (e.g. clarithromycin, azithromycin) or tetracyclines (e.g. doxycycline). Effectiveness was assessed in terms of the rate of first-line clinical failures, of second-line treatments required, of hospitalizations required, and of mortality. A strategy is said to dominate the comparator when it is both less expensive and more effective.

Clinical Failure

The economic evaluations were based on the premise that clinical failure can occur due to two main reasons: lack of response to treatment in patients with susceptible pathogens and failure due to the presence of antimicrobial-resistant pathogens.

The failure rate in susceptible pathogens was estimated on the basis of antimicrobial success rates from published clinical trials in CAP. Meta-analyses were not suitable for use in the models as they did not focus on the population of patients suffering from mild-to-moderate CAP. A wide range of efficacy data was found in the literature due to differences in trial design, treatment setting, patient population, duration of treatment, trial size, outcome measures used, etc. The estimates were based on those clinical trials that could be matched as far as possible to the patient population, causative pathogens, time horizon, dosage and outcome measures considered in the economic evaluations.

The failure rate in antimicrobial-resistant pathogens was estimated on the basis of data from published surveillance studies. The majority of samples considered in surveillance studies related to hospitalized patients. However, a recent study showed that the prevalence of resistant isolates in a hospitalized and community setting is similar for community-acquired pathogens [21], thus making it possible to generalize surveillance data to the community setting. Antimicrobial resistance data related to each country considered or were derived from published sources in the absence of country-specific data. The models considered resistance to various first-line antimicrobial treatments, including fluoroquinolones (e.g. moxifloxacin), beta-lactams (e.g. co-amoxiclav,

cefuroxime), macrolides (e.g. clarithromycin, azithromycin) and tetracyclines (e.g. doxycycline). The models also made assumptions about clinical failure rates due to resistance for each CAP pathogen. There is no published literature documenting the link between resistance and clinical failure. Therefore, the calculations of failure rates were based on the opinion of clinical experts. The model developed for the United States was compared to empirical data on treatment failure and results were very comparable, thus validating assumptions [17].

The economic evaluations for France, Germany, the United States, and Canada accounted for multi-drug resistance in *Streptococcus pneumoniae* isolates, where isolates resistant to the first-line antimicrobial agent also demonstrate resistance to the second-line antimicrobial [17, 19]. For instance, according to 1998-2000 data from the Alexander Project, resistance to more than five antimicrobial drug classes amounted to 11.7% in France [22]. Therefore, the models calculated resistance prevalences for second-line antimicrobial treatment of CAP adjusted for the presence of multi-drug resistance. Multi-drug resistance did not play a role in the Belgian model given that the four treatment strategies considered included either moxifloxacin or co-amoxiclav, either first-line or second-line, and both treatments lacked any level of resistance for *Streptococcus pneumoniae* [18].

Sensitivity Analysis

As there is uncertainty surrounding local resistance rates, deterministic and probabilistic sensitivity analyses were carried out. One-way deterministic sensitivity analyses were conducted to ascertain the robustness of cost-effectiveness results by varying key input parameters over plausible ranges. To assess the impact of changes in resistance level, resistance rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* were changed from -50% to +50% of base case rates for each of the antimicrobials considered.

Probabilistic sensitivity analyses based on a Monte Carlo simulation were performed. Such an analysis requires that a probability distribution is assigned to the resistance rate. The beta distribution was chosen for resistance rates. Spontaneous cure rates and clinical failure rates for resistant isolates were assumed to be distributed as uniform random variables. For each iteration, the simulation drew input parameters at random from their statistical distributions and calculated cost and effectiveness pairs. At the end of the iteration process, the joint statistical distribution for costs and effectiveness was represented as a cloud of points on the cost-effectiveness plane.

Results

The impact of antimicrobial resistance on cost-effectiveness was investigated in two ways: first, resistance levels were varied in each economic evaluation by means of sensitivity analyses; second, cost-effectiveness results can be compared between economic evaluations (and thus between countries with different levels of resistance), although factors other than resistance may explain differences in cost-

effectiveness results between economic evaluations (e.g. costs of care, treatment protocols).

The sensitivity analyses and the comparison between countries indicated that varying levels of antimicrobial resistance in CAP pathogens and multi-drug resistance in *Streptococcus pneumoniae* isolates affected costs and clinical outcomes of antimicrobial treatment [17-20]. However, cost-effectiveness conclusions did not change: treatment of CAP with moxifloxacin was more effective and less expensive than other antimicrobial treatment strategies in Belgium, France, Germany, Spain and the United States.

In Canada, the deterministic sensitivity analysis showed that a 50% increase in fluoroquinolone resistance would raise the incremental cost-effectiveness ratio of moxifloxacin treatment as compared with azithromycin to CAN\$ 101.47 per first-line clinical failure avoided [19]. Canada has faced a steady increase in macrolide resistance in *Streptococcus pneumoniae* over time [23], and further increases in macrolide resistance rates cannot be ruled out. Increases in macrolide resistance would result in more favourable cost-effectiveness ratios for treatment with moxifloxacin.

The probabilistic sensitivity analyses demonstrated that treatment of CAP with moxifloxacin was more effective and less expensive in nearly all scenarios [17-19]. For instance, in France, moxifloxacin had a probability of 100% and 99.8% of being more effective and less expensive than co-amoxiclav and clarithromycin, respectively. In the United States, the probability that moxifloxacin was more effective and less expensive than co-amoxiclav, azithromycin and doxycycline was 100%, 99.8% and 99.8%, respectively. In Germany, these probabilities amounted to 67.1%, 54.4% and 100% as compared to amoxicillin, roxithromycin and cefuroxime, respectively. Finally, moxifloxacin was more effective and less expensive than co-amoxiclav, cefuroxime and clarithromycin in 99.4%, 99.9% and 92.6% of cases, respectively, in Belgium.

CONCLUSIONS

Few economic evaluations have examined clinical outcomes and costs of empirical antimicrobial treatment of CAP in the community taking into account resistance. When resistance levels were varied in sensitivity analyses, the current body of evidence demonstrated that levels of antimicrobial resistance in CAP pathogens and multi-drug resistance in *Streptococcus pneumoniae* isolates had a minimal impact on costs and clinical outcomes of antimicrobial treatment. In nearly all scenarios, treatment of CAP with moxifloxacin is the most cost-effective option. At the moment, worldwide resistance of CAP pathogens to moxifloxacin is low [13], but continued vigilance with regard to the evolution of antimicrobial resistance and its impact on the cost-effectiveness of moxifloxacin and of other antimicrobials is indicated. For instance, the association between moxifloxacin use and the rate of extended-spectrum beta-lactamase (ESBL) resistance needs to be considered and followed up [24].

CONFLICT OF INTEREST

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