Farmeconomia. Health economics and therapeutic pathways 2024; 25(1): 35-45
https://doi.org/10.7175/fe.v25i1.1562

ORIGINAL RESEARCH

Decatecholaminization of septic shock patients in intensive care unit: an economic assessment in the Italian setting

Alfredo Del Gaudio [1], Assunta Caiazza [2], Luana Bortone [3], Sonia Tomasso [3], Ilaria Bozzari [4], Laura Vincenzi [4], Gianluca Furneri [4], Luigi Tritapepe [2]

[1] Anesthesia and Resuscitation Department, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy
[2] Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy
[3] AOP Orphan Pharmaceuticals Italy S.r.l., Pisa, Italy
[4] PharmaLex Italy S.p.A., Milan, Italy

ABSTRACT

INTRODUCTION: Prolonged administration of norepinephrine to critically ill patients can lead to serious adverse events. In this context, the concept of "decatecholaminization" has emerged over the past decade, involving the association of vasopressin with norepinephrine to reduce catecholamines need. Additionally, beta-blockers can help prevent increased heart rate resulting from sepsis treatments. This study presents an economic analysis evaluating the economic implications of the decatecholaminization use in patients with septic shock treated in intensive care unit (ICU) from the Italian National Health Service (NHS) perspective.

METHODS: Two analyses were conducted: (1) a patient-level comparison of costs between two real-world cases, one treated with decatecholaminization and one without this approach, and (2) a cohort-level analysis using a pharmacoeconomic model to project cost differences for the Italian National Health Service (NHS) before and after implementing decatecholaminization.

RESULTS: In the patient-level analysis, the use of decatecholaminization results in increased pharmacological expenses (+€210), and cost reduction in resource utilization (-€30,412). Similarly, the cohort-level shows higher pharmacological costs (+€192 per patient) and lower cost for other resources (-€1,264 per patient) in the future vs current scenario, resulting in a cumulative cost reduction of -€1,072 per patient. Considering an eligible population of 39,207 patients, decatecholaminization results in a total cost reduction of approximately €42.4 million.

CONCLUSION: This analysis supports the economic viability of decatecholaminization as an effective treatment for comprehensive management of septic shock. Further evaluation in real-world settings is needed to validate these findings and optimize clinical application.

Keywords

Decatecholaminization; Catecholamine sparing; Sepsis; Vasopressin; Landiolol

INTRODUCTION

Sepsis is a life-threatening condition triggered by pathological and biochemical abnormalities resulting from an infection [1]. Septic shock is of the most severe progression of sepsis, marked by circulatory system collapse that lead to reduced mean arterial pressure (MAP) (causing hypotension) and peripheral vascular resistance, compromised cardiac output, and a deterioration in oxygen exchange [1,2].

Sepsis and septic shock affect millions of people each year, with a mortality rate ranging from 20 to 30% [3–5]. In Italy, the number of death certificates citing sepsis rose by almost 40% from 2003 to 2015, accounting for 3% to 8% of all recorded deaths in the country during these years [6]. According to the Italian Project for Prospective Surveillance of Nosocomial Infections in Intensive Care Units (SPIN-UTI) report, about 15% of all hospital-acquired infection culminate in septic shock [7]. Therefore, sepsis and septic shock constitute both a clinical challenge and a public health concern.

According to the 2021 International Guidelines for the Management of Sepsis and Septic Shock, the primary approach to diagnosed sepsis involves administering antimicrobials,

Corresponding author
Laura Vincenzi
laura.vincenzi@pharmalex.com

Received: 26 July 2024
Accepted: 4 November 2024
Published: 19 November 2024

restoring blood volume using crystalloids, and infusing norepinephrine to achieve a MAP of 65 mmHg [2].

The predominant vasoactive agents employed in the management of hypotension during septic shock currently consists of catecholamine, such as norepinephrine and dobutamine [8]. Norepinephrine, a neurotransmitter and hormone classified within the catecholamines group [9], is used to attain hemodynamic objectives with high efficacy during the initial phases of resuscitation [8,10]. Nevertheless, prolonged administration or the assertive pursuit of hemodynamic objectives has proved ineffective in non-responder patients [8,11,12], potentially yielding adverse effects, such as immunological response disturbance and myocardial dysfunction exacerbation [13–16]. Results from a large trial suggested comparable clinical outcomes between norepinephrine alone and a combined regimen of argipressin (vasopressin) and norepinephrine [8,17].

Given the deleterious effects of norepinephrine, on critically ill patients, the concept of "decatecholaminization" has been advanced over the past decade [18,19]. Potential treatments for implementing decatecholaminization include arginine vasopressin (AVP) receptor agonists, infused at low-doses to restore vascular tone and spare the use of catecholamines, and beta-blockers, with cardioprotective properties, employed for the treatment of non-compensatory supraventricular tachycardia (SVT) arising from adrenergic hypertone [20]. The primary aim of decatecholaminization is to partially or entirely spare exogenous norepinephrine use, thereby achieving cardiovascular protection with non-adrenergic pathways [20].

Based on findings of the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial and the Vasopressin and Septic Shock Trial (VASST), it was established that norepinephrine in association with vasopressin is non-inferior to norepinephrine as an initial therapy for septic shock [17,21]. The administration of vasopressin did not lead to higher rates of adverse events, particularly ischemic events [17,21]. On this subject, Sacha et al. conducted a retrospective study wherein patients with septic shock, who received a fixed dose of vasopressin in association with norepinephrine, demonstrated improved prognosis when the vasopressin infusion led to an increase in MAP [22]. The vasopressin responders group exhibited significantly better outcomes in terms of mortality, intensive care unit (ICU) and hospital free days than the non-responders [22].

An early association, or synergism, between norepinephrine and argipressin should be considered to reduce cardiovascular risks related to medium-high dosages of norepinephrine. For example, as reported in Good Clinical Practice of SIAARTI (Italian scientific society of anesthesiologists and intensivists), the early association of vasopressin with norepinephrine is considered appropriate in patients with less severe septic shock (dosages of norepinephrine from 5 to 14 μg/min) to reduce mortality [23].

Moreover, tachycardia and atrial fibrillation are considered significant prognostic factors in patients with sepsis; therefore, reducing heart rate to less than 95 beats per min within 24 h of onset might improve prognosis [24]. In some patients, protracted endogenous and exogenous sympathetic overstimulation, marked by persisting tachycardia, has been shown to be harmful despite initial improvement in hemodynamic response. In this context, the duration and the total dose of catecholamine therapy, and the detrimental effects of tachycardia are associated with poor outcomes [14,25]. Conventional treatments of sepsis, including fluid resuscitation and vasopressors, might exacerbate sympathetic nervous system activity, causing increased heart rate. β-blockers can help prevent these effects [24].

The implementation of decatecholaminization could potentially enhance patient prognosis, consequently reducing the utilization of hospital resources and yielding both clinical and economic benefits.

In this paper, we present two real-world (patient-level) cases and a cohort-level analysis. The second analysis is based on an economic model developed to evaluate the clinical and economic implications of introducing decatecholaminization for treating septic shock patients in ICU, from the Italian National Health Service (NHS) perspective.

METHODS

In the present paper, two analyses were conducted:

1. A patient-level analysis, in which data of two real-world cases treated at Sant'Andrea Hospital (Rome, Italy) were used to compare costs between a patient who underwent decatecholaminization and one who did not.
2. A cohort-level analysis, in which a pharmacoeconomic model was developed to compare cost difference before (current scenario) and after (future scenario) the implementation of decatecholaminization to the Italian NHS system.

Healthcare resource	Unit costs (€)* [27–31]	Frequency [48]	
		Patient 1—without decatecholaminization	Patient 2 — with decatecholaminization
Cardiac surgery	6,876.00	3.0	0.0
ICU stay	1,941.80	6.0	3.0
CT scan	100.89	5.0	2.0
X rays scan/Ultrasound	42.52	4.0	1.0
Transfusion	468.40	4.0	0.0
CPR/Extracorporeal circulation	4,048.00	1.0	1.0
Respiratory failure	1,654.61	1.0	0.0
Consultations	20.66	3.0	0.0

Table I. *Resource consumption and unitary costs in patient-level analysis*
* Unit costs have been discounted to 2024 monetary value
CPR: cardiopulmonary resuscitation; CT: computerized tomography; ICU: Intensive Care Unit

Patient-level analysis: clinical inputs based on real-world data

In this first analysis, clinical data were extracted from two case reports provided by Sant'Andrea Hospital in Rome.

Patient 1 (74 years-old) was affected by arterial hypertension, depressive syndrome, along with schizophrenia and a compulsive hoarding disturbance. The patient was rescued after a fall and transported to the emergency room. He reported dizziness started in the previous days and severe asthenia. After a psychiatric and cardiac consultations, a coronary artery bypass graft (CABG) surgery was requested to stabilize the clinical picture. Septic shock raised following a cardiac surgery. A conservative approach (without decatecholaminization) was employed to treat the patient, including high dose norepinephrine, esmolol and metoprolol (Table S1 in Supplementary material). The patient died after 6 days.

Patient 2 (72 years-old), previously in good health, presented to the hospital in a critically severe condition, characterized by confusion, hypotension, and a tense, painful abdomen. Septic shock developed subsequent to a recent vertebroplasty which caused perivisceral and endo-peritoneal free air. Despite the administration of high-dose norepinephrine, an optimal hemodynamic status was not achieved. Consequently, the decatecholaminization process was initiated. Argipressin infusion was administered until the MAP exceeded 65 mmHg. Subsequently, to facilitate the patient's withdrawal from catecholamines, the norepinephrine dosage was reduced, and landiolol was started. After 3 days, the patient was extubated and continued the recovery.

Based on the treatment pathway of the two real-world cases, costs for pharmacological therapies (Table S1 in Supplementary material) and additional resource consumption (Table I) were considered for the patient-level analysis. Unit costs were retrieved from national tariffs [26,27] and literature data [28–30]. Unit costs been discounted to 2024 monetary value.

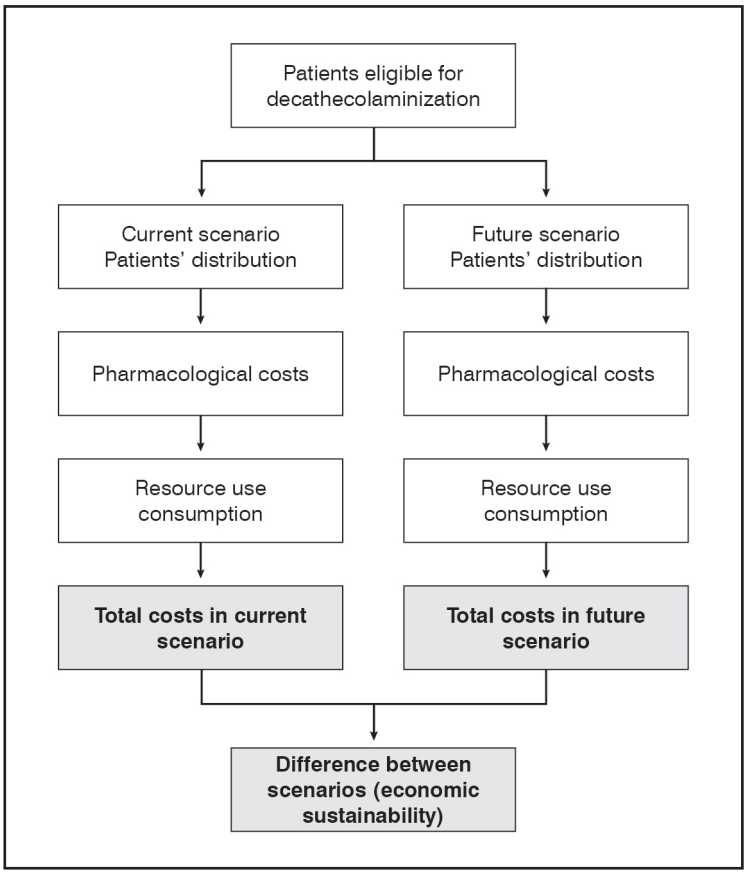

Figure 1. *Structure of the model*

Cohort-level analysis: extension to the Italian population

Starting from the patient-level analysis, a pharmacoeconomic model was developed to extend the analysis to the Italian population.

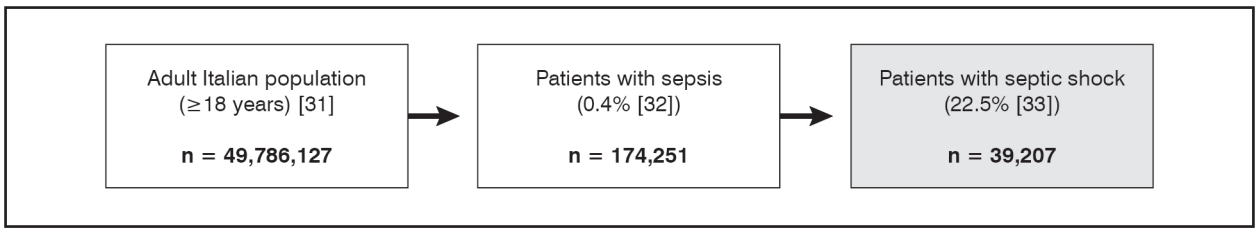

Figure 2. *Eligible population funnel*

The cohort-level analysis compares a current scenario, in which decatecholaminization is not or scarcely considered as treatment option for patients with septic shock, and a future scenario, where decatecholaminization is introduced among treatment options (Figure 1). The analysis was conducted from the Italian NHS perspective.

Due to the limited availability of scientific literature and the impracticality of basing the analysis on only two real-world cases, three clinical experts in the fields of anesthesiology and reanimation were consulted to validate the input data for the analysis. In particular, the clinical experts (n = 2 Directors of the Department of Anesthesia and Intensive Care and n = 1 Hospital Pharmacist) supported in the definition of the patient population, validation of the patient treatment pathway and additional resource consumption. The eligible population was calculated starting from the adult Italian population [31] and applying the rates of patients with sepsis [32], and septic shock [33]. Overall, approximately 39,000 eligible patients were eligible to the treatment with decatecholaminization. Figure 2 illustrates the patient population funnel employed to calculate the eligible pool in the scenario analysis [31–33].

As for the patient-level analysis, the model takes into account the costs associated with the use of:

- Pharmacological treatments.
- Other healthcare resources (interventions, length of hospital stay, etc.).

Unit costs have been discounted to 2024 monetary value considering the average annual inflation rate for the period.

According to available literature data and expert opinion, treatment options were divided in two steps [34]. In the first step norepinephrine was considered as first-line treatment in both the current and future scenarios (0.5 µg/kg/min). In the second step, norepinephrine was considered either alone at a high dose (0.8 µg/kg/min), or in combination with a second vasopressor at a low dose (0.5 µg/kg/min; decatecholaminization).

Literature evidence and additional case reports suggests that implementing norepinephrine sparing strategies (i.e., decatecholaminization) is associated with lower morbidity and lower ICU length of stays [35–37]. Decatecholaminization involves an initial administration of norepinephrine, followed by the subsequent use of an alternative vasopressor or inotrope to

Step	Treatment		Current scenario (%)	Future scenario (%)
1st step	NE		100,0	100,0
2nd step	NE, high dose		75.0	25.0
	NE, low dose + vasopressors / inotropes		25.0	75.0
	Vasopressors / inotropes	Argipressin	45.0	75.0
		Dobutamin	33.0	5.0
		Terlipressin	10.0	0.0
		Levosimendan	12.0	20.0
Additional treatment	Landiolol		0.0	17.5
	Esmolol		10.0	17.5
	Metoprolol		10.0	10.0
	Amiodarone		30.0	15.0
	No treatment		50.0	40.0

Table II. *Pharmacological treatment distribution used in cohort-level analysis [34]*
NE: norepinephrine

preserve peripheral perfusion. In cases where patients remain tachycardic, additional administration of beta-blockers or antiarrhythmic drugs may be necessary.

Vasopressors or inotropes considered to be associated with norepinephrine were argipressin, dobutamine, terlipressin and levosimendan. An additional treatment step was evaluated for patients experiencing non-compensatory tachycardia (~24% [14]), involving the use of landiolol, esmolol, metoprolol, or amiodarone. The patients' treatments distribution was initially assessed by market research involving 358 Italian departments of anesthesia, reanimation, and ICUs, and further validated by expert opinion (Table II) [34].

Data on length of stay were retrieved from the two real-world cases, additional literature and validated by the clinical experts. In particular, available data indicates:

- Septic shock treatment duration ranging from 4 and 7 days [17,34,35,38].
- Hospital length of stay ranging between 23 and 28 days [17,34,38–40].
- Of the total time spent in the hospital, approximately 60% is in the ICU [17,34,38,41].

After expert validation, for the cohort-level analysis, it was assumed that patients not receiving decatecholaminization spend 25 days in hospital and receive sepsis treatment for 6 days (Figure S1 in Supplementary material). Sepsis treatment is divided into:

- Step-1: norepinephrine 0.5 µg/kg/min, for 1 day.
- Step-2: high-dose norepinephrine, for 5 days.

Similarly, it was considered that patients undergoing decatecholaminization spend 24 days in hospital and receive sepsis treatment for 4 days. Sepsis treatment is divided into:

- Step-1: norepinephrine 0.5 µg/kg/min, for 1 day.
- Step-2: low-dose norepinephrine, for 3 days (in combination with vasopressor/inotrope for 1 to 3 days depending on the drug).

Table S2 in Supplementary material provides additional details on treatments.

It is important to note that, according to expert opinion, with the implementation of decatecholaminization, patients should experience a decrease in the hospital stay, with a potential reduction ranging from 1 to 5 days (4-20% decrease). This reduction is confirmed by published clinical cases [35]. Since there is a lack of literature evidence supporting a direct association between decatecholaminization and reduced hospital stay days, a conservative estimate of a 1-day decrease in hospital stay was assumed. However, potential outcomes associated with more substantial reductions, examining scenarios involving 3 and 5 days of hospital stay reduction, were considered.

The other healthcare resources considered in the analysis are described in detail in Table III [42]. Unit costs were retrieved from national tariff [26,27] and literature data and actualized to 2024 [29,30].

Sensitivity analysis

Some assumptions used in the model, such as the number of days of hospital stay, drugs posology and frequencies of resource consumption were based on market research and literature data confirmed by experts' opinion [34,42]. To take account of such variability, a deterministic (one-way) sensitivity analysis was carried out to identify the input values with the largest effect on the results of the economic analysis.

For the deterministic sensitivity analysis, the baseline value of each of the following parameter was modified to the upper and lower limits of ± 15% variation: length of hospital stay; proportion of patients with sepsis; proportion of patient using high dose norepinephrine, argipressin, levosimendan, terlipressin or dobutamine; patient weight; proportion of patients with non-compensatory tachycardia; renal replacement therapy, respiratory failure and consulting frequency.

Healthcare resource	Unit cost (€)° [27,28,30,31]	Frequency [18,22,35,36,39–41,48]	
		Without decatecholaminization	With decatecholaminization
Hospital stay*	1,481.59	25 days	24 days
Respiratory failure	1,654.61	60.0%	40.0%
Renal replacement therapy	3,734.00	35.0%	18.0%
Consultations	20.66	3	0

Table III. *Unitary costs and frequencies of resource consumption in cohort-level analysis*
* Considering 60% of stay in ICU (€1,654) and 40% in general ward (€674) [18,49,50]
° Unit costs have been discounted to 2024 monetary value
ICU: Intensive Care Unit

RESULTS

Patient-level analysis

The results of the patient-level analysis are shown in Figure 3. Costs were classified based on pharmacological treatments, ICU length of stay, diagnostic exams (which include CT scan and X rays scan) and interventions (including cardiac surgery, transfusion, cardiopulmonary resuscitation (CPR)/extracorporeal circulation, respiratory failure, renal replacement therapy and consultations). It is evident that, despite the marginal rise in pharmacological expenses (+€210), the use of decatecholaminization results in substantial cost reduction associated with healthcare resource utilization (€30,412). The cumulative cost reduction amount to €30,202. The main drivers of cost reduction are the costs related to the ICU stay and interventions.

Cohort-level analysis

The results obtained in the cohort-level analysis are illustrated in Figure 4. Similar to the patient-level analysis, the use of decatecholaminization leads to a slight increase in pharmacological costs (+€192 per patient) but delivers a significant reduction in the costs related to

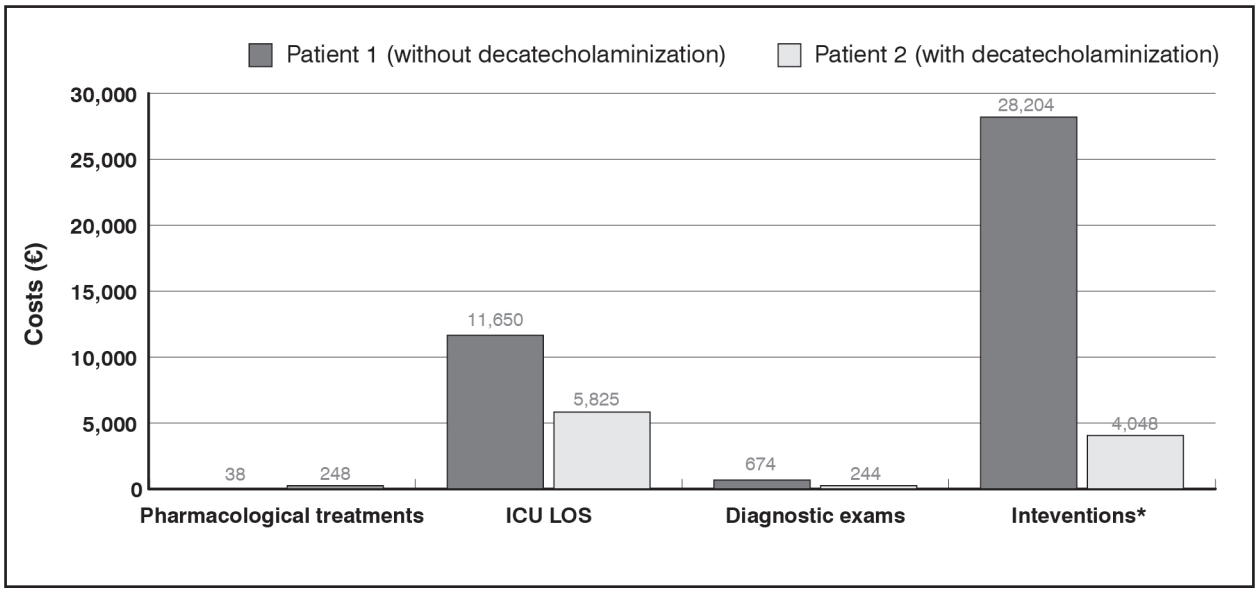

Figure 3. *Results of patient-level analysis*
* Including cardiac surgery, transfusion, CPR/extracorporeal circulation, respiratory failure, renal replacement therapy and consultations
CPR: Cardiopulmonary Resuscitation; ICU: Intensive Care Unit; LOS: Length of Stay

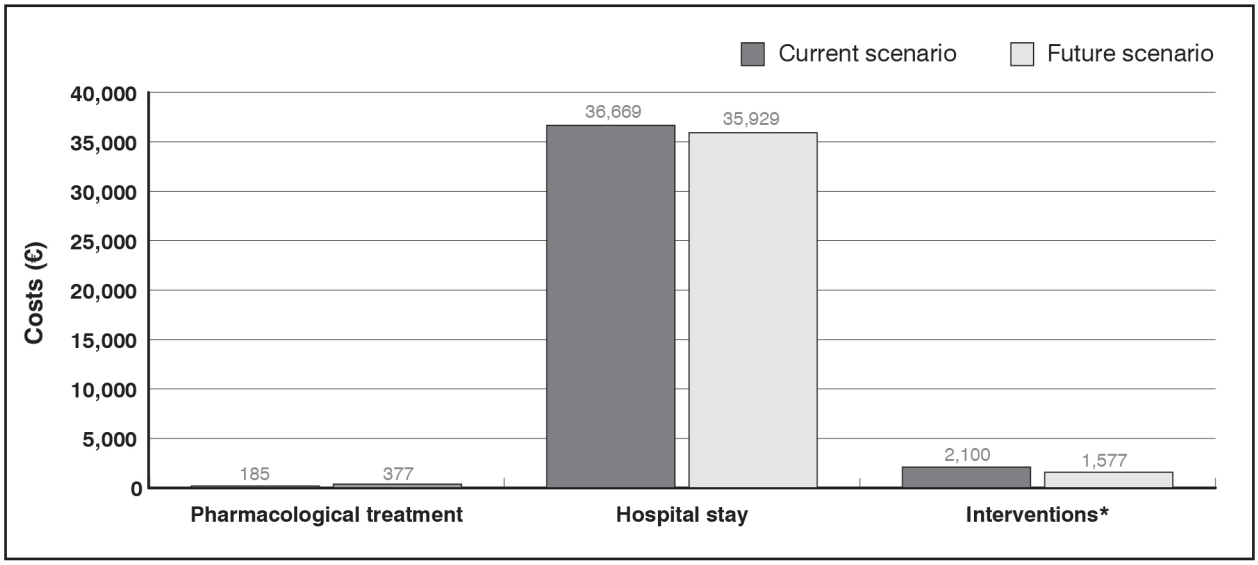

Figure 4. *Results per patient of cohort-level analysis*
*Including respiratory failure, renal replacement therapy and consultations

Data type	Per patient		Cumulative (n = 39,207)	
	Current scenario	Future scenario	Current scenario	Future scenario
Drug costs (€)	185	377	7,131,979	14,246,538
Other resources costs (€)	38,769	37,505	1,520,013,808	1,470,457,883
Total costs (€)	**38,955**	**37,882**	**1,527,145,786**	**1,484,704,421**
Difference (€)	**1,072**		**-42,441,366**	

Table IV. *Summary of results of cohort-level analysis*

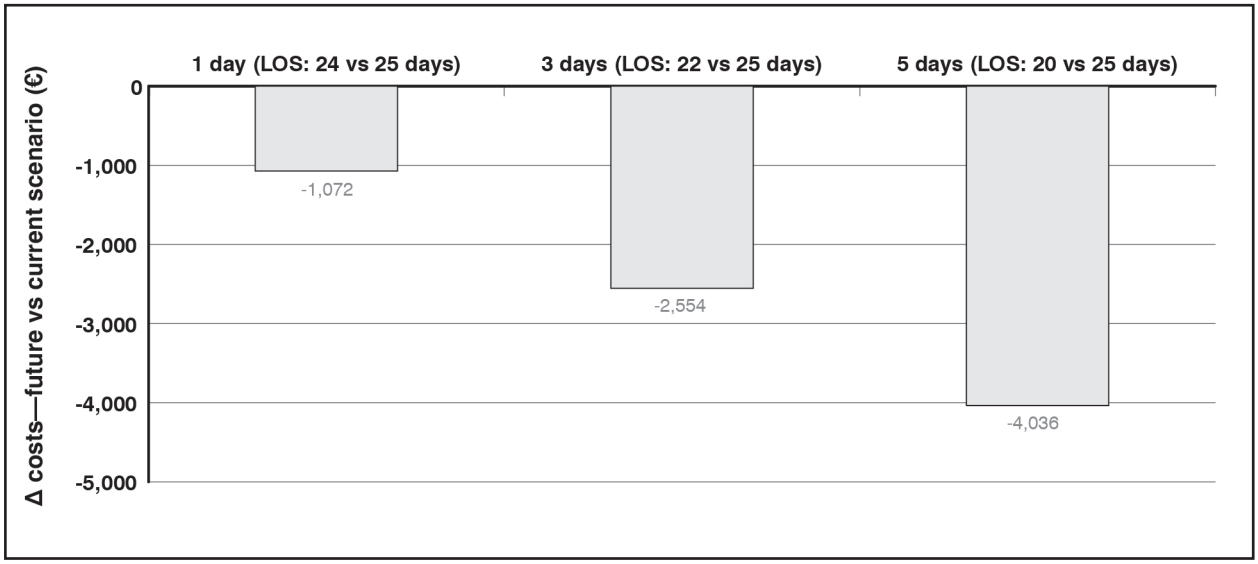

Figure 5. *Cost reduction breakdown per patient based on hospital days reduction in future scenario*
LOS: Length of stay

other healthcare resources consumption (-€1,264 per patient). The main driver of cost reduction is the costs related to the hospital stay.

Taking into account the entire eligible population of 39,207 patients, decatecholaminization results in a total cost reduction of approximately €42.4 million. Table IV presents a summary of the results from the cohort-level analysis, categorized by individual patients or cumulative.

In the cohort-level analysis a conservative hypothesis of 1-day hospital stay reduction in the future scenario was considered, resulting in a cost reduction of -€1,072 per patient. However, estimating a potential reduction in atrial fibrillation rate of 25-30% [34,43,44], a further decrease in hospital stay could be anticipated. The implementation of decatecholaminization led to incremental cost reduction proportional to the reduction in hospital days, with reductions of 3 and 5 days resulting in cost reduction of -€2,554 and -€4,036 per patient, respectively (Figure 5). Applying this reduction to the entire eligible population, a total cost reduction of -€101 million and -€159 million could be achieved, with 3 and 5 days reduction, respectively. These findings offer valuable insights into the potential benefits of decatecholaminization, laying the foundation for further investigations on its impact on patient outcomes.

Sensitivity analysis

Sensitivity analyses showed that results were robust and did not change significantly when assumptions were modified within plausible ranges (Figure S2 in Supplementary material). In all but one deterministic analyses tested, the future scenario, with a massive implementation of decatecholaminization, was found to achieve cost reduction vs the current scenario. The only instance in which the future scenario did not lead to cost reduction is when a longer hospital stay for the decatecholaminized patient (27 days; +15%) vs non-decatecholaminized patient (25 days) is considered. However, it is important to highlight that this occurrence is unlikely, as literature evidence suggests that the implementation of decatecholaminization is correlated with the reduction of atrial fibrillation of 25-30% [34,43,44] and is associated with a decrease morbidity and hospital stay [36,37]. The assumption of a 1-day reduction in

hospital stay following decatecholaminization implementation, adopted in the cohort-level analysis, is quite conservative. Indeed, the prolonged hospital stay is associated with patients' extreme severity rather than the therapeutic approach. Additional evidence are needed to validate the considered assumptions.

DISCUSSION

The concept of "decatecholaminization" has gained traction in recent years due to the recognition of the detrimental effects of catecholamines, such as norepinephrine. Norepinephrine plays a crucial role in regulating cardiovascular function, but excessive or prolonged exposure to exogenous norepinephrine can lead to adverse outcomes, particularly in critically ill patients [18,19]. Decatecholaminization represents a novel approach aimed at minimizing reliance on exogenous catecholamines, thereby reducing the potential for adverse effects while still achieving cardiovascular support through alternative non-adrenergic pathways [20]. One of the primary concerns with high-dose norepinephrine therapy is its association with peripheral ischemia and cardiac complications, which can significantly impact patient outcomes. By adopting decatecholaminization strategies, clinicians seek to improve patient safety. The effectiveness of decatecholaminization in attenuating the severity of side effects has been documented in the medical literature. These studies have demonstrated the potential benefits of decatecholaminization in reducing the incidence of adverse events, improving hemodynamic stability, and optimizing organ perfusion in critically ill patients [45–47]. The integration of decatecholaminization into clinical practice not only could improve overall patient care, but also allow the optimization of treatment protocols, contributing to a significant reduction in the required duration of treatment.

Despite the potential clinical advantages of decatecholaminization, its implementation may encounter certain challenges. One consideration is the possibility of increased treatment costs associated with the use of adjunctive therapies or alternative vasopressors. However, the present analysis suggests that any rise in treatment cost is negligible and largely balanced out by potential cost lowering derived from reduced length of stay and decreased utilization of resources, such as continuous renal replacement therapy (CRRT) and mechanical ventilation. Particularly noteworthy is the potential reduction in CRRT usage by up to 90% in cases, indicating significant reduction of resource use and enhanced healthcare system efficiency. These findings are supported by a recent meta-analysis that pooled data from 23 trials [48]. This study suggested that the concomitant use of non-catecholamine vasopressors and norepinephrine treatment is associated with shortened the length of mechanical ventilation, improved renal function, and improved cardiac function [48]. Additionally, careful patient selection and personalized treatment approaches may help optimize the cost-effectiveness of decatecholaminization strategies.

It is important to recognize the limitations inherent in the data sources and analytical approaches used. Modelling studies are valuable tools for assessing the potential impact of decatecholaminization strategies; however, they are based on certain assumptions and simplifications that may affect their validity and generalizability. These models often rely on data inputs derived from existing literature or expert opinion, which may not fully capture the complexity of clinical scenarios. Indeed, individual case reports and observational studies can provide valuable real-world insights, but their designs may be susceptible to biases, such as selection bias or confounding variables, which can impact the accuracy and reliability of the findings. Additionally, the retrospective nature of many observational studies can limit the ability to establish causality or generalize results to broader patient populations. As a result, the findings of modelling studies should be interpreted with caution and validated through empirical research in diverse patient populations and clinical settings.

Robust, prospective studies are needed to validate the efficacy and safety of decatecholaminization in critically ill patients. Randomized controlled trials with adequate sample sizes and long-term follow-up are crucial for establishing evidence-based guidelines and informing clinical practice.

Overall, while decatecholaminization shows promise as a therapeutic strategy for mitigating the adverse effects of high-dose catecholamine therapy, further research is necessary to elucidate its clinical utility. By addressing existing knowledge gaps and overcoming methodological challenges, clinicians can enhance their ability to provide safe and effective care for critically ill patients requiring vasopressor support.

CONCLUSION

In conclusion, decatecholaminization stands as a promising therapeutic approach for managing critically ill patients by reducing dependence on high-dose norepinephrine and mitigating associated risks, thereby enhancing patient outcomes and safety within intensive care settings. Despite certain methodological limitations, data gaps, and simplifications, this analysis gives confidence in the value and economic viability of decatecholaminization as an effective treatment to ensure comprehensive management of patients with septic shock. Further evaluation in broader real-world settings is warranted to validate these findings and optimize clinical application.

Funding

This study was financially supported by AOP Orphan Pharmaceuticals Italy S.r.l.

Conflicts of Interest

A.D.G., A.C. report support for the submitted work from PharmaLex Italy S.p.A.
L.B., S.T. are employees of AOP Orphan Pharmaceuticals Italy, which financially supported the submitted work.
I.B., L.V., G.F., are employees of PharmaLex Italy S.p.A., which received support for the submitted work from AOP Orphan Pharmaceuticals Italy.
L.T. reports support for the submitted work from PharmaLex Italy S.p.A., and consulting fees from Chiesi, AOP Orphan Pharmaceuticals Italy, Edwards, Viatris, Baxter, GE, outside the submitted work.

REFERENCES

1. Singer M, Deutschman CS, Seymour C, et al. The Third International Consensus Definitions for Sepsis and SepticShock (Sepsis-3). *JAMA*. 2016;315: 801; https://doi.org/10.1001/JAMA.2016.0287
2. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49: E1063–E1143; https://doi.org/10.1097/CCM.0000000000005337
3. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med*. 2016;193: 259–272; https://doi.org/10.1164/RCCM.201504-0781OC
4. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46: 1552–1562; https://doi.org/10.1007/S00134-020-06151-X
5. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA*. 2017;318: 1241–1249; https://doi.org/10.1001/JAMA.2017.13836
6. Ministry of Health. Giornata mondiale per lotta alla sepsi. 2022. Available at: https://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=5987 (last accessed Febraury 2024)
7. Agodi A, Barchitta M, Mura I. Prospective active surveillance of nosocomial infections in intensive care units (SPIN-UTI Project). 2021; 1–21
8. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012;165: 2015–2033; https://doi.org/10.1111/J.1476-5381.2011.01588.X
9. Nagatsu T. The catecholamine system in health and disease -Relation to tyrosine 3-monooxygenase and other catecholamine-synthesizing enzymes. *Proc Jpn Acad Ser B Phys Biol Sci*. 2007;82: 388–415; https://doi.org/10.2183/PJAB.82.388
10. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345: 1368–1377; https://doi.org/10.1056/NEJMOA010307
11. Alía I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Chest. 1999;115: 453–461; https://doi.org/10.1378/CHEST.115.2.453

12. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333: 1025–1032; https://doi.org/10.1056/NEJM199510193331601

13. Kumar A, Schupp E, Bunnell E, Ali A, Milcarek B, Parrillo JE. Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock. *Critical Care*. 2008;12: R35; https://doi.org/10.1186/CC6814

14. Schmittinger CA, Torgersen C, Luckner G, Schröder DCH, Lorenz I, Dünser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. *Intensive Care Med*. 2012;38: 950–958; https://doi.org/10.1007/S00134-012-2531-2

15. Hartmann C, Radermacher P, Wepler M, Nußbaum B. Non-Hemodynamic Effects of Catecholamines. *Shock* (Augusta, Ga). 2017;48: 390–400; https://doi.org/10.1097/SHK.0000000000000879

16. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330: 1717–1722; https://doi.org/10.1056/NEJM199406163302404

17. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358: 877–887; https://doi.org/10.1056/NEJMOA067373

18. Singer M. Catecholamine treatment for shock--equally good or bad? *Lancet*. 2007;370: 636–637; https://doi.org/10.1016/S0140-6736(07)61317-8

19. Singer M, Matthay MA. Clinical review: Thinking outside the box--an iconoclastic view of current practice. *Crit Care*. 2011;15; https://doi.org/10.1186/CC10245

20. Coquerel D, Sainsily X, Dumont L, et al. The apelinergic system as an alternative to catecholamines in low-output septic shock. *Crit Care*. 2018;22; https://doi.org/10.1186/S13054-018-1942-Z

21. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA*. 2016;316: 509–518; https://doi.org/10.1001/JAMA.2016.10485

22. Sacha GL, Lam SW, Duggal A, et al. Predictors of response to fixed-dose vasopressin in adult patients with septic shock. *Ann Intensive Care*. 2018;8; https://doi.org/10.1186/S13613-018-0379-5

23. Girardis M, Tritapepe L, Antonelli M, et al. Good Clinical Practices - Use of vasopressin and its analogues in critically ill patients. 2021. Available at: https://www.siaarti.it/news/431114 (last accessed February 2024)

24. Kakihana Y, Nishida O, Taniguchi T, et al. Efficacy and safety of landiolol, an ultra-short-acting β1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. 2020;8: 863–872; https://doi.org/10.1016/S2213-2600(20)30037-0

25. Sander O, Welters ID, Foëx P, Sear JW. Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications. *Crit Care Med*. 2005;33: 81–88; https://doi.org/10.1097/01.CCM.0000150028.64264.14

26. Ministero della Salute. GU n.23. Allegato 1. Tariffario delle prestazioni ospedaliere. 2013.

27. Ministero della Salute. GU n.23. Allegato 3. Tariffario delle prestazioni ambulatoriali. 2013.

28. Montrella S. In Italia i ragazzi non donano più sangue. 2019. Available at: https://www.agi.it/salute/news/2019-06-14/giornata_mondiale_donazione_sangue-5662025/ (last accessed February 2024)

29. Ruggeri M, Signorini A, Drago C, Rosiello F, Marchetti M. Model for estimating the healthcare costs and capacity of intensive care units in Italy in the treatment of patients with COVID-19: remdesivir impact assessment. AboutOpen. 2020;7: 95–102; https://doi.org/10.33393/ABTPN.2020.2213

30. Foglia E, Ferrario L, Schettini F, Pagani MB, Dalla Bona M, Porazzi E. COVID-19 and hospital management costs: the Italian experience. *BMC Health Serv Res*. 2022;22: 1–10; https://doi.org/10.1186/S12913-022-08365-9/TABLES/3

31. National Institute of Statistics of Italy (ISTAT). Adult Italian Population in 2023. 2023. Available at: https://demo.istat.it/app/?i=POS&l=it (last accessed February 2024)

32. Accorgi D, Alti E, Barnini S, et al. Lotta alla sepsi. 2019. Available at: https://www.ars.toscana.it/lotta-alla-sepsi/toscana-agenzia-sanita-microbiologia-rischio-clinico-call-to-action-infezioni-pdta-linee-di-indirizzo.php (last accessed February 2024)

33. Agodi A, Barchitta M, Auxilia F, et al. Epidemiology of intensive care unit-acquired sepsis in Italy: Results of the SPIN-UTI network. *Annali di Igiene Medicina Preventiva e di Comunita*. 2018;30: 15–21; https://doi.org/10.7416/ai.2018.2247

34. Expert opinion – Data on file. 2023.

35. Barile A, Tonti MP. La decatecolaminizzazione nel paziente settico in terapia intensiva - Raccolta di casi clinici su landiololo e argipressina. *Questioni di Clinica*. 2023; 1–16; https://doi.org/10.48265/QdC20-23

36. Guinot PG, Martin A, Berthoud V, et al. Vasopressor-Sparing Strategies in Patients with Shock: A Scoping-Review and an Evidence-Based Strategy Proposition. *J Clin Med*. 2021;10: 3164; https://doi.org/10.3390/JCM10143164

37. Guinot PG, Abou-Arab O, Guilbart M, et al. Monitoring dynamic arterial elastance as a means of decreasing the duration of norepinephrine treatment in vasoplegic syndrome following cardiac surgery: a prospective, randomized trial. *Intensive Care Med*. 2017;43: 643–651; https://doi.org/10.1007/S00134-016-4666-Z

38. Sant'Andrea Hospital (Rome). Case report. 2023.

39. Malacarne P, Langer M, Nascimben E, et al. Building a continuous multicenter infection surveillance system in the intensive care unit: findings from the initial data set of 9,493 patients from 71 Italian intensive care units. *Crit Care Med*. 2008;36: 1105–1113; https://doi.org/10.1097/CCM.0B013E318169ED30

40. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA*. 2019;321: 654; https://doi.org/10.1001/JAMA.2019.0071

41. Wu KS, Gu DY, Wang TT, Yu BW, Pan KH, Zhou JC. Factors associated with outcomes of septic shock patients receiving high dose noradrenaline according to three primary infection sites. *J Int Med Res*. 2020;48: 300060519874545; https://doi.org/10.1177/0300060519874545

42. AMOMED Globaldatasupport. Mapping of intensive care departments. 2020.

43. McIntyre WF, Um KJ, Alhazzani W, et al. Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. *JAMA*. 2018;319: 1889; https://doi.org/10.1001/JAMA.2018.4528

44. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. *Anesthesiology*. 2017;126: 85–93; https://doi.org/10.1097/ALN.0000000000001434

45. Lescroart M, Pequignot B, Kimmoun A, Klein T, Levy B. Beta-blockers in septic shock: What is new? *J Intensive Med*. 2022;2: 150–155; https://doi.org/10.1016/J.JOINTM.2022.01.004

46. Rudiger A, Singer M. Decatecholaminisation during sepsis. *Crit Care*. 2016;20; https://doi.org/10.1186/S13054-016-1488-X

47. Ferreira JA, Bissell BD. Misdirected Sympathy: The Role of Sympatholysis in Sepsis and Septic Shock. *J Intensive Care Med*. 2018;33: 74–86; https://doi.org/10.1177/0885066616689548

48. Zhong L, Ji XW, Wang HL, Zhao GM, Zhou Q, Xie B. Non-catecholamine vasopressors in the treatment of adult patients with septic shock-evidence from meta-analysis and trial sequential analysis of randomized clinical trials. *J Intensive Care*. 2020;8; https://doi.org/10.1186/S40560-020-00500-0