Clinical factors affecting costs in patients receiving systemic antifungal therapy in intensive care units in Greece: Results from the ESTIMATOR study

A. Armaganidis1 | S. Nanas2 | E. Antoniadou3 | K. Mandragos4 | K. Liakou5 | A. Koutsoukou6 | G. Baltopoulos7 | G. Nakos8 | A. Kounougeri9 | K. Ganas10 | A. Prekates11 | M. Kompoti12 | D. Georgopoulos13 | I. Pneumatikos14 | E. Zakynthinos15

1Second Critical Care Department, ATTIKON University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece
2First Critical Care Department, General Hospital of Athens “Evangelismos”, National and Kapodistrian University of Athens Medical School, Athens, Greece
3Intensive Care Unit, “G. Gennimatas” General Hospital, Thessaloniki, Greece
4Intensive Care Unit, “Korgialenio Benakio” Red Cross General Hospital, Athens, Greece
5Medical Department, Astellas Pharma, Athens, Greece
6Intensive Care Unit, 1st Department of Respiratory Diseases, Sotiria Chest Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece
7Athens University Faculty of Nursing, ICU “Agioi Anargyroi” Hospital of Kifissia, Athens, Greece
8Intensive Care Unit, University Hospital of Ioannina, Ioannina, Greece
9Intensive Care Unit, Konstantopoulio General Hospital “Agia Olga”, Athens, Greece
10Intensive Care Unit, General Hospital of Nikaia “Agios Panteleimonas”, Piraeus, Greece
11Intensive Care Unit, Tzaneio General Hospital, Piraeus, Greece
12Intensive Care Unit, General Hospital of Eleusis “Thrassion”, Athens, Greece
13Intensive Care Unit, University Hospital of Heraklion, Crete, Greece
14Department of Intensive Care Medicine, University Hospital of Alexandroupolis, Alexandroupoli, Greece
15Department of Critical Care, University Hospital of Larissa, Larissa, Greece

Summary
Invasive fungal infections are common in intensive care units (ICUs) but there is a great variability in factors affecting costs of different antifungal treatment strategies in clinical practice. To determine factors affecting treatment cost in adult ICU patients with or without documented invasive fungal infection receiving systemic antifungal therapy (SAT) we have performed a prospective, multicentre, observational study enrolling patients receiving SAT in participating ICUs in Greece. During the study period, 155 patients received SAT at 14 participating ICUs: 37 (23.9%) for proven fungal infection before treatment began, 10 (6.5%) prophylactically, 77 (49.7%) empirically and 31 (20.0%) preemptively; 66 patients receiving early SAT (55.9%) were subsequently confirmed to have proven infection with Candida spp. (eight while on treatment). The most frequently used antifungal drugs were echinocandins (89/155; 57.4%), fluconazole (31/155; 20%) and itraconazole (20/155; 12.9%). Mean total cost per patient by
Candida bloodstream infections (BSIs) are increasingly common worldwide in intensive care units (ICUs) and are the third most common cause of nosocomial BSIs among critically-ill ICU patients. Although culture-directed (proven, defined as patients with a diagnostic confirmation of a fungal infection) antifungal therapy provides specific pathogen and susceptibility results for targeted therapy, the wait for a positive result is considered unsatisfactory because of its association with high crude mortality rates and substantial excess costs. To improve outcomes, early antifungal intervention strategies are increasingly being considered. Such strategies include prophylaxis (defined as treatment to prevent fungal infections in high-risk patients), preemptive (defined as initiation of antifungal treatment in patients suspected of a fungal infection but without the diagnostic confirmation of fungal infection), and empiric therapy (defined as antifungal treatment given to patients with fever of unknown origin, which was not responding to broad spectrum antibacterial therapy).

Defining the patient populations that would benefit from early antifungal treatment remains a challenge. Colonisation with Candida spp. precedes infection and, in conjunction with other known risks factors, may be an early predictor of candidaemia. In practice, in an attempt to decrease Candida-related morbidity and mortality, an increasing number of patients in ICUs without documented candidaemia receive early antifungal therapy based on the presence of specific risk factors.

The identification of appropriate antifungal therapy for patients in ICUs with sepsis and Candida colonisation also remains a challenge. Studies have shown that inappropriate antifungal treatment (e.g. resistance to the antifungal agent, inadequate drug dosage or delayed therapy) is related to worse clinical outcomes, increased length of stay (LOS) and increased associated costs compared with appropriate treatment. In a cost-containment environment, clinicians are expected to choose the optimal strategy to provide appropriate antifungal therapy while controlling costs. However, to our knowledge, there is limited information on the cost of antifungal therapy for proven candidiasis compared with cost of early antifungal therapy for patients without documented candidaemia. Data regarding physicians’ choices for specific antifungal therapy and related costs in Greece are also lacking.

We conducted this study to assess the impact on overall hospital costs of different strategies for systemic antifungal therapy (SAT) in patients in Greek ICUs, and to identify clinical factors that may affect these costs.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective, multicentre, non-interventional study (NIS) of patients receiving SAT was carried out in compliance with the protocol, the principles of the Helsinki Declaration (version October 1996), the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Harmonised Tripartite Guideline for Good Clinical Practice, and the applicable legislation on NISs. The study protocol was approved by the scientific committees of the participating hospitals, and written informed consent was obtained from the patients or the nearest relative. Recruitment was carried out between July 2011 and February 2012 with a target sample size of 160 patients receiving SAT in 14 Greek ICUs. Additional information about the study design, data collection and statistical analyses are provided in the Appendix S1.

2.2 | Outcomes

The primary study objectives were to provide an estimate of the total ICU treatment cost for patients receiving SAT, from the Greek social insurance perspective, and to describe the different therapeutic approaches of antifungal treatment and their association with treatment effectiveness. The present manuscript summarises the total ICU treatment cost and the clinical factors that directly affect this cost.
2.3 | Patients and treatment

Inclusion criteria were as follows: (i) provision of informed consent, prior to any study specific procedure; (ii) age ≥18 years at the time of consenting; (iii) Acute Physiology and Chronic Health Evaluation (APACHE) score ≥15; and (iv) the patient was already receiving SAT in the ICU for no more than 1 day. Pregnant women or women who were breast-feeding were excluded from the study.

Antifungal treatment was administered to patients by the attending clinician according to the approved drug labels and usual clinical practice in each ICU. The treatment strategy for SAT (prophylaxis, preemptive, empiric, proven infection before treatment, as defined previously) was classified by the treating clinician. Treatment failure was determined by the investigators based on clinical failure, resistance or intolerance to the selected antifungal agent.

2.4 | Data collection

The study data were recorded on an electronic data capture system for subsequent analysis. The following data were collected about the patient: demographics, patient’s origin, type of admission, underlying conditions, pre-disposing risk factors and disease severity (APACHE II and Sepsis-related Organ Failure Assessment [SOFA] score). The following information was collected regarding infections, SAT and outcomes: infection during study, Candida score, antifungal agent administered, type of treatment (prophylaxis, preemptive, empirical, proven), total duration of SAT, LOS in the ICU (from ICU admission) and survival status, routine laboratory tests, radiology or other interventions, fungal species epidemiology and susceptibility tests. Costs were obtained from the latest available tariffs of antifungal agent costs, diagnostic tests, and fixed reimbursement rate (direct medical costs only) for critically-ill patients in Greek ICUs. The reference year for all costs was 2012, which describes the fixed reimbursement rate tariff of the payer for their time in ICU (Greek sickness “EOPPY” and the official price bulletin used to calculate costs). In this respect, discounting and sensitivity analysis are not applicable since the costs refer only to the reference year. Therefore, since no discounting of costs was performed, patients treated in 2011 were adapted to 2012 costs.

2.5 | Statistical analysis

Sample size calculation was based on a one-sample mean test (two-sided at 5% significance level with 90% power), where a range of possible values for the mean total cost under H₀ (€10 000–€40 000) and the mean total cost under H₁ (€15 000–€50 000) was assessed. Standard deviation (SD) ranged from €15 000–€37 000. The maximum required sample size of the tested scenarios was 152 patients. Since this was an ICU study where the dropout rate was expected to be minimal, there was a minor adjustment to the sample size for drop outs to 160 patients.

Prior to the application of the multivariate analyses, specific univariate analyses were performed with the Kruskal–Wallis test (the non-categorical factors were categorised based on their distributional profile) to identify important bivariate correlations. Data were analysed using a step-wise multiple regression model including, at the beginning, all factors found to be statistically significantly (at the 5% level of significance) correlated with total cost (cost of LOS was excluded since it was the major cost component) in the univariate analysis.

Statistical significance for the factors remaining in the model was declared at the 10% level using backward selection. Several adjustment factors were included in the model regardless of statistical significance (APACHE II score, patient’s origin, first line SAT, survival status at the end of the ICU stay and study site). All analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patients

In total, 155 patients receiving SAT as instructed by the lead physician were included in the study (Table 1). In 37 (23.9%) cases, SAT was initiated as targeted therapy for proven candidaemia, while in 118 (76.1%) cases early antifungal treatment was initiated. Of these 118 patients, 66 (55.9%) were subsequently confirmed to have candidaemia 3.6±2.2 days after treatment initiation. In these 118 patients, the Candida score had a positive predictive value of 65.4% and a negative predictive value of 43.9% (using 2.5 as a cut-off).

All patients had at least two predisposing factors on initiation of antifungal therapy, with the majority (106, 68.4%) having six or more. The most common pre-disposing risk factors were systemic antibiotic therapy (98.8%), presence of central venous catheter (CVC) (93.6%), sepsis (82.0%), fever (78.0%), bacteraemia (37.4%) and renal dysfunction (52.2%).

3.2 | Antifungal treatment

Total ICU patients days studied were 5766 of which 1891 (32.8%) were days when antifungal therapy was administered. Antifungal strategy, day of treatment initiation and duration of therapy, are shown in Table 2. The mean number of days for antifungal treatment to be initiated was 12.9±22.4 days. In all strategies, the most frequently prescribed antifungal drugs were echinocandins (n=89; 57.4%), followed by fluconazole (n=31; 20%), itraconazole (n=20; 12.9%), liposomal amphotericin B (n=7; 4.5%), voriconazole (n=5; 3.2%) and amphotericin B (n=3; 2%). Initial antifungal treatment was modified in 13/155 (8.4%) patients due to resistance or clinical failure; these patients were initially treated with fluconazole or itraconazole (n=7), an echinocandin (n=3) or liposomal amphotericin B (n=3). Seven patients had a de-escalation of antifungal therapy (treatment initiation before switching to a more narrow spectrum drug) governed by subsequent susceptibility results.

3.3 | Outcomes

Table 3 summarises the outcomes for the 155 patients included in the analysis. Mean LOS in the ICU was 37.2±33.8 days, mean duration of antifungal therapy was 12.2±9.0 days and 77 patients (49.7%) died. Patients who switched antifungal treatment during the study had a significantly
longer LOS in the ICU (53.8±36.1 vs 35.5±33.8 days; \( P = .0204 \)) and duration of antifungal therapy (27.3±13.7 vs 13.1±8.6 days; \( P \leq .0001 \)) compared with those without a treatment switch, but no significant difference in mortality rate was observed (38.5% vs 51.1%; \( P = .5633 \)).

### 3.4 | Costs

Mean total cost per patient was €22 013 (95% CI: €19 553-€24 472) with SD €15 500 (95% CI: €13 945-€17 447). LOS was the major cost component with a mean value of €17 787 (Figure 1). Cost per patient by type of treatment is shown in Table 4. For the 155 patients in this study, associated antifungal drug costs accounted for €0.57 million (16.7%) of the €3.4 million total costs.

In the univariate analysis there was no statistically significant difference in cost between different strategies, although prophylaxis was associated with a €7000 decrease in total cost (mean €15 054). Additionally, there were no statistically significant differences among the different strategies in daily total and antifungal drug costs. Total cost was significantly correlated with treatment switch (\( P = .0048 \)), with the mean cost for patients who received only one drug €20 790 (95% CI: €18 240-€23 340) vs €33 540 (95% CI: €22 730-€44 350) for those who switched.

Multivariate analysis revealed that factors associated with increased costs for patients receiving SAT were: switching antifungal agents (additional €11 128; \( P = .0001 \)), presence of fever (additional €418; \( P = .0487 \)), and documentation of candidaemia (additional €359; \( P = .0471 \); Table 5). The effect of the different study drugs on cost is shown in Figure 2.

### 4 | DISCUSSION

The most important finding from our study was that the administration of an antifungal drug was not a substantial component of total costs.
hospital costs. Other important factors associated with increased cost in critically ill patients receiving SAT were treatment failure requiring switching to another antifungal agent, ICU-LOS before starting antifungal treatment, presence of fever, and proven candidaemia.

Only 8.4% of patients required a switch in antifungal treatment when susceptibility results were available. Nevertheless, this group substantially contributed to total cost (€436 000 out of the €3.4 million [12.8%]). Patients with therapy changes (excluding de-escalation) had significantly longer ICU-LOS and duration of antifungal therapy as well as total cost compared with those without therapy changes. The significance of an increased cost of initial inappropriate SAT choice should be interpreted with caution due to the small percentage of patients that had ineffective therapy. However, when the effect of therapy switch on cost (€12 750) was adjusted in the multivariate model, it remained high (€11 128). Our findings are consistent with other reports that inappropriate antifungal therapy is related to worse clinical outcomes and to an escalation in cost due to prolonged LOS. Others showed that inappropriate antifungal treatment prolonged LOS by 8 days, and contributed an extra $13 000 to total costs and increased mortality (28.8% vs 0%). Therefore choosing an appropriate first-line antifungal agent is crucial for better outcomes, reduced LOS and lower hospital cost of managing candidiasis.

An important distinction from our study is that the duration of previous ICU-LOS is an important contributor of total LOS and overall cost. Also, antifungal therapy was started a mean of 12.9±22.4 days after ICU admission, suggesting that earlier administration of antifungal therapy may be appropriate, especially in patients with a high APACHE II score. In accordance with our findings, another study found that each additional day lag prior to initiating SAT therapy for aspergillosis was associated with 1.28 days longer LOS and a 4% increase in total cost. Others have shown the mean pre-ICU-LOS may be a significant risk factor for the development of candidaemia and subsequent increase to the costs of care. These findings support the need for more rapid diagnostic methods for IC in ICU patients and earlier initiation of antifungal therapy. In critically ill patients, there should always be a high degree of suspicion that IC may occur.

In our study, the APACHE II score used as an adjustment covariate had a negative association with total cost indicating that severely ill patients with a high APACHE II score had higher early mortality and lower LOS and ICU care, which decreased total cost. Baddley et al., [26] which excluded patients with early mortality, found that severity of illness (extreme vs major) was associated with a 57% increase in

TABLE 3  Clinical outcomes

| Patients | N | 155 | 155 |
|------------------|---|-----|-----|
| LOS before initiation of antifungal treatment | Mean (SD) | 12.9 (22.4) | 15.4 (32.6) | 11.6 (14.9) | 12.7 (13.8) | 11.0 (15.6) |
| Total LOS (days) | Mean (SD) | 37.2 (33.8) | 36.7 (44.5) | 37.4 (27.0) | 33.6 (28.0) | 39.5 (26.4) |
| 1st line SAT duration | Mean (SD) | 12.2 (9.0) | 10.2 (6.1) | 13.2 (10.1) | 11.7 (8.3) | 14.1 (10.9) |
| ICU mortality | n (%) | 77 (49.7) | 30 (57.7) | 47 (45.6) | 21 (56.8) | 26 (39.4) |

ICU, intensive care unit; LOS, length of stay; SAT, systemic antifungal treatment; SD, standard deviation.

TABLE 4  Mean (SD) cost (€) per patient by type of treatment

| Type of treatment | Total | Prophylaxis | Pre-emptive | Empiric | Proven |
|-------------------|-------|------------|------------|---------|-------|
| N | 155 | 10 | 31 | 77 | 37 |
| Total cost | 22 013 (15 500) | 15 054 (10 884) | 22 184 (18 776) | 23 594 (14 943) | 20 458 (14 546) |
| Cost of LOS from ICU admission | 17 787 (13 892) | 12 025 (9 225) | 19 350 (18 610) | 18 595 (13 169) | 16 354 (11 609) |
| Cost of SAT | 3680 (3372) | 2586 (2411) | 2411 (2184) | 4426 (3389) | 3486 (4003) |
| Cost of tests and investigations | 545 (371) | 444 (205) | 423 (334) | 572 (384) | 618 (388) |
| Cost of LOS from start of SAT | 10 949 (9234) | 6965 (6842) | 13 639 (13 608) | 11 138 (7569) | 9377 (8033) |
| Daily cost of SAT | 130 (113) | 149 (146) | 129 (127) | 140 (113) | 107 (88) |

ICU, intensive care unit; LOS, length of stay; SAT, systemic antifungal treatment; SD, standard deviation.
Numerically more patients died in the non-switching group, which could account for the shorter LOS and treatment duration. Others reported that a high APACHE II score contributed to total cost and Candida infections were associated with a cost of $230/ICU/patient-day and an increased ICU-LOS of 8 days. Thus, the mortality adjusted APACHE II effect analysis showed that an increased score was a significant contributor of total cost, as might be expected, since more severely ill patients require prolonged or specific care.

It is well documented that fever is associated with illness severity and mortality. Indeed, patients with febrile septic shock who receive external cooling to achieve normothermia have significantly decreased vasopressor dose requirements after 12 h of treatment ($P<.001$) and lower 14-day mortality ($P=.013$) and shock reversal is also more common ($P=.021$) vs those whose fever is untreated, inferring that persistent fever is related to increased cost due to increased duration of shock.

The mean total cost in our study population receiving antifungal therapy was €22 013 (SD 15 500). Our findings in patients receiving antifungal treatment are similar to other studies, which reported costs associated with candidaemia of between $25 000 and $55 000. We identified that candidaemia may affect total costs for patients receiving antifungal therapy. This may have several explanations including the need for prolonged antifungal therapy until resolution of candidaemia (mean duration of antifungal therapy in proven before treatment vs unproven candidaemia was 13.2±10.1 days vs 10.2±6.1 days, respectively). Furthermore, proven candidaemia was associated with a one day additional stay in the ICU. Patients with proven candidaemia have increased ICU stay, are more severely ill and require additional prolonged therapies. Candidaemia increases the cost of care in patients with septic shock, with attributable costs of candidaemia in patients with severe sepsis of €7 713,
representing an increased cost of 19.4% compared with septic patients without candidaemia. This difference is mainly governed by the higher costs of sepsis therapy (antimicrobials and catecholamine administration), significantly more days of sepsis therapy (28 days vs 16.4 days), more blood disorder therapy and a trend to more days of renal replacement therapy in the *Candida* group.

Limitations of our study include that the study was not a randomised clinical trial aiming to draw causal relationships. However, it is an observational real life study reflecting clinical practice, the value of each therapeutic approach and related total costs. In such a real life study with a subjectively selected group of ICU patients, the observed values of actual and predicted mortality, as well as the accuracy of the *Candida* score cannot be compared with the results of large epidemiological studies. Furthermore, because all participating ICUs were in Greece, the effect of SAT on costs may not reflect clinical practice in other countries and inter-country differences in ICUs. Therefore several other local factors that may influence LOS and costs in different ICUs cannot be excluded.

In conclusion, we found that the most important clinical factors affecting cost were switching treatment (due to failure of initial treatment), presence of fever, diagnosis of candidaemia, previous antifungal use and ICU-LOS. Accordingly, strategies that decrease ICU-LOS and improve the earlier selection of appropriate antifungal agents in antifungal strategies should be prioritised in order to decrease the costs for patients receiving SAT. In accordance with the literature, these findings highlight the importance of awareness of potential candidiasis, timely diagnosis and appropriate early treatment of ICU patients in order to improve patient outcomes while containing direct medical costs. Further research including cost effectiveness and budget impact analysis is warranted.

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**CONFLICT OF INTEREST**

K Liakou is an employee of Astellas Pharma AE and participated in study design. Dr. Nakos, Dr. Kounougeri, Dr. Nanas, and Dr. Ganas have nothing to disclose. Prof. Armaganidis reports personal fees from Astellas Pharma AE for lectures, outside the submitted work; Dr. Antoniadou reports personal fees from Astellas Pharma AE, outside the submitted work (honorarium for lecture). Dr. Mandragos reports personal fees from Astellas Pharma AE, outside the submitted work (honoraria for lecture). Dr. Koutsoukou reports personal fees from Astellas Pharma AE (honorarium for lecture), outside the submitted work. Dr. Baltopoulos reports personal fees from Astellas Pharma AE (honorarium), outside the submitted work; Dr. Prekates reports personal fees from Astellas Pharma AE, outside the submitted work (honoraria for lecture). Dr. Kompotis reports personal fees (investigator fees) from Astellas Pharma AE, during the conduct of the study; Dr. Georgopoulos reports personal fees from Astellas Pharma AE, outside the submitted work. Dr. Zakythinos reports personal fees from Astellas Pharma AE, outside the submitted work (honoraria for lecture).

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.