Health Care Costs of Target Attainment for Beta-Lactam Antibiotics in Critically Ill Patients: A Retrospective Analysis of the EXPAT Study

Tim M. J. Ewoldt, MD,* Alan Abdulla, PharmD,† Nicole G. M. Hunfeld, PharmD,*†
Anouk E. Muller, MD,‡§ Diederik Gommers, MD,* Suzanne Polinder, PhD,¶ Birgit C. P. Koch, PharmD,†
and Henrik Endeman, MD*

Background: Optimizing beta-lactam antibiotic treatment is a promising method to reduce the length of intensive care unit (ICU) stay and therefore reduce ICU costs. We used data from the EXPAT trial to determine whether beta-lactam antibiotic target attainment is a cost determinant in the ICU.

Methods: Patients included in the EXPAT trial were divided into target attainment and target nonattainment based on serum antibiotic levels. All hospital costs were extracted from the hospital administration system and categorized.

Results: In total, 79 patients were included in the analysis. Target attainment showed a trend toward higher total ICU costs (€44,600 versus €28,200, $P = 0.103$). This trend disappeared when correcting for ICU length of stay (€2680 versus €2700). Renal replacement therapy was the most important cost driver.

Conclusions: Target attainment for beta-lactam antibiotics shows a trend toward higher total costs in ICU patients, which can be attributed to the high costs of a long stay in the ICU and renal replacement therapy.

Key Words: beta-lactam, antibiotic, microcost, critically ill, target attainment

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levels. All hospital costs were extracted from the hospital administration system and categorized.

BACKGROUND

Optimizing antibiotic treatment is a promising method to reduce the length of intensive care unit (ICU) stay and therefore reduce ICU costs.[1,2] During ICU stay, nearly 70% of ICU patients receive antibiotic treatment.[3] When treating serious infections with antibiotics, 3 major pillars need to be considered: rapid initiation of therapy, proper antibiotic exposure, and choice of an appropriate antibiotic for the likely pathogen.[4,5] Reaching the target attainment for antibiotics is essential for therapeutic success.[6,7] In critically ill patients, target attainment for widely used beta-lactam antibiotics can be as low as 40%–60%.[8,9] Moreover, improper antibiotic exposure and antimicrobial resistance result in longer lengths of stay (LOSs).[10]

Individualizing treatment by using therapeutic drug monitoring (TDM) has been proposed to optimize the dosing of selected antibiotics.[6] Individualized dosing increases target attainment. The benefits of TDM have been established for vancomycin and aminoglycosides.[11,12] However, these antibiotics have a narrower therapeutic index, and TDM is primarily used to prevent toxicity. TDM of frequently prescribed beta-lactam antibiotics is commonly proposed to increase efficacy while preventing toxicity.[4]

Few studies have examined the effects of target attainment on ICU costs. To explore this relationship, we evaluated data from EXPAT trial.[8] In this article, we investigated the impact of beta-lactam antibiotic target attainment on

the costs of intensive care and identified factors that may have contributed to any differences in costs.

MATERIALS AND METHODS

Primary Aim

The primary aim of this study was to describe the difference in total ICU costs between patients with beta-lactam target attainment and those with target nonattainment.

Secondary Aims

The secondary aim was to describe the difference in daily ICU costs between patients with beta-lactam target attainment and those with target nonattainment, as well as to identify cost determinants.

Population

We conducted our analyses using data from the EXPAT trial, a prospective, observational pharmacokinetic/pharmacodynamic (PK/PD) study including 2 centers.[8] In the current study, we only included patients admitted to the Erasmus University Medical Center (Erasmus MC) study site. We assessed patients admitted to the ICU between January 2016 and June 2017 and those treated with beta-lactam antibiotics.

Target attainment was defined as reaching the pharmacodynamic target (PDT) for the antibiotic. The PDT of these antibiotics was defined as an unbound plasma concentration above at least one time the minimal inhibitory concentration (MIC) for 100% of the dosing interval ($100\%fT > 1MIC$). MIC is the minimum concentration required to prevent the visible growth of a bacterium in vitro. Patients were divided into 2 study groups based on blood sampling: target attainment and target nonattainment.

Data Extraction

Patient characteristics were extracted from the electronic health records on the first day of antibiotic administration in the EXPAT trial. ICU costs between January 2016 and June 2017 were extracted from the hospital administration system. All declared hospital costs during ICU admission of included patients were collected and categorized into 10 categories: specialist consultation, renal replacement therapy (RRT), bedside procedures, laboratory diagnostics, microbiology, surgery, pathology, radiology, transfusion (blood-derived products), and fixed ICU admission costs.

Economic Evaluation

Cost analyses were performed from a health care perspective using the Dutch guidelines for cost studies.[13] If treatment costs were unavailable, the costs of the most fitting diagnosis–treatment combination were used as defined by the Dutch Health care Authority (Nederlandse Zorgautoriteit).[14]

All costs are described as the total costs during ICU admission and daily costs. Daily costs were calculated by dividing the total costs by ICU LOS. ICU costs consist of variable and fixed costs. Fixed ICU admission costs were the declared daily

costs of admission and included aggregated costs of staff, maintenance and acquisition of devices, hospital space, and preparation of medication. Variable costs were defined as total costs minus the fixed ICU admission costs. Costs that were not declared in 2016 were adjusted to the standard inflation defined by the Dutch Central Bureau of Statistics (CBS) to match the costs in 2016.[15]

Statistical Analysis

Patient characteristics are expressed as mean values with SDs for normally distributed data; alternatively, they are expressed as median values with interquartile ranges (IQRs). Categorical data are expressed as counts with percentages. Normality was tested using the Shapiro–Wilk test. Differences in patient characteristics were calculated with an independent 2-tailed Student *t* test or Mann–Whitney *U* test, as appropriate. Categorical differences were tested using the χ^2 or Fisher exact test, as appropriate.

For our primary aim, we assessed differences between costs using the Mann–Whitney *U* test in addition to a 2-tailed *t* test with bootstrapping (×1000). As costs generally tend to present a right-skewed distribution, they are expressed in Euro (€) as median with IQR.

For our secondary aims, we explored whether beta-lactam target attainment is a cost determinant. We performed a general linear regression analysis of the total costs. Both patients with target attainment and target nonattainment were included in this analysis. For the regression model, we selected 4 relevant variables for costs: sex, age, Sequential Organ Failure Assessment (SOFA) score, and RRT. Target attainment was included as the most important factor in the model. Furthermore, we analyzed a model without RRT because RRT strongly affects both reaching the target attainment and LOS. Effects were reported as mean differences or odds ratios (ORs) with corresponding confidence intervals (CIs). McFadden R^2 was used to determine the proportion of the variance in the total cost predicted by the model. Analysis of variance was used to calculate statistical differences.

All analyses were performed with "R" version 3.6.3 (2020, Vienna, Austria). In all analyses, a *P* value below 0.05 was considered significant, unless stated otherwise.

RESULTS

Patient Characteristics

In total, 79 patients were included in the analysis. Based on serum antibiotic analyses, 50 patients were allocated to antibiotic target attainment and 29 to antibiotic target nonattainment. The population demonstrating target attainment presented a higher age, higher SOFA score at the initiation of antibiotic therapy, and increased RRT (Table 1). Although not significant, there was an important difference in ICU LOS, which was 15 days (IQR 7–28) in patients with target attainment when compared with 7 days (IQR 5–18) in those with target nonattainment. Although not significant, but important, mortality at 30 days was higher in patients with target attainment (24%) than in those with target nonattainment (13.8%).

TABLE 1. Baseline Characteristics and Clinical Outcomes

	Target Attainment (N = 50)	Target Nonattainment (N = 29)	*P*
Age	63.0 [56.3–68.8]	58.0 [51.0–64.0]	**0.047**†
Male	28 (56.0%)	24 (82.8%)	**0.026**‡
BMI (kg/m^2)	26.0 [23.6–28.9]	24.9 [21.8–26.3]	0.127†
Target antibiotic			
Trough concentration (mg/L)			**0.001**‡
Cefotaxim	12 (24.0%)	16 (55.2%)	
	18.0 [10.7–27.8]	2.13 [1.10–3.75]	
Ceftazidim	4 (8.0%)	0 (0%)	
	72.2 [50.9–104]		
Ceftriaxon	15 (30.0%)	1 (3.4%)	
	5.55 [2.73–9.56]	1.94 [1.94–1.94]	
Cefuroxime	0 (0%)	2 (6.9%)	
		5.22 [4.06–6.38]	
Augmentin	4 (8.0%)	4 (13.8%)	
	30.8 [17.9–54.5]	3.78 [3.20–7.12]	
Meropenem	15 (30.0%)	6 (20.7%)	
	12.2 [3.83–37.0]	1.36 [0.966–1.52]	
Sepsis at admission	10 (20.0%)	2 (6.9%)	0.116‡
APACHE Score	22.2 (6.24)	20.8 (5.95)	0.331*
SOFA score	8.70 (3.48)	7.00 (3.47)	**0.040***
Albumin (g/L)	23.5 [20.3–29.0]	31.0 [25.0–35.0]	**0.009**†
Serum creatinine (umol/L)	118 [70.3–158]	77.0 [60.0–100]	**0.019**†
Leukocyte count (×10^9/L)	12.3 [7.63–18.1]	16.3 [11.1–18.0]	0.106†
CRP (mg/L)	86.5 [47.5–221]	62.0 [10.0–144]	**0.038**†
Transfusion received	40 (80%)	15 (51.7%)	**0.011**‡
RRT	11 (22.0%)	1 (3.4%)	**0.047**‡
30-day mortality	12 (24.0%)	4 (13.8%)	0.386‡
ICU LOS	15.0 [7.00–28.0]	9.00 [5.00–18.0]	0.133†

Bold *P* values are significant (lower than 0.05).
*t test.
†Mann–Whitney *U* test.
‡Fisher exact test.
APACHE, Acute Physiology And Chronic Health Evaluation version 2; BMI, body mass index; CRP, C-reactive protein.

Hospital Costs

Fixed admission costs accounted for 60.1% of the total costs, leaving the variable costs at 39.9%. Target attainment, compared with target nonattainment, showed a trend toward higher total ICU costs (€44.600 and €28.200, $P = 0.103$) (Table 2). Furthermore, the same trend was observed in variable costs (€16.500 and €11.800, $P = 0.076$), RRT costs (€0 and €0, $P = 0.065$), and medical microbiology costs (€2.270 and €1.840, $P = 0.065$). Target attainment was significantly associated with the increased transfusion of blood product costs (€1.050 and €229, $P = 0.010$).

The RRT and pathology costs are described as €0, with an IQR of €0–€0. This can be explained by the fact that less than 25% of patients account for all costs in these categories. Total RRT costs for the patients who incurred these costs were €2500 (1610–5850) for target attainment when compared with €1270 (933–1610) for target nonattainment. Similarly, for total pathology costs, these numbers were €245 (66.6–834) for target attainment and 699 (328–703) for target nonattainment. Fixed

ICU costs varied marginally according to the need for extra-corporeal circulation and disease severity.

On presenting daily costs (Table 3), the aforementioned trends in total, microbiology, and variable costs were no longer observed. Costs associated with the transfusion of blood products were significantly higher in patients with target attainment (€90.60 and €12.70, $P = 0.023$), with a strong trend toward higher RRT costs in this patient category (0 and 0, $P = 0.063$). For patients who received RRT, the daily RRT costs were €90.1 (63.6–109) for those with target attainment when compared with €29.3 (24.9–33.8) for those with target nonattainment. The daily costs for pathology were €7.97 (2.85–39.6) for patients with target attainment when compared with €54.1 (39.2–117) for those with target nonattainment, on examining only those patients who incurred costs in this category.

Cost Determinants

Table 4 describes models 1 and 2. Model 1 shows that target attainment is not a determinant of cost (OR 1.05; CI

TABLE 2. Total ICU Costs Split by Cost Categories

Categories	Target Attainment (N = 50)		Target Nonattainment (N = 29)		P	
	Median	IQR1–IQR3	Median	IQR1–IQR3	Mann–Whitney *U* Test	Bootstrapped *t* test
Total	€44.600	22.100–70.900	€28.200	16.800–48.000	0.10	**0.05**
Variable	€16.500	8.640–28.900	€11.800	6.610–18.600	0.08	**0.04**
Fixed admission	€29.400	13.600–52.300	€19.600	8.310–34.600	0.23	0.06
Consultation	€1.340	549–3.220	€1.780	660–2.780	0.79	0.28
RRT	€0	0–0	€0	0–0	0.07	**<0.01**
Bedside procedures	€747	361–1.220	€722	143–1.110	0.55	0.18
Laboratory diagnostics	€2.600	1670–4.660	€1.830	947–2.870	0.09	**0.03**
Radiology	€993	476–2.010	€1.130	344–2.610	0.83	0.95
Transfusion	€1.050	459–4.650	€229	0–1.470	**0.01**	0.06
Microbiology	€2.270	856–5.690	€1.840	525–3.190	0.06	**<0.01**
Pathology	€0	0–0	€0	0–0	0.68	0.89
Surgery	€450	0–2.290	€346	0–1.260	0.58	0.74

0.90–1.23, $P = 0.54$). However, RRT during ICU admission was a clear predictor of cost (OR, 1.84; CI 1.50–2.27, $P = 0.001$). On omitting RRT from linear regression (model 2), target attainment was still not a predictor for total costs (OR 1.18 CI 0.98–1.42, $P = 0.09$). The omission of RRT resulted in a significantly worse prediction of total costs ($P < 0.001$).

Only RRT therapy during admission proved to be an independent cost determinant for high total ICU costs. Our most important factor, target attainment, was not a factor in both multivariate analyses.

DISCUSSION

Contrary to our hypothesis, we observed a trend toward higher total ICU costs when antibiotic target attainment was achieved. Costs for blood product transfusions were significantly higher in patients with target attainment. We observed

that these trends disappeared when correcting for the LOS, except for the aforementioned costs for transfusion and RRT. The latter is the most influential cost determinant, which mainly explains the differences in costs between the 2 groups.

To explain this paradoxical finding of higher ICU costs in patients with target attainment, we further analyzed both patient groups. There were some major patient differences between both groups, with the most relevant being ICU LOS, disease severity scores, RRT use, and the use of blood products. Target attainment seems to be a surrogate marker for patient illness because it relates to a decrease in renal function, greater ICU LOS, a higher illness severity score, and therefore an increased prevalence of multiple organ failure. These risk factors of target attainment have also been confirmed in previous research.[16–18] Logically, health care costs in this population are also expected to be higher because they need pronounced and prolonged ICU care. Bootstrapped

TABLE 3. Daily ICU Costs Split by Cost Category

Categories	Target Attainment (N = 50)		Target Nonattainment (N = 29)		P	
	Median	IQR1–IQR3	Median	IQR1–IQR3	Mann–Whitney *U* Test	Bootstrapped *t* test
Total	€2.680	2.420–3.290	€2.700	2.930–3.370	0.95	0.95
Variable	€1.080	889–1.630	€1.090	783–1.570	0.76	0.80
Fixed admission	€1.790	1700–1.880	€1.820	1.760–1.890	0.33	0.90
Consultation	€98.3	57–163	€111	68–242	0.42	0.25
RRT	€0	0–0	€0	0–0	0.06	**<0.01**
Bedside procedures	€48.9	19.1–98.1	€52.9	28.9–83.9	0.85	0.97
Laboratory diagnostics	€181	141–232	€164	134–217	0.38	0.66
Radiology	€93.2	33.4–167	€86.7	49.5–277	0.45	0.17
Transfusion	€90.6	14.4–208	€12.7	0–91.4	**0.02**	0.16
Microbiology	€149	85.3–223	€110	83.7–154	0.17	0.48
Pathology	€0	0–0	€0	0–0	0.79	0.80
Surgery	€29.2	0–124	€42.7	0–159	0.67	0.31

Bold *P* values are significant (lower than 0.05).

TABLE 4. Multivariate Linear Regression With Logarithmic Transformation on Total ICU Costs

Model 1	OR (95% CI)	*P*	Model 2	OR (95% CI)	*P*
Target attainment	1.05 (0.90–1.23)	0.54	Target attained	1.18 (0.98–1.42)	0.09
Female sex	0.93 (0.80–1.09)	0.39	Female sex	0.95 (0.79–1.14)	0.59
Age	1.00 (0.99–1.00)	0.46	Age	0.99 (0.99–1.00)	0.06
SOFA score	1.00 (0.98–1.02)	0.98	SOFA score	1.01 (0.98–1.03)	0.47
RRT	1.84 (1.50–2.27)	**<0.001**	McFadden R^2 = 0.10		
McFadden R^2 = 0.52					

Bold *P* values are significant (lower than 0.05).

t tests revealed distorted significance: a small number of outliers can easily lead to a low *P* value, such as in RRT and pathology costs.

Target attainment was not a significant cost driver for the total ICU costs in our analysis. On examining a model excluding RRT, target attainment was still not a predictor. In our model, the most important determinant of costs was RRT. This variable seemed to be solely responsible for explaining high costs, considering that most patients receiving RRT achieved target attainment. Moreover, on visually inspecting the data in Figure 1, no patient receiving RRT had a LOS of less than 20 days. In **Supplemental Digital Content 1** (see **Table**, http://links.lww.com/TDM/A490), we explored a statistical method to identify cost determinants that might not be clinically explained. In this analysis, RRT and blood product transfusions are both independent determinants of high costs. The trend toward significance (P = 0.126) of target attainment in the univariate analysis did not translate in the multivariate analysis. This can be explained by the aforementioned relationship between RRT and target attainment.

The ICU contributes to a major part of total hospital costs, with relatively high costs per admission day when compared with other clinical wards.[19,20] In addition, costs can markedly vary between ICU patients owing to heterogeneous ICU populations.[17,21] In this study, the total ICU costs are approximately 40% higher when compared with a Dutch study conducted in 2008,[22] which is significantly higher than the reported inflation of 13%.[15,23] This difference can mainly be explained by the higher illness severity score in the current study and the greater number of patients requiring blood products or RRT. The same 2008 study described that these patients incurred higher ICU costs. RRT and the use of blood products have been described in other studies as cost determinants.[20,24,25] Furthermore, costs were highly dependent on the admission diagnosis and site of infection.[18,26,27] In addition, renal failure (with or without RRT), sepsis, and comorbidities were described as predictors. We were unable to confirm these predictors in our analyses; however, we confirmed trends toward significance. Similar results were observed when selecting a PDT of 100% ƒ T > 4 × MIC MIC (see **Table 1**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A491).

TDM is considered to be cost-effective for some antibiotics, including glycopeptides and aminoglycosides, because it might prevent costly adverse events.[12] However, as beta-lactam antibiotics have a wide therapeutic window, it is logical that adverse events that could be prevented with TDM are less frequent. For these antibiotics, TDM is mostly aimed at preventing underexposure to desired treatment, making it more difficult to research cost-effectiveness. Owing to the heterogeneity of the ICU population, TDM is probably not beneficial in every patient receiving beta-lactam antibiotics. Patients with a higher chance of target nonattainment will need to be specifically examined, such as those presenting augmented renal clearance.[28] A planned secondary analysis of the DOLPHIN trial, a randomized controlled trial designed to assess the efficacy and cost-effectiveness of model-based TDM of beta-lactams and fluoroquinolones, will evaluate whether reaching target attainment after TDM results in a difference in ICU costs and therefore assessing whether TDM is cost-effective for beta-lactam antibiotics.[29]

This study has a few limitations, mostly attributed to the observational nature of our data. First, we only examined the costs of ICU admittance. No costs could be analyzed from subsequent hospital wards. Second, as this study was performed in a tertiary university hospital, external validity
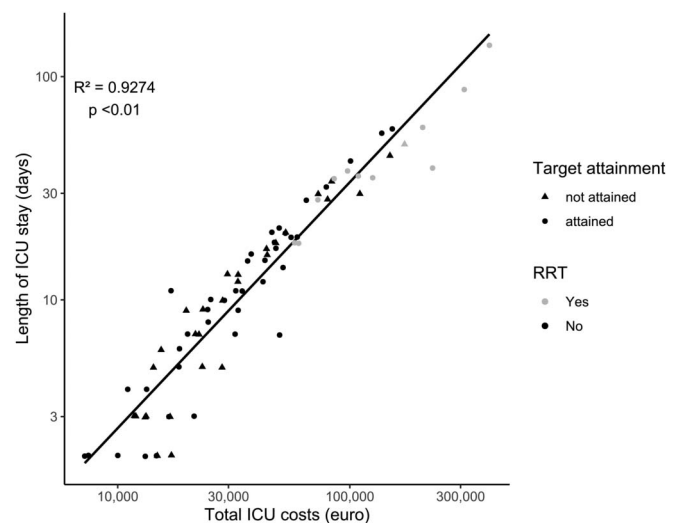
FIGURE 1. Correlation plot of ICU LOS and total ICU costs split by target attainment and use of renal replacement therapy. Both axes are log10 transformed.

should be considered when interpreting these results. The total or variable costs might not well translate to a different case-mix or less academic patient care facility. Finally, we were unable to extract all costs related to the patients; for example, costs of all medications included in the standard daily admission costs. An inquiry showed that these account for 7% of the standard daily admission costs. However, most beta-lactam antibiotic patents have expired and are therefore relatively inexpensive when compared with other ICU costs.

This is the first study to describe the relationship between ICU costs and beta-lactam antibiotic target attainment. Although we did not determine a significant difference in total costs, interesting trends toward significance were identified. Further research in an ICU population at risk of target nonattainment is needed to assess the efficacy and cost-effectiveness of TDM of beta-lactam antibiotics.

CONCLUSIONS

Target attainment for beta-lactam antibiotics shows a trend toward higher total costs in ICU patients. As RRT is the major cost determinant for total ICU costs, differences in these costs are mainly explained by the fact that patients achieving beta-lactam target attainment are more likely to receive RRT.

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