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Antoine Lafuma, Francis Fagnani & Gilles Berdeaux

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Cost and effectiveness of ciprofloxacin + hydrocortisone versus neomycin + polymyxin B + hydrocortisone in France for the treatment of acute otitis externa

Antoine Lafuma MD[1], Francis Fagnani PhD[1], Gilles Berdeaux MD PhD[2]

Summary

The cost-effectiveness of two topical otic combinations, ciprofloxacin + hydrocortisone and polymyxin B — neomycin — hydrocortisone (PNH), was assessed in the treatment of acute otitis externa (AOE). Two randomised controlled double-masked trials compared their clinical and bacteriological efficacy and safety after 7 to 10 days of qid treatment. The treatment failure cost was established from a panel of ENT specialists and GPs. A decision-tree analysis was constructed to reproduce the results of empirical treatment. The most often encountered species were *Pseudomonas aeruginosa* (82.4%) and *Staphylococcus aureus* (9.7%). Patients documented with *P aeruginosa* had a better ciprofloxacin + hydrocortisone bacterial and clinical efficacy. The cost of AOE first-line failure was EUR 94.44 (Societal) and EUR 57.24 (Sécurité Sociale). The savings associated with ciprofloxacin + hydrocortisone (Cipro HC ®*) were respectively EUR 3.87 and EUR 2.85. This model shows that topical ciprofloxacin + hydrocortisone could be a cost saving alternative in the treatment of AOE, provided its public price does not exceed EUR 10.60.

Key words : acute otitis externa, ciprofloxacin, neomycin, polymixin, economics, cost of failure

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[1] Cemka-Eval, 43, Boulevard du Maréchal Joffre, F-92340 Bourg-la-Reine, France

[2] Alcon France, 4, Rue Henri Sainte-Claire Deville, F-92563 Rueil-Malmaison Cedex, France

Address for correspondence: Gilles Berdeaux, Alcon France, 4, Rue Henri Sainte-Claire Deville, F-92651 Rueil-Malmaison Cedex, France.
Tel: +33 1 47 10 48 60, fax: +33 1 47 10 48 41, e-mail: gilles.berdeaux@alconlabs.com.

* Cipro HC® is a registered trademark of Alcon, France.

Introduction

Acute Otitis Externa (AOE) is defined by the inflammation of the skin of the external auditory canal (EAC) with edema associated with tenderness when moving the pinna and otalgia[1,2,3]. The origin is commonly bacterial, although the diagnosis is based on clinical signs (pain and lesion of the external auditory canal). Bacterial flora of the EAC plays a role of protection against pathoges[4,5]. On some occasions, commensal species become pathogenic due to humidity, use of antiseptic topical solutions, surgical procedures, skin lesions, and so on. AOE is unilateral in about 90% of cases suggesting that other factors play a role: partial obstruction of the canal due to wax, foreign bodies, exostosis and trauma to the canal lining from scratching fingers or attempts at self-cleaning.

A severe form (the malignant AOE) concerns mainly older diabetic patients and can lead to death. Intravenous antibiotics are needed in these cases to control the risk of cranial infection. The causative organism is exclusively *Pseudomonas aeruginosa* (*P aeruginosa*).

The incidence of acute otitis externa (AOE) is estimated between 3–10% of the general population. Life-time incidence has been estimated 10% by Poncet[6]. The highest incidence rate is in the age group of 5 to 10 years[7].

Very few microbiologic studies have been performed in France on AOE[8,9].

P aeruginosa was encountered in 45 to 70% of the patients and *Staphylococcus aureus* (*S aureus*) in 7 to 27%. These figures were similar to the data issued from the international literature[10–18]. All studies presenting results on causative organisms in AOE confirm the increasing predominance of *P aeruginosa* and *S aureus* over time.

From a macro-economic point of view, AOE represents between 5 and 50% of ear-nose-throat (ENT) visits[5,19]. In France 507,000 visits per year were related to AOE, 266,000 to general practitioners (GPs) and 211,000 performed by ENT specialists[20]. According to IMS[21], about 68% of patients were treated by GPs, 24% by ENT specialists and the remainder by pediatricians. Practitioners prescribed mainly topical antibiotics[22] in fixed combination with topical corticoids, and in 47% of the cases an oral antibiotic was also prescribed. Antibiotic treatment was mainly empirical and based on the frequency of the most often encountered organisms. In France, topical treatments are mainly constituted[23] of fixed combinations: an aminosid (i.e. neomycin), a polypeptid (i.e. polymixin) and a corticoid (i.e. dexamethasone).

Ciprofloxacin, a new fluoro-quinolone, has been developed for the treatment of AOE, in combination with hydrocortisone (Cipro HC ®*). Ciprofloxacin is known to be more efficacious than neomycin on *P aeruginosa*, the most often encountered species in AOE, with similar efficacy on *S aureus*[24-27].

* Cipro HC ® is a registered trademark of Alcon, France.

This health economics study estimated the cost and the consequences of treatment with ciprofloxacin + hydrocortisone in comparison to the French standard treatment based on polymyxin B–neomycin–hydrocortisone otic drops (PNH).

Material and methods

Experimental design

The clinical outcome of the empirical topical treatment of AOE conducted by practitioners (GP and ENT specialists) in France was simulated through a model based on epidemiological data related to the type of species and the relative clinical efficacy of ciprofloxacin + hydrocortisone and PNH.

This model (Figure 1) took into account four situations that might occur during empirical treatment: (1) the infecting organism was not documented; (2) the species was either *P aeruginosa*; or (3) *S aureus*; or (4) another species. The success rates varied according to the four possibilities and the topical antibiotic used. The efficacy rates according to causative organism and topical antibiotic used were estimated from clinical trials. The epidemiology of species encountered in AOE in France was also estimated from the clinical trials since very few data are available from the literature on this point. The clinical outcome of this model was first-line success rate.

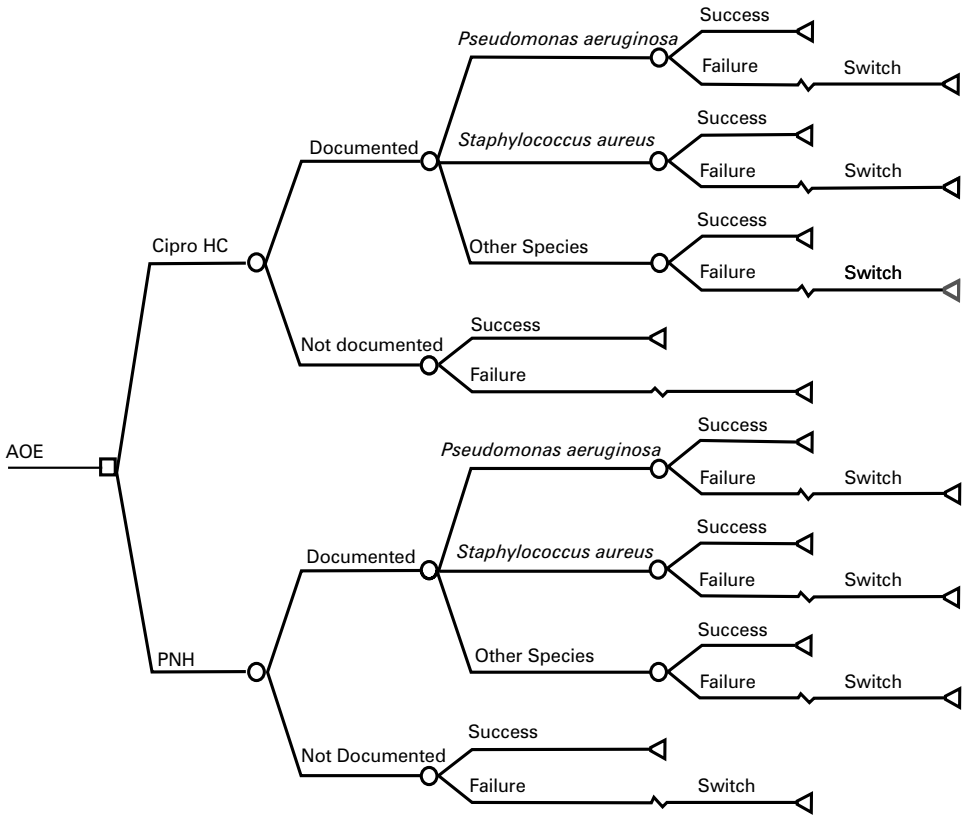
Efficacy data were derived from two international Phase III clinical trials, one performed in the US and one in Europe (Belgium, Switzerland, Germany, Denmark, Spain, France, United Kingdom, Greece, and Ireland). Results in terms of efficacy were issued from the analysis of: (1) each study; (2) French patients of the European study; (3) pooled data from both trials. For first-line therapy, the only relevant difference was the price of the products: study drugs and one medical visit were taken into account. As rescue treatment was not collected in the clinical trials, a survey among French practitioners (GP and ENT specialist) was conducted in order to document the standard medical management of AOE treatment failure.

Clinical efficacy and effectiveness

Two prospective, open-label, randomised multi-center trials (US and Europe)[28,29] estimated the efficacy and safety of ciprofloxacin versus ciprofloxacin + hydrocortisone versus PNH in the treatment of AOE. Patients older than 2 years had to present with an acute bacterial diffuse external otitis associating edema of the EAC, tenderness when moving the pinna and otalgia. At baseline, a bacteriological sample was analysed. Treatment was given for 7–10 days, qid. Two follow-up visits were performed, one during the period 7–10 days and the other 11–31 days after, to document possible recurrences.

The clinical efficacy was evaluated at the end of the follow-up visits. Since antibacterial efficacy was not statistically different from ciprofloxacin + hydrocortisone treated patients, the results (bacterial and clinical) of the Cipro and Cipro-HC patients were pooled.

Figure 1. Model description comparing ciprofloxacin + hydrocortisone treated patients with PNH



Clinical failure was defined as "No change, worsening or reappearance of the signs and symptoms of infection; patients requiring additional anti-microbial therapy".

Resource utilisation

First-line therapy included the costs of the study compounds and one visit. Cost of drugs was only available for PNH since the French price of ciprofloxacin + hydrocortisone was not fixed at the time of this model. Second-line therapy included a switch to another preparation and related second-line therapy items.

A specific survey was performed to estimate resources consumed by patients who failed first-line therapy. Although no information was available on second-line therapy in AOE, it was assumed that a small sample of practitioners would be sufficient to estimate commonly experienced costs, since almost all these patients are treated in an out-patient setting. As a matter of fact, no dramatic differences between practitioners were noticed in their reported medical management.

An ENT specialist interviewed five GPs and five ENT specialists, randomly selected from a list of practitioners in the Paris area[30], using a standardised interview guide. This distribution (1GP:1ENT) is close to the ratio

observed in the CREDES survey[20]. They were asked to describe how they manage patients who fail AOE first-line therapy, including all the out-patient medical resources they utilise. Indirect costs were estimated by schooldays and workdays lost.

Economic analysis

This study was conducted according to the recommendations issued in the "Guidelines and Recommendations for French Pharmaco-Economic Studies" [31].

Average savings associated with avoided failures were estimated based on expenses associated with the second-line treatment. The time horizon of the model was the short-term healing of the AOE episode and, therefore, no discounting was performed. Sensitivity analyses were performed on clinical results observed on the French sample and on the range (extreme sensitivity analysis) of cost values associated with second-line treatment.

Third party payer (*Sickness Fund*) and societal perspectives were considered. Third party payer perspective included the part paid by the *Sécurité Sociale* on drugs, bacteriological and laboratory examinations. Societal perspective included the reimbursement plus patient copayment of the same items plus indirect costs.

Unit costs estimates were based on three main sources: (1) "Nomenclature Générale des Actes Professionnels"[32], listing the tariffs and reimbursement rates of visits and laboratory examinations; (2) "Tariff Inter-Ministériel des Prestations Sanitaires"[33], listing the tariffs and reimbursement of medical devices; (3) Dictionnaire VIDAL for drugs[23]. Cost of one treatment strategy was estimated by probability of success multiplied by its cost plus probability of failure multiplied by its cost. The breakeven price (equal cost of both strategies) of Cipro-HC was estimated.

Costs are expressed in Euros 2000 (EUR 1 = 6.55957 FF; *Journal Officiel des Communautés Européennes*; [35]).

Table 1. Main characteristics of the 2 clinical trials: description of bacteriological species. Europe included France

	Europe	*France*	*USA*	*Both trials*
Number of patients	682	242	728	1,410
Number of patients with documented infection (%)	457 (67.0%)	165 (68.2%)	468 (64.3%)	925 (65.6%)
Number of patients without documented infection	225 (33.0%)	77 (31.8%)	260 (35.7%)	485 (34.4%)
Number of documented patients with *P aeruginosa* (%)	354 (77.5%)	128 (77.6%)	408 (87.2%)	762 (82.4%)
Number of documented patients with *S aureus* (%)	56 (12.3%)	22 (13.3%)	34 (7.3%)	90 (9.7%)
Number of documented patients with other organisms (%)	47 (10.3%)	15 (9.1%)	26 (5.6%)	73 (7.9%)

Results

Clinical efficacy and effectiveness

Table 1 describes the main characteristics of the patients enrolled in the clinical trials. 1,410 were included in both trials and treatment groups were found comparable at baseline. In the US, patients were younger (mean age 24 versus 37), more women (50 % versus 40 %) were enrolled, and patients presented with a lower percentage of previous AOE episodes during prior 12 months (16 % versus 30 %). AOE infections were more frequently bilateral in the US (14% versus 8.5%). Bacteriological characteristics at baseline showed a predominance of *P aeruginosa* (82.4% in patients with documented infections).

Table 2 describes the bacteriological results by treatment group, by study and type of species. On the sample of documented species, ciprofloxacin-treated patients had approximately half as many bacterial failures as PNH-treated patients, both in the EU and USA. These differences were statistically significant. On the French sample of patients, the odds ratio estimate was lower and not statistically significant. This was due to the lesser efficacy of ciprofloxacin and PNH on *P aeruginosa* where the odds ratio was two.

Table 2. Bacterial efficacy according to the type of species and studies

	Europe	*France*	*USA*	*Both trials*
All patients				
Cipro	85.8%	87.3%	93.7%	89.9%
PNH	73.9%	78.4%	87.4%	81.2%
Odds ratio	2.137	1.89	2.129	2.06
p-value	0.006	0.20	0.034	0.0008
P aeruginosa				
Cipro	85.6%	84.6%	93.4%	90.0%
PNH	68.5%	73.3%	86.6%	78.7%
Odds ratio	2.745	2.00	2.214	2.434
p-value	0.0009	0.18	0.033	0.0001
S aureus				
Cipro	89.2%	100%	91.3%	90.0%
PNH	93.3%	100%	90.0%	92.0%
Odds ratio	0.589	na	1.167	0.783
p-value	0.65	–	0.91	0.77
Other species				
Cipro	82.8%	88.9%	100%	89.1%
PNH	100%	100%	100%	100%
Odds ratio	na	na	1.00	na
p-value	0.98	0.98	1	0.97

na, not applicable, since the variance of the OR is too big.

Europe included France.

p-value estimated through Fisher's exact test.

Cipro, ciprofloxacin.

PNH, polymixin B + neomycin + hydrocortisone.

Table 3. Clinical efficacy according to the type of species and studies

	Europe	*France*	*USA*	*Both trials*
All patients				
Cipro	95.3%	95.8%	91.5%	93.3%
PNH	94.4%	91.7%	87.2%	90.7%
Odds ratio	1.19	2.05	1.57	1.43
p-value	0.63	0.21	0.08	0.09
P aeruginosa				
Cipro	97.9%	96.7%	90.5%	94.0%
PNH	93.1%	88.6%	87.4%	90.0%
Odds ratio	3.40	3.79	1.37	1.75
p-value	0.04	0.09	0.35	0.05
S aureus				
Cipro	89.7%	93.3%	95.7%	91.9%
PNH	100%	100%	80.0%	92.3%
Odds ratio	na	na	5.50	0.95
p-value	0.98	0.98	0.19	0.95
Other species				
Cipro	84.4%	90.0%	94.1%	87.8%
PNH	100%	100%	85.7%	95.2%
Odds ratio	na	na	2.67	0.358
p-value	0.97	0.98	0.51	0.36

na, not applicable, since the variance of the OR is too big.

Europe included France.

p-value estimated through Fisher's exact test.

Cipro, ciprofloxacin.

PNH, polymixin B + neomycin + hydrocortisone.

Table 3 describes the clinical efficacy of ciprofloxacin + hydrocortisone and PNH. The clinical efficacy of ciprofloxacin tended to be higher on all patients, although the differences were not statistically significant in most cases. The probability of failure when treating with ciprofloxacin was 1.43 times less frequent according to the pooled analysis. On the patients documented with *P aeruginosa*, the clinical efficacy of ciprofloxacin-treated patients was found higher than PNH-treated patients in the EU study ($p<0.04$) and in the pooled analysis ($p<0.05$). The probability of failure with ciprofloxacin was found 3.40 times less in the EU study and 1.75 less in the pooled analysis. In the French population the odds ratio was found to be higher (3.79) although it was not statistically significant ($p<0.09$).

Lastly, the safety of both drugs was found comparable in both studies. Adverse drug reactions were rare, not severe, and very few patients dropped-out from the study for safety reasons (0.2% in the EU study and 1.2% in the USA study).

Economic analysis

Resource utilisation after first-line failure is described in Table 4. There were no major differences between GP and ENT specialists excepted for the latter who prescribed two times more systemic

Table 4. Second line treatment failure: prescription description according to the type of practitioners

	GPs	*ENT specialists*	*Total*
Prescription of oral antibiotics	92 %	92 %	92 %
Prescription of oral anti-inflammatory	38 %	63 %	51 %
Other prescription	44 %	40 %	42 %
Bacteriological samples	21 %	20 %	21 %
Laboratory examination	20 %	0 %	10 %

GP, general practitioner.

ENT specialist, ear nose throat specialist.

anti-inflammatory drugs (corticoids or NSAIDs). Most of the prescriptions included oral antibiotics for 5–10 days (92%) and one-fifth had a bacteriological sample. Oral anti-inflammatory consisted in NSAIDs and corticoids. Other prerscriptions were mainly analgesic. Laboratory examination consisted mainly of blood glucose test. None of the practitioners prescribed staying home from school or work, leading to no indirect costs.

Cost of one bottle of PNH was EUR 2.56, public price.

The unit cost of success was EUR 15.07 when PNH was used according to the French Sickness Fund point of view and EUR 31.05 according to the societal point of view. The costs of one first-line failure (10th–90th percentile) were EUR 57.24 (35.46; 86.17) and EUR 94.44 (33.24; 131.75) respectively. The latter figures represent about four times the cost of a first-line empirical treatment, according to the French Sickness Fund, and three times according to societal viewpoint. According to the societal perspective, antibiotics represent 36% of the total cost of failure, while 20% is due to other treatment, another 20% is for procedures and the remaining is visits.

The results of the main analysis based on the pooled analysis and the sensitivity analyses, based on the French sample of patients are presented in Table 5.

On the main analysis, patients treated with ciprofloxacin + hydrocortisone had 2.7% fewer failures. This new topical antibiotic allowed an average saving of EUR 2.55 per AOE episode according to the Societal perspective and EUR 1.54 according to the Sickness Fund perspective.

The difference observed on the French sub-sample of patients was larger: patients treated with ciprofloxacin + hydrocortisone developed 4.1% less failures. Consequently, the average savings were also larger: EUR 3.87 for Society and EUR 2.35 for the French Sickness Fund.

Sensitivity analyses (Table 5) were run on the French sample of patients. On average, savings with ciprofloxacin + hydrocortisone varied between EUR 1.31

Table 5. Economic analysis and sensitivity analyses according to the pooled analysis and the sub-sample of French patients

	Ciprofloxacin + hydrocortisone	*PNH*	*Difference*
Main analysis: pooled analysis			
Failure rate estimated from the model	6.6%	9.3%	–2.7%
Failure cost – Societal perspective	EUR 6.23	EUR 8.78	– EUR 2.55
Failure cost – Séc-Soc perspective	EUR 3.78	EUR 5.32	– EUR 1.54
Sensitivity analyses : French sample			
Failure rate estimated from the model	4.3%	8.4%	– 4.1%
Average failure cost – Society	EUR 4.06	EUR 7.93	– EUR 3.87
Average failure cost – Séc-Soc	EUR 2.46	EUR 4.81	– EUR 2.35
Minimal failure cost – Society	EUR 1.36	EUR 2.67	– EUR 1.31
Minimal failure cost – Séc-Soc	EUR 0.88	EUR 1.72	– EUR 0.84
Maximal failure cost – Society	EUR 6.56	EUR 12.82	– EUR 6.26
Maximal failure cost – Séc-Soc	EUR 4.15	EUR 8.12	– EUR 3.97

Difference, ciprofloxacin + hydrocortisone minus PNH

Two perspectives, society and third party payer.

Ciprofloxacin + hydrocortisone, ciprofloxacin hydrocortisone.

PNH, polymixin B + neomycin + hydrocortisone.

Séc Soc, *Sécurité Sociale*.

and EUR 6.26 according to the societal perspective and between EUR 0.84 and EUR 3.97 according to Fund's perspective. The public breakeven price according to the societal perspective was EUR 10.60.

Discussion and conclusion

AOE is a common problem related to conditions of living. Analysis of the literature showed that the predominance of *P aeruginosa* as the causative organism is increasing. France was chosen, as the bulk of the EU patients came from this country. PNH was chosen as the comparator since it represented the most often prescribed and the cheapest drug in France[21]. This follows the French pharmacoeconomics guidelines[36].

Two studies were conducted in order to demonstrate the clinical equivalence of PNH and ciprofloxacin + hydrocortisone. The analysis of each study concluded that the two one-sided tests allowed for inference of equivalence. Switching from equivalence to superiority is possible provided certain statistical points are verified as described in the CPMP working party entitled "Points to be considered on

Bio-statistical / Methodological issues arising from recent CPMP discussions on licensing applications: superiority, noninferiority and equivalence[37]. These applied to these two studies.

Our results were based on modelling since no economic parameters were collected alongside the clinical trials. However, it has to be emphasised that the primary clinical endpoint definition of the two trials specified that the patients had to be treated by another antibiotics in case of failure. The unit cost of failure after first-line treatment was estimated using a standard cost approach based on a small sample of ophthalmologist and GPs since we did not expect large variability. This was confirmed by our findings. We chose at random GP and ENT specialists only in the Paris area. National inference is not too questionable since outpatient medical care is rather homogenous in France, especially when the items dedicated to care for first line treatment failures were medically simple. No costs related to safety were included in this model, since the tolerance of both drugs was found to be similar, and therefore they would not have contributed to the cost difference between the two strategies. We took efficacy measures from the clinical trials as a proxy of effectiveness, since, at that time, no national data were available (ciprofloxacin + hydrocortisone had an approved MAA but it was still not available on the French market). This is in accordance with most of the international health economics guidelines. We chose to work both on estimates coming from the pooled analysis, leading to the more precise results, and from the sub-sample of French patients, leading to the better external validity. So, despite the methodological difficulties we had to face, the sensitivity analyses we performed showed the robustness of our findings, including the extreme sensitivity analysis based on the minimal and maximal cost reported during the practitioner interviews.

Ciprofloxacin + hydrocortisone treated patients had an average savings of EUR 2.55 per episode of AOE according to the societal point of view when effectiveness was based on the pooled analysis, and EUR 3.87 when based on the French sample of patients. Although the clinical effectiveness difference did not reach statistical significance due to a lack of power, we ran the sensitivity analysis on this population in order to take into account the specificity of the bacterial species met in France.

Nothing, as far as we know, has been published on cost-effectiveness in AOE. The cost of PNH is very low in France reflecting the fact that drug prices are lower than in the other EU countries, a fact which is even more pronounced with topical drugs (Le secteur de l'ophtalmologie pharmaceutique, 1999). Therefore, to meet an economic breakeven point, the incremental efficacy in such situations is very high and some ceiling effects could even jeopardise the valuation of innovation.

According to the convention signed with the *Sécurité Sociale*, some practitioners are allowed to charge more than the tariff fixed

by the Sick Fund. According to Dumesnil, it amounts to 21% of GP and 63% of ENT specialist fees. We decided not to take these extra fees in our evaluation to stay on a conservative side.

In a budgeting approach, knowing that about 2,050,000 episodes of AOE are treated with topical antibiotics per year (IMS 1999) in France, and according to the effectiveness measured on the French subset of patients, 84,000 failures could be avoided per year, representing EUR 7.9 M in the societal perspective. IMS data were chosen to extrapolate at a national level since (1) there is a monthly update; (2) in AOE, one patient has rarely more than one prescription. From a macro-economic point of view, the cost-shifting generating these savings should occur since it is directly linked to the incremental efficacy of ciprofloxacin + hydrocortisone and therefore does not require any adaptations to the organisation of the health care system. Ciprofloxacin + hydrocortisone avoids some visits only due to its better efficacy (cost-shifting within and only within the out-patient envelope).

Lastly, besides the economic consequences, a more efficacious treatment is a way to avoid short and long-term complications of AOE, which were not taken into account in our short-term modelling approach. This is especially true on the subset of patients with diabetes mellitus where malignant AOE is one of the more severe complications. Although its incidence has never been clearly estimated, malignant AOE is a rather rare disease. Its treatment usually includes long term (up to 6 months) antibiotics (oral and/or infusion), local iterative surgeries with hospitalisation[39-43].

For these patients, the cost of failure would be much higher, and ciprofloxacin + hydrocortisone might be even more cost saving.

In conclusion, this economic study showed that a first-line treatment with ciprofloxacin + hydrocortisone in AOE at a public price of EUR 10.60 did not increase the French Sickness Fund expenses.

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