

Cost-Effectiveness Analysis of Polymyxin-B Immobilized Fiber Column and Conventional Medical Therapy in the Management of Abdominal Septic Shock in Italy

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Key Words

Apache score • Blood • Cost-effectiveness analysis • Critical care • Economics • Endotoxins • Hemoperfusion • Hospital mortality • Intensive care units • Polymyxin • Polymyxin B • Septic shock

Abstract

Introduction: Severe abdominal sepsis and septic shock are common problems in intensive care units (ICUs), and carry high mortality. The purpose of this economic analysis was to determine the cost-effectiveness of polymyxin B immobilized fiber column (PMX-F) plus conventional therapy (CT) (PMX-F-CT) versus CT alone for patients with severe sepsis/septic shock of abdominal origin, in the perspective of the Italian hospital. **Methods:** This was a retrospective cost-effectiveness analysis (CEA) based on data of clinical efficacy and consumption of resources collected alongside an Italian randomized clinical trial. 64 patients were enrolled following emergency surgery for intra-abdominal infection in 10 tertiary care ICUs from December 2004 to December 2007. Direct medical costs analyzed in the study included the consumption of hospital days, ICU days, catecholamine treatment days, renal replacement therapy days, mechanical

ventilation treatment days, and the use of the PMX-F device. Resources were valued using published 2010 tariffs and market values. All-cause hospital mortality was extrapolated to survival as expected life years (LY) per patient/arm: for each survivor, average age-gender-related years of life expectancy were retrieved from national life tables; for deceased patients, only the number of CRF reported survival days was retained. Baseline expected years of survival were weighed by the severity of sepsis, according to individual Acute Physiology and Chronic Health Evaluation (Apache) II scores, showing that age/disease severity were comparable in the two groups before treatment initiation. Life expectancy per patient in each treatment group was thus calculated as the combination of life expectancy from Italian National Statistics Institute life tables and intra-hospital mortality detected in the Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study. After all costs and 3% discounted survival years were calculated per patient per treatment arm, the incremental CEA was run to obtain the incremental cost-effectiveness ratio (ICER). Univariate sensitivity analyses and 2,000 bootstrap replications were run to test the robustness of the study results. **Results:** Based on the expected survival years (mean discounted PMX-F-CT 9.37 LY/patient, CT 4.92 LY/patient; difference for PMX-F-CT 4.45 LY/

patient; mean undiscounted PMX-F-CT 13.92 LY/patient, CT 7.19 LY/patient; difference +6.73 LY/patient), and the expected mean cost (PMX-F-CT mean 59,922 EUR/patient, CT mean 42,712 EUR/patient; difference for PMX-F-CT 17,211 EUR/patient), the mean ICER for PMX-F-CT resulted in 3,864 EUR/life year gained (LYG; ICER 2,558/undiscounted LYG). Results of the base-case CEA were confirmed by all sensitivity analyses, with ICER values always well below commonly accepted value thresholds. **Conclusion:** PMX-F-CT versus CT is a cost-effective intervention for treatment of severe sepsis/septic shock of abdominal origin and could be considered for use in the Italian National Health System hospital setting.

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Key Messages

- Severe abdominal sepsis and septic shock are common problems in intensive care units (ICUs), and carry high mortality.
- The Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study showed significantly reduced mortality, organ dysfunction and improved hemodynamics in a population of Italian ICU patients treated with polymyxin B immobilized fiber column plus conventional therapy (PMX-F-CT) for severe sepsis/septic shock of intra-abdominal origin.
- This retrospective cost-effectiveness analysis compared PMX-F-CT versus conventional therapy (CT), based on calculated costs and survival years per patient per treatment arm.
- This analysis shows that PMX-F-CT versus CT can save on average 4.45 discounted (6.73 undiscounted) life years (LY)/patient, at an additional expected cost of 17,211 EUR/patient, with a mean incremental cost of EUR 3,864 per discounted LY (EUR 2,558/undiscounted LY) gained.
- PMX-F-CT could be considered a cost-effective intervention for treatment of severe sepsis/septic shock of abdominal origin and, under the specific clinical indication investigated in the EUPHAS study, it may represent a valuable and appropriate treatment for use in the Italian hospital setting.

Introduction

Severe sepsis and septic shock are common problems in intensive care units (ICUs) and carry high mortality. Endotoxin, one of the principal components on the outer membrane of Gram-negative bacteria, is considered relevant to their pathogenesis [1]. High levels of endotoxin activity are associated with worse clinical outcomes [2]. Septic shock of intra-abdominal origin is likely to be due to Gram-negative pathogens and consequently associated with high endotoxin levels. Thus, it represents a condition in which endotoxin-targeted therapy may be of par-

ticular benefit. Polymyxin B (PMX) is a cationic cyclic polypeptide antibiotic which binds with high affinity to endotoxin, neutralizing its effects. However, it has significant nephrotoxic and neurotoxic effects, and these toxicities preclude its systemic use. This subsequently led to the development of an adsorptive cartridge in which PMX is covalently bound to polystyrene fibers [polymyxin B immobilized fiber column (PMX-F)] [3]. The device can effectively bind endotoxin both in vitro and in vivo thus interrupting the biological cascade of sepsis. It has been approved for use in Japan since 1993 and in Europe since 1998. More than 70,000 patients have been treated with PMX-F in Japan and Italy over the last 15 years [4]. In a recent systematic review, direct hemoperfusion with PMX-F has shown favorable effects on mean arterial pressure, use of vasopressive drugs, PaO₂/FiO₂ ratio and mortality. Pooled mortality rates were 61.5% in the conventional therapy (CT) group and 33.5% in the PMX-F group. In the pooled estimate, PMX-F appeared to significantly reduce mortality compared with conventional medical therapy (RR 0.53; 95% CI 0.43–0.65). The results were similar in both randomized controlled trials (RR 0.50; 95% CI 0.37–0.68) and non-randomized controlled trials (RR 0.55; 95% CI 0.38–0.81) [5]. However, it should be noted that very few of the included studies were planned or powered to specifically assess mortality [6].

The Italian National Health System (NHS) is basically a social security system with healthcare mainly financed by taxation and delivered by public and private structures and medical professionals. Concerning the hospital sector, which represents the elective market of PMX-F, financing of healthcare delivery is based on the DRG payment system (similar to the US Medicare hospital payment method), which basically consists of tariffs set in advance by the NHS and/or by the regions to fund hospital admissions. Despite the optimal acceptance by reanimators, PMX-F is facing significant challenges for use in the hospital setting, mainly due to the barriers to adoption generated by local financial constraints and by the absence of specific funding for ICUs. In fact, PMX-F being used in ICUs, and ICUs being classified as service providers to the medical and surgical wards of the hospital, and not as profit centers, the product is considered as an additional expenditure for the hospital and a potential harm to the global hospital budget, thus not fully recognizing its life-saving relevance. Not much is known about the economic value of PMX-F in comparison with alternative strategies for the management of severe sepsis/septic shock: a MEDLINE search using the terms 'Polymyxin B' and 'Economic' or 'Cost' (limits: Humans, English) pro-

duced 15 results, none of which actually reports results of cost-effectiveness analysis (CEA), cost-utility analysis or other commonly applied types of economic analysis.

The most recent clinical evidence on the use of PMX-F was published in 2009 by Cruz et al. [7]: the Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study showed significantly reduced mortality, organ dysfunction and improved hemodynamics in a targeted population of Italian patients admitted in ICUs for severe sepsis/septic shock from intra-abdominal Gram-negative infections. The clinical record form collected a number of variables that collectively well represent the consumption of resources and the mortality due to the disease and to the treatment for each treatment arm. Thus, this retrospective economic analysis was carried out in order to determine the cost-effectiveness of PMX-F plus CT (PMX-F-CT) versus CT alone, for severe sepsis/septic shock. The economic study was focused on the Italian healthcare provider's perspective and was retrospectively based on the clinical efficacy and consumption of resources collected in the Italian EUPHAS clinical study.

Materials and Methods

CEA is probably the most used healthcare economic evaluation technique [8–10]. Its main characteristics are: (i) assessment of the decision problem, study population and definition of the alternatives under study; (ii) definition of study perspective, which should be that of the decision-maker who is in charge of the delivery and funding of treatments and, accordingly, (iii) definition of the type of costs and outcomes which are relevant under the selected perspective; (iv) assessment of the consumption of resources needed in order to deliver each of the treatments under evaluation; (v) identification of the unit costs for each of the identified resources; (vi) assessment of efficacy of the alternatives, i.e. health gains in terms of number or percentage of patients successfully treated, or life years gained (LYG), or quality-adjusted life years (QALY); (vii) calculation of average cost and outcome for each alternative and calculation of the incremental cost-effectiveness ratio (ICER; i.e. the added cost of each additional unit of efficacy gained by one technology versus the alternative/s); (viii) production of a number of sensitivity analyses in order to test the robustness of the economic evidence. According to these principles, the following paragraphs will present in detail each of the assumptions of the retrospective economic study.

Study Population and Treatment Alternatives

This economic analysis was based on the EUPHAS study, a prospective, multi-center, randomized, controlled trial conducted between December 2004 and December 2007 in 10 Italian tertiary care ICUs, which enrolled 64 patients with severe sepsis/septic shock who had emergency surgery for intra-abdominal infection. Clinical characteristics of study patients, as well as clinical outcomes of the comparison between PMX-F-CT and CT,

Table 1. Patient demographics

	CT (n = 30)	PMX-F-CT (n = 34)	p
Male subjects, n (%)	18 (60.0)	24 (70.6)	n.s.
Mean age \pm SD, years	66.8 \pm 15.0	61.0 \pm 13.1	n.s.
Mean Apache II score \pm SD	19.1 \pm 6.9	20.7 \pm 5.7	n.s.
Deaths, n (%)	20 (67.7)	14 (41.2)	0.026

have been reported in detail in a previous paper [7]. Table 1 summarizes the main characteristics of study patients.

Study Perspective

This economic study adopted the perspective of the Italian provider of medical treatments, for patients affected by severe sepsis, that is, the hospital institution offering medical services to patients listed in the Italian NHS. Accordingly, the costs to be analyzed under the hospital perspective are typically those accrued in the hospital setting (direct medical costs), and the outcomes are those which better match the institutional scope of hospital assistance, in this case, the estimated number of life years (LY) saved by the alternatives in the treatment of severe sepsis, according to clinical study mortality by patient and by treatment arm.

Consumption of Resources

According to the study perspective, the direct medical costs considered for each alternative include the following resources which were collected for each patient during the clinical study data collection and recorded in the patient's clinical record form: length (number of days) of ICU stay; length (number of days) of hospital ward stay; length (number of days) of catecholamine treatment; length (number of days) of renal replacement therapy (RRT); length (number of days) of mechanical ventilation treatment (MVT), and use of the PMX-F device (number of cartridges) (only in the PMX-F-CT study arm). Consumption of resources per treatment arm is reported in table 2.

Identification of Unit Costs

Consumption of resources was valued by applying 2010 unit costs/tariffs as follows: hospital ward days (excluding days in ICU) were valued 487 EUR/day [11]; ICU days were valued 1,669 EUR/day [12]; days of catecholamine treatment were valued 9.97 EUR/day considering a daily dose of 0.25 g/kg/min, average patient weight of 70 kg, 24 h of continuous administration at a hospital price of EUR 3.96 per 5 vials of noradrenaline of 2 mg in 1 ml [13]; days of RRT were valued 297 EUR/day using the day-hospital tariff from the National DRG Tariff List for DRG-317 [14]; days of MVT were valued 258 EUR/day using the day-hospital tariff from the National DRG Tariff List for DRG-418 [14]; the use of PMX-F cartridges was valued 6,000 EUR/unit according to the official market price. Notably, costs were not discounted, as: (i) in Italy most costs are indeed NHS's tariffs, which are used as proxies to actual costs; in this study either 2010 tariffs or values derived from other studies which, in turn, used NHS tariffs were applied; (ii) the consumption of resources was indeed collected during the 3 years' duration of the EUPHAS study, but it only refers to re-

Table 2. Consumption of resources

	CT (n = 30)			PMX-F-CT (n = 34)			p*	EUR	Ref.
	total	mean	median	total	mean	median			
Hospital ward, days	411.0	13.7	0.0	576.0	16.9	14.0	n.s.	487.00	11
ICU, days	549.0	18.3	7.5	689.0	20.3	16.0	0.0263	1,669.00	12
MVT, days	452.0	15.1	7.5	539.0	15.9	10.5	0.0387	258.00	14
RRT, days	155.0	5.2	0.0	192.0	5.6	2.5	0.0308	297.00	14
Catecholamine, days	221.0	7.4	4.5	274.0	8.1	6.5	n.s.	9.97	13
PMX-F	0.0	0.0	0.0	68.0	2.0	2.0	n.a.	6,000.00	market price

* p value calculated using non-parametric two-sided Wilcoxon rank-sum (Mann-Whitney) test.

sources and costs which are borne during the acute phase of the disease, with no projection to the future. Unit cost of resources and respective references are listed in table 2.

Efficacy of the Alternatives

The main result of the clinical study was the lower all-cause hospital mortality rate in the PMX-F group versus the CT group, 41.2 versus 67.7%, respectively [adjusted hazard ratio (HR) 0.43, 95% CI 0.21–0.90, $p = 0.026$] [7]. For the purpose of the CEA, it was necessary to extrapolate from mortality to expected survival, to obtain the number of remaining LY per patient per treatment arm, which represents the denominator of the cost-effectiveness calculation. For each survivor, in each treatment arm, the average life expectancy (in years) by age and sex was retrieved using the Italian National Statistics Institute (ISTAT) life tables [15, 16], whilst for each deceased patient, the exact number of survival days reported in the CRF was retained. It could be noted that life expectancy of a subject affected by severe sepsis/septic shock cannot be considered equal to that of an 'average' age-gender-matched individual in the general population (i.e. the one reported in the ISTAT life expectancy tables); in fact, to account for the severity of the disease, expected baseline survival (at enrolment) per patient was weighed using the predicted death rate based on individual Acute Physiology and Chronic Health Evaluation (Apache) II scores (which were also collected in the clinical study patient record form). The Apache score is a physiologically based classification system for measuring severity of illness in groups of critically ill patients, which is commonly used in ICUs [17]. The current version of this system assigns points to a number of variables, all contributing to the severity of disease, namely the Acute Physiology Score (including physiological variables such as blood pressure, respiratory rate, arterial pH, electrolytes, etc.), age, chronic nature of the disease, and the Glasgow Coma Score including other signs and symptoms (eyes open, verbal response, motor response, flexion) [18]. Baseline expected survival in years was therefore weighed by the severity of sepsis, based on individual Apache II scores, showing that the two groups were comparable before treatment initiation, in terms of age/severity of disease. Life expectancy per patient in each treatment group was thus calculated as the combination of life expectancy from ISTAT life tables and intra-hospital mortality detected in the EUPHAS study. Furthermore, according to the Italian economic guidelines [10], 3%

discounting was applied to the expected survival years calculated for each patient in each study group. Survival data in years (discounted and undiscounted) per treatment group and differences between groups are reported in table 3.

Statistical Analysis

The non-parametric two-sided Wilcoxon-Mann-Whitney test was applied to analyze the differences of resources consumption (measured as number of hospital ward days, ICU days, catecholamine treatment days, RRT days, and MVT days) of the outcome (LY of survival) and per-patient cost between the two treatment groups, with a significance level of $\alpha = 0.05$. The Wilcoxon-Mann-Whitney test, one of the most powerful non-parametric tests, was chosen as all the variables were asymmetrically distributed, and therefore postulates of the t test could not be envisaged as valid. All analyses were performed using Stata® Release 9 (Stata Corp., College Station, Tex., USA).

Cost-Effectiveness Calculations

Once all costs and survival years were calculated per patient, in each treatment arm, the incremental CEA was run using the formula

$$\frac{\text{Costs (EUR)}_{\text{PMX-F}} - \text{Costs (EUR)}_{\text{CT}}}{\text{Outcome (years)}_{\text{PMX-F}} - \text{Outcome (years)}_{\text{CT}}} = \text{ICER}$$

thus obtaining the ICER which represents the additional EUR to be spent in order to obtain one additional LY with PMX-F versus CT.

Sensitivity Analysis

In order to test the robustness of the economic findings, a number of univariate sensitivity analyses were run on costs, and the ICER was recalculated using: 50% reduction/increase of consumption of all medical resources, this was done in multiple steps: increasing by 50% consumption of resources in both treatment arms, decreasing by 50% consumption of resources in both treatment arms, decreasing by 50% in the CT arm and simultaneously increasing by 50% in the PMX-F-CT arm and vice versa; applying 50% reduction/increase on the cost of the PMX-F device; also as the ICU cost/day was the highest cost/unit among the resources considered in this study, this was also tested by as much as $\pm 50\%$.

Table 3. Survival (life years)

	CT (n = 30)	PMX-F-CT (n = 34)	Difference
Mean age at enrolment, years	66.80	61.03	
Mean age-related life expectancy, years	19.06	21.95	+2.89
Mean sepsis-related predicted survival rate, %	47.32	46.21	
Mean age- and sepsis-related life expectancy, years	10.17	10.30	+0.13
Mean EUPHAS survival rate, %	33.00	58.82	
Mean EUPHAS life expectancy, years undiscounted	7.19	13.92	+6.73
Mean EUPHAS life expectancy, years discounted	4.92	9.37	+4.45

Table 4. Cost-effectiveness analysis

	Effect, years			Cost, EUR			ICER
	CT (n = 30)	PMX-F-CT (n = 34)	difference	CT (n = 30)	PMX-F-CT (n = 34)	difference	
Undiscounted survival years							
Mean	7.19	13.92	6.73	42,712	59,922	17,211	2,558
SD	12.51	14.55		57,659	31,338		
SE	2.67	3.10		12,293	6,681		
Median	0.08	11.23		25,081	49,857		
p value*	0.0112				0.0005		
Discounted survival years							
Mean	4.92	9.37	4.45	42,712	59,922	17,211	3,864
SD	7.69	8.95		57,659	31,338		
SE	1.64	1.91		12,293	6,681		
Median	0.08	9.41		25,081	49,857		
p value*	0.0112				0.0005		

* p value calculated using non-parametric two-sided Wilcoxon rank-sum (Mann-Whitney) test.

Efficacy was also tested via 50% reduction/increase which was applied to the expected difference in survival, measured in LYG, between the two treatment groups. In addition, according to a widely used economic methodology, cost and expected discounted survival for the 64 patients in the original dataset were used to extrapolate 2,000 bootstrap simulations, in order to estimate percentile CIs and 95% CIs for the resulting median ICER [19–21].

Results

We undertook a CEA based on mortality data and consumption of resources collected alongside the EUPHAS trial. The clinical study enrolled 64 patients (PMX-F-CT n = 34; CT n = 30) with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection. The main outcome measures were change in mean

arterial pressure and vasopressor requirement, and secondary outcomes were the PaO₂/FiO₂ (fraction of inspired oxygen) ratio, change in organ dysfunction measured using sequential organ failure assessment (SOFA) scores, and 28-day mortality. The 28-day mortality was 32% (11/34) in the PMX-F-CT group and 53% (16/30) in the CT group (p = 0.13). Adjusted for SOFA score, the PMX-F-CT group had a significant difference in 28-day survival time (adjusted HR 0.36, 95% CI 0.16–0.80, p = 0.012). Hospital mortality was 67% (20/30) in the CT group, as compared with 41% (14/34) in the PMX-F-CT group (p = 0.049). Adjusted for SOFA score, the PMX-F-CT group had a significant difference in hospital survival time (adjusted HR 0.43, 95% CI 0.21–0.90, p = 0.026) [22].

Results of the Italian CEA are reported in table 4. Based on the estimated discounted number of survival years of

Table 5. Univariate sensitivity analysis

	CT (n = 30)		PMX-F-CT (n = 34)		Difference		ICER EUR
	effect years	cost EUR	effect years	cost EUR	effect years	cost EUR	
Base-case analysis (undiscounted LY)	7.19	42,712	13.92	59,922	6.73	17,211	2,558
Base-case analysis (discounted LY)	4.92	42,712	9.37	59,922	4.45	17,211	3,864
<i>Use of resources</i>							
+50% use (both groups)		64,067		83,883	4.45	19,816	4,449
-50% use (both groups)		21,356		35,961	4.45	14,605	3,279
+50% (for PMX-CT), -50% (for CT)		21,356		83,883	4.45	62,527	14,038
-50% (for PMX-CT), +50% (for CT)		64,067		35,961	4.45	-28,106	-6,310
<i>Cost</i>							
+50% cost of PMX-F		42,712		65,922	4.45	23,210	5,211
-50% cost of PMX-F		42,712		53,922	4.45	11,210	2,517
+50% cost of ICU days		57,982		76,832	4.45	18,850	4,232
-50% cost of ICU days		27,441		43,012	4.45	15,571	3,496
<i>Difference in efficacy (LYG)</i>							
+50% of the difference					6.68	17,210	2,576
-50% of the difference					2.23	17,210	7,727

Table 6. Bootstrap analysis

	Effect LY	Cost EUR	ICER EUR
Base-case mean	4.45	17,211	3,864
Bootstrap mean	4.45	17,565	4,958
Median	4.42	18,196	4,070
25th percentile	3.01	9,692	2,194
75th percentile	5.86	25,473	6,176
Interquartile range	2.85	15,781	3,981
2.5th CI	-	-	-3,498
97.5th CI	-	-	20,567

4.92 (7.19 undiscounted years) for CT and 9.37 (13.92 undiscounted years) for PMX-F-CT, the mean difference in survival was calculated and yielded an estimated increase in survival of 4.45 (6.73 undiscounted) LYG for PMX-F-CT (median on discounted years 0.08 LY for CT vs. 9.41 LY for PMX-F-CT, $p = 0.0112$), at an additional cost of EUR 17,211 (median EUR 25,081 for CT vs. EUR 49,857 for PMX-F-CT, $p = 0.0005$). This corresponds to a mean ICER of EUR 2,558 per incremental undiscounted LYG and EUR 3,864 per incremental discounted LYG.

Results of the base-case CEA were confirmed by the results of the sensitivity analyses, which are reported in table 5. Noteworthy, large variations in the consumption

of resources ($\pm 50\%$ of the base-case values) in both groups yielded marginal changes in the ICER values of respectively EUR 4,449 and 3,279 per additional LYG with PMX-F-CT versus CT alone. In the worst scenario, represented by a reduction of 50% in the consumption of resources for the CT group and a simultaneous increase of 50% in the PMX-F-CT group, the net difference in costs was EUR 62,527, with a resulting ICER of EUR 14,038 per additional LYG. Similarly, $\pm 50\%$ variations of the base-case unit cost of PMX-F cartridges only marginally altered the ICER, yielding values of EUR 5,211 and 2,517 per additional LYG, respectively, using upper and lower unit cost estimates. Finally, even a reduction of 50% of the difference in expected discounted survival between PMX-F-CT and CT (i.e. 2.23 vs. 4.45 LYGs of the base-case analysis) produced a very modest increase of the ICER (i.e. 7,727 vs. 3,864 EUR/LYG of the base-case).

Results of the bootstrap simulation are presented in figure 1 and summary statistics are presented in table 6. As shown in figure 1, a large majority of bootstrap simulations lie in the upper right quadrant of the graph, confirming that PMX-F-CT is more effective and more costly than CT alone, with all ICER values lying well below the commonly accepted value thresholds for the ICER, according both to the international [23, 24] and the Italian literature [25] on cost-effectiveness estimates, that is, a value below EUR 60,000 per incremental LY. According

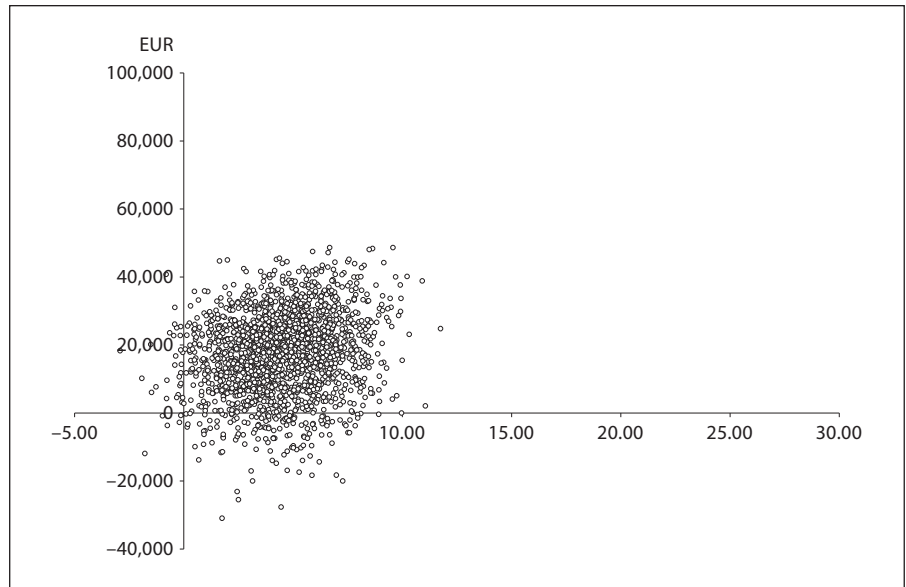


Fig. 1. Multivariate sensitivity analysis: results of 2,000 bootstrap replications.

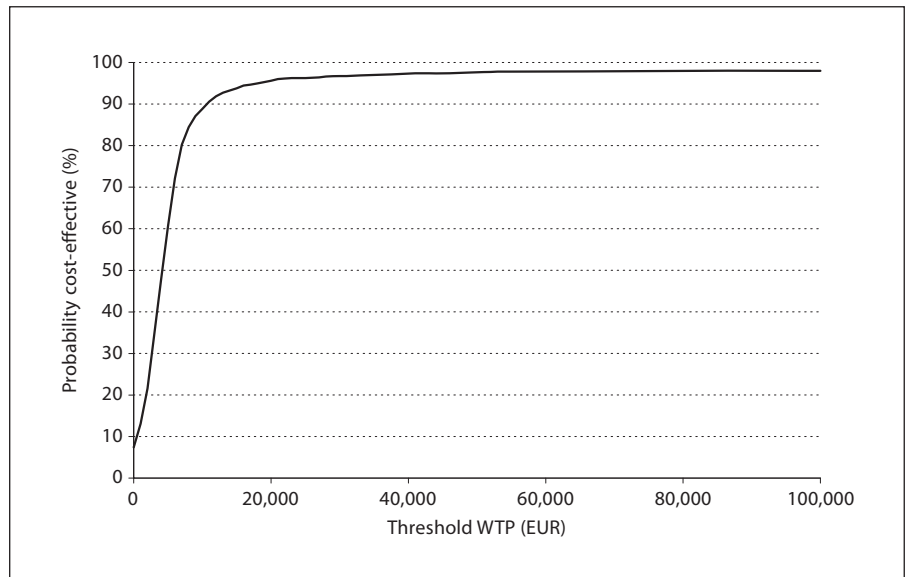


Fig. 2. Cost-effectiveness acceptability curve.

to this analysis, in comparison with CT alone, PMX-F-CT yielded a median of 4.42 (interquartile range 2.85; 3.01–5.86) additional LY, with a median per-patient cost of EUR 18,196 (interquartile range EUR 15,781; 9,692–25,473) and was associated with a median ICER of EUR 4,070 per additional LYG (interquartile range EUR 3,981/LYG; 2,194–6,176; 95% CI –3,498 to 20,567). Figure 2 shows the cost-effectiveness acceptability curve: only 1.7% of the extrapolated bootstrap replications lie in the *dominated* area (meaning that PMX-F-CT may be less effective and more costly than CT); conversely, 97.8% of the

replications lie below the willingness-to-pay threshold of EUR 60,000/LYG (with more than 95% of the simulations lying actually below EUR 20,000/LYG), thus confirming the robustness of this economic evaluation.

Discussion

This study attempts to quantify the economic value of PMX-F-CT versus CT alone from information collected alongside a clinical trial and, as such, carries a number of

potential limitations, due to the characteristics of the trial itself, the methods which were applied to extrapolate survival and costs and the clinical characteristics of the study patients.

A limitation of this retrospective CEA may be due to the fact that the study is based on data collected in one single and relatively small clinical trial, the EUPHAS study, which itself presented a number of limitations, as correctly pointed out in a recent paper [22]. Of particular note, for use of the trial results in the economic evaluation, was the consideration that the trial was stopped early, based on the results of the interim analysis, according to accepted standards for trial interruption. On these topics the authors commented that despite the relatively modest sample size, trial results were noteworthy and in line with the results of the meta-analysis on a varied population [5]; also of note is the comment that the 20% relative reduction in 28-day mortality, as indicated by the higher value of the 95% CI, could in any case be considered clinically relevant in this highly fatal condition [22].

The survival data used in this economic analysis are based on the consideration that patients who were alive at hospital discharge or at the latest follow-up day would have lived the rest of their life, according to their expected individual age-gender-related survival probability. Indeed, our study is based on the hypothesis that individuals who survive an episode of severe sepsis may subsequently enjoy the same life expectancy than individuals in the general population. We are aware of the fact that patients who experiment severe sepsis may in fact have permanent sequelae, such as chronic renal failure. Previous papers suggested that patients treated with PMX-F may in fact benefit from a lower incidence of long-term adverse events [26, 27], and therefore we think that our analysis could be considered to all effects conservative. We believe the mean number of LYG between the two treatment arms, as estimated in this economic study, may be considered as a good representation of the clinical effect of PMX-F-CT versus CT alone, in a surgical population affected by severe sepsis of abdominal origin, in Italy.

Another potential limitation of the analysis may be due to the type of costs that were considered in the economic evaluation: as a matter of fact, the use of cost/day as a proxy of actual costs incurred by the hospital is a common procedure in the economic literature, and it is also endorsed by the Italian guidelines [10]; our analysis includes the cost of days spent in the general ward, as well as days spent in the ICU, under mechanical ventilation, and under RRT, encompassing also the use of catecholamines. We believe this represents a very realistic picture

of the costs incurred by hospitals in delivering the technology.

Also, a limitation concerning the costing of the study could refer to the fact that only 28 days of in-hospital costs were considered, while survival data was extrapolated to the lifetime horizon. Given the nature of the Italian NHS, which is based on principles of welfare and subsidiarity, the decision of delivering the technology (in our case, PMX-F-CT or CT alone) relies entirely on the hospital which acts on behalf of the ASL (the local healthcare unit which represents locally the national healthcare system) and is funded by the ASL itself; this means that the hospital – acting as a public (not private) payer – is interested in the long-term value provided by the technology. Though, an analysis that would have investigated cost and effectiveness at 28 days would not have been a meaningful exercise and would not produce sensible information to the payer. Conversely, any attempt to estimate costs outside the hospitalization period, that is outside the data collection of the EUPHAS study, would have been open to criticism. We strongly believe that this study is a correct and conservative, albeit preliminary, source of evidence on the economics of PMX-F.

Importantly, due to the clinical nature of the data on which this economic study is based, the results of the CEA must be considered with caution, in that they should be limited to the type of patients who were enrolled in the EUPHAS study: specifically, individuals affected by severe sepsis or septic shock of abdominal origin, managed with conventional treatment or PMX-F and conventional treatment, after emergency surgery. Furthermore, due to the premature interruption of the original study, the encouraging data on survival time cannot be considered as conclusive, and the doubts on the efficacy of the therapy on crude mortality are not completely dispelled. Results of the EUPRHATES study [4, 28], currently ongoing in the United States, aimed at treating septic shock patients positive to the endotoxin activity assay test, should confirm the effect on mortality and provide a more specific therapeutic window to further improve the appropriateness of this therapeutic approach. Also, the use of patient registries to collect real-practice costs and outcomes [29] may trigger production of effectiveness (rather than efficacy) data, allowing clinicians and public decision-makers to pursue appropriateness of use, which also implies better use of the limited available resources.

Another limitation may be due to the fact that data used in this economic analysis was collected alongside a clinical trial and may be influenced by trial design and procedures: as a matter of fact, the production of eco-

nomic analysis from the consumption of resources for a given disease always has to deal with a trade-off between the limited representativeness of data collected during a randomized clinical trial and the limited value of resource use data retrieved by an observational study whose population and setting may, in turn, do not fully match with the clinical outcome that also represents a key feature of the cost-effectiveness calculation. We believe that this issue is effectively targeted by the sensitivity analyses which were used to test the robustness of the incremental cost per LYG calculation: in fact, even in the worst-case scenario in which the difference between costs of the two treatment arms is the largest (EUR 62,527), the resulting ICER of EUR 14,038 per additional discounted LYG remains below the commonly accepted threshold, thus supporting the consideration that hemoperfusion with PMX-F-CT may represent an efficient use of hospital resources in the management of these patients.

Conclusion

This study represents the first attempt to estimate the cost-effectiveness of PMX-F used in association with CT in the treatment of severe sepsis/septic shock in the perspective of the Italian NHS. According to the results, PMX-F-CT versus CT alone can save a mean incremental 4.45 discounted LY per patient (6.73 undiscounted) at an expected average cost of EUR 17,211 with a corresponding ICER of EUR 3,864 per discounted (EUR 2,558 undiscounted) LYG. Sensitivity analyses showed that cost-effectiveness calculations are robust and not affected by

the cost of the medical device or by the amount of resources used in the clinical trial. Importantly, all bootstrap ICER values lie well below the commonly accepted value thresholds according both to the international [23, 24] and the Italian literature [25] on cost-effectiveness estimates: this implies that PMX-F-CT could be considered a cost-effective intervention for treatment of severe sepsis/septic shock of abdominal origin and, under the specific clinical indication investigated in the EUPHAS study, it may represent a valuable and appropriate treatment for use in the Italian hospital setting.

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Disclosure Statement

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References

- 1 Cruz DN, Bellomo R, Ronco C: Clinical effects of polymyxin B-immobilized fiber column in septic patients. *Contrib Nephrol. Basel, Karger, 2007, vol 156, pp 444–451.*
- 2 Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, Opal S, Abraham E, Brett SJ, Smith T, et al: Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. *J Infect Dis 2004;190:527–534.*
- 3 Shoji H: Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). *Ther Apher Dial 2003;7:108–114.*
- 4 Rachoïn JS, Foster D, Dellinger RP: Endotoxin removal: how far from the evidence? From EUPHAS to EUPHRATES. *Contrib Nephrol. Basel, Karger, 2010, vol 167, pp 111–118.*
- 5 Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, Lentini P, Nalesso F, Ueno T, Ranieri VM, et al: Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care 2007; 11:R47.*
- 6 Cruz DN, de Cal M, Piccinni P, Ronco C: Polymyxin-B hemoperfusion and endotoxin removal: lessons from a review of the literature. *Contrib Nephrol. Basel, Karger, 2010, vol 167, pp 77–82.*
- 7 Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, et al: Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA 2009;301:2445–2452.*
- 8 Drummond M, Stoddard G, Torrance G: *Methods for the Economic Evaluation of Healthcare Programmes.* New York, Oxford University Press, 1987.
- 9 Gold MR, Siegel JE, Russel LB, Weinstein MC: *Cost-effectiveness in health and medicine.* New York, Oxford University Press, 1996.

- 10 Gruppo di Lavoro AIES Coordinato da G. Fattore: Proposta di linee guida per la valutazione economica degli interventi sanitari: documento per la discussione. *Pharmacoecon Ital Res Art* 2009;11:83–93.
- 11 Di Loreto P: L'approccio della Regione dell'Umbria alla determinazione del tariffario per la remunerazione delle prestazioni di ricovero. *Pharmacoecon Ital Res Art* 2006;8:74–81.
- 12 Torbica A, Tarricone R, Calciolari V, Branca V, Gaini SM: Analisi dei costi del trattamento dell'aneurisma intracranico in Italia. *Pharmacoecon Ital Res Art* 2009;11:25–37.
- 13 Prontuario Farmaci del Sistema Sanitario Nazionale. <http://www.giofil.it> (accessed 20.7.2009).
- 14 Aggiornamento delle tariffe delle prestazioni di assistenza ospedaliera. Decreto Ministeriale 13/12/2006.
- 15 ISTAT. Tavole di mortalità della popolazione italiana – Ripartizione: Italia – Femmine Anno: 2006. <http://demo.istat.it> (accessed 20.7.2009).
- 16 ISTAT. Tavole di mortalità della popolazione italiana – Ripartizione: Italia – Maschi Anno: 2006. <http://demo.istat.it> (accessed 20.7.2009).
- 17 Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE: Apache – acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981;9:591–597.
- 18 Knaus WA, Draper EA, Wagner DP, Zimmerman JE: Apache II: a severity of disease classification system. *Crit Care Med* 1985;13:818–829.
- 19 Briggs AH, Wonderling DE, Mooney CZ: Pulling CEA up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Econ* 1997;6:327–340.
- 20 Desgagne A, Castilloux AM, Angers JF, LeLorier J: The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. *Pharmacoeconomics* 1998;13:487–497.
- 21 Hunink MG, Bult JR, de Vries J, Weinstein MC: Uncertainty in decision models analyzing cost-effectiveness: the joint distribution of incremental costs and effectiveness evaluated with a nonparametric bootstrap method. *Med Decis Making* 1998;18:337–346.
- 22 Antonelli M, Fumagalli R, Cruz DN, Brienza N, Giunta F: PMX endotoxin removal in the clinical practice: results from the EUPHAS trial. *Contrib Nephrol. Basel, Karger*, 2010, vol 167, pp 83–90.
- 23 Appleby J: Data briefing. The NICE threshold. *Health Serv J* 2007;117:21.
- 24 Appleby J, Devlin N, Parkin D, Buxton M, Chalkidou K: Searching for cost-effectiveness thresholds in the NHS. *Health Policy* 2009;91:239–245.
- 25 Messori A, Santarlasci B, Trippoli S, Vaiari M: Controvalore economico del farmaco e beneficio clinico: stato dell'arte della metodologia di applicazione di un algoritmo farmacoeconomico. *Pharmacoecon Ital Res Art* 2003;5:53–67.
- 26 Cantaluppi V, Assenzio B, Pasero D, Romanazzi GM, Pacitti A, Lanfranco G, Puntorieri V, Martin EL, Mascia L, Monti G, et al: Polymyxin-B hemoperfusion inactivates circulating proapoptotic factors. *Intensive Care Med* 2008;34:1638–1645.
- 27 Vincent JL, Laterre PF, Cohen J, Burchardi H, Bruining H, Lerma FA, Wittebole X, De BD, Brett S, Marzo D, et al: A pilot-controlled study of a polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. *Shock* 2005;23:400–405.
- 28 Clin Tri Id.NCT01046669: Safety and efficacy of polymyxin B hemoperfusion (PMX) for septic shock (EUPHRATES). <http://www.clinicaltrials.gov> (accessed 20.7.2009).
- 29 EUPHAS2: a web-based prospective multicentered, collaborative data collection project. <http://www.euphas2.eu/en> (accessed 20.7.2009).