SHORT COMMUNICATION

Managing hospitalized patients with bacterial infections: the price-to-pay upon site of infection

AUTHORS

Karolina Akinosoglou[1] MD, PhD, Internist – Infectious Diseases Specialist *

Christos Davoulos[2] MD, Researcher

Anne-Lise deLastic[3] MD, PhD, Researcher

Martha Kolosaka[4] MD, Researcher

Vasiliki Niarou[5] MD, Researcher

Spyridoula Theodoraki[6] MD, Researcher

Dimitrios Ziazias[7] MD, Researcher

Foteini Kosmopoulou[8] MD, Researcher

Christina- Panagiota Koutsouri[9] MD, Researcher

Charalambos Gogos[10] MD, PhD, Professor

CORRESPONDENCE

*A/Prof Karolina Akinosoglou akin@upatras.gr

AFFILIATIONS

[1, 10] Department of Internal Medicine and Department of Infectious Diseases, University Hospital of Patras, Rio, Greece

[2, 3, 4, 5, 6, 7, 8, 9] Department of Internal Medicine, University Hospital of Patras, Rio, Greece

ABSTRACT:

Introduction: Infections impose a significant burden on healthcare costs worldwide. We aimed to explore antibiotic- and hospital-related costs of infections needing admission in a tertiary university hospital in Greece.

Methods: We performed a prospective cohort study in the medical care unit of a tertiary university hospital in Greece, for the period May 2016 to May 2018. Patients admitted with respiratory, urinary, gastrointestinal tract, skin, soft tissue and bone infections or primary bacteremia were included in this study. Costs of hospitalization and unit cost of antibiotic regimen were retrieved from a database for Greek hospitals containing data for each International Classification of Diseases (ICD-10) code and the national formulary respectively, and manually calculated for each patient.

Results: Antibiotic costs represent approximately 14–40% of total hospital-related costs depending on infection studied. Skin, soft tissue and bone infections and primary bacteremia led hospital- and antibiotic-related costs, with median costs of €6370 (interquartile range (IQR) 3330.90–11 503.90), €2519.90 (IQR 431.50–8371.10), €4418.10 (IQR 2335–8281.90) and €1394.30 (IQR 519.12–6459.90), respectively. Antibiotic- and hospital-related costs significantly differs with site of infection ($p<0.0001$). Length of stay is strongly correlated with antibiotic- and hospital-related costs, while site of infection is moderately related to antibiotic cost (eta value 0.445), and hospital-related cost (eta value 0.387).

Conclusion: Healthcare-related costs vary substantially depending on site of infection. Information about real-life costs can drive best decisions and help to reduce healthcare expenditures.

Keywords:

antibiotic costs, Greece, healthcare-related costs, infection.

FULL ARTICLE:

Introduction

Infections requiring hospitalization impose significant costs on healthcare systems worldwide. Many economic reports are derived from readily available volume data including bulk costs and pharmacy supply statistics, which do not necessarily correspond to actual costs of antibiotic and resource utilization, as well as everyday clinical practice[1]. A recent effort to overcome this obstacle has been made in Greece in relation to community-acquired pneumonia[2]. This indicated that hospitalization, medication and diagnostic tests mainly drove inpatient costs in cases of community-acquired pneumonia. Data is scarce regarding other sites of infection. We hypothesized that, other than for antibiotic misuse, infection site has a significant impact on antibiotic- and hospital-related cost variability.

Methods

This prospective study was carried out in the medical ward of a tertiary university hospital in Greece between 1 May 2016 and 1 May 2018. Adult patients admitted at the medical ward with established respiratory tract infection (RTI), urinary tract infection (UTI), gastrointestinal infection (GI), skin, soft tissue and bone infection (SSTBI) or primary bacteremia (PB) were included in this

study and followed up until discharge. Epidemiological characteristics, assessment of disease severity as per Sepsis-II[3] and Sepsis-III definitions[4], empiric antibiotic therapy and in-hospital outcome (survival rate and length of stay (LOS)) were recorded. Costs of hospitalization and unit cost of antibiotic regimen were retrieved from a national health system database for Greek hospitals containing data for each International Classification of Disease (ICD-10) code[5] and the national formulary respectively, and manually calculated for each patient.

Statistical analyses

All statistical analyses were performed using SPSS for Windows v25 (IBM International; http://www.spss.com).

Continuous variables are presented as mean ± standard deviation, with ranges or with 95% confidence intervals. Categorical variables are presented as proportions of the sample as a whole. The significance of differences between two independent samples for continuous variables was measured with student t-tests or the Mann–Whitney U-test, also depending on the normality of the data distribution (Kolmogorov–Smirnov test results). For comparisons of continuous variables among three or more groups, we used one-way ANOVA or the Kruskal–Wallis test, again

depending on the normality of the data distribution. Linear correlations between key variables were tested by Spearman's and eta correlation coefficients. The strength of each correlation was assessed according to Cohen's kappa (≥0.5, extremely strong; 0.3–0.49, moderate; ≤0.29, weak). The level of statistical significance was set at $p<0.05$.

Ethics approval

This study was approved by the University Hospital of Patras ethics committee (number 96/15.04.16) and carried out in accordance with relative regulations, following subjects' consent.

Results

In total, 629 patients fulfilled inclusion criteria during the study period. Characteristics of patients, infections and antibiotics, costs and outcome are shown in Tables 1 and 2 respectively. Patients with PB and SSTBI generally presented in more severe condition and this reflected in the percentage of patients with a qSOFA sepsis score ≥2 and the percentage of patients with sepsis compared to those with RTIs, UTIs and SSTIs. PB presented the lowest survival rates. The majority of infections were community acquired, except for PB and SSTBI, which were equally divided between hospital and community origin. PB and SSTBI infections presented the longer LOS, similar to increased antibiotic and hospital-associated cost compared to other sites of infection. LOS, antibiotic- and hospital-related costs all significantly differed between infections. Antibiotic- and hospital related costs are strongly related with LOS in all infections ($p<0.001$ for all sites). Site of infection is moderately related to length of stay (eta value 0.444), antibiotic cost (eta value 0.445) and hospital-related cost (eta value 0.387).

Table 1: Characteristics of patients admitted with bacterial infections to a tertiary university hospital, Greece, May 2016 – May 2018

Characteristic	Infection n (%)/median (IQR)					
	Respiratory tract (*n*=132)	Urinary tract (*n*=232)	Skin, soft tissue and bone (*n*=15)	Primary bacteremia (*n*=47)	Gastrointestinal tract (*n*=104)	Hepatobiliary tract (*n*=99)
Age, years	68 (48–81)	74 (51–80)	65 (58–83)	61 (50–71)	55 (37–72)	76 (60-86)
Male	69 (53)	79 (34)	12 (80)	24 (51)	60 (58)	62 (63)
Sepsis	72 (55)	171 (74)	14 (93)	46 (98)	52 (50)	71 (72)
Community acquired	113 (86)	214 (92)	8 (53)	7 (15)	100 (96)	89 (90)
qSOFA≥2	16 (12)	29 (13)	4 (27)	10 (22)	6 (5.7)	11 (11)
Pathogen identified	25 (19)	52 (28)	13 (87)	47 (100)	6 (6)	23 (23)
Gram (+) (% pathogen identified)	5 (20)	15 (29)	10 (77)	15 (32)	1 (17)	5 (22)
Gram (−) (% pathogen identified)	20 (80)	37 (71)	3 (23)	32 (68)	5 (83)	18 (78)
Antibiotic used (alone or in combination)						
Quinolone	47 (36)	112 (48)	3 (20)	2 (4.3)	55 (52.9)	49 (49.5)
Piperacillin/tazobactam	40 (30)	90 (39)	3 (20)	14 (29.8)	12 (11.5)	34 (34.3)
Cephalosporin	45 (34)	54 (23)	0 (0)	3 (6.4)	21 (20.2)	6 (6.4)
Glycopeptide	8 (6)	26 (11.2)	7 (46.7)	22 (46.8)	8 (7.7)	17 (17.2)
Macrolide	16 (12)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)
Carbapenem	7 (5.3)	19 (8.2)	5 (33.3)	8 (17)	3 (2.9)	7 (7.0)
Aminoglycoside	0 (0)	10 (4.3)	2 (13.3)	1 (2.1)	1 (0.9)	2 (2.0)
Metronidazole	0 (0)	2 (0.8)	2 (13.3)	1 (2.1)	53 (50.9)	19 (19.2)
Antifungal agent	0 (0)	1 (0.4)	0 (0)	5 (10.5)	0 (0)	0 (0)
Other	6 (4.5)	14 (6)	5 (33.3)	10 (21)	11 (10.6)	9 (9.0)
Survival	109 (83)	215 (93)	14 (93)	31 (66)	102 (98)	85 (86)

Table 2: Cost and length of stay for patients admitted with bacterial infections to a tertiary university hospital, Greece, May 2016 – May 2018

Characteristic	Infection n (%)/median (IQR)						
	Respiratory tract (*n*=132)	Urinary tract (*n*=232)	Skin, soft tissue and bone (*n*=15)	Primary bacteraemia (*n*=47)	Gastrointestinal tract (*n*=104)	Hepatobiliary tract (*n*=99)	*p*-value
LOS, days	5 (3–8)	5 (3–8)	29 (10–45)	21 (12.5–31.3)	4 (3–6)	7(6–12)	<0.0001
Total hospital-related cost for LOS, euro	637.0 (458.40–1168.50)	846.0 (586.50–1368.50)	6370 (3330.90–11 503.90)	4418.1 (2335–8281.90)	746.4 (502–1196.40)	1074.1 (880–1723.30)	<0.0001
Antibiotic-related cost for LOS, euro (% of total cost)	129.8 (64.50–305.90) (20.4)	124.6 (66.60–248.50) (14.5)	2519.9 (431.50–8371.10) (39.6)	1394.30 (519.12–6459.90) (31.6)	106.9 (45.90–172.70) (14.3)	230.3 (140.60–474.40) (21.4)	<0.0001

IQR, interquartile range. LOS, length of stay.

Discussion

We performed a prospective study exploring the healthcare costs in relation to site of infection. We found that antibiotic- and hospital-related costs significantly varied among different infections, and is correlated strongly to LOS and moderately to type of infection. We observed that PB and SSTI appear to be the most costly infections, increasing the average antibiotic cost 10-fold compared to other infections, representing approximately one-third of total hospital-associated related costs.

In the case of SSTI, increased cost seems to be attributed to extended LOS, mostly driven by bone infection requiring long courses of intravenous therapy, despite recent data favouring oral therapy, hence antibiotic misuse[1,6]. Antibiotic misuse has been previously recorded in the setting of community-acquired pneumonia in Serbia, significantly elevating healthcare related costs[7]. Similarly, PB requiring specific days of intravenous therapy

is responsible for increased LOS, thus increasing cost. However, in the case of PB it seems that a high percentage of hospital-acquired PB with potential drug-resistant pathogens, complicated by secondary infections and demand for multiple rounds of antibiotics, increased the total expenditure[8]. It is notable that, at the time of this study, dalbavancin, ceftolozane/tazobactam and ceftazidime/avibactam were not available in the host institution.

The costs of antibiotic therapy have been assessed in the past in relation to guideline-adherent appropriateness of initial therapy or use of broad-spectrum antibiotics[1,9,10]. Absolute costs vary significantly between settings, and this could be attributed to antibiotic production of individual countries, supplies, pharma negotiation and federal policies. Most information is derived from cases of respiratory tract infection[2], because no comparative data between infections exist[11,12]. In all cases, inappropriate empirical antibiotic therapy, which is defined by later pathogen identification or clinical failure, significantly increases LOS (by approximately 2 days), and antibiotic- and hospital-related costs (also observed in our group; unpublished data). The present study found that antibiotic costs seem to represent approximately 15–20% of total hospital costs, in contrast to recent data from US hospital cohorts attributing 3–5% of hospital-associated costs to antibiotics[9]. Bearing in mind that this study was performed during the financial crisis in Greece, this observation is important.

Even though the hospital in this study is a tertiary university teaching hospital, conforming with international guidelines on antibiotic therapy, one cannot predict variance among doctors' prescription habits and compliance with stewardship programs[13]. Hospital administrations should begin to consider the importance of appropriate choice of antibiotic therapy rather than simply the pharmacy budget (eg including solely generic regimens to improve costs). A recent evaluation in Kazakhstan of implementation of drug literacy interventions among healthcare workers showed positive outcomes for antibacterial consumption, hence decreasing associated costs[14]. Alternative interventions that require added outlays to improve mortality should be weighed against competing demands[15]. Infectious disease specialist consultation strategies and strict implementation of local stewardship protocols have had variable results in the past[16]. Specialist nursing or self-administered intravenous therapy in an outpatient setting could prove cost effective for both short- and long-term infections[17].

Potential solutions should be explored in the context of ageing populations and their needs, and take advantage of innovation in digital health to allow for self-care and greater independence and cost-effectiveness, while weighing this against limited healthcare expenditure[15,18]. Also to be considered are needs and realities created by the COVID-19 pandemic, which has overstretched healthcare expenditure through irrational and increased use of antibiotics both in wards and intensive care units[19,20]. Reallocated priorities have held back antibiotic surveillance, possibly placing us in the midst of rising antimicrobial resistance in the years following the pandemic[21].

Our study has inherent limitations. Although it spanned a 2-year period, blunting potential variations in time (such as antibiotic class cycling), it remains a single-centre study. Variable antimicrobial resistance environments may complicate and elongate antibiotic management, thus adding costs. Also, our study was designed to record in-hospital costs of infection management. Costs following discharge were beyond the scope of this study. A larger multi-centre study would allow for a multivariable analysis to show other potential independent predictors of cost variability, including site of infection, with greater certainty. Beyond these limitations, this study is one of the first studies to explore real-world antibiotic and hospitalization costs in a Greek setting, examining different sites of infection.

Conclusion

Healthcare-related costs vary substantially depending on site of infection. Information about real-life costs can drive best decisions and help us reduce healthcare expenditures. This was the first study to attain real-world cost data in Greece, pertaining to different sites of infection, providing a greater picture of antibiotic use while suggesting integrated curative and preventive interventions on how this can be moderated in a setting of stringent budget and high antimicrobial resistance.

REFERENCES:

1 Silva ML, Cargnello C, Aulois-Griot M, Dumartin C. Antibiotic misuse: how to evaluate the costs? *Médecine et Maladies Infectieuses* 2019; **49(7):** 485-494. DOI link, PMid:30954321

2 Naoum P, Athanasakis K, Kyriopoulos I, Liapikou A, Toumbis M, Kyriopoulos J. Community acquired pneumonia: a cost-of-illness analysis in Greece. *Rural and Remote Health* 2020; **20(2):** 5400. DOI link, PMid:32536183

3 Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine* 2003; **31(4):** 1250-1256. DOI link, PMid:12682500

4 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315(8):** 801-810. DOI link, PMid:26903338

5 Athens Medical Society in collaboration with Onassis Cardiac Surgery Centre and Ministry of Health and Social Solidarity. *Kleista Enopoiimena Nosileia (KEN).* Available: web link (Accessed December 2021).

6 Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus Intravenous Antibiotics for bone and joint infection. *New England Journal of Medicine* 2019; **380(5):** 425-436. DOI link, PMid:30699315

7 Cupurdija V, Lazic Z, Petrovic M, Mojsilovic S, Cekerevac I, Rancic

N, et al. Community-acquired pneumonia: economics of inpatient medical care vis-a-vis clinical severity. *Jornal Brasileiro de Pneumologia* 2015; **41(1):** 48-57. DOI link, PMid:25750674

8 Stone PW. Economic burden of healthcare-associated infections: an American perspective. *Expert Review of ClinicoEconomics and Outcomes Research* 2009; **9(5):** 417-422. DOI link, PMid:19817525

9 Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. 30-day readmission, antibiotics costs and costs of delay to adequate treatment of Enterobacteriaceae UTI, pneumonia, and sepsis: a retrospective cohort study. *Antimicrobial Resistance, Infection and Control* 2017; **6:** 124. DOI link, PMid:29225798

10 Lucidi C, Di Gregorio V, Ceccarelli G, Venditti M, Riggio O, Merli M. A cost analysis of a broad-spectrum antibiotic therapy in the empirical treatment of health care-associated infections in cirrhotic patients. *ClinicoEconomics and Outcomes Research* 2017; **9:** 385-390. DOI link, PMid:28721080

11 Lee KK, Wan MH, Fan BS, Chau MW, Lee VW. A cost-minimisation analysis comparing different antibiotic regimens used in treating all-cause bacterial pneumonia in Hong Kong. *Journal of Medical Economics* 2009; **12(1):** 46-55. DOI link, PMid:19450064

12 Purba AKR, Ascobat P, Muchtar A, Wulandari L, Dik JW, d'Arqom A, et al. Cost-effectiveness of culture-based versus empirical antibiotic treatment for hospitalized adults with community-acquired pneumonia in Indonesia: a real-world patient-database study. *ClinicoEconomics and Outcomes Research* 2019; **11:** 729-739. DOI link, PMid:31819563

13 Maltezou HC, Mougkou K, Iosifidis E, Katerelos P, Roilides E, Theodoridou M. Prescription of antibiotics and awareness of antibiotic costs by paediatricians in two hospitals in Greece. *Journal of Chemotherapy* 2014; **26(1):** 26-31. DOI link, PMid:24410189

14 Zhussupova G, Skvirskaya G, Reshetnikov V, Dragojevic-Simic V, Rancic N, Utepova D, et al. The evaluation of antibiotic consumption at the inpatient level in Kazakhstan from 2011 to 2018. *Antibiotics (Basel)* 2020; **9(2):** 57. DOI link, PMid:32024295

15 Global Burden of Disease 2016 Greece Collaborators. The burden of disease in Greece, health loss, risk factors, and health financing, 2000-16: an analysis of the Global Burden of Disease Study 2016. *Lancet Public Health* 2018; **3(8):** e395-e406.

16 Krivoy N, El-Ahal WA, Bar-Lavie Y, Haddad S. Antibiotic prescription and cost patterns in a general intensive care unit. *Pharmacy Practice (Granada)* 2007; **5(2):** 67-73. DOI link, PMid:25214920

17 Vargas-Palacios A, Meads DM, Twiddy M, Czoski Murray C, Hulme C, Mitchell ED, et al. Cost-effectiveness of outpatient parenteral antibiotic therapy: a simulation modelling approach. *Journal of Antimicrobial Chemotherapy* 2017; **72(8):** 2392-2400. DOI link, PMid:28505278

18 Lamnisos D, Giannakou K, Jakovljevic MM. Demographic forecasting of population aging in Greece and Cyprus: one big challenge for the Mediterranean health and social system long-term sustainability. *Health Research Policy and Systems* 2021; **19(1):** 21. DOI link, PMid:33588876

19 Grau S, Echeverria-Esnal D, Gomez-Zorrilla S, Navarrete-Rouco ME, Masclans JR, Espona M, et al. Evolution of antimicrobial consumption during the first wave of COVID-19 pandemic. *Antibiotics (Basel)* 2021; **10(2):** 132. DOI link, PMid:33573070

20 Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. . Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clinical Microbiology and Infection* 2020; **26(12):** 1622-1629. DOI link, PMid:32711058

21 Knight GM, Glover RE, McQuaid CF, Olaru ID, Gallandat K, Leclerc QJ, et al. Antimicrobial resistance and COVID-19: Intersections and implications. *Elife* 2021; **10:** e64139. DOI link, PMid:33588991