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Clarithromycin Leads to Long-Term Survival and Cost Benefit in Ventilator-Associated Pneumonia and Sepsis

Thomas Tsaganos,[a] Maria Raftogiannis,[a] Maria Pratikaki,[b] Sofia Christodoulou,[a] Anastasia Kotanidou,[b] Evangelos Papadomichelakis,[c] Apostolos Armaganidis,[c] Christina Routsi,[b] Evangelos J. Giamarellos-Bourboulis[a]

4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece[a]; 1st Department of Critical Care Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece[b]; 2nd Department of Critical Care Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece[c]

Increasing numbers of admissions for sepsis impose a heavy burden on health care systems worldwide, while novel therapies have proven both expensive and ineffective. We explored the long-term mortality and hospitalization costs after adjunctive therapy with intravenous clarithromycin in ventilator-associated pneumonia (VAP). Two hundred patients with sepsis and VAP were enrolled in a published randomized clinical trial; 100 were allocated to blind treatment with a placebo and another 100 to clarithromycin at 1 g daily for three consecutive days. Long-term mortality was recorded. The hospitalization cost was calculated by direct quantitation of imaging tests, medical interventions, laboratory tests, nonantibiotic drugs and antibiotics, intravenous fluids, and parenteral and enteral nutrition. Quantities were priced by the respective prices defined by the Greek government in 2002. The primary endpoint was 90-day mortality; cumulative hospitalization cost was the secondary endpoint. All-cause mortality rates on day 90 were 60% in the placebo arm and 43% in the clarithromycin arm ($P = 0.023$); 141 patients were alive on day 28, and mortality rates between days 29 and 90 were 44.4% and 17.4%, respectively ($P = 0.001$). The mean cumulative costs on day 25 in the placebo group and in the clarithromycin group were €14,701.10 and €13,100.50 per patient staying alive, respectively ($P = 0.048$). Respective values on day 45 were €26,249.50 and €19,303.10 per patient staying alive ($P = 0.011$); this was associated with the savings from drugs other than antimicrobials. It is concluded that intravenous clarithromycin for three consecutive days as an adjunctive treatment in VAP and sepsis offers long-term survival benefit along with a considerable reduction in the hospitalization cost. (This study has been registered at ClinicalTrials.gov under registration no. NCT00297674.)

Severe sepsis is among the leading causes of morbidity worldwide; it strikes more than 1.5 million people in the United States and a similar number in Europe, requiring urgent and often prolonged hospitalization (1). The increasing number of hospitalizations for sepsis worldwide imposes a heavy financial burden on health care systems (2).

Treatment of sepsis has evolved to one of the most difficult and most expensive medical problems in the modern era. Guidelines for its management focus on early diagnosis and on early administration of fluids and antimicrobials (3). Despite the decrease of mortality these guidelines offered, mortality from sepsis remains unacceptably high. Research in the recent years has focused on development of expensive agents that aim to interfere with the pathogenesis of sepsis by modulating inflammation and coagulation. Unfortunately, incomplete comprehension of the underlying mechanisms of sepsis and of the most appropriate timing for intervention has led to failure of most clinical trials investigating these agents, with the PROWESS-SHOCK study being one of the most expensive failures (4).

Almost 10 years ago, our group conducted a randomized clinical trial (RCT) in which patients with ventilator-associated pneumonia (VAP) and sepsis were blindly allocated to receive intravenously either a placebo or clarithromycin for three consecutive days (5). The results showed that clarithromycin treatment was accompanied by earlier resolution of VAP, from a median of 15.5 days for the placebo group to 10.0 days, and by earlier weaning from mechanical ventilation, from a median of 22.5 days for the placebo group to 16.0 days. In addition, there was a decrease of the odds ratio (OR) for death by septic shock and multiple-organ dysfunction syndrome (MODS) from 19.00 in the placebo group to 3.78 in the clarithromycin group. However, it was puzzling that despite the earlier resolution of VAP, the overall all-cause mortality rates between the two groups were similar. In order to confirm the findings, another RCT was conducted by our group in a population of 600 patients with sepsis developing after clinically suspected or microbiologically proven infections of Gram-negative origin; 298 patients were allocated to placebo treatment and 302 patients to clarithromycin treatment (6). In that study, the period of treatment was extended to 4 days. Results confirmed the significant decrease of the OR for death by septic shock and MODS from 6.21 to 3.58 and the earlier resolution of severe infections from 10 days to 6 days. A salient exploratory finding of our second RCT was a significant decrease of the hospitalization cost in the clarithromycin group.

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Address correspondence to Evangelos J. Giamarellos-Bourboulis, egiamarel@med.uoa.gr.

M.R. and M.P. contributed equally to this article.

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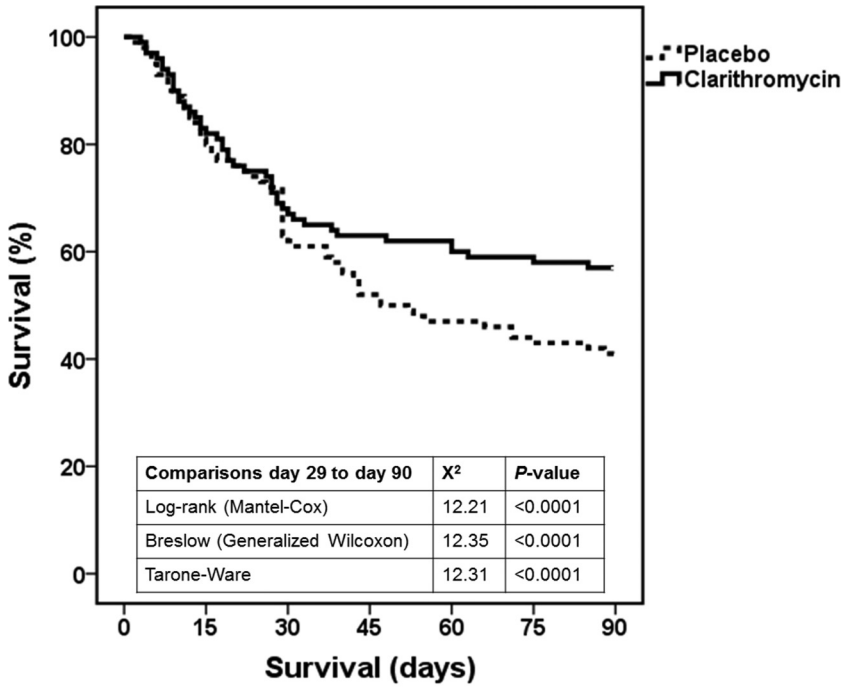

FIG 1 Comparative survival until day 90 of patients enrolled in the study. *P* values for comparison between patients staying alive after day 28, using the indicated test, are provided.

When the results of the second RCT were known, we asked ourselves whether clarithromycin treatment would have affected the hospitalization costs of patients with VAP enrolled in the first RCT as well. The aim of the present retrospective study was to report on the effect of clarithromycin on the long-term (90-day) mortality and on the cost of hospitalization of patients with VAP and sepsis enrolled in this RCT.

(Findings from this study were presented at the 24th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 10 to 13 May 2014.)

MATERIALS AND METHODS

Study design. As the design of the study has been published before (5), it is briefly reported here. Between June 2004 and November 2005, 200 male or female adult patients were enrolled in a prospective, double-blind, randomized, placebo-controlled, multicenter clinical trial in two intensive care units (ICUs) and one department of internal medicine of the University of Athens after written informed consent by their first-degree relatives. The study was approved by the ethics committees of the hospitals and by the National Organization for Medicines of Greece (Clinicaltrials.gov identifier NCT00297674). Inclusion criteria were the development of VAP and at least two signs of the systemic inflammatory response syndrome. Patients with HIV infection or neutropenia and patients under treatment with any other macrolide, drotregocin-alpha, or corticosteroids were excluded from the study. Patients were randomized to receive either intravenous placebo or clarithromycin along with the standard-of-care antimicrobial treatment. Blind treatment was administered at a volume of 250 ml as a 1-h infusion through a central venous line for three consecutive days. The dose of clarithromycin was 1 g, and it was diluted in normal saline; normal saline was administered to patients allocated to the placebo group.

On June 2012, following licensing by the regulatory authorities of Greece (license 3896/03-06-2011), all medical and nursing charts were retrospectively reviewed by a team of physicians who were completely blind to the allocated treatment. The following information per patient was registered into a case report form (CRF) starting from the day of start of the blind intervention until day 90: (i) survival status, (ii) discharge from the ICU, (iii) discharge from the general ward, and (iv) absolute quantities of the following until day 90: radiology tests, interventions (i.e., catheterizations, tracheostomies, and hemodialysis) and respective consumables, laboratory tests (including blood cell counting, biochemistry, blood gas, and microbiology), antimicrobials, antifungals, and nonantimicrobial drugs comprising intravenous fluids, cardiology drugs, anesthetics, and parenteral and enteral nutrition. The hospitalization cost per day was estimated by the sum of multiplications of each counted item with its price in Euros and the addition of the nominal cost of daily stay for the ICU or general ward. The unit price for each counted item was derived from the official pricelist as defined in 2002 by the Greek government (provided in the supplemental material). Counting of the items was performed by three investigators who were also completely blind to the allocated treatment. The cost of human resources (e.g., salaries of nursing and medical personnel) was not counted.

The primary study endpoint was 90-day mortality. Secondary study endpoints were the cumulative total hospitalization cost and the cumulative cost of cost categories included in the hospitalization cost.

Statistical analysis. Mortality rates between the two groups were compared by the chi-square test. ORs and 95% confidence intervals (CIs) were calculated by Mantel and Haenzel's statistics. Survival analysis was done

by all three relevant tests, i.e., log rank test, Breslow's test, and Tarone-Ware's test. Cumulative cost was expressed as mean ± standard error (SE); comparisons between the two groups were done on each separate day by the Mann-Whitney U test. Adjustments for mortality were done so that the cumulative cost of patients staying alive onto each day of follow-up was included in the analysis.

Any two-sided P value of <0.05 after Bonferroni corrections for multiple comparisons was considered statistically significant. Statistical analysis was performed by the software package IBM Statistics SPSS 22.0.

RESULTS

Long-term mortality. Of the 200 patients, 100 were allocated to receive placebo and the other 100 were allocated to receive clarithromycin. As described in the original publication (5), the two treatment groups did not differ in their baseline demographics, clinical characteristics, or degrees of disease severity, and the appropriateness of antimicrobial treatment and the rates of eradication of the implicated pathogens were similar between the two treatment groups.

All-cause mortality rates were similar in the two groups on day 28, 28% in the placebo arm and 31% in the clarithromycin arm. However, when mortality follow-up was prolonged to 90 days, the rates were 60% in the placebo arm and 43% in the clarithromycin arm (Fisher exact test = 5.79; $P = 0.023$). The OR for death by any cause on day 90 was 0.50 (95% CIs, 0.28 to 0.58; $P = 0.024$).

Thus, although all-cause mortality rates did not differ between the two groups until day 28, a large survival benefit from clarithromycin treatment became apparent between days 29 and 90. Of the 200 enrolled patients, 141 were alive on day 28, 72 in the placebo group and 69 in the clarithromycin group. Survival of these patients treated with clarithromycin was significantly prolonged compared with that in the placebo arm (shown in Fig. 1). More precisely, the mortality rates between days 29 and 90 were 44.1% in the placebo arm (32 deaths) and 17.4% in the clarithromycin arm (12 deaths) (Fisher exact test = 12.01; $P = 0.001$). The OR for death between days 29 and 90 with clarithromycin treatment was 0.26 (95% CIs, 0.12 to 0.57; $P = 0.001$).

Cost analysis. Cumulative hospitalization costs from baseline day 1 until day 45 are presented in Fig. 2A. The cumulative costs did not differ between the two groups for patients staying alive until day 24; however, by day 25, the mean cumulative costs were €14,701.10/patient staying alive in the placebo group and €13,100.50/patient staying alive in the clarithromycin group ($P = 0.048$). The mean cumulative hospitalization cost remained lower for clarithromycin-treated patients from day 25 until day 45 than for placebo-treated patients (Fig. 2), mounting to €19,303.10/patient staying alive in the clarithromycin group on day 45, in comparison to €26,249.50/patient staying alive in the placebo group ($P = 0.011$). Although cost data were available for the entire follow-up period of 90 days, we decided to limit analysis to day 45 because the number of patients staying in the hospital after that day was relatively small compared to the number of patients of each group at the baseline.

Subanalysis comprising only survivors until day 45 showed that the cumulative cost was greater in the placebo group than in the clarithromycin group (Fig. 2B). The two groups start to differ on day 21, when mean cumulative hospitalization costs/patient were €12,205.0 in the placebo group and €10,682.0 in the clarithromycin group ($P = 0.036$). On day 45, the respective costs were €27,089.71/patient and €19,382.32/patient ($P = 0.004$). Analysis comprising only patients who died by day 45 did not show any differences between the two groups (data not shown).

Cost-related characteristics were compared between the two groups for patients remaining alive on day 28 (Table 1). The only difference was that the rate of discharge of alive patients from the general ward was significantly greater in the clarithromycin group.

Separate analysis was done by breaking the hospitalization costs into cost categories, namely, costs of antimicrobials, drugs other than antimicrobials, laboratory and radiology examinations, interventions, and hospital beds (Fig. 3). The only difference was found for the cost of the nonantimicrobial drugs (Fig. 4). Their mean cumulative cost was lower for clarithromycin-treated patients than for placebo-treated patients from day 23 through day 45: on day 23, the mean cumulative costs of nonantimicrobial drugs were €2,568.70/patient staying alive in the placebo group and €1,892.41/patient staying alive in the clarithromycin group ($P = 0.048$); they were €6,664.76/patient staying alive and €3,614.50/patient staying alive on day 45, respectively ($P = 0.040$).

DISCUSSION

In this study, we found that intravenous clarithromycin administration for three consecutive days as an adjunctive treatment in patients with sepsis and VAP provided a long-term survival benefit along with considerable reduction of the hospitalization cost. These results were not totally unexpected since the original analysis of the first 28 days of follow-up of these patients reported earlier resolution of VAP and earlier weaning from mechanical ventilation. To assess the potential survival benefit, we used the customary 28-day mortality when we analyzed the data of the RCT back in 2008. When we designed the study, we had not forseen that the survival curves of the clarithromycin group and the placebo group would further divert beyond day 28. Unblinding for allocated treatment was done only when data for all enrolled patients were entered into the database. This happened well after the completion of follow-up of all patients for 90 days. As a consequence, there was no early withdrawal of support that could explain the rapid drop of survival from day 28 to day 30 in the placebo group. Two hypotheses can be provided to explain this divergence to high death rate after day 28: (i) VAP is an entity with slow progression and long-lasting sequelae, and (ii) in this group of patients, clarithromycin treatment was documented to provide efficient resolution of sepsis-induced immunosuppression, providing better immune protection of the host (7). These findings also teach that for the analysis of sepsis and VAP trials, a longer monitoring is necessary to assess the effect on survival. Such analysis should probably be done for other trials.

Although our group is the only one that has conducted RCTs to assess the benefit of clarithromycin treatment in sepsis management, another recent RCT with patients with community-acquired pneumonia (CAP) confirmed the benefit coming from this intervention. Patients with CAP were assigned to treatment with β-lactams and placebo ($n = 291$) or β-lactam and intravenous or oral clarithromycin ($n = 289$) (8). Although the study was powered to demonstrate noninferiority of the adjunctive treatment, 33.6% of patients of the combination arm

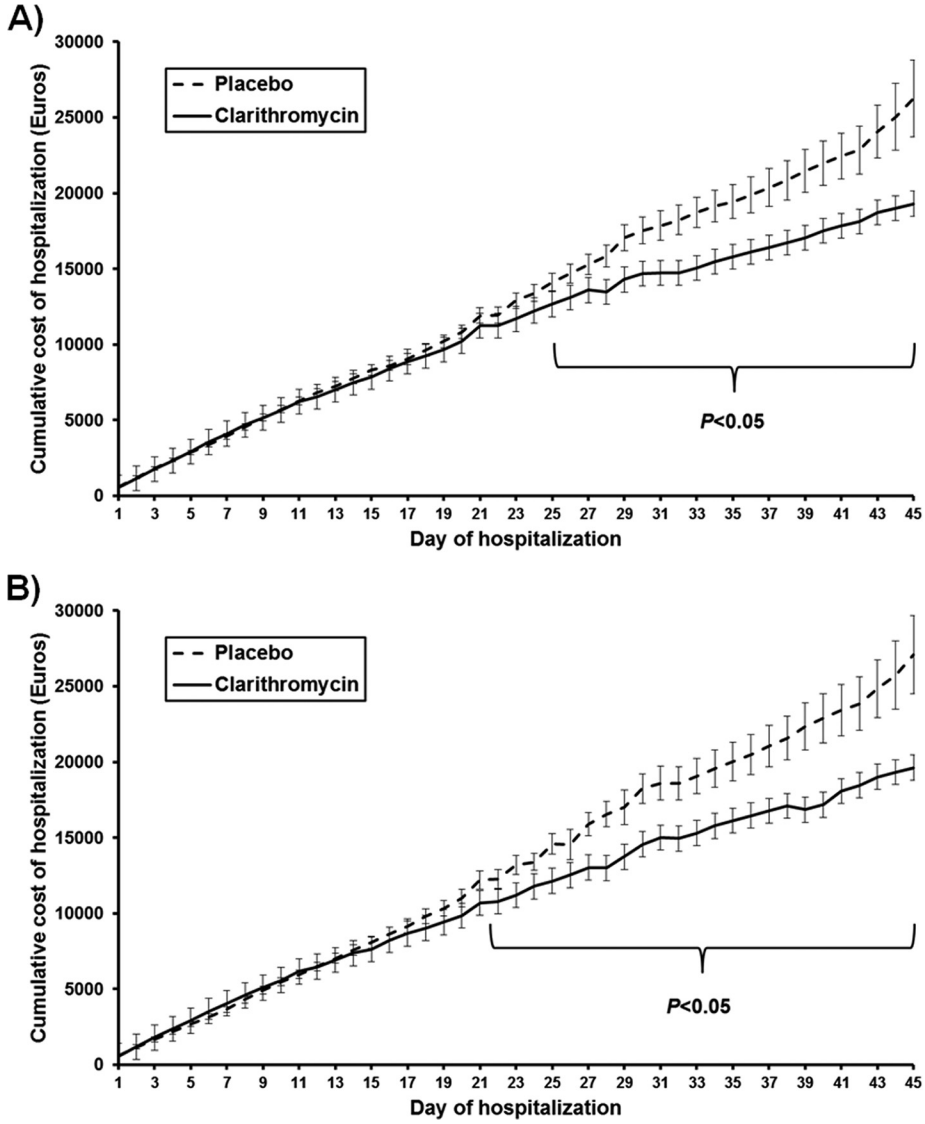

FIG 2 Comparative cumulative hospitalization cost. (A) Analysis included all 100 patients of the placebo group (dashed line) and all 100 patients of the clarithromycin group (solid line); cumulative cost refers to patients staying alive on the indicated day. (B) Analysis included 51 patients of the placebo group (dashed line) and 62 patients of the clarithromycin group (solid line) who survived until day 45. The cost was calculated by investigators who were blind to the allocated treatment. The time points at which statistically significant differences ($P < 0.05$) were achieved between the two arms are indicated.

met the primary endpoint, hemodynamic instability on day 7; the respective rate for the monotherapy arm was 41.2% ($P = 0.070$). A big gap between the two groups was found for the secondary endpoint, hospital readmission on day 30; the values were 3.1% and 7.9%, respectively ($P = 0.010$). Both our results (5, 6) and those of the recent CAP trial (8) confirm retrospective reports that addition of a macrolide offers survival benefit in patients with CAP (9).

TABLE 1 Cost-related characteristics of hospitalization for patients who survived after day 28[a]

Parameter	Value for patients receiving:		*P* value
	Placebo	Clarithromycin	
Days under mechanical ventilation [median (range)]	16 (1–38)	12 (2–40)	0.115
Total days of ICU stay [median (range)]	29 (3–161)	32 (3–179)	0.410
Total days of hospital stay [median (range)]	41 (3–289)	48 (3–283)	0.531
Discharged alive from the ICU [no. (%)]	53 (73.6)	55 (79.7)	0.431
Transferred to the general ward and discharged alive [no. (%)]	38 (52.8)	53 (76.8)	0.005

[a] The analysis comprised 72 patients allocated to placebo treatment and 69 patients allocated to clarithromycin treatment and who were alive on day 28.

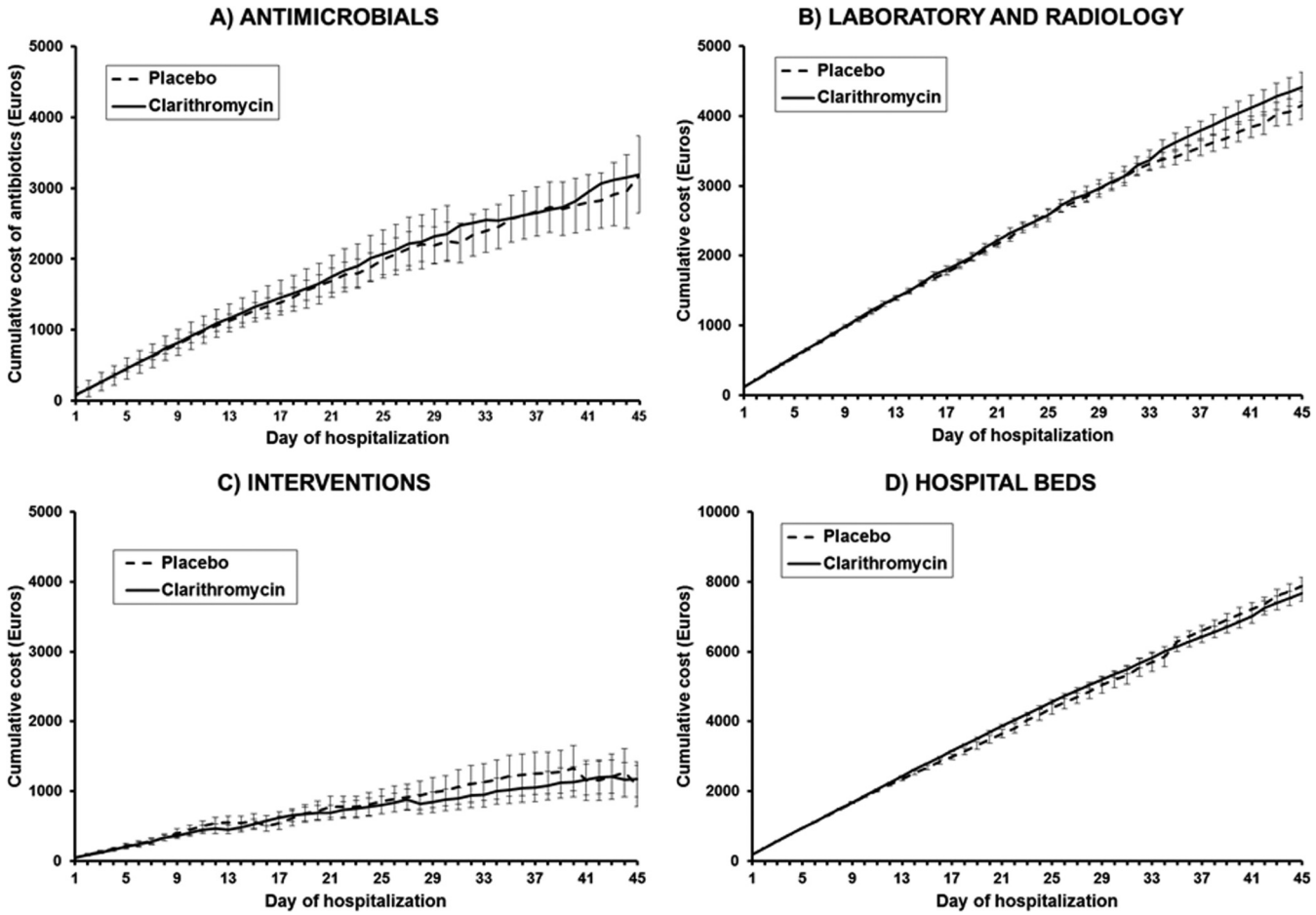

FIG 3 Comparative cumulative hospitalization cost by category: antimicrobials (A), laboratory and radiology examinations (B), interventions and surgical operations (C), and hospital beds (D). The analysis included all 100 patients of the placebo group (dashed line) and all 100 patients of the clarithromycin group (solid line); cumulative cost refers to patients staying alive on the indicated day. The cost was calculated by investigators who were blind to the allocated treatment.

The financial crisis has hit the southern countries of the European continent hard, putting in danger even the more prosperous nations of northern Europe (10). As a consequence, reductions of expenditure for health care may have a negative impact on the number of available ICU beds and available resources for the treatment of severely ill patients. The increasing number of hospitalizations for sepsis generates the need for more ICU beds and consequently increased health care costs, which results in a disequilibrium between available and required health care resources (2, 11).

The benefit of clarithromycin adjunctive treatment in sepsis extends beyond mortality; at an exchange of €20 Euros, there is almost €7,000 savings per patient after 45 days. These savings are attributed to the beneficial clinical effect of clarithromycin treatment, mainly alive discharges from the hospital. Our analysis disclosed that savings were associated with the discontinuation of expensive supportive treatments, such as parenteral nutrition and human albumin solutions.

A major strength of this study is that it used real counting of the amounts of utilized drugs, diagnostics, and interventions. In many studies, these estimates are indirect. For instance, in a study on the cost-effectiveness of albumin in severe sepsis and septic shock (12), cost was estimated based on the corresponding diagnosis-related group costs plus the additional daily fixed price for ICU stays. In a meta-analysis of studies with intravenous immunoglobulin for severe sepsis and septic shock, a decision model was developed to estimate the cost-effectiveness of the intervention (13); in another meta-analysis of nine randomized clinical trials (RCTs) with various dosing regimens of M-enriched immunoglobulin (14), the cost-effectiveness analysis was based on mean daily costs derived from a previous study of severe sepsis. After the publication of the PROWESS study, several studies were conducted on the cost-effectiveness of drotrecogin-alpha in severe sepsis; all of them supplemented the clinical data from the original study with local financial data from the United States (15), Canada (16), Germany (17), and the United Kingdom (18, 19). The present study avoids such systemic bias.

The presented results merit careful consideration for a number of reasons. First, there is the remarkable and significant long-term mortality benefit, which is of clinical relevance. Second, the considerable cost benefit of the intervention is important in view of the rising costs of hospital care. Third, the observation that survival benefit is sustained and even clearer beyond 28 days is highly

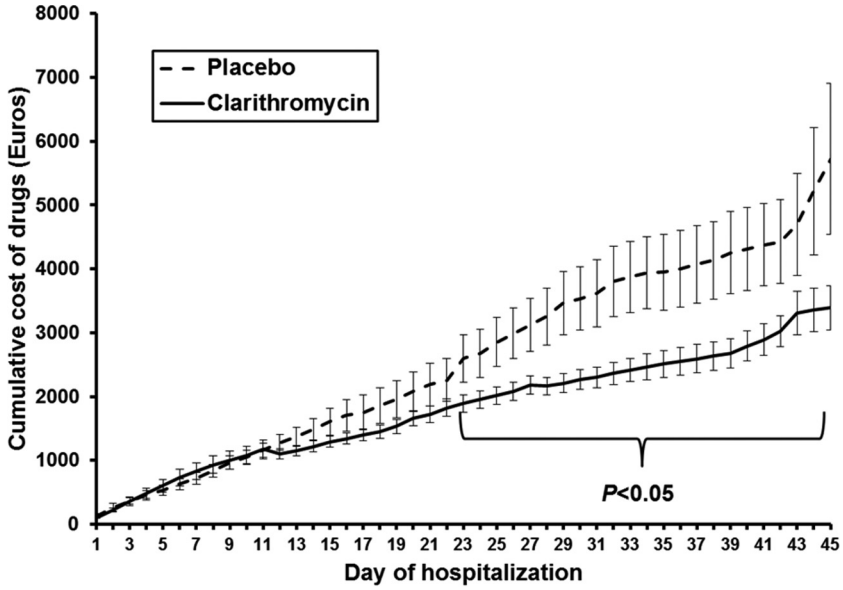

FIG 4 Cumulative cost of drugs other than antimicrobials. The analysis included all 100 patients of the placebo group (dashed line) and all 100 patients of the clarithromycin group (solid line); cumulative cost refers to patients staying alive on the indicated day. The cost was calculated by investigators who were blind to the allocated treatment. The time points at which statistically significant differences ($P < 0.05$) were achieved between the two arms are indicated.

relevant for other studies from the past and the future. Finally, no adverse events have been attributed to this intervention (5, 6), rendering intravenous clarithromycin an indispensable adjunctive tool for severe infections in light of the difficult financial situation of our times.

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The other authors have no conflict of interest to declare.

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