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Impact of an antimicrobial stewardship program indicator on the appropriateness of the empiric antibiotic treatment of urinary source *Escherichia coli* bacteraemia

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ABSTRACT

A prospective multicentre study was carried out between 2017 and 2021 to assess (1) the appropriateness of the empirical treatment to the local guidelines of urinary source *Escherichia coli* bacteraemia, (2) the appropriateness of empirical treatment to antibiotic sensitivity results and (3) the degree of error in the local guidelines regarding the antibiotic sensitivity reported in acute care hospitals enrolled in the vigilància de les infeccions relacionades amb l'atenció sanitària de Catalunya program. During the study period, 79.0% of the empirical treatments analysed complied with the guidelines and 88.1% were appropriate in view of the in vitro activity of the isolated strain. The rate of appropriateness rose from 73.8% in 2017 to 81.0% in 2021 ($P < 0.001$). The degree of error in the recommendations regarding the in vitro activity of the isolated strains was 5.9% and remained stable during the study period. Antibiotic families correctly prescribed according to the guidelines were third-generation cephalosporins (54.9%), carbapenems (16.8%) and combinations of penicillins and beta-lactamase inhibitors (16.4%). Of the 8009 *E. coli* strains, 19.0% were extended-spectrum beta-lactamases producers, 36.8% were resistant to quinolones and 0.5% were resistant to carbapenems. The broad implementation of an antimicrobial stewardship program with quality indicators of antibiotic use improved compliance to local guidelines in the empiric treatment of urinary tract *E. coli* bacteraemia. The degree of error in local guidelines was low but higher in more complex hospitals and in healthcare-associated infections. Guidelines need to be constantly updated with the

Abbreviations: ESBL, extended-spectrum beta-lactamases; ASPs, antimicrobial stewardship programs; VINCat, vigilància de les infeccions relacionades amb l'atenció sanitària de Catalunya; ICU, intensive care units; RDT, rapid diagnostic tests; HCAI, healthcare-associated infections; EARS-Net, European Antimicrobial Resistance Surveillance Network; UTI, urinary tract infections.

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See Members of the E. coli Study Group in Appendix.

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use of epidemiological data, rapid diagnostic tests and the analysis of patient risk factors specific to each geographical area.

1. Introduction

Bacteraemia is a common and serious systemic infection that affects approximately 600 000 people in the United States and 1.2 million people in Europe each year [1]. *Escherichia coli* is the main cause of bacteraemia in developed countries, surpassing other pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae* [2–6]. Recently, a systematic review of the epidemiology of *E. coli* bacteraemia in developed countries showed an annual increase in its prevalence of 7% [4]. Possible reasons for this rise are population aging, since most episodes occur between 65 and 74 y of age, and the increased complexity in the management of pathologies.

Urinary tract infection (UTI) is the main source of bacteraemia, representing more than 50% of cases [7]. Thirty-day mortality rates due to *E. coli* bacteraemia of 9.6%–12% have been reported [4,8]. The highest rates of mortality and admission to intensive care units (ICUs) are associated with the severity of the disease and also with a non-urinary focus [9].

The greatest changes in the epidemiology of *E. coli* are the emergence of strains resistant to fluoroquinolones and third-generation cephalosporins, with the proportion of isolates in blood cultures with extended-spectrum beta-lactamases (ESBL)-producing *E. coli* reaching 20% [10]. In Spain, from 2000 to 2006, the prevalence of ESBL-producing *E. coli* increased eight times, rising to 4.04% (range 0.4%–20.3%) [11], and in 2017 it reached 8.1% in urine cultures [12].

The appropriateness of the empirical treatment of bacteraemia is an indicator included in the antibiotic stewardship programs (ASPs) [13,14]. Selecting the appropriate empirical antibiotic treatment is increasingly complex due to the rising rates of resistance, and for this reason, treatment algorithms should incorporate both patient-related factors such as severity, the focus of infection and local resistance patterns.

In Catalonia, the vigilància de les infeccions relacionades amb l'atenció sanitària de Catalunya (VINCat) nosocomial infection surveillance program includes among its objectives the application of an ASP in hospitals, in the community and in long-term care facilities [15]. Since its creation in 2006, the VINCat program has incorporated indicators related to the use of antimicrobials, such as the standardized monitoring of consumption and sensitivities, surveillance of multi-resistant microorganisms and the assessment of the appropriateness of antibiotic prophylaxis in colorectal surgery [16]. The VINCat ASPs in the hospital setting began in 2012 following the indications laid out in the Hospital-acquired infections Study Group of the Spanish Society of Infectious Diseases and Clinical Microbiology, Spanish Society of Hospital Pharmacists and Sociedad Española de Medicina Preventiva, Salut Pública y Gestión Sanitaria consensus document [17] and its activities include the design and execution of strategies aimed at reducing antibiotic resistance through the optimization of antimicrobial treatments, especially with regard to the management of infections with the highest incidence and relevance. The process indicator that is the object of this study was introduced to monitor the appropriateness of the empirical treatment of urinary source *E. coli* bacteraemia, in order to identify areas for improvement for ASPs teams to work on.

Thus, the objectives of this study were: to analyse the appropriateness to local therapeutic guidelines for the empirical treatment of urinary source *E. coli* bacteraemia; to assess the appropriateness of empirical treatment with regard to the results of antibiotic sensitivity; and to determine the degree of error in the guidelines with regard to antibiotic sensitivity (i.e., the percentage of bacteraemias administered adequate empirical treatment according to the local protocol, but not in accordance with the antibiotic sensitivity of the isolated strain).

2. Methodology

2.1. Study design

A prospective multicentre study was carried out between 2017 and 2021 to assess (1) the extent to which the empirical treatment of bacteraemias due to *E. coli* of urinary origin complied with the recommendations of the local guidelines, (2) the suitability of the choice of empirical treatment prescribed in view of the results of antibiotic sensitivity tests and (3) the degree of error in the local guidelines regarding the antibiotic sensitivity reported in acute care hospitals enrolled in the VINCat program [15]. This study was subject to a public surveillance program for healthcare-associated infections (HCAI) and was, therefore, open for any hospital to participate. The incorporation of new hospitals was done at the beginning of the year and all centres have to maintain the indicator throughout the year. Those centres that drop the indicator must do so at the beginning of the following year in order to maintain the coherence of the data series. During the study period: 23 centres participated in 2017, 41 in 2018, 45 in 2019, 49 in 2020 and 53 in 2021, representing, respectively, 40.6% (1457 239 stays), 61.7% (2291 261 stays), 62.8% (2349 191 stays), 69.3% (2496 121 stays) and 68.0% (2516 700 stays) of the total annual hospital stays at centres participating in the VINCat program, and included centres in the four provinces of Catalonia. The average time of participation of the centres in the study was 3.65 y and the median was 4 y. The hospitals were classified into three groups according to the number of beds: group I > 500 beds, group II 200–500 beds and group III < 200 beds. Group III includes one urology and nephrology monographic hospital and three oncology monographic hospitals.

At each centre, local researchers performed a prospective follow-ups of all consecutive *E. coli* bacteraemias diagnosed in adult patients. Specific training was given to the assessors prior to the start of the study. They evaluated the appropriateness of the empirical treatment to the local guidelines (1) of the centre. A prescription was considered appropriate to the guidelines if the antibiotic prescription followed guidelines recommendations used by the centres considering the type of patient. They also evaluated the appropriateness of the empirical treatment according in vitro sensitivity of the isolated microorganism (2). A prescription was considered appropriate according to antimicrobial susceptibility testing if the isolated strain was sensitive to the empirically prescribed antibiotic.

Participating centres received an annual report on the appropriateness of empirical treatments with regard to local guidelines and to antibiotic sensitivity. They were encouraged to develop strategies such as the discussion of the results with the ASP team at the centre, improving the dissemination of the guidelines among the centre's prescribing physicians through information sessions and publicity campaigns, and reviewing the guidelines in view of local

Table 1
Quality indicators and definitions for monitoring the appropriateness of the treatment of urinary source *Escherichia coli* bacteraemia.

Indicator	Definition	Numerator description	Denominator description
Appropriateness of empirical treatments according to the local guidelines	Percentage of antibiotics prescribed empirically indicated in the guideline used by the centre	Urinary source *E. coli* bacteraemia with appropriate empirical treatment with regard to local guidelines[a]	Urinary source *E. coli* bacteraemia with empirical treatment
Appropriateness of the empirical treatment prescribed with regard to antibiotic sensitivity test results *according to antimicrobial susceptibility testing*	Percentage of empirical antibiotic prescription that covers the isolated strain	Urinary source *E. coli* bacteraemia with appropriate empirical treatment with regard to antibiotic sensitivity	Urinary source *E. coli* bacteraemia with empirical treatment
Degree of error in the guidelines	Percentage of antibiotics prescribed empirically indicated in the guideline that do not cover the isolated strain	Urinary source *E. coli* bacteraemia with appropriate empirical treatment with regard to the local guidelines but not with regard to the in vitro activity of the isolated *E. coli* strain	Urinary source *E. coli* bacteraemia with appropriate empirical treatment to the local guidelines

[a] If no local guidelines are available, prescribe according to national guidelines. If no national guidelines are available, prescribe according to international guidelines.

sensitivity data. The overall aim was to improve adherence to local guidelines and to encourage the revision of these guidelines if necessary. Each centre was able to design and implement local interventions aimed at improving the proposed indicators. The STROBE recommendations were followed to strengthen the reporting of the study results [18].

2.2. Selection of cases

All patients aged ≥18 y attended in any area of the participating centres who required hospital admission and were hospitalized at the time of diagnosis and prescription of empirical treatment were included.

Urinary source *E. coli* bacteraemia was considered as any isolation of *E. coli* in a blood culture in a patient who simultaneously had a urine culture with more than 10^5 CFU of this microorganism with compatible symptoms and the absence of an alternative focus.

2.3. Microbiological study and antibiotic sensitivity of the strains

The identification of the isolated *E. coli* strains and the antibiotic sensitivity study were carried out using standard techniques, as described elsewhere [19,20].

Antibiotic sensitivity and ESBL production were determined using the European Committee on Antimicrobial Susceptibility Testing breakpoints and following the recommendations of the Spanish Antibiogram Committee and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Strains classified as 'susceptible' (S) or 'susceptible, increased exposure' (I) were considered sensitive [20].

Samples from participating centres were processed in 42 laboratories. In all except one, in which disk diffusion was used, the broth microdilution method was performed [VITEK (bioMérieux, Marcy L'Etoile, France) in 23, MicroScan (Beckman Coulter, Brea, CA, USA) in 15, Phoenix system (BD Diagnostic Systems, Sparks, MD) in 2 and MicroScan and VITEK in 1]. In 36/41 (87,8%) they undergo quality programs (ISO 9001:2015 or 15816:2015) and 6 do not have a quality certificate, but they carry out internal and external quality controls and send the isolates to accredited reference laboratories, when necessary.

2.4. Demographic, clinical and epidemiological variables

The following variables were recorded for each case: patient's age and sex; area of acquisition of the bacteraemia (nosocomial, healthcare associated, community); area of hospitalization at the time of diagnosis and prescription of empirical treatment (medical, surgical or ICU); empirical antibiotic(s) prescribed, whether they complied with the guidelines used by the centre (yes/no), and whether they were appropriate according to the in vitro sensitivity of the *E. coli* strain (yes/no); and the resistance profile of the isolate (ESBL-producing, quinolone-resistant, carbapenem-resistant). bacteraemia was defined as nosocomial if identified >48 h after the admission [21] and before discharge; as HCAI if it began in the community or within 48 h of admission in patients discharged from a health centre ≤4 weeks before the onset of symptoms; and as community-acquired if it began in the community or within 48 h of admission in patients discharged from a health centre >4 weeks before the onset of symptoms [22].

Table 1 shows the definition of the indicators used to assess the appropriateness of the choice of empirical treatment of urinary source *E. coli* bacteraemia at the participating centres.

2.5. Statistical study

The evolution of the appropriateness of the empirical treatments, the degree of error of the guidelines and the resistance profiles of the isolated *E. coli* strains were analysed by comparing the results from the first and the last year of the study period. For categorical variables, Pearson's Chi-square test or Fisher's exact test was used. Associations were measured using odds ratios (OR).

We also analysed the evolution of all global indicators by simple linear regression. The linear relationship was tested by ANOVA tests, and Pearson's correlation coefficient was obtained. However, as we only have five analysis points (2017–2021) this has less statistical power and has been included only in Supplementary Figure 1.

For all analyses, 95% confidence intervals were calculated and a P value < 0.05 was considered statistically significant. A two-tailed distribution was assumed for all P values. The analysis was performed using the SPSS v.20 statistical package.

2.6. Confidentiality and ethical aspects

No diagnostic tests were made or samples taken from any participant other than those required by routine care. The study complied with the principles of the Declaration of Helsinki, with international human rights, and with the legislation regulating biomedicine and personal data protection. All data were treated as confidential, and records were accessed anonymously. This study was approved by the Ethics Committee of Bellvitge Hospital (Ref. PR066/18). Patient data were anonymized, and so the requirement for informed consent was waived by the Ethics Committee for Clinical Research.

Table 2
Evolution of quality indicators to assess appropriateness of the empirical treatment according to the site of acquisition, hospitalization area and type of hospital.

		2017	2018	2019	2020	2021	Total
% of appropriate empirical treatments according to the local guidelines		73.8% (628)	75.9% (1415)	80.0% (1560)	82.2% (1308)	81.0% (1419)	79.0% (6330)
Site of acquisition	Community	78.2% (433)	75.6% (815)	85.4% (1008)	85.5% (837)	85.8% (865)	**82.5% (3958)**
	Nosocomial	56.6% (43)	61.2% (93)	67.9% (129)	76.8% (146)	70.7% (147)	**68.4% (558)**
	HCAI	68.8% (152)	80% (507)	72.8% (423)	76.8% (325)	76.1% (407)	**75.8% (1814)**
Hospitalization area	Medical	74.8% (493)	76.3% (1165)	80.4% (1266)	82.7% (1064)	81.0% (1166)	**79.5% (5154)**
	Surgical	71.1% (108)	74.2% (198)	78.0% (231)	79.3% (180)	80.0% (184)	**76.9% (901)**
	ICU	67.5% (27)	74.3% (52)	78.8% (63)	81.0% (64)	84.1% (69)	**78.3% (275)**
Hospital group	Group I	72.1% (238)	75.6% (360)	88.4% (442)	83.6% (368)	85.3% (401)	**81.6% (1809)**
	Group II	70.7% (164)	76.1% (632)	76.9% (516)	83.3% (478)	80% (424)	**78% (2214)**
	Group III	78.2% (226)	75.9% (423)	77.2% (602)	79.9% (462)	79.1% (594)	**78.1% (2307)**
% of appropriate treatments according to the sensitivity of the isolated strain		**88.2% (751)**	**87.1% (1624)**	**88.3% (1723)**	**88.8% (1414)**	**88.2% (1544)**	88.1% (7056)
Site of acquisition	Community	89.4% (495)	88.9% (958)	91.2% (1076)	91.4% (895)	91.7% (924)	**90.6% (4348)**
	Nosocomial	88.2% (67)	78.9% (120)	84.7% (161)	89.5% (170)	83.7% (174)	**84.8% (692)**
	HCAI	85.5% (189)	86.1% (546)	83.6% (486)	82.5% (349)	83.4% (446)	**84.8% (2016)**
Hospitalization area	Medical	88.0% (580)	86.7% (1324)	88.1% (1387)	88.2% (1134)	87.4% (1257)	**87.6% (5682)**
	Surgical	87.5% (133)	88.0% (235)	87.8% (260)	91.2% (207)	90.9% (209)	**87.6% (1044)**
	ICU	95.0% (38)	92.9% (659)	95.0% (76)	92.4% (73)	95.1% (78)	**94.0% (330)**
Hospital group	Group I	87.0% (287)	84.5% (402)	90.8% (454)	89.5% (394)	87.7% (412)	**88.0% (1949)**
	Group II	87.5% (287)	89.9% (402)	88.8% (454)	89.4% (394)	89.2% (412)	**89.2% (1949)**
	Group III	90.3% (261)	85.3% (475)	86.3% (673)	87.7% (507)	87.7% (659)	**87.1% (2575)**
Degree of error in guidelines		**5.6% (48)**	**5.6% (104)**	**6% (117)**	**6.1% (97)**	**6% (105)**	5.9% (471)
Site of acquisition	Community	6.1% (34)	5.8% (63)	5.7% (67)	5.1% (50)	6.2% (62)	**5.8% (276)**
	Nosocomial	1.3% (1)	5.9% (9)	5.8% (11)	4.2% (8)	4.8% (10)	**4.8% (39)**
	HCAI	5.9% (13)	5% (32)	6.7% (39)	9.2% (39)	6.2% (33)	**6.5% (156)**
Hospitalization area	Medical	5.8% (38)	5.6% (86)	6.6% (104)	6.4% (82)	6.4% (92)	**6.2% (402)**
	Surgical	5.9% (9)	6.4% (17)	4.1% (12)	4.8% (11)	5.2% (12)	**5.2% (61)**
	ICU	2.5% (1)	1.4% (1)	1.2% (1)	5.1% (4)	1.2% (1)	**2.3% (8)**
Hospital group	Group I	7.3% (24)	8.6% (41)	5.2% (26)	5.9% (26)	6.6% (31)	**6.7% (148)**
	Group II	4.7% (11)	2.9% (24)	5.7% (38)	6.8% (39)	6.8% (36)	**5.2% (148)**
	Group III	4.5% (13)	7% (39)	6.8% (53)	5.5% (32)	5.1% (38)	**5.9% (175)**

The bold values highlight titles and total percentages and number of patients/strains.
HCA, healthcare-associated.

3. Results

Between 2017 and 2021, 60 hospitals in Catalonia (six in group I, 15 in group II and 39 in group III) participated in the evaluation of the three objectives of the study (the compliance of empirical treatments for urinary source *E. coli* bacteraemias with local guidelines, the appropriateness of the empirical treatment prescribed in view of the results of antibiotic sensitivity tests, and the degree of error of the local guidelines with respect to the antibiotic susceptibility reported).

In total, the empirical antibiotic prescriptions of 8009 cases were analysed (851 in 2017, 1864 in 2018, 1951 in 2019, 1592 in 2020 and 1751 in 2021). Just over a quarter of cases (27.7%, 2216) were recorded in group I hospitals, 35.4% (2838 cases) in group II hospitals and 36.9% (2955 cases) in group III hospitals. Women accounted for 55.8% of cases (4472) and the mean age was 72.7 y (range 18–103 y).

Regarding the site of bacteraemia acquisition, 59.9% (4799 cases) occurred in the community, 29.9% (2394 cases) were HCAI and 10.2% (816 cases) were nosocomial. In all, 81.0% (6486) of cases were admitted to medical wards, 14.6% (1172) to surgical wards and 4.4% (351) to the ICU.

3.1. Appropriateness of empirical treatment with regard to the local guidelines and to the in vitro activity

During the study period, 79.0% (6330) of the empirical treatments analysed complied with the guidelines (Table 2). The highest level was recorded in group I hospitals: 81.6% (1809 cases) versus 78.0% (4521 cases) in groups II and III, (OR: 1.251; 95% CI: 1.104–1.416; $P < 0.001$), and in community-acquired infections: 82.5% (3958 cases) versus 73.9% for the other sites of acquisition (2372 cases), (OR: 1.663; 95% CI: 1.492–1.853; $P < 0.001$).

In total, 88.1% (7056) of the empirical treatments were appropriate in view of the in vitro activity of the isolated strain. The highest level was recorded in group II hospitals: 89.2% (2532 cases) versus 87.5% in groups I and III (4524 cases) (OR: 1.183; 95% CI: 1.024–1.367; $P = 0.022$), in community-acquired infections: 90.6% (4348 cases) versus 84.4% (2708 cases) for the other sites of acquisition (OR: 1.787; 95% CI: 1.560-2.043; $P < 0.001$), and in the cases admitted to the ICU: 94.0% (330 cases) versus 87.8% (6726 cases) in the other hospitalization areas (OR: 2.177; 95% CI: 1.393–3.403; $P = 0.001$).

3.2. Degree of error in the guidelines

During the study period, the degree of error in the recommendations established in local guidelines regarding the in vitro activity of the isolated strains was 5.9% (471 cases) (Table 2). It was more frequent in patients admitted to the medical ward (6.2%, 402 cases) than in the admissions to the other hospital areas (4.5%, 69 cases) (OR: 1.392; 95% CI: 1.072–1.809; $P = 0.013$). As for the site of acquisition, the HCA cases presented the highest degree of error, although the differences were not significant.

3.3. Antibiotic sensitivity of the strains analysed

Of the 8009 strains studied, 1521 (19.0%) were ESBL producers, 2951 (36.8%) were resistant to quinolones, and 41 (0.5%) were resistant to carbapenems (Table 3). In all, 16.6% (1331) of the strains analysed were ESBL-producing and quinolone-resistant, and 0.2% (15 strains) were ESBL producers and resistant to both quinolones and carbapenems.

Table 3
Evolution of the resistance profile of the isolated strains according to the site of acquisition, hospitalization area and type of hospital.

ESBL strains		2017 16.6% (141)	2018 16.1% (300)	2019 20.3% (396)	2020 19.7% (314)	2021 21.1% (370)	Total 19.0% (1521)
Site of acquisition	Community	9.9% (55)	11.0% (119)	11.0% (130)	11.6% (114)	12.1% (122)	**11.3% (540)**
	Nosocomial	25.0% (19)	21.1% (32)	27.4% (52)	24.2% (46)	24.0% (50)	**24.4% (199)**
	HCAI	30.3% (67)	23.5% (149)	36.8% (214)	36.4% (154)	37.0% (198)	**32.7% (782)**
Hospitalization area	Medical	17.3% (114)	16.2% (247)	19.9% (314)	20.2% (260)	21.2% (305)	**19.1% (1240)**
	Surgical	15.1% (23)	16.9% (45)	23.0% (68)	15.0% (34)	19.6% (45)	**18.3% (215)**
	ICU	10.0% (4)	11.4% (8)	17.5% (14)	25.3% (20)	24.4% (20)	**18.8% (66)**
Hospital group	Group I	20.9% (69)	21.4% (102)	19.2% (96)	22% (97)	22.6% (106)	**21.2% (470)**
	Group II	11.6% (27)	12.5% (104)	18.5% (124)	16.2% (93)	21.5% (114)	**16.3% (462)**
	Group III	15.6% (45)	16.9% (94)	22.6% (176)	21.5% (124)	20% (150)	**19.9% (589)**
Quinolone-resistant strains		**37.8% (322)**	**34.6% (645)**	**38.7% (756)**	**36.2% (576)**	**37.2% (652)**	**36.8% (2951)**
Site of acquisition	Community	28.5% (158)	30% (323)	30.1% (355)	28.4% (278)	28.4% (286)	**29.2% (1400)**
	Nosocomial	40.8% (31)	43.4% (66)	41.1% (78)	34.2% (65)	40.4% (84)	**39.7% (324)**
	HCAI	60.2% (133)	40.4% (256)	55.6% (323)	55.1% (233)	52.7% (282)	**51.3% (1227)**
Hospitalization area	Medical	36.1% (238)	33.6% (513)	38.1% (600)	36.5% (470)	36.9% (531)	**36.3% (2352)**
	Surgical	45.4% (69)	40.4% (108)	42.9% (127)	33.9% (77)	38.3% (88)	**40% (469)**
	ICU	37.5% (15)	34.3% (24)	36.3% (29)	36.7% (29)	40.2% (33)	**37% (130)**
Hospital group	Group I	40.9% (135)	42.9% (204)	36.8% (184)	35.7% (157)	35.1% (165)	**38.1% (845)**
	Group II	38.8% (90)	30% (249)	38.3% (257)	34.1% (196)	37.2% (197)	**34.8% (989)**
	Group III	33.6% (97)	34.5% (192)	40.4% (315)	38.6% (223)	38.6% (290)	**37.8% (1117)**
Carbapenem-resistant strains		**0.7% (6)**	**0.7% (13)**	**0.5% (10)**	**0.3% (4)**	**0.5% (8)**	**0.5% (41)**
Site of acquisition	Community	0.5% (3)	0.6% (6)	0.3% (4)	0.2% (2)	0.5% (5)	**0.4% (20)**
	Nosocomial	1.3% (1)	0.7% (1)	1.6% (3)	0% (0)	0% (0)	**0.6% (5)**
	HCAI	0.9% (2)	0.9% (6)	0.5% (3)	0.5% (2)	0.6% (3)	**0.7% (16)**
Hospitalization area	Medical	0.3% (2)	0.6% (9)	0.5% (8)	0.2% (2)	0.5% (7)	**0.4% (28)**
	Surgical	2.6% (4)	1.1% (3)	0.7% (2)	0.4% (1)	0.4% (1)	**0.9% (11)**
	ICU	0% (0)	1.4% (1)	0% (0)	1.3% (1)	0% (0)	**0.6% (2)**
Hospital group	Group I	1.2% (4)	0.8% (4)	0.6% (3)	0.5% (2)	0.4% (2)	**0.7% (15)**
	Group II	0.4% (1)	0.6% (5)	0.4% (3)	0.2% (1)	0.4% (2)	**0.4% (12)**
	Group III	0.3% (1)	0.7% (4)	0.5% (4)	0.2% (1)	0.5% (4)	**0.5% (14)**

The bold values highlight titles and total percentages and number of patients/strains.
HCA, healthcare-associated.

The presence of ESBL strains was significantly associated with group I hospitals: 21.2% (470 strains) versus 18.1% (1051 strains) in the other two groups combined (OR: 1.215; 95% CI: 1.075–1.372; $P = 0.002$), with health-care acquisition (32.7%, 782 strains) versus 13.2% (739 strains) in the other two sites (OR: 3.201; 95% CI: 2.852–3.592; $P > 0.000$) and with nosocomial acquisition (24.4%, 199 strains) versus 18.4% (1322 strains) (OR: 1.432; 95% CI: 1.208–1.699; $P < 0.001$).

Strains resistant to quinolones were significantly associated with the site of acquisition. In HCAI , 51.3% (1227 strains) were quinolone-resistant versus 30.7% (1724 strains) in infections acquired in the other sites (OR: 2.373; 95% CI: 2.151–2.618; $P < 0.001$). In patients admitted to the surgical service, 40.0% (469 strains) were quinolone-resistant versus 36.3% (2482 strains) in patients admitted to the other hospital areas (OR: 1.171; 95% CI: 1.031–1.329; $P = 0.015$).

3.4. Prescription of empirical antibiotics with regard to the guidelines

Overall, the families of antibiotics correctly prescribed according to the guidelines were (in order of frequency) third-generation cephalosporins (3726 prescriptions, 54.9%), carbapenems (1140 prescriptions, 16.8%) and combinations of penicillins and beta-lactamase inhibitors (1111 prescriptions, 16.4%).

In the medical wards, third-generation cephalosporins were the most frequently prescribed agents in cases of community-acquired infections (2522 prescriptions, 72.2%) and healthcare-acquired infections (519 prescriptions, 32.3%), and carbapenems (124 prescriptions, 31.4%) in cases of nosocomial acquisition (Supplementary Table 1).

In the surgical ward, third-generation cephalosporins were the most frequently prescribed in cases of community acquisition (368 prescriptions, 70.6%) and health-care acquisition (101 prescriptions, 35.2%), and combinations of penicillins and beta-lactamase (54 prescriptions, 34.0%) in cases of nosocomial acquisition (Supplementary Table 1).

In the ICU, carbapenems were the most widely prescribed antibiotics overall (128 prescriptions, 38.7%) and in cases of nosocomial (49.2%) and HCAI (43.3%). In community-acquired infections, carbapenems and third-generation cephalosporins were both prescribed in 32.6% of cases (Supplementary Table 1).

3.5. Evolution of quality indicators

The rate of appropriate empirical treatment of urinary source *E. coli* bacteraemia according to the recommendations of the local guidelines rose from 73.8% in 2017 to 81.0% in 2021 ($P < 0.001$). This increase was statistically significant for all sites of acquisition, for all hospitalization areas and for group I and II hospitals (Table 4).

The rate of appropriate treatment with regard to the in vitro activity of the isolated strains did not vary significantly, remaining close to 88% throughout the study period. The degree of error in the guidelines did not change significantly either, with rates of 5.6% in 2017 and 6.0% in 2021 ($P = 0.717$) (Table 4).

A statistically significant increase in the percentage of ESBL strains was observed, from 16.6% in 2017 to 21.1% in 2021 ($P = 0.006$), especially in the medical ward (17.3%–21.2%; $P = 0.039$) and in group II hospitals (11.6%–21.5%; $P = 0.001$). The percentage of quinolone and carbapenem-resistant strains did not vary significantly, remaining close to 37% and 0.5% respectively throughout the study period (Table 4). Supplementary figure 1 shows the graphic evolution and the Pearson's correlation coefficient of global quality indicators and resistance profile during the study period.

Table 4
Evolution of the quality indicators and resistance profile during the study period according to the site of acquisition, hospitalization area and hospital group.

		2017	2021	IC	*P*
% of appropriate empirical treatments according to the local guidelines		628 (73.8%)	1419 (81.0%)	1.250–1.843	**<0.001**
Site of acquisition	Community	433 (78.2%)	865 (85.8%)	1.293–2.210	**<0.001**
	Nosocomial	43 (56.6%)	147 (70.7%)	1.075–3.183	**0.025**
	HCAI	152 (68.8%)	407 (76.1%)	1.020–2.042	**0.038**
Hospitalization area	Medical	493 (74.8%)	1166 (81.0%)	1.154–1.792	**0.001**
	Surgical	108 (71.1%)	184 (80.0%)	1.012–2.625	**0.044**
	ICU	27 (67.5%)	69 (84.1%)	1.051–6.212	**0.035**
Hospital group	Group I	238 (72.1%)	401 (85.3%)	1.582–3.191	**<0.001**
	Group II	164 (70.7%)	424 (80.0%)	1.164–2.363	**0.005**
	Group III	226 (78.2%)	594 (79.1%)	0.758–1.467	0.752
% of appropriate treatments according to the sensitivity of the isolated strain		751 (88.2%)	1544 (88.2%)	0.770–1.281	0.958
Site of acquisition	Community	495 (89.4%)	924 (91.7%)	0.924–1.861	0.13
	Nosocomial	67 (88.2%)	174 (83.7%)	0.313–1.510	0.351
	HCAI	189 (85.5%)	446 (83.4%)	0.547–1.315	0.462
Hospitalization area	Medical	580 (88.0%)	1257 (87.4%)	0.710–1.247	0.671
	Surgical	133 (87.5%)	209 (90.9%)	0.737–2.744	0.294
	ICU	38 (95.0%)	78 (95.1%)	0.180–5.854	0.977
Hospital group	Group I	287 (87.0%)	412 (87.7%)	0.698–1.623	0.772
	Group II	203 (87.5%)	473 (89.2%)	0.736–1.909	0.484
	Group III	261 (90.3%)	659 (87.7%)	0.492–1.201	0.248
Degree of error of the guidelines		48 (5.6%)	105 (6.0%)	0.751–1.517	0.717
Site of acquisition	Community	34 (6.1%)	62 (6.2%)	0.651–1.544	0.991
	Nosocomial	1 (1.3%)	10 (4.8%)	0.477–30.10	0.208
	HCAI	13 (5.9%)	33 (6.2%)	0.543–2.039	0.881
Hospitalization area	Medical	38 (5.8%)	92 (6.4%)	0.756–1.648	0.58
	Surgical	9 (5.9%)	12 (5.2%)	0.359–2.129	0.768
	ICU	1 (2.5%)	1 (1.2%)	0.029–7.902	0.55
Hospital group	Group I	24 (7.3%)	31 (6.6%)	0.518–1.564	0.71
	Group II	11 (4.7%)	36 (6.8%)	0.732–2.930	0.281
	Group III	13 (4.5%)	38 (5.1%)	0.594–2.156	0.707
ESBL strains		141 (16.6%)	370 (21.1%)	1.089–1.671	**0.006**
Site of acquisition	Community	55 (9.9%)	122 (12.1%)	0.892–1.749	0.194
	Nosocomial	19 (25.0%)	50 (24.0%)	0.516–1.745	0.867
	HCAI	67 (30.3%)	198 (37.0%)	0.965–1.890	0.080
Hospitalization area	Medical	114 (17.3%)	305 (21.2%)	1.013–1.632	**0.039**
	Surgical	23 (15.1%)	45 (19.6%)	0.787–2.366	0.268
	ICU	4 (10.0%)	20 (24.4%)	0.920–9.163	0.088
Hospital group	Group I	69 (20.9%)	106 (22.6%)	0.782–1.551	0.580
	Group II	27 (11.6%)	114 (21.5%)	1.325–3.268	**0.001**
	Group III	45 (15.6%)	150 (20.0%)	0.940–1.949	0.103
Quinolone-resistant strains		322 (37.8%)	652 (37.2%)	0.823–1.154	0.766
Site of acquisition	Community	158 (28.5%)	158 (28,5%)	0.789–1.249	0.951
	Nosocomial	31 (40.8%)	31 (40,8%)	0.576–1.679	0.951
	HCAI	133 (60.2%)	133 (60,2%)	0.536–1.014	0.060
Hospitalization area	Medical	238 (36.1%)	238 (36,1%)	0.854–1.253	0.729
	Surgical	69 (45.4%)	69 (45,4%)	0.492–1.129	0.165
	ICU	15 (37.5%)	15 (37,5%)	0.516–2.443	0.771
Hospital group	Group I	135 (40.9%)	135 (40,9%)	0.585–1.044	0.095
	Group II	90 (38.8%)	90 (38,8%)	0.680–1.282	0.67
	Group III	97 (33.6%)	97 (33,6%)	0.936–1.656	0.131
Carbapenem-resistant strains		6 (0.7%)	8 (0.5%)	0.224–1.869	0.417
Site of acquisition	Community	3 (0.5%)	5 (0.5%)	0.218–3.846	1.000
	Nosocomial	1 (1.3%)	–	–	0.268
	HCAI	2 (0.9%)	3 (0.6%)	0.102–3.721	0.633
Hospitalization area	Medical	2 (0.3%)	7 (0.5%)	0.333–7.751	0.728
	Surgical	4 (2.6%)	1 (0.4%)	0.018–1.460	0.084
	ICU	–	–	–	–
Hospital group	Group I	4 (1.2%)	2 (0.4%)	0.063–1.913	0.237
	Group II	1 (0.4%)	2 (0.4%)	0.079–9.698	1.000
	Group III	1 (0.3%)	4 (0.2%)	0.172–13.856	1.000

The bold values highlight titles and total percentages and number of patients/strains.
HCA, healthcare-associated.

4. Discussion

Inappropriate antibiotic use is one of the main causes of antimicrobial resistance. It has been shown that ASPs can improve the clinical evolution of patients with infection, reducing inappropriate use of antibiotics and healthcare costs without increasing the adverse effects. In order to identify areas in need of improvement and prioritize targeted actions, it is essential to have access to process indicators that measure the appropriateness of hospital antibiotic use. However, finding a process indicator that is feasible, valid and reliable is difficult because the evidence is scarce [23,24].

The prescription quality indicator proposed by the VINCat ASP, which measures the adequacy of empirical treatment of *E. coli* bacteraemia, has been applied successfully by ASPs teams at VINCat hospitals in Catalonia over the last 5 y. This has made it possible to achieve the objective of improving the empirical treatment of urinary source *E. coli* bacteraemia in hospitals of different levels of complexity. There has been a significant increase in adherence to the local empirical treatment guidelines, which has risen from 73.8% to 81%. As for the degree of error in the guidelines has not risen significantly, despite the increase in the percentage of ESBL-producing *E. coli*.

Periodically updated empirical treatment guidelines based on local sensitivity data constitute an invaluable tool not just for the early initiation of appropriate treatment in severe cases, but also for reducing the use of very broad-spectrum antibiotics and as a result lowering antimicrobial resistance. The VINCat ASP indicator made it possible to determine the degree of compliance with the recommendations and to monitor the effectiveness of improvement interventions (e.g., training sessions, dissemination of the guidelines) organized by the ASPs teams at the hospitals over the course of the study. Our data highlighted the greater adherence to the guidelines at more complex hospitals and in cases of community-acquired bacteraemia.

E. coli bacteraemia accounts for 50% of all bacteraemias and for approximately 73% of antibiotic-resistant bacteraemia in some countries [25]. The urinary tract is the focus of *E. coli* bacteraemia in half of the cases [4,9], with 75% being community-acquired [26]. In our study, 59.9% of urinary bacteraemias were community-acquired and 29.9% were health-care adquired. Only 10.2% were nosocomially acquired, a percentage lower than that obtained in other series [4,9,27] where rates of 27%–29% have been reported. The mean age was 72.7 y. These results suggest that strategies for the prevention of *E. coli* bacteraemia and ASPs actions aimed at the diagnosis and treatment of UTIs may be more successful when applied in the community setting, in hospital emergency rooms and in long-term care centres, where the majority of residents are elderly.

UTIs are the cause of 12%–25% of emergency room visits, especially in the elderly, and are responsible for a large proportion of antibiotic prescriptions in this area. This, together with the increase in resistance observed in *E. coli*, highlights the importance of ASPs teams' attempts to improve the management of UTI in this setting [4]. In an ASP intervention aimed at treating UTI in the emergency room, Hecker et al. [28] achieved an increase in adherence to recommended antibiotics from 70% pre-intervention to 89% post-intervention, rates that are very similar to ours.

In our study, the most prescribed empirical treatment comprised third-generation cephalosporins, and 88.1% of the treatments were appropriate in view of the in vitro sensitivity. According to a recent publication, *E. coli* was the second most frequent cause of death worldwide among microorganisms, after *S. aureus* [29]; however, studies of the clinical evolution when the empirical treatment of bacteraemia is inappropriate with respect to in vitro sensitivity are conflicting [30–32]. In some, the urinary focus of *E. coli* bacteraemia has been associated with lower mortality than the non-urinary focus [9]. In our study, despite the significant increase in ESBL *E. coli* over the years, especially in the medical ward and in group II hospitals, the degree of error in the guidelines has not increased excessively (rising only from 5.6% to 6%). This finding, together with the low mortality reported for urinary source *E. coli* bacteraemia, supports the recommendations of empirical treatment of UTI with a reduced spectrum antibiotic and subsequent targeted treatment according to the in vitro sensitivity of the strain isolated [33]. In this regard, it is important to implement rapid diagnostic tests (RDT) to identify the microorganisms that cause the infection and determine their sensitivity. The combination of RDT, ASPs and the presence of a microbiologist 24/7 has proved its usefulness in the early optimization of the use of antibiotics [34].

In recent years, the incidence of UTIs due to ESBL-producing *E. coli* has increased in the community and in tertiary hospitals in the USA, from 4.6% in 2011 to 9.2% in 2019 [35]. In Europe, the EARS-Net report published in 2021 [36] recorded a prevalence of ESBL-producing *E. coli* of 5.5%–37.3%. Our data reflect a significant increase in the percentage of bacteraemia due to ESBL-producing *E. coli*, which rose from 16.6% in 2017 to 21.1% in 2021.

In agreement with other reports [17,30], we found the presence of ESBL-producing *E. coli* to be mainly associated with the healthcare system (32.7%) and secondly with the nosocomial setting (24.4%). This alerts us to the fact that patients in the community who have recently had contact with the healthcare system and those residing in long-term care centres have a higher risk of being carriers of ESBL *E. coli* in the gastrointestinal microflora and therefore of developing UTI and bacteraemia caused by this microorganism.

The presence of ESBL-plasmids with additional genes that affect resistance to fluoroquinolones and sulphonamides is frequent in *E. coli*. In our study, 36.8% of the strains were resistant to ciprofloxacin and there were no significant variations over the years. This percentage is identical to that obtained in the SMART study [12] carried out in Spain in 2016 and 2017. In 2020, the VINCat ASP was implemented in primary care, one of the indicators being the reduction in the use of quinolones. Studies like that of Peñalva et al. [37] show that educational, non-restrictive ASPs interventions, developed continuously in primary care, reduce the consumption of quinolones and cephalosporins, which may in turn lower the rates of ESBL-producing *E. coli* UTI. In our health environment, the high but stable percentage of resistance to quinolones and the increase in ESBL *E. coli* demonstrate the need to strengthen ASPs actions in both primary care and hospital settings.

Due to the growing resistance observed in the causative agents of UTI, there is a risk that the consumption of carbapenems will also rise, which may contribute to the spread of *Enterobacteriaceae* resistant to this group of antibiotics. Although in our study the percentage of empirical treatment of nosocomial bacteraemia with carbapenems was 31.4% and in the ICU setting 49.2%, the percentage of carbapenemase-producing *E. coli* remained stable at 0.5% over the 5-y period, with the country-range in Europe being 0–1.1 [36].

During the last 2 y of the study, the COVID-19 pandemic occurred. As a consequence, antibiotic consumption increased in our area, especially of third-generation cephalosporins [38] mainly at de beginning of the pandemic [39]. These antibiotics are also the most commonly used treatment for *E. coli* bacteraemia of urinary origin. As for the participating centres, 84.6% of the centres continued to conduct the study during the first wave of the pandemic, despite a significant reduction in human resources, and normal activity was restored in 2021 [40]. With regard to the evolution of susceptibility, although there was an increase in the number of ESBL-producing strains, this occurred before the pandemic as shown in Table 2. All these facts, as well as the fact that the pathology studied does not have a respiratory origin, allow us to assume that the COVID-19 pandemic did not have a major impact on this study beyond a slight decrease in the number of cases recorded in 2020 compared to 2019 and 2021.

Our study has several limitations. First, it is an observational study designed to determine compliance with local treatment protocols and the appropriateness of the treatment with regard to the sensitivity of the isolated strain. Therefore, it does not analyse the actions carried out by the ASPs teams over the course of the study period to improve adherence to the guidelines. Each centre has its local treatment guideline or, failing that, adheres to national or international guidelines, so there may be differences in the empirical treatment of UTIs between the participating hospitals. Besides, the centre teams had to assess their own adherence of the prescribed treatments to the guidelines, which could cause some bias. To minimize this, specific training was given to the assessors prior to the start of the study. We also consider that this assessment might be subject to minimal interpretation as the treatments and cases set out in the clinical guidelines are clear. Secondly, the data obtained correspond to the reality of a health system and to specific epidemiology and sensitivity patterns, which may not be reproducible in other settings. Finally, the clinical evolution of the patients was not followed up in order to determine the mortality related to this infection.

In summary, at a time when *E. coli* resistance is increasing, adherence to local guidelines in the empiric treatment of urinary tract *E. coli* bacteraemia leads to better use of antibiotics and may contribute to reducing the emergence of resistance. Our study shows that the broad implementation of an ASPs quality indicator that incorporates the degree of adherence to therapeutic guidelines allows for better compliance with UTI treatment protocols, especially in hospital emergencies. However, although the degree of error in the local guidelines is low, it is higher in more complex hospitals and in HCAI, mainly due to the sustained growth in the percentage of *E. coli* isolates resistant to third-generation cephalosporins in these areas. To improve the appropriateness of the choice of empirical treatment of UTI with regard to antibiotic sensitivity, especially in severe cases, the guidelines need to be constantly updated with the use of RDTs, epidemiological data, and the analysis of patient risk factors specific to each geographical area.

Declarations

Ethical approval: This study was approved by the Ethics Committee of Bellvitge Hospital (Ref. PR066/18).

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Data availability statement: The research data is prospectively registered and belongs to the Nosocomial Infection Surveillance System in Catalonia (VINCat), a program from the Catalan Health Service, Department of Health, Generalitat de Catalunya. Anonymous data extraction was approved by the Institutional Research Board of the VINCat. All data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107202.

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