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Pharmacology applied to geriatric medicine

# Pharmacoeconomic and clinical aspect of a sequential intravenous to oral therapy plan in an acute geriatric ward

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ABSTRACT

*Introduction:* Sequential antibiotic therapy (SAT) is an important phase of treatment and an attempt to bring the change to oral treatment forward. We assessed the impact of SAT on the costs of antibiotic treatment on hospitalized elderly patients.
*Methods:* This was a prospective study in which 204 patients were assessed. Duration and costs of IV and oral treatment were recorded, as well as the day for switching from IV to oral treatment, mean stay and readmissions, and the results were confronted between the two phases of the study: observational and interventional. Mean antibiotic intake was defined as defined daily dose per every 100 stays (DDD/100S).
*Results:* Fifty-two were included in the observational phase and 59 in the interventional phase, mean age $80.0 \pm 7.4$, 52.3% women. Changeover of treatment was brought forward an average of 1.7 and 1.3 days with ciprofloxacin and levofloxacin, respectively, during the intervention phase compared to the observational phase ($P < 0.001$). The mean cost per unit in the intervention phase was reduced by 28.64 € with levofloxacin and by 24.28 € with ciprofloxacin. Intravenous DDDs/100S were reduced from $0.069 \pm 0.023$ to $0.042 \pm 0.006$ ($P < 0.001$) for levofloxacin and from $0.068 \pm 0.029$ to $0.038 \pm 0.012$ ($P < 0.001$) for ciprofloxacin.
*Conclusions:* Pharmaceutical intervention based on a SAT achieved reduction of the length of treatment of antibiotic IV treatment and thus also achieved a reduction in treatment costs. The intervention was not associated to an increase in relapse and was therefore efficient and cost effective.


## 1. Introduction

Efficient treatment of infections includes selection of the most appropriate medication and the adequate dose during enough time to eradicate the infection and minimize secondary effects and selection of resistant strains.

In addition, the channel for medication delivery is an important factor.

Sequential therapy is viewed as a method for more efficient use of antibiotics. Sequential therapy is defined as a changeover from the intravenous (IV) formulation to oral administration of the same medication, maintaining the same pharmacological strength [1,2].

IV administration of medication achieves immediate plasma levels and guarantees therapeutic compliance, which makes it useful in emergencies or in certain pathologies where, due to the type of microorganism, or location of the infection, it is necessary to use this mode of delivery exclusively. Therefore in illnesses such as meningitis, endocarditis or sepsis the use of a sequential antibiotic therapy is counter-indicated (SAT) [3].

Keep in mind that swallowing problems and the size of the tablets can reduce the salary possibility to switch to oral administration, especially in geriatric populations.

However, in other circumstances (such as pneumonia, genito-urinary infections, skin and soft tissue infections, gastrointestinal infections and febrile neutropenia) and depending on the evolution of the infection, SAT has been shown to be a cost-effective alternative [3,4].

The main inconveniences of IV are that it causes a considerable increase of both direct and indirect costs [4–9], reduces patient mobility, and increasing the risk of bed rest [10].

The principal advantages of oral administration are: that it is more comfortable and less aggressive for patients, it avoids the risk of phlebitis, it allows early mobilisation of hospitalized patients and, especially, that it is more economic in terms of direct costs of treatment (vials, solvents, galenic formulation) as well as indirect

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costs (vascular catheters, infusion systems, human resources, length of hospital stay) [11,12]. Furthermore, contrary to what might be thought, oral treatment is not less efficient than IV [13,14].

A complication of antibiotics in general, and fluoroquinolones in particular, is the increased risk of *Clostridium difficile* infections (CDIs) [15]. The bioavailability of fluoroquinolones not depends on the route of administration, and probably this is the reason why the risk of CDIs is the same between the oral or intravenous administration [16].

These facts mean that, as long as a patient's situation is appropriate and there is a therapeutic arsenal, which is efficient when orally administered, it is recommended that the administration route is changed as soon as possible [3,13].

The first step in order to carry out a correct SAT is training about the main aspects of this type of therapy [1,17]. After this, patients who are possible candidates for SAT must be properly selected and, finally, the treatment's effectiveness must be assessed.

Antimicrobial medication use optimization programmes are included as a quality and effectiveness criterion in therapeutic audits in order to optimize the use of antimicrobials and reduce the risk of selecting resistant strains through improper use [18].

The most appropriate antibiotics for sequential therapy should have a similar antimicrobial spectrum, be readily available in oral format and have a pharmacokinetics that allows administration every 12 or 24 hours, to make their administration easier and, especially, should have good tolerance (gastro-intestinal tolerance above all), a low potential for resistance selection and be relatively inexpensive [11,13]. One of the families of antibiotics that best fits these criteria is the fluoroquinolone group [13].

The main aim of this study is to assess the impact of pharmaceutical intervention on the costs of treatment via the implementation of sequential therapy with ciprofloxacin and levofloxacin in a geriatrics department.

## 2. Methods

Prospective study carried out at the Geriatrics Unit of the San Juan de Dios Hospital in León, Spain, which has 252 beds.

The study was carried out in two sequential phases of five months duration each. The first, observational, phase (Ph 1) took place between August and December 2010, during which time no intervention was carried out and contact was not established with the doctor and to select the control group. Later, there was a second, pharmaceutical intervention, phase (Ph 2) (January–May 2011) during which a sequential antimicrobial therapy programme using fluoroquinolones was implemented on all candidate patients, whilst informing the doctors in charge of these patients.

The study was approved by the Steering Committee and the Pharmacy Commission in agreement with the hospital Geriatrics Service and approved by the hospital Ethics Committee.

### 2.1. Patient selection

We prospectively included in the study all patients aged 65 or above in the Geriatrics Unit and who had been prescribed IV ciprofloxacin or levofloxacin, who had good oral tolerance, were haemodynamically stable and in whom a decrease in body temperature was observed.

Patients were selected from the unitary dose medication dispensation, with an assisted electronic prescription programme.

Patients receiving treatment with almagate, sucralfate, calcium or iron (due to a potential reduced absorption of fluoroquinolones), patients with nausea, vomiting, serious diarrhoea, a naso-gastric tube or intestinal motility alterations as well as patients with sepsis, endocarditis, meningitis or with endovascular prosthesis infections were all excluded.

### 2.2. Pharmaceutical intervention programme

During phase 2, on the third day of IV treatment, the pharmacist (JdP), sent a note to the doctor with the electronic prescription system, advising him of the possibility of changing the administration route and stating the bioavailability of oral administration and the benefits of such a changeover. In the cases when the doctor continued to prescribe IV, the researchers spoke directly to him in order to inform him of the SAT programme.

### 2.3. Effectiveness variables used

The researchers used the following variables: number of days with IV and oral treatment, total duration of antibiotic treatment and of hospital stay, day of changeover from IV to oral, readmissions due to re-infection during the 30 days following discharge, diagnosis upon discharge in order to assess whether early readmission (within 30 days) could be considered a relapse due to infection. We also calculated the mean cost of antimicrobial treatment by group and by laboratory sale price (LSP) and mean antibiotic intake defined as Defined Daily Dose per 100 stays (DDD/100S). DDD/100S, is the assumed average maintenance dose per day for a drug used for its main indication in adults, established by the World Health Organization [19]. It is calculated with the following formula: DDD/100S = (annual intake in grams $\times$ DDD in grams)/(100 $\times$ stays in a year). The defined daily dose (DDD) is the most widespread measurement for antibiotic intake in a hospital setting and allows comparisons to be drawn between hospitals in different countries.

### 2.4. Statistical analysis

A descriptive analysis of the studied variables was carried out by calculating averages and proportions. Values are expressed as numbers and percentages for the categorical values and as mean $\pm$ standard deviation for continuous variables with a normal distribution.

Variables that do not fulfil the normality assumption (Kolmogorov-Smirnov test) were non-parametrically analysed, so the averages were compared using the Mann-Whitney U test and proportions were compared using the chi-square test ($\chi^2$).

Bilateral $P < 05$ values were considered significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS inc., Chicago, IL).

## 3. Results

A total of 204 patients were assessed, of which 111 were recruited, 57 were treated with levofloxacin (27 in the observational phase and 30 in the intervention phase) and 54 with ciprofloxacin (25 in the observational phase and 29 in the intervention phase).

Of the 86 patients excluded during the observational phase, 56.9% were women, mean age 87.8, 42.1% were men aged 81.6 on average. The reasons for excluding these patients were: on adherence to treatment ($n = 31$), palliative care patients ($n = 10$), oral intolerance ($n = 25$), or because they presented haemodynamic instability (n 20)

During the pharmaceutical intervention phase, 66 patients were considered to be candidates for SAT, 36 for ciprofloxacin and 30 for levofloxacin, of which a total of 59 interventions were accepted (89.4%): 30 for levofloxacin (100%) and 29 for ciprofloxacin (80.5%).

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**Table 1**
Descriptive characteristics of patients who were candidates for intervention with respect to the comparison group, and diagnosis upon discharge for both groups.

| | Levofloxacin ($n=57$) | | | Ciprofloxacin ($n=54$) | | |
|---|---|---|---|---|---|---|
| | Observational phase ($n=27$) | Intervention phase ($n=30$) | $P$ value | Observational phase ($n=25$) | Intervention phase ($n=29$) | $P$ value |
| Age (years) | 80.7 (5.6) | 82.5 (6.5) | 0.396 | 79.4 (8.8) | 77.3 (8.9) | 0.546 |
| Men $n$ (%) | 12 (44.4) | 17 (56.6) | 0.659 | 10 (40) | 14 (48.3) | 0.578 |
| IV dose, mg/day | 500 (0.0) | 500(0.0) | 1.000 | 598.42 (203.93) | 670.28 (203.98) | 0.145 |
| Oral dose, mg/day | 505.3 (99.3) | 505.4 (73.2) | 1.200 | 997.95 (344.2) | 1.056.35 (232.94) | 0.192 |
| Readmission due to reinfection, $n$ | 0 | 0 | | 0 | 0 | |
| Community acquired pneumonia, $n$ (%) | 12 (44.4) | 13 (43.3) | 0.841 | 0 | 0 | |
| Other respiratory infections, $n$ (%) | 10 (37.0) | 11 (36.6) | 0.845 | 2 (8) | 2 (6.89) | 0.993 |
| Genito-urinary infection, $n$ (%) | 2 (7.4) | 2 (6.7) | 0.695 | 15 (60) | 14 (48.3) | 0.909 |
| Skin infection, soft tissues, $n$ (%) | 1 (3.7) | 1 (3.3) | 0.695 | 3 (12) | 4 (13.8) | 0.822 |
| Gastro-intestinal infection, $n$ (%) | 1 (3.7) | 1 (3.3) | 0.695 | 2 (8) | 5 (17.2) | 0.209 |
| Other infections, $n$ (%) | 1 (3.7) | 2 (6.7) | 0.904 | 3 (12) | 4 (13.8) | 0.779 |

Results are expressed as mean (±SD), unless stated otherwise.

The reasons for which there was no acceptance of our pharmaceutical recommendation for seven of the patients (four women, three men, mean age 82.6) were: oral intolerance in four cases and febrile peaks in the other three patients.

There was no statistically significant difference between the excluded patients and those included in the study.

The general characteristics of the population and infection locations are detailed in Table 1.

We found no significant differences in terms of age, sex, IV and oral antibiotic doses of levofloxacin and ciprofloxacin, and diagnosis upon discharge. There were no readmissions due to infection in the 30 days following discharge.

## 4. Duration of treatment and of hospital stay

The duration in days of the IV treatment was statistically shorter in the intervention phase with levofloxacin and with ciprofloxacin, going from $4.4 \pm 0.9$ to $2.1 \pm 0.4$ days in the former ($P < 0.001$) and from $5.1 \pm 1.0$ to $3.3 \pm 0.7$ in the latter ($P < 0.001$) (Table 2). Mean duration of oral treatment in the group with levofloxacin was 10.0 days $\pm$ 2.0 in the observational phase and of $12.3 \pm 1.6$ days in the intervention phase ($P < 0.001$) whilst in the groups treated with ciprofloxacin it was $9.8 \pm 2.7$ and $11.8 \pm 1.7$ respectively ($P = 0.001$) (Table 2, Fig. 1 Panel A). The total duration of treatment in days was not modified in either of the two phases of the study.

Conversion from IV to oral treatment took place earlier during the intervention phase compared to the observational phase, going from $5.2 \pm 2.0$ to $3.5 \pm 0.2$ days in the group treated with ciprofloxacin, and from $4.3 \pm 1.0$ to $3.0 \pm 0.5$ days in the group treated with levofloxacin; these differences being statistically significant ($P < 0.001$) (Table 2, Fig. 1 panel B).

Hospital stay was shortened in the intervention group, going from $17.6 \pm 2.6$ to $16.3 \pm 2.3$ days, respectively, in the observation phase and the intervention phase, in the group treated with levofloxacin and from $18.0 \pm 3.2$ to $17.8 \pm 3.5$ in the group treated with ciprofloxacin, although the difference was not statistically significant ($P = 0.789$ for levofloxacin and $P = 0.873$ for ciprofloxacin) (Table 2, Fig. 1 panel B).

### 4.1. Costs of medication and intake in DDDs/100 stays

Average cost of treatment per unit in the observational phase in the group with levofloxacin was $63.05 \pm 11.81$ € and $100.94 \pm 28.06$ € in the ciprofloxacin group, and in the intervention phase these costs decreased to $34.41 \pm 8.11$ € ($P < 0.001$) and $76.66 \pm 11.72$ € ($P = 0.001$) with levofloxacin and ciprofloxacin respectively (Table 2, Fig. 2 panel A). Mean savings per patient were 28.64 € for levofloxacin and 24.28 € for ciprofloxacin.

The total cost of treatment in the observational phase was $1765.20 \pm 316.00$ € for levofloxacin and 2584.50 € for ciprofloxacin, whilst in the intervention phase it was $1032.40 \pm 179.00$ € ($P < 0.001$) and 2146.50 € $\pm$ 350.00 € ($P = 0.001$) for levofloxacin and ciprofloxacin respectively, generating a significant decrease of the total cost of antimicrobial treatment (Table 2, Fig. 2 panel B). Thus, in this study a mean saving of 732.80 € was achieved in treatment with levofloxacin and 438.00 € in treatment with ciprofloxacin.

**Table 2**
Effects of intervention on treatment duration and costs.

| | Levofloxacin ($n=57$) | | | Ciprofloxacin ($n=54$) | | |
|---|---|---|---|---|---|---|
| | Observational phasetd:paraenter ($n=27$) | Intervention phasetd:paraenter ($n=30$) | $P$ value | Observational phasetd:paraenter ($n=25$) | Intervention phasetd:paraenter ($n=29$) | $P$ value |
| *IV duration (days)* | 4.4 (0.9) | 2.1 (0.4) | <0.001 | 5.1 (1.0) | 3.3 (0.7) | <0.001 |
| *Oral duration (days)* | 10.0 (2.0) | 12.3 (1.6) | <0.001 | 9.8 (2.7) | 11.8 (1.7) | 0.001 |
| *Conversion day (days)* | 4.3 (0.93) | 3.0 (0.5) | <0.001 | 5.2 (2.0) | 3.5 (0.2) | <0.001 |
| *LOS (days)* | 17.6 (2.6) | 16.3 (2.3) | 0.789 | 18 (3.2) | 17.8 (3.5) | 0.873 |
| *Duration of antibiotic treatment (days)* | 14.3 (2.0) | 14.4 (1.5) | 0.549 | 14.8 (2.2) | 15.0 (1.6) | 0.701 |
| *Total intake (DDD/100S)* | | | | | | |
| Oral | 3.168 (0.94) | 4.110 (0.57) | 0.001 | 2.724 (1.07) | 3.884 (1.04) | <0.001 |
| IV | 1.112 (0.63) | 0.726 (0.18) | <0.001 | 1.717 (0.72) | 1.087 (0.34) | <0.001 |
| *Intake/patient (DDD/100S)* | | | | | | |
| Oral | 0.113 (0.035) | 0.134 (0.019) | 0.001 | 0.092 (0.043) | 0.139 (0.036) | <0.001 |
| IV | 0.069 (0.023) | 0.042 (0.006) | 0.001 | 0.068 (0.029) | 0.038 (0.012) | <0.001 |
| *Cost per patient, €** | 63.05 (11.81) | 34.41 (8.11) | <0.001 | 100.94 (28.06) | 76.66 (11.72) | 0.001 |
| *Total cost, €** | 1765.20 (316.00) | 1032.40 (179.00) | <0.001 | 2584.50 (361.00) | 2146.50 (350.00) | 0.001 |

Results are expressed as mean (±SD), unless stated otherwise.
IV: intravenous; LOS: length of stay; € = Euro.

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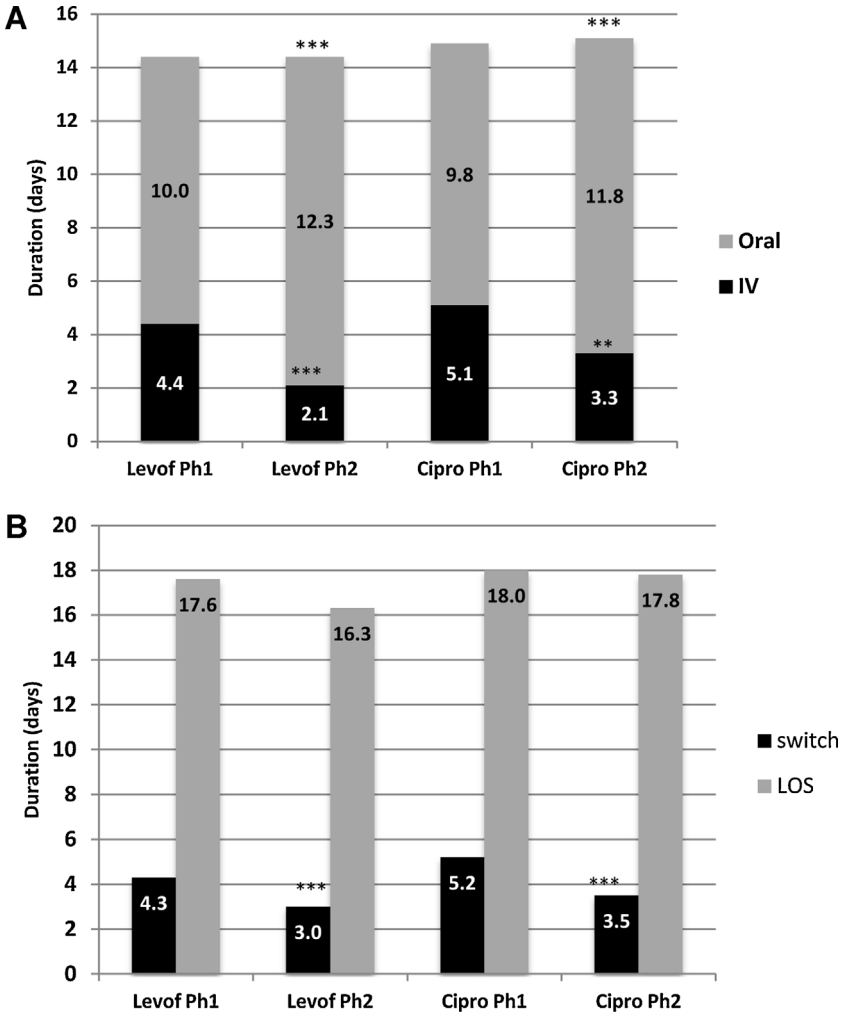


**Fig. 1.** Duration of treatment and of hospital stay. Panel A: showing the duration of oral treatment (black), and IV treatment (grey) of levofloxacin (Levof) and ciprofloxacin (Cipro) treatment during the observational phase (Ph1) and during intervention phase (Ph2). The height of accumulated columns represents the total duration of antibiotic treatment. Panel B: conversion days (black) and total hospital stay (grey). ***$P < 0.001$.

Intravenous DDDs/100S were reduced from $0.069 \pm 0.023$ to $0.042 \pm 0.006$ ($P < 0.001$) for levofloxacin and from $0.068 \pm 0.029$ to $0.038 \pm 0.012$ ($P < 0.001$) for ciprofloxacin. Oral DDD/100S increased from $0.113 \pm 0.035$ to $0.134 \pm 0.019$ ($P = 0.001$) for levofloxacin and from $0.092 \pm 0.043$ to $0.139 \pm 0.036$ ($P < 0.001$) for ciprofloxacin (Table 2, Fig. 3 panel A).

Total ciprofloxacin and levofloxacin DDD/100S increased significantly in oral treatment from $3.17 \pm 0.94$ to $4.11 \pm 0.57$ ($P = 0.001$) with levofloxacin and from $2.72 \pm 1.07$ to $3.88 \pm 1.04$ with ciprofloxacin ($P < 0.001$). A reduction in IV DDD/100S was observed, going from $1.11 \pm 0.63$ to $0.73 \pm 0.18$ in levofloxacin and from $1.72 \pm 0.72$ to $1.09 \pm 0.34$ ($P < 0.001$) in patients treated with ciprofloxacin (Table 2, Fig. 3 panel B).

## 5. Discussion

The fundamental purpose of this study was to promote a programme of sequential antimicrobial therapy by the Pharmacy Service in the Geriatrics Unit, and to analyze its impact upon costs (whether direct or indirect), and on hospital stay.

We found good level of approval among the doctors, as can be seen by the increase of oral administration and the fact that it was brought forward [5,11,20].

According to various studies, doctors show a tendency to continue with IV therapy due to uncertainty about patients' response to oral treatment or due to a lack of information about the oral bioavailability of ciprofloxacin and levofloxacin [7,20]. All this indicates the need for pharmacy services to promote SAT for hospitalized patients.

IV antibiotic intake decreased, while oral intake increased, causing a significant reduction in costs. An extrapolation of these results to the number of patients treated with fluoroquinolones in this hospital during one year, suggests direct savings of 5339.20 € in levofloxacin and 6152.60 € in ciprofloxacin. To this we must add the savings in indirect costs and in nurse hours which, according to other studies, has been estimated at 350 per hour per year [21,22].

Intervention achieved a statistically significant reduction in the length of IV treatment with both antibiotics by over two days on average and an equivalent increase in the length of oral treatment. Published papers on promoting SAT in various hospitals show similar results, with conversion to oral treatment being brought forward in time [3,11,21,23–25] and, together with a reduction in the duration of IV treatment, a significant reduction in antibiotic intake in DDD/100S whilst also causing a lower incidence of adverse effects and greater safety for patients [21].

This study found no differences between the groups studied in terms of the mean dose of ciprofloxacin and levofloxacin whether orally or intravenously, or in the mean length of antimicrobial treatment; both of which results were expected, in that these factors are independent of the SAT programme [3,11,21,24–26].

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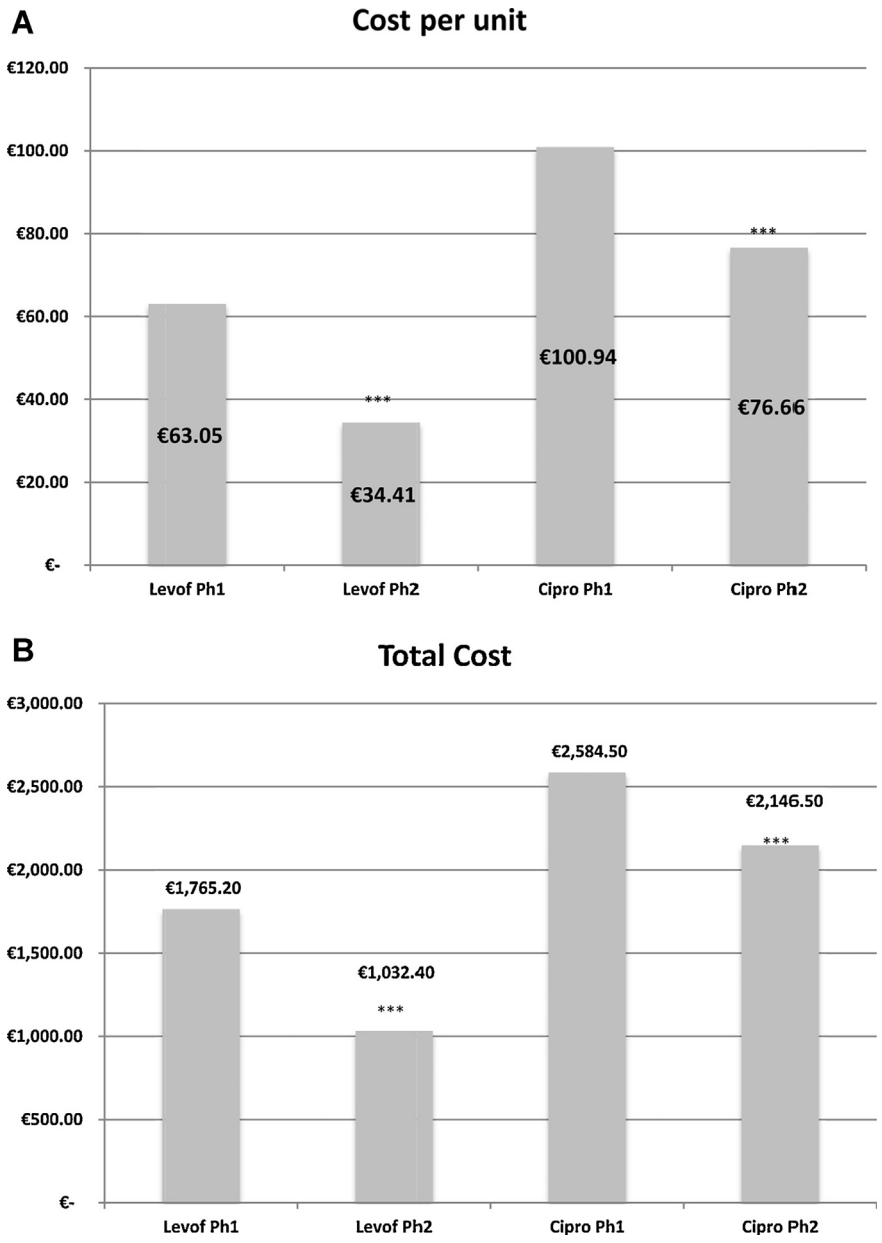


**Fig. 2.** Cost of medication of levofloxacin (Levof) and ciprofloxacin (Cipro) treatment during the observational phase (Ph1) and during intervention phase (Ph2). Panel A: average cost of treatment per unit. The cost, in Euro (€), in the intervention phase was significantly lower than in the observational phase. Panel B: total cost was significantly lower in the intervention phase than in the observational phase. $^{***}P < 0.001$.

As to variations in length of hospital stay, results are diverse, depending on the study, with a significant reduction in length of stay in some of the studies [11], whilst in others the reduction was not significant [21,24,25,27]. In our study we found a reduction in length of stay in the intervention group, although it was not significant.

There is a range of factors that concur in causing relatively lengthy hospital stay periods in geriatrics departments [21,24,25]. Advanced mean age, the presence of comorbidities and, often, a precarious social situation, polypharmacy, functional abilities, frailty/sarcopenia, can mean that patients prefer to remain in hospital despite being clinically stable and the possibility of continuing oral antibiotic treatment at home, and therefore only looking on the way of drug administration may be biased. This may amount to bias affecting the comparison of hospital stay duration between different studies, as it can vary depending on the resources available to social services in different countries.

The nonexistence or readmissions to hospital shows the effectiveness of these therapy programmes, as observed in earlier studies [11,21,24].

Introduction of SAT programmes has been shown to be one of the most efficient systems for pharmaceutical care of hospitalized patients [9,11,13,21,24].

Intervention by pharmacists is often not enough and an information exchange with doctors is required, in order to gain knowledge of clinical data and implement a solid decision-making process [23,28–31]. This leads to pharmacists becoming part of the care team and carrying out multidisciplinary work [32].

This study has a number of limitations. Indirect costs associated to materials required for IV infusion and to nursing hours were not calculated. There was also no assessment of approval by patients, a measured result associated to greater quality of care. Finally, the date when the doctor considered it appropriate to discharge patients and the reasons that may have influenced delays in discharge were

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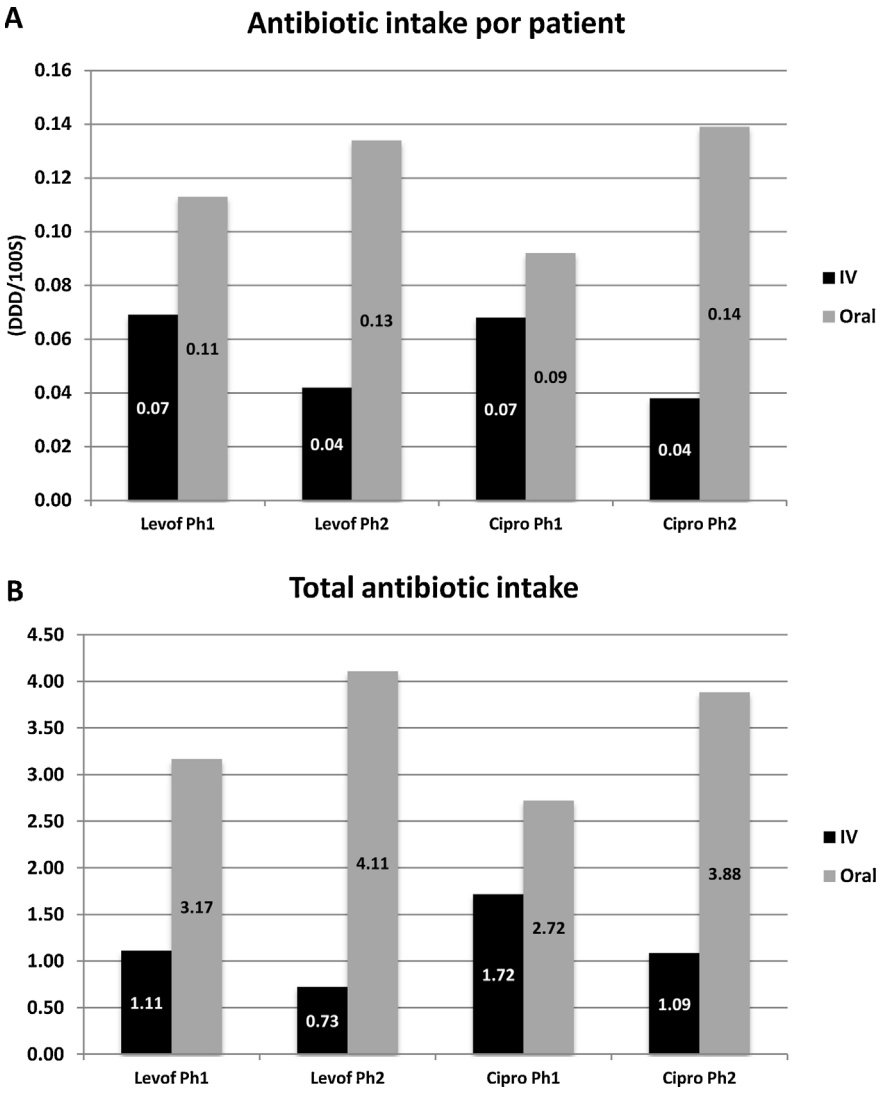


**Fig. 3.** Medication intake of levofloxacin (Levof) and ciprofloxacin (Cipro) treatment during the observational phase (Ph1) and during intervention phase (Ph2). Panel A: different intake defined as defined daily dose per 100 stays (DDD/100S) of IV and oral levofloxacin and ciprofloxacin for patients in the different phases of the study. All the differences are statistically significant. Panel B: total antibiotic intake. All the differences are statistically significant. $^{***}P < 0.001$.

not recorded. It would be interesting to do future research into whether stable patients receiving oral treatment can be discharged and finish their antibiotic treatment at home. Research carried out in the USA showed that reduction of hospitalization by one single day in turn reduces cost by approximately $2200 per patient. This would lead to a reduction in costs linked to admission but, particularly, it would drastically reduce the negative consequences of admission and confinement to bed in elderly patients [33].

Despite its limitations, the main strengths of this study are, firstly, that it is the first piece of research of this kind carried out entirely in a geriatric population, which is the largest user of social-health resources and the population that suffers the most complications secondary to admission (functional loss, pressure ulcers and acute confusional syndrome are all among the main complications). Secondly, the observational phase was prior to the pharmacist's intervention. This reduced possible bias stemming from prior knowledge of the aims of the study.

## 6. Conclusions

Establishment of a sequential antibiotic therapy programme is an opportunity to expand the role of hospital clinical pharmacists, aiding their integration into the multidisciplinary care teams, which are typical of geriatrics units.

In the light of the results obtained by this study, programmes for optimization of the use of antimicrobial drugs, such as this one, achieve, on the one hand, an important reduction of both direct and indirect costs and, on the other hand, an optimization of antimicrobial therapeutics – specifically, rational use of fluoroquinolones – reducing the length of IV treatment whilst maintaining the same level of effectiveness. This demonstrates that the implementation of such programmes is a cost-effective alternative for hospitals.

## Disclosure of interest

The authors declare that they have no competing interest.

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