Original article

Impact of septic episodes caused by *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in a tertiary hospital: clinical and economic considerations in years 2018–2020

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ABSTRACT

Objective: To evaluate incidence, therapy and antibiotic resistance trends in septic episodes caused by three multi-drug resistant bacteria in a tertiary hospital, by also estimating their economic impact.
Methods: An observational, retrospective-cohort analysis was based on data related to patients admitted to the "SS. Antonio e Biagio e Cesare Arrigo" Hospital in Alessandria (Italy) between 2018 and 2020, that developed sepsis from multi-drug resistant bacteria of the examined species. Data were retrieved from medical records and from the hospital's management department.
Results: Inclusion criteria led to enrolment of 174 patients. A relative increase in *A. baumannii* cases ($p < 0.0001$) and an increasing resistance trend for *K. pneumoniae* ($p < 0.0001$) were detected in 2020 compared to 2018–2019. Most patients were treated with carbapenems (72.4%), although the use of colistin rose significantly in 2020 (62.5% vs 36%, $p = 0.0005$). Altogether, these 174 cases caused 3295 additional hospitalisation days (mean 19 days/patient): the consequent expenditure attained ≈ 3 million Euros, 85% of which (≈2.5 million Euros) due to the cost of extra hospital stay. Specific antimicrobial therapy accounted for 11.2% of the total (≈336,000 €).
Conclusions: Healthcare-related septic episodes cause a considerable burden. Moreover, a trend could be spotted towards higher relative incidence of complex cases recently.

Background

Healthcare-associated infections (HAIs), i.e. infections contracted in healthcare settings and not manifest (nor in incubation) prior to admission [1], are a major public health issue in Europe: according to the European Centre for Disease Prevention and Control (ECDC), the average HAI prevalence in European Countries is around 5.7–6.5%, corresponding to an incidence of approximately 3.7 HAI cases per 100 admissions [2].

Antimicrobial resistance (AMR), particularly in the case of multi-drug resistant (MDR) organisms, is an additional issue in the frame of HAIs, especially in the European Union/European Economic Area (EU/EEA): every year, more than 670,000 infections occur owing to antibiotic-resistant bacteria, and around 33,000 people die as a direct consequence of these infections [3]. Specifically, some Gram-negative bacteria – such as *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [4] – have shown a wide trend towards AMR, and may reach resistance rates averagely ranging between 31% and 37%, in some cases attaining 53% [3].

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Research has shown that HAIs are responsible for high costs in terms of disability, hospitalisation days and economic losses: according to the most recent World Health Organisation (WHO) estimates, every year in the EU/EEA, HAIs cause 2.5 million disability-adjusted life years (DALYs) [5] and 16 million hospitalisation days [6], and the relevant attributable costs were estimated at around 7 billion Euros in 2011 [5]. However, this figure – besides having been computed more than a decade ago (it would correspond to more than 9 billion Euros after discounting to 2022) – probably underestimates the current cost of HAIs, given the increasing trend already detected up to 2015 [6].

Moreover, AMR itself is associated with higher mortality [7] and higher medical resource consumption [8]. AMR infections have been shown to result into hospital stays longer by 1–6 days compared to non-AMR cases, with average extra costs attaining 1.7–3.8 thousand Euros per case in the event of bloodstream infections [9]. Moreover, studies concerning methicillin-resistant *Staphylococcus aureus* and based on the Diagnosis-Related Group (DRG) payment system showed that AMR infections led not only to longer hospital stays [10], but also to greater average bed-day costs [11].

An additional variable affecting HAIs has been represented by COVID-19: whilst the pandemic produced many changes (sometimes disruptive) in hospital management, it was also associated with particular trends in incidence and types of HAIs, with a significant rise in the number of MDR *K. pneumoniae* and *A. baumannii* isolates [12–14], and an increased incidence of healthcare-associated septic episodes [15,16].

In Italy, where HAI prevalence (about 7%) and AMR rates are slightly higher than the European average [2], a list of bacteria have been deemed as "alert microorganisms" (in consideration of their high infectivity, persistence on environmental surfaces, and/or resistance to antimicrobial agents) and subjected to specific monitoring, as part of the surveillance conducted by the National Institute of Health [17]. In our hospital, a 700-bed hospital in North-West Italy serving around 600,000 inhabitants in the area and participating in this surveillance, we had previously noticed an increasing trend in the incidence of colonisations, infections, and particularly septic episodes, caused by three Gram-negative multidrug resistant micro-organisms belonging to the "alert" group, namely *K. pneumoniae*, *A. baumannii* and *P. aeruginosa*, in years 2018–2020 [18].

Therefore, the aim of this study was to evaluate the economic impact of septic episodes caused by these bacteria in 2018–2020, by providing numerical data about resource deployment for these septic cases, in terms of both extra length of hospital stay and attributable diagnostic and therapeutic procedures. Furthermore, starting from these data, our study tried to produce a reasonable estimate of such impact in terms of monetary value.

Methods

Study design

This analysis was conceived with an observational, retrospective cohort study design. Data on patients admitted to the "SS. Antonio e Biagio e Cesare Arrigo" Hospital in Alessandria (North-West Italy), who developed septic episodes from *A. baumannii*, *K. pneumoniae* and/or *P. aeruginosa* between 1st January 2018 and 31 December 2020, were retrospectively collected. The study was conducted in conformity with the Helsinki Declaration on ethical research principles, and with the Italian (Legislative Decree 2003/196) and European law framework (GDPR 2016/679) concerning data protection and privacy. The research was performed after approval by the Inter-institutional Ethical Board of the Local Health Authority "ASL Alessandria" and "SS. Antonio e Biagio e Cesare Arrigo" Hospital (protocol n. 0009981, 7 May 2021), and subsequent authorisation by

the General Hospital Direction (resolution 2021/776 on 10 May 2021).

Inclusion/exclusion criteria

All (and only those) patients admitted to the "SS. Antonio e Biagio e Cesare Arrigo" Hospital between 1st January 2018 and 31 December 2020 and meeting the following inclusion criteria were considered as eligible and then enrolled for the study: (1) age ≥ 18 years on admission; (2) positive blood cultures showing infection by *A. baumannii*, *K. pneumoniae* and/or *P. aeruginosa*, resistant to at least 2 antimicrobial agent categories according to the ECDC classification [3]; (3) diagnostic finding obtained at least 48 h after admission, as established by the current international definition of HAIs [1]. Further details about inclusion criteria are reported in the Supplementary Material (§1.1).

Data collection

The data collection process is detailed in the Supplementary Material (§1.2). For each subject, data on baseline characteristics, hospital stay and outcome were collected from different sources: Table S1a reports details about collected variables and respective sources, by also specifying relevant retrieval methodologies where necessary. The length of hospital stay ascribable to sepsis (extra length of stay, extra-LOS) was computed from the day of the first positive blood culture until either the last day of antibiotic therapy (in case of remission), or the day of discharge (for transferred patients) or death. Unitary cost data were retrieved from databases of the hospital's pharmacy and the Department of Quality Management and Control (Table S1b).

Hospital costs considered for this analysis include staffing, support therapy, medical devices, and costs of all items and services used for ordinary patient, ward and hospital management, but not – for instance – initial building or land costs, as we assumed they could be considered negligible given the conspicuous amount of time for which the hospital has been in operation (more than 200 years). A hospital perspective was adopted for cost evaluations, and all costs were calculated in 2020 Euros (€).

Statistical analysis

For descriptive purposes, septic episodes were grouped into 2018–2019 (first group, before COVID) and 2020 (second group, during COVID). After the results of the Shapiro-Wilk normality test, quantitative variables were reported as medians and interquartile ranges, and compared between groups through the Mann-Whitney-Wilcoxon U test. Categorical variables were expressed as absolute frequencies and percentages, and compared through Fisher's exact test.

Sepsis outcomes were represented by plotting cumulative incidence curves, taking into account the two potential outcomes of each case (i.e., healing or death) besides follow-up losses. To evaluate the extent of resource consumption due to sepsis, unitary costs of exams, drugs and replaced devices were multiplied by the respective number of diagnostic/therapeutic procedures. Then, the average daily cost of hospital stay (stratified by ward) was multiplied by the extra-LOS: presence of possible bias in the computation of the extra-LOS, arising from the heterogeneity of hospitalisation days prior to sepsis between subjects [19], was inspected through correlation (Kendall's tau) between LOS before sepsis and extra-LOS due to sepsis. To provide a measure of the relative uncertainty of overall costs, the corresponding 95% confidence interval was computed via Monte-Carlo simulations, with a number of iterations equal to the number of septic cases (overall and by year).

Table 1
General descriptive characteristics of the sample.

Sample characteristics		Total (n = 174)	2018–2019 (n = 86)	2020 (n = 88)	*p*-value
Baseline characteristics	**Age** [years]	**69 [56–76]**	**70 [58–77]**	**67 [56–76]**	**0.5300**
	Gender, male	**119 (68.4%)**	**53 (61.6%)**	**66 (75.0%)**	**0.0729**
	Main bacterium				**< 0.0001***
	A. baumannii	**35 (20.1%)**	**6 (7.0%)**	**29 (33.0%)**	
	- resistant to:				0.3176
	2 classes	*2/35 (5.7%)*	*1/6 (16.7%)*	*1/29 (3.4%)*	
	3 classes	*33/35 (94.3%)*	*5/6 (83.3%)*	*28/29 (96.6%)*	
	K. pneumoniae	**102 (58.6%)**	**57 (66.3%)**	**45 (51.1%)**	
	- resistant to:				< 0.0001*
	2 classes	*21/102 (20.6%)*	*19/57 (33.3%)*	*2/45 (4.4%)*	
	3 classes	*44/102 (43.1%)*	*26/57 (45.6%)*	*18/45 (40.0%)*	
	4 classes	*37/102 (36.3%)*	*12/57 (21.1%)*	*25/45 (55.6%)*	
	P. aeruginosa	**37 (21.3%)**	**23 (26.7%)**	**14 (15.9%)**	
	- resistant to:				0.3650
	2 classes	*15/37 (40.5%)*	*11/23 (47.8%)*	*4/14 (28.6%)*	
	3 classes	*8/37 (21.6%)*	*3/23 (13.0%)*	*5/14 (35.7%)*	
	4 classes	*4/37 (10.8%)*	*2/23 (8.7%)*	*2/14 (14.3%)*	
	5 classes	*10/37 (27.0%)*	*7/23 (30.4%)*	*3/14 (21.4%)*	
	Number of considered micro-organisms				**0.7942**
	1 bacterium	158 (90.8%)	79 (91.9%)	79 (89.8%)	
	2 bacteria (co-infection)	16 (9.2%)	7 (8.1%)	9 (10.2%)	
	Charlson Index	**4** [2–6]	**5** [3–6]	**4** [2–5]	**0.0595**
	Major surgery in the 6 months before infection	**86 (49.4%)**	**47 (54.7%)**	**39 (44.3%)**	**0.2250**
	Previous colonisation by the same bacteria ≤6 months before infection	**18 (10.3%)**	**13 (15.1%)**	**5 (5.7%)**	**0.0484***
	LOS prior to sepsis (median)	**14** [8–25]	**14** [7–22]	**14** [11–28]	**0.1280**

In all tests, the significance level was set at α = 0.05. Data analysis, computation and plotting were performed using the statistical software R, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) [20].

Results

In years 2018–2020, among patients admitted to the "SS. Antonio e Biagio e Cesare Arrigo" Hospital, 1471 cases of colonisations by the three considered bacteria were detected: *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* were responsible for 141, 573 and 757 cases respectively.

Among these colonisations, 174 patients (11.8%) developed septic infections and were then enrolled for the study (38 in 2018, 48 in 2019 and 88 in 2020). The proportion of colonised cases developing sepsis was different between *P. aeruginosa* (37 patients, 6.5% of those colonised), *K. pneumoniae* (102 cases, 13.5%), and *A. baumannii* (35 episodes, 24.8%).

Among enrolled patients, more than two thirds (119/174, 68.4%) were males, and median age was 69, with no significant differences between the pre-COVID and COVID periods. Median hospital stay prior to developing sepsis, considering patients that actually contracted it, was 15 days (14 for *A. baumannii* and *K. pneumoniae* cases, 21 for *P. aeruginosa*).

Data analysis showed that frequency distributions of the three bacteria have changed from 2018 to 2019–2020, with a relative increase in *A. baumannii* cases compared to the other two species (*p* < 0.0001). With regard to resistance patterns, no significant differences emerged between the two periods for *A. baumannii* (generally resistant to at least three antibiotics) or *P. aeruginosa*, whilst the proportion of *K. pneumoniae* cases resistant to 3–4 classes of antimicrobials was significantly higher in 2020 (*p* < 0.0001). Descriptive statistics are detailed in Table 1, and additional considerations about baseline characteristics are available in the Supplementary Material (§1.3).

Concerning therapy, most patients were treated with carbapenems (72.4%), although – after comparing the COVID period in relation to the pre-COVID – a significant rise could be detected in the use of polymyxins, particularly colistin (62.5% vs 36%, *p* = 0.0005).

Moreover, also the administration of glycopeptides (i.e. vancomycin, teicoplanin) experienced an increase, although not statistically significant. Interestingly, use of the most expensive antibacterial agents was required by a significantly higher proportion of patients in 2020 compared to 2018–2019 (52.3% vs 37.2% respectively, *p* = 0.0493).

Diagnostic procedures performed on enrolled patients included both laboratory – blood counts, inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT), and culture tests – and imaging exams (mainly chest X-rays). Comparison between pre-COVID and COVID periods yielded a generally rising trend for all considered diagnostic procedures, particularly significant for those used for routine patient monitoring such as X-rays, computed tomographies, blood counts, CRPs, PCTs and broncho-alveolar lavage cultures (Table 2).

Eventually, concerning the final outcome of sepsis-related hospital stay, no substantial differences were recorded between pre-COVID and COVID period: in both cases, most patients recovered (53–57%), around one third died (30.4%), while a low proportion of them (12–16%) were discharged or transferred to other hospitals, and were consequently considered as lost to follow-up. All details related to hospital stay, diagnostic/therapeutic procedures and outcomes are reported in Table 2. The cumulative incidence plot (Fig. 1) shows different final outcomes according to the infecting bacteria, generally better for *P. aeruginosa* and worse for *A. baumannii* (more deaths and fewer recoveries), while *K. pneumoniae* attained outcomes closest to average.

Altogether, the 174 cases of sepsis caused 3295 extra hospitalisation days (median 14, mean 19 extra days/case due to the presence of a right-hand tail of cases with an extra-LOS above 100 days), in which 901 imaging procedures and 7365 laboratory exams were performed, reasonably attributable to the septic episodes (Table 3). Interestingly in 2020, compared to the previous years, a noticeable rise was recorded in all evaluated parameters, due to the increase in the number of cases (Table 3a). However, an increasing trend could be detected also in the number of diagnostic procedures performed per single septic episode, with 16.4 blood counts, 14.7 CRP tests, 10.9 PCT tests and 5.6 X-rays prescribed per case in 2020, compared to corresponding figures equal to, respectively, 11.5, 10.6, 5.4 and 2.9 per case in 2018 (Table 3b).

Table 2
Descriptive characteristics of patients' hospital stay and outcomes.

Sample characteristics		Overall (n = 174)	2018–2019 (n = 86)	2020 (n = 88)	p-value
Characteristics of the extra stay at hospital (ascribable to sepsis)	**Extra-LOS (per episode)**	**14** [9–22]	**14** [9–22]	**14** [10–22]	**0.6987**
	Administered antimicrobials				
	Carbapenems	126 (72.4%)	64 (74.4%)	62 (70.5%)	0.6127
	Cephalosporins	86 (49.4%)	39 (45.3%)	47 (53.4%)	0.2938
	Polymyxins	86 (49.4%)	31 (36.0%)	55 (62.5%)	0.0005*
	Penicillins	56 (32.2%)	33 (38.4%)	23 (26.1%)	0.1048
	Aminoglycosides	52 (29.9%)	31 (36.0%)	21 (23.9%)	0.0979
	Glycopeptides	51 (29.3%)	21 (24.4%)	30 (34.1%)	0.1845
	Tetracyclines	11 (6.3%)	7 (8.1%)	4 (4.5%)	0.3678
	Fluoroquinolones	6 (3.4%)	4 (4.7%)	2 (2.3%)	0.4409
	Sulphonamides	5 (2.9%)	3 (3.5%)	2 (2.3%)	0.6802
	Macrolides/Lincosamides	3 (1.7%)	2 (2.3%)	1 (1.1%)	0.6185
	Others (Phosphomycin, Linezolid, Daptomycin)	45 (25.9%)	22 (25.6%)	23 (26.1%)	1.0000
	Use of the most expensive (newest-generation) antimicrobial agents[†]	**78 (44.8%)**	**32 (37.2%)**	**46 (52.3%)**	**0.0493***
	Imaging procedures (per case of sepsis)				
	X-rays	2 [1–7] Range: 1 – 35	2 [1–4] Range: 1 – 35	4 [1–8] Range: 1 – 32	0.003*
	Computed tomographies	0 [0 – 0] Range: 0 – 4	0 [0 – 0] Range: 0 – 3	0 [0 – 1] Range: 0 – 4	0.0016*
	Ultrasound and echocardiograms	0 [0 – 0] Range: 0 – 3	0 [0 – 0] Range: 0 – 3	0 [0 – 1] Range: 0 – 3	0.0883
	Laboratory exams (per case of sepsis)				
	Blood counts	11 [5–18] Range: 1–131	8 [5–16] Range: 1–115	12 [7–21] Range: 1–131	0.0364*
	C-Reactive protein (CRP)	10 [5–16] Range: 0–118	8 [5–14] Range: 0–100	11 [7–20] Range: 1–118	0.0261*
	Procalcitonin (PCT)	6 [3–11] Range: 0 – 72	4 [1–8] Range: 0 – 46	9 [5–14] Range: 0 – 72	< 0.0001*
	Blood cultures	2 [1–3] Range: 0 – 22	2 [1–3] Range: 1 – 17	2 [1–3] Range: 0 – 22	0.1426
	Urine cultures	1 [0 – 2] Range: 0 – 13	1 [0 – 2] Range: 0 – 13	1 [1,2] Range: 0 – 7	0.6031
	Broncho-alveolar lavage cultures	0 [0 – 1] Range: 0 – 3	0 [0 – 0] Range: 0 – 3	0 [0 – 1] Range: 0 – 3	0.0242*
	Other culture exams	1 [0 – 2] Range: 0 – 29	1 [0 – 2] Range: 0 – 29	1 [0 – 2] Range: 0 – 29	0.1572
	Device replacement manoeuvres	**1 [0 – 3]** Range: 0 – 16	**1 [0 – 3]** Range: 0 – 6	**1 [0 – 2]** Range: 0 – 16	**0.0021***
	Specialist consultancy services	**2** [1–4]	**2** [1–3]	**2** [1–4]	**0.3844**
Outcomes	**Final outcome**				**0.5347**
	Recovery	96 (55.2%)	49 (57.0%)	47 (53.4%)	
	Death	53 (30.4%)	23 (26.7%)	30 (34.1%)	
	Discharge (loss to follow-up)	25 (14.4%)	14 (16.3%)	11 (12.5%)	

[†]Most expensive drugs include newest-generation cephalosporins such as Ceftaroline (48.22 €/ampoule) and Ceftobiprole (53.21 €/ampoule), as well as Ceftazidime/Avibactam (63.49 €/ampoule) and Ceftolozane/Tazobactam (166.71 €/ampoule) combinations.
 * Statistically significant differences ($p < 0.05$)

As a result of the aforementioned elements, costs relatable to septic episodes caused by multi-resistant *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*, in years 2018–2020, might be reasonably estimated in almost 3 million Euros, i.e. an average of 17,200 € per capita (Table 4). Most of the expenditure was represented by extra hospitalisation costs (≈2.5 million Euros, i.e. almost 85% of the total). However, therapy specifically oriented to infection treatment had a substantial impact, entailing 11.2% of the total expenditure (336,000 Euros, Table 4a). Along with the increase in diagnostics and – partially – in hospitalisation days, besides the higher number of cases, even costs per capita have been facing a rising trend, from 15,830 € in 2018–17,970 € in 2020 per septic episode (Table 4b).

Stratification by infecting bacteria showed that, owing to the greater number of cases, *K. pneumoniae* infections appeared to be responsible for the highest expenditure (more than 1.7 million Euros, Tab. S2). However, considering costs per capita, a rising trend was particularly evident for *A. baumannii* and – to a lesser extent – for *K. pneumoniae*, i.e. the bacteria with increasing AMR, while costs per capita appeared to be decreasing for *P. aeruginosa* infections (Tab. S3). Diagnostics about the possible bias due to the relationship between before-sepsis hospitalisation and extra hospitalisation days

showed the absence of correlation between these two variables (Fig. S1, $\tau = 0.10$, p = 0.0633).

Discussion

This study aimed at providing an overview of trends in septic infections due to the bacteria that were represented in most cases of colonisation, i.e. *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*. Our analysis, based on real data coming from medical records and not on simple estimations, offered some quantitative insights about the trends in relative incidences, antimicrobial resistance, and resource consumption in a tertiary hospital of a developed country (Italy).

Starting from the obtained results, the first consideration regards the increase in the number of septic cases from the three examined bacteria in 2020 compared to the previous years (+83% and +132% in comparison with 2019 and 2018 respectively). These numbers probably mirror the different healthcare framework ascribable to the COVID-19 pandemic, as previously reported in literature, where a significantly higher incidence of sepsis was recorded since the beginning of the pandemic wave [15,16].
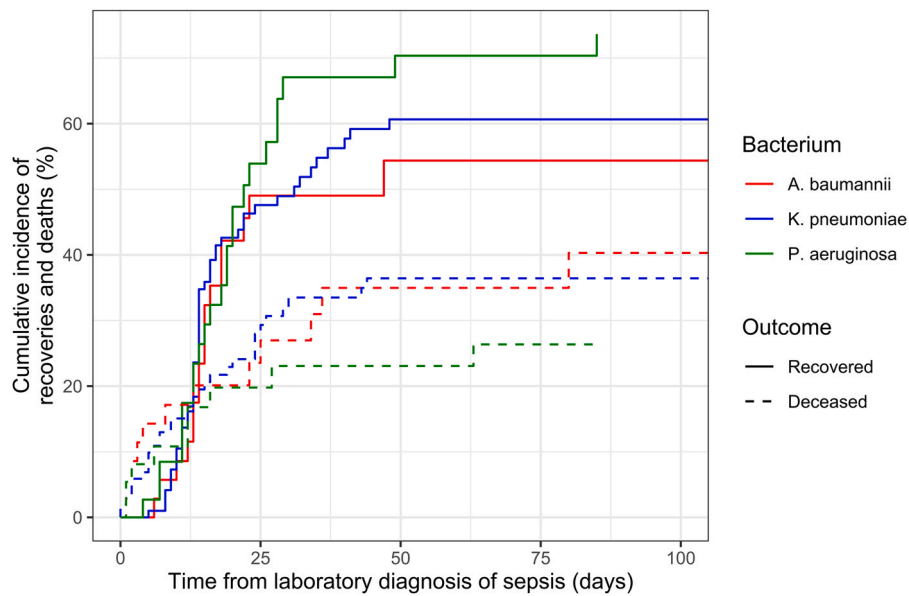
Fig. 1. Cumulative incidences of recoveries and deaths as a function of hospitalisation time, grouped by infecting bacterium. Solid and dashed lines represent recovered and deceased patients, respectively.

Another remarkable element is the number of classes of antimicrobials to which microorganisms are resistant: for all the examined species, considering overall data, resistance rates appeared to be aligned with ECDC estimates [3]. However, the comparison between 2018 and 2019 and 2020 showed a variation in *K. pneumoniae*'s resistance pattern, with a significant increase in the proportion of cases resistant to four antibiotic classes (third-generation cephalosporins, fluoroquinolones, aminoglycosides and carbapenems), and proportionally more cases by *A. baumannii*, at the expense of the other examined bacteria, after the pandemic. These results confirm trends recorded in previous studies, which showed a significant increase in *A. baumannii* isolates [12,13], a higher

occurrence of multi-resistant *K. pneumoniae* [12,14] and a lower incidence of sepsis by *P. aeruginosa* [13] after the outbreak.

Considering the different frequency distribution of the infecting microorganisms, and their mutating AMR pattern, helps to understand the reason for the increased use of colistin in 2020, as that drug remains the first-line therapy for multi-resistant *A. baumannii* infections [21]. Moreover, uncertainty about treatment of clinical cases connected to sepsis explains the use of antimicrobial agents such as glycopeptides, not specifically targeted for contrasting Gram-negative pathogens but primarily used for empirical therapy. It must be noted that these trends appear to be reliable since they were recorded in the absence of any significant changes in the policy

Table 3
Overview of the enrolled sample, considering hospitalisation variables on aggregate.

(a) Overall data, considering all subjects together		2018 (n = 38)	2019 (n = 48)	2020 (n = 88)	Overall (n = 174)
Extra hospitalisation days (ascribable to sepsis)		628	935	1732	3295
Imaging	X-rays	110	183	492	785
	Computed tomographies	6	10	47	63
	Ultrasound/echocardiograms	10	10	33	53
Laboratory	Blood counts	436	670	1443	2549
	C-Reactive Protein (CRP)	403	580	1291	2274
	Procalcitonin tests	207	296	958	1461
	Blood cultures	97	122	250	469
	Urine cultures	54	70	120	244
	Broncho-alveolar lavage cultures	8	19	43	70
	Other culture exams	43	92	163	298
Consultancy services by specialists from other wards		87	140	272	499
Device (e.g. catheter) replacement manoeuvres		49	72	167	288
(b) Average data per subject		2018 (n = 38)	2019 (n = 48)	2020 (n = 88)	Overall (n = 174)
Extra hospitalisation days (ascribable to sepsis)		16.5	19.5	19.7	18.9
Imaging	X-rays	2.9	3.8	5.6	4.5
	Computed tomographies	0.2	0.2	0.5	0.4
	Ultrasound/echocardiograms	0.3	0.2	0.4	0.3
Laboratory	Blood counts	11.5	14.0	16.4	14.6
	C-Reactive Protein (CRP)	10.6	12.1	14.7	13.1
	Procalcitonin tests	5.4	6.2	10.9	8.4
	Blood cultures	2.6	2.5	2.8	2.7
	Urine cultures	1.4	1.5	1.4	1.4
	Broncho-alveolar lavage cultures	0.2	0.4	0.5	0.4
	Other culture exams	1.1	1.9	1.9	1.7
Consultancy services by specialists from other wards		2.3	2.9	3.1	2.9
Device (e.g. catheter) replacement manoeuvres		1.3	1.5	1.9	1.7

Table 4
Costs ascribable to septic episodes, classified by item.

(a) Overall costs, considering all subjects together (expressed in thousand Euros)					
		2018 (n = 38)	2019 (n = 48)	2020 (n = 88)	TOTAL (n = 174)
Extra-LOS (ascribable to sepsis)		509.7	710.0	1312.3	**2532.0**
Diagnosis	Imaging	3.2	4.8	15.8	**23.8**
	Laboratory	14.4	20.3	56.1	**90.8**
Therapy (antimicrobial agents)		73.2	73.1	189.8	**336.1**
Replaced devices		1.1	1.7	7.4	**10.2**
Grand total		**601.6**	**809.9**	**1581.4**	**2992.9**
[95% CI]		**[550.0–653.2]**	**[751.2–868.6]**	**[1504.1 – 1658.7]**	**[2894.0 – 3091.8]**
(b) Average costs per subject (expressed in Euros)					
		2018 (n = 38)	2019 (n = 48)	2020 (n = 88)	TOTAL (n = 174)
Extra-LOS (ascribable to sepsis)		13,413	14,792	14,913	**14,552**
Diagnosis	Imaging	83	99	180	**136**
	Laboratory	378	423	638	**522**
Therapy (antimicrobial agents)		1927	1522	2156	**1931**
Replaced devices		29	36	84	**59**
Grand total		**15,830**	**16,870**	**17,970**	**17,200**
[95% CI]		**[14,470–17,190]**	**[15,650–18,100]**	**[17,090–18,850]**	**[16,630–17,770]**

adopted by the hospital for antibiotic use: in fact, the hospital's current antibiotic policy was agreed by the antibiotic stewardship group at its establishment in 2017, shortly after the updates issued by the World Health Organisation on antimicrobial use and stewardship priorities [4].

Specific antimicrobial therapy played a secondary role in determining costs associated with MDR sepsis (11.2% of the total amount). However, disaggregated tables show that therapy-related costs heavily increased in 2020, along with the greater incidence of *A. baumannii* infections and the higher proportion of extensively drug-resistant *K. pneumoniae*. In fact, the COVID outbreak appears to have affected also AMR patterns [12–14], often requiring use of new-generation antimicrobials and combinations to ensure greater effectiveness in treating multi-resistant pathogens, yet at the price of higher purchase costs [22,23]. Not coincidentally, the highest expenditures for therapy (what's more, with a rising trend) could be reported for bacteria with increasing resistance, i.e. *K. pneumoniae* and *A. baumannii*: while the latter does not allow reliable economic trend analyses due to the extremely low number of cases in 2018–2019, the increase in antibiotic resistance appeared to result into tangibly higher therapy costs for *K. pneumoniae*, as resistant *Klebsiella* strains demand using combinations such as ceftazidime/avibactam [24] or latest-generation drugs such as ceftaroline [25].

However, the variable with the greatest impact on the total expenditure (84.6% of the total) is represented by the extra-LOS attributable to sepsis, responsible for around 2.5 million out of the overall 3 million Euros (i.e. around €14,500 per case). For patients enrolled in our study, the mean extra hospitalisation attained 19 days, which is consistent with previous studies reporting hospital stays longer by 12–19 days for patients with hospital-onset sepsis [26].

In our study, extra-LOS was determined from the onset of infection, defined as the day of the first positive culture, to the assumable end of the infection itself. However, costs of the extra-LOS may be even higher, as the effects of infections may well begin even before any diagnostic test is performed or antibiotic treatment is started, or last beyond the end of antimicrobial therapy (e.g., in terms of recovery time).

Nevertheless, this method might represent a plus of the study, as it overcomes many shortcomings of model-based studies, one of which is typically the already cited correlation between later onset of bacteraemia and longer extra hospitalisation [19]: in fact, the potential impact of this biasing factor appears to be scarce in our

sample (Fig. S1), hence the results of our extra-LOS computation seem to be quite generalisable.

On the other hand, monetary results are hardly comparable with those of other studies, first because of the many differences in healthcare systems and – therefore – in staffing, device and management costs, and second because of methodological differences between studies: in fact, many studies did not report the cost of a bed-day as a separate variable, as some aggregated all measured costs into an overall estimated burden of AMR on hospitals, while some authors separated fixed from variable costs without listing single items, and other analyses accounted single cost categories used in the clinical management of the infection without quantifying comprehensive costs of bed-days [27].

This analysis has strengths and limitations: among the former, the study design must be mentioned, as our analysis was conceived after careful evaluation of the available literature regarding determinants of the clinical and economic impact of sepsis by multiresistant microorganisms. Moreover, an added value is represented by the sample, consisting of all patients meeting inclusion criteria, and by the data collection process, simultaneously performed by two skilled researchers after matching data from all available sources in digital or paper format. Methods used for this study are based on single cost items, which overcomes the methodological shortcomings of many studies that, for instance, concentrate only on treatment costs incurred by inpatients or set LOS-related costs as economic outcome [28]. Moreover, this study reports the breakdown of costs, which could indicate how interventions might be targeted and how financial incentives could be set to improve HAI prevention [29].

Among the limitations, first this is a single-centre study, thus possibly affected by peculiar characteristics of patients' characteristics and/or hospital and care organisation: hence, further similar evaluations in diverse settings would be needed. Moreover, like all hospital-based studies, this study considers costs of the included septic episodes from the healthcare provider's perspective and, therefore, fails to capture the burden represented by indirect costs, and this should be carefully considered while projecting estimates on a national or global level or while assessing the potential impact of prevention measures.

In terms of generalisability of the achieved results, an intrinsic limitation affects cost computation in a comparative prospective, because sepsis-attributable costs can be measured using several different approaches, given both the various methods to estimate

the extra-LOS ascribable to each episode [30] and the widely variable pricing parameters of healthcare items between different regions or countries.

Eventually, this analysis was performed on a subset of septic episodes, i.e. those caused by particularly resistant micro-organisms (all MDR), as this was originally conceived as a pilot study, ahead of a more complete evaluation of healthcare-related sepsis burden: however, reasonably unbiased and adjusted estimates show that, in case of a HAI, the extra-LOS is much more heavily affected by the presence of bacteraemia, rather than from AMR itself [26].

Conclusions

The analysis performed above shows the relevance of the clinical and economic impact of septic episodes caused by MDR bacteria such as *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*. Specifically, the study points out a rising trend in septic cases over years, particularly for extensively resistant strains, with a steep increase in 2020 (concurrently with the COVID outbreak) compared to the previous years (2018–2019).

The occurrence of more episodes entailed a higher sepsis-related burden, mostly due to the extra-LOS (almost 85%): the computation of this parameter is key to understand the real extent of the economic impact of sepsis, and the conduction of further analyses with different methodologies would be of interest, since it would be possible to quantify the range in which extra hospitalisation days may fluctuate.

Although, under current circumstances, the potential saving from HAI prevention might be limited by the fact that most fixed costs (e.g., capital costs, overheads, or staffing contracts) are unlikely to be affected in the short term, the obtained results open up the prospect to further studies performing cost-effectiveness analyses. Since the DRG system computes hospital remuneration based on patients' diseases, rather than on LOS, preventing infections would probably lead to financial benefits, as well as offer healthcare to more patients and shorten waiting lists: resources absorbed by fixed costs could be redeployed to reduce barriers to healthcare services.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.02.007.

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