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ORIGINAL ARTICLE

Secular trends in the appropriateness of empirical antibiotic treatment in patients with bacteremia: a comparison between three prospective cohorts

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Abstract

The objective of this study was to explore whether the percentage of inappropriate empirical antibiotic treatment in patients with bacteremia changed over time and to understand the factors that brought on the change. Three prospective cohorts of patients with bacteremia in three different periods (January 1st, 1988 to December 31st, 1989; May 1st, 2004 to November 30, 2004; May 1st, 2010 to April 30, 2011) were compared. Analysis was performed on a total of 811 patients. In 2010–2011, 55.9% (76/136) of patients with bacteremia received inappropriate empirical treatment, compared with 34.5% (170/493) and 33.5% (55/164) in the first and second periods, respectively, in a significant upward trend ($p = 0.001$). Resistance to antibiotics increased significantly during the study period. The following variables were included in the multivariate analysis assessing risk factors for inappropriate empirical treatment: study period (third period) [odds ratio, OR = 2.766 (95% confidence interval, CI, 1.655–4.625)], gender (male) [OR = 1.511 (1.014–2.253)], pathogen carrying extended-spectrum beta-lactamases [OR = 10.426 (4.688–23.187)], multidrug-resistant *Acinetobacter baumannii* [OR = 5.428 (2.181–13.513)], and skin/soft infections [OR = 3.23 (1.148–9.084)]. A model excluding microbiological data included: gender (male) [OR = 1.648 (1.216–2.234)], study period (third period) [OR = 2.446 (1.653–3.620)], hospital-acquired infection [OR = 1.551 (1.060–2.270)], previous use of antibiotics [OR = 1.815 (1.247–2.642)], bedridden patient [OR = 2.019 (1.114–3.658)], and diabetes mellitus [OR = 1.620 (1.154–2.274)]. We have observed a worrisome increase in the rate of inappropriate empirical treatment of bacteremia. We need tools that will allow us better prediction of the pathogen and its susceptibilities during the first hours of managing a patient suspected of a severe bacterial infection.

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Introduction

Bacteremia is a major cause of morbidity and mortality in both hospitalized and community-dwelling patients. In Europe, the annual number of bacteremia episodes is estimated at over 1.2 million, with more than 157,000 deaths per year [1]. Delays in appropriate antimicrobial treatment for severe bacterial infections are associated with higher mortality rates [2]. Consequently, when identifying a patient with a suspected severe bacterial infection, the attending physician needs to decide on an empirical treatment as soon as possible while considering the benefits of the treatment against the potential resistance selection.

A systematic review of prospective studies reporting the association between appropriate empirical antibiotic treatment and all-cause mortality among adult inpatients with sepsis demonstrated a concerning rate of 46.5% of inappropriate

empirical antibiotic treatment [3]. Inappropriate empirical antibiotic treatment was associated with a higher 30-day mortality [odds ratio, OR = 1.60 (95% confidence interval, CI, 1.37–1.86)] [3].

Among the factors that contribute to high rates of inappropriate empirical treatment are the lack of knowledge of pathogen resistance patterns, pathogen distribution, and patients' risk factors. These factors have changed over the years and we cannot be sure that physicians are aware of these factors and take the changes into account when prescribing empirical antibiotic treatment.

In the present study, we aimed to explore whether there was a specific trend in the percentage of inappropriate empirical antibiotic treatment in patients with bacteremia over time and to understand the factors that brought on the change.

Materials and methods

Design and setting

We examined three prospective cohorts in three different periods from 1988 to 2011.

The first cohort was collected between January 1st, 1988 and December 31st, 1989; the second between May 1st, 2004 and November 30, 2004; and the third between May 1st, 2010 and April 30, 2011. The first two cohorts were a part of previous studies [4–8]. The third cohort was assembled for this study. The study population consisted of inpatients with a suspected bloodstream infection from six departments of medicine in Beilinson Hospital, Petah Tikva, Israel. Data were collected at four time points: the beginning of the episode (day 0), day 2, day 4, and day 30. The study protocol was approved by the research ethics committee of the hospital.

Inclusion/exclusion criteria

We included patients older than 17 years of age with clinically significant positive blood cultures that fulfilled the systemic inflammatory response syndrome diagnostic criteria. Isolates such as coagulase-negative staphylococci and other skin microorganisms were defined as contaminants if they were isolated from a single set of blood cultures. Exclusion criteria were suspected travel infection and pregnancy.

Data collection

Patients fulfilling the inclusion/exclusion criteria were prospectively identified by daily review of patient charts. The following details were collected: background conditions, devices, signs and symptoms, and all available laboratory data. At follow-up, data on the final diagnosis, treatment, and microbiological cultures were collected.

The primary outcome was inappropriate empirical antibiotic treatment, which was defined as inappropriate if the antibiotic treatment given within the first 24 h after blood cultures were taken did not match the in vitro susceptibility of the pathogen.

In order to assess the extent of bacterial resistance, two variables were created: Gram-positive bacteria resistance index and Gram-negative bacteria resistance index. The variables were computed with an arithmetic summation of resistance: susceptible, 0; intermediate, 1; resistant, 2, and divided by the number of antibiotics tested for each isolate.

Statistical analysis

A sample of at least 131 patients in each period was sufficient to detect a statistically significant difference in the primary outcome ($\alpha = 0.05$, $1 - \beta = 0.8$).

Analyses were performed using the Statistical Package for the Social Sciences 19 (SPSS Inc.). Proportions were tested by univariate analysis: χ^2 or Fisher's exact test for comparison of categorical variables, Student's *t*-test for comparison of two independent continuous variables, Mann–Whitney test for comparison of two independent variables with abnormal distributions, and analysis of variance (ANOVA) test for comparison of three continuous variables. The significance of differences in the ORs between different variables and inappropriate empirical antibiotic treatment in each period was examined with the Breslow–Day test.

Logistic regression in the stepwise method was used for multivariate analysis to assess the impact of risk factors on inappropriate antibiotic treatment with and without microbiological variables. Due to the similar rates of inappropriate antibiotic treatment in the first and second periods, we merged those two periods and recoded the study period as a dichotomous variable (0, first and second periods; 1, third period). We entered all variables significantly associated with the outcome on univariate analysis ($p < 0.1$) and not correlated (Spearman correlation > 0.5). We examined interactions that seemed reasonable to us, but none reached significance. The Hosmer–Lemeshow statistic was used for goodness of fit.

Results

Analysis was performed on 811 patients, comprising 493 patients in the first period, 171 patients in the second period, and 147 patients in the third period. In 2010–2011, 55.9% (76/136) of patients with bacteremia received inappropriate empirical treatment, compared with 34.5% (170/493) and 33.5% (55/164) in the first and second periods, respectively, in a significant upward trend ($p = 0.001$).

Table 1 Baseline patient and infection characteristics by study period

Characteristic	First period (1988–1989) [*n*/*N* (%)]	Second period (2002–2003) [*n*/*N* (%)]	Third period (2010–2011) [*n*/*N* (%)]	*p*-Value linear-by-linear association	*p*-Value
Inappropriate empirical treatment	170/493 (34.5%)	55/164 (33.5%)	76/136 (55.9%)	0.000	0.000
Thirty-day mortality	130/493 (26.4%)	30/171 (17.5%)	35/147 (23.8%)	0.213	0.067
Previous use of antibiotics	107/493 (21.7%)	21/171 (12.3%)	36/147 (24.5%)	0.908	0.011
Septic shock	47/487 (9.7%)	9/171 (4.4%)	22/147 (15%)	0.094	0.003
Demographics					
Age (mean ± SD)	71.01 ± 15.44	71.38 ± 16.79	70.41 ± 17.84		0.822
Gender (male)	250/492 (50.8%)	84/171 (49.1%)	70/147 (47.6%)	0.475	0.774
Place of acquisition					
Hospital	108/493 (21.9%)	28/170 (16.5%)	21/147 (14.3%)	0.023	0.068
Nursing home	95/490 (19.4%)	13/170 (7.6%)	28/147 (19.0%)	0.268	0.001
Devices					
Mechanical ventilation	1/493 (0.2%)	5/171 (2.9%)	19/147 (12.9%)	0.000	0.000
Central IV line	14/488 (2.9%)	10/171 (5.8%)	12/146 (8.2%)	0.003	0.014
Source of infection					
Lower respiratory	49/493 (9.9%)	18/171 (10.5%)	21/147 (14.3%)	0.167	0.327
UTI	223/493 (45.2%)	66/171 (38.6%)	48/147 (32.7%)	0.004	0.017
Abdominal	34/493 (6.9%)	14/171 (8.2%)	5/147 (3.4%)	0.244	0.199
Skin/soft tissue	40/493 (8.1%)	11/171 (6.4%)	9/147 (6.1%)	0.353	0.622
Primary/unknown	149/493 (30.2%)	62/171 (36.3%)	64/147 (43.5%)	0.002	0.009
Antibiotic treatment					
First-generation cephalosporins	29/493 (5.9%)	1/171 (0.6%)	4/147 (2.7%)	0.018	0.007
Second-generation cephalosporins	360/493 (73.0%)	11/171 (6.4%)	0/147 (0%)	0.000	0.000
Third-generation cephalosporins	58/493 (11.8%)	71/171 (41.5%)	77/147 (52.4%)	0.000	0.000
Aminoglycosides	24/493 (4.9%)	12/171 (7.0%)	4/147 (2.7%)	0.542	0.21
Vancomycin	17/493 (3.4%)	15/171 (8.8%)	10/147 (6.8%)	0.026	0.016
Other	66/493 (13.4%)	101/171 (59.1%)	88/147 (59.9%)	0.000	0.000
Resistance profile					
Extended-spectrum beta-lactamase	23/493 (4.7%)	16/171 (9.4%)	15/147 (10.2%)	0.007	0.017
Multidrug-resistant *Acinetobacter baumannii*	13/493 (2.6%)	12/171 (7.0%)	13/147 (8.8%)	0.001	0.002
Methicillin-resistant *Staphylococcus aureus*	36/493 (7.3%)	17/171 (9.9%)	12/147 (8.2%)	0.412	0.431
Carbapenem-resistant Enterobacteriaceae	2/493 (0.4%)	15/171 (8.8%)	14/147 (9.5%)	0.000	0.000
Vancomycin-resistant *Enterococcus*	1/493 (0.2%)	0/171 (0.0%)	1/147 (0.7%)	0.438	0.453
Gram-negative pathogens					
Escherichia coli	167/493 (33.9%)	72/171 (42.1%)	50/147 (34.0%)	0.554	0.138
Pseudomonas sp.	45/493 (9.1%)	18/171 (10.5%)	33/147 (22.4%)	0.000	0.000
Klebsiella sp.	56/493 (11.4%)	29/171 (17.0%)	30/147 (20.4%)	0.003	0.011
Proteus sp.	34/493 (6.9%)	19/171 (11.1%)	15/147 (10.2%)	0.104	0.156
Acinetobacter sp.	13/493 (2.6%)	17/171 (9.9%)	15/147 (10.2%)	0.000	0.000
Enterobacter sp.	19/493 (3.9%)	8/171 (4.7%)	2/147 (1.4%)	0.262	0.246
Gram-positive pathogens					
Staphylococcus aureus	59/493 (12.0%)	32/171 (18.7%)	23/147 (15.6%)	0.102	0.076
Enterococcus sp.	23/493 (4.7%)	13/171 (7.6%)	20/147 (13.6%)	0.000	0.001

Table 2 Risk factors for inappropriate empirical treatment in each period; univariate analysis

Characteristic	First period (1988–1989) [*n*/*N* (%)]		Second period (2002–2003) [*n*/*N* (%)]		Third period (2010–2011) [*n*/*N* (%)]		Breslow–Day *p*-value
	Inappropriate empirical treatment	Appropriate empirical treatment	Inappropriate empirical treatment	Appropriate empirical treatment	Inappropriate empirical treatment	Appropriate empirical treatment	
Previous use of antibiotics	53/170 (31.2%)*	54/323 (16.7%)*	8/55 (14.5%)	13/109 (11.9%)	24/76 (31.6%)*	10/60 (16.7%)*	0.524
Septic shock	13/168 (7.7%)	34/319 (10.7%)	3/50 (6.0%)	5/102 (4.9%)	15/76 (19.7%)*	4/60 (6.7%)*	0.056
Demographics							
Age (mean ± SD)	70.5 ± 16.2	71.3 ± 14.9	72.03 ± 16.0	71.66 ± 16.6	72.95 ± 16.5*	66.66 ± 19.0*	
Gender (male)	95/170 (55.9%)	155/322 (48.1%)	40/55 (72.7%)*	41/109 (37.6%)*	38/76 (50.0%)	27/60 (45%)	0.009
Place of acquisition							
Community	93/170 (54.7%)*	214/323 (66.3%)*	39/55 (70.9%)	84/109 (77.1%)	40/76 (52.6%)*	50/60 (83.3%)*	0.056
Hospital	51/170 (30.0%)*	57/323 (17.6%)*	10/54 (18.5%)	18/109 (16.5%)	14/76 (18.4%)	6/60 (10.0%)	0.508
Nursing home	31/168 (18.5%)	64/322 (19.9%)	6/54 (11.1%)	7/109 (6.4%)	22/76 (28.9%)*	4/60 (6.7%)*	0.007
Background conditions							
Bedridden patient	11/58 (19.0%)*	7/117 (6.0%)*	11/55 (20.0%)	12/109 (11.0%)	7/76 (9.2%)	5/60 (8.3%)	0.417
Congestive heart failure	21/170 (12.4%)	30/323 (9.3%)	12/55 (21.8%)	22/109 (20.2%)	21/76 (27.6%)*	7/60 (11.7%)*	0.273
Diabetes mellitus	45/170 (26.5%)	73/323 (22.6%)	18/55 (32.7%)	24/109 (22.0%)	33/76 (43.4%)*	12/60 (20.0%)*	0.124
Liver cirrhosis	5/170 (2.9%)	10/323 (3.1%)	0/55 (0.0%)	3/109 (2.8%)	3/76 (3.9%)	1/60 (1.7%)	0.339
Chronic renal failure	11/170 (6.5%)	19/323 (5.9%)	12/55 (21.8%)	21/109 (19.3%)	29/75 (38.7%)	17/59 (28.8%)	0.789
Devices							
Mechanical ventilation	0/170 (0.0%)	1/323 (0.3%)	4/55 (7.3%)*	1/109 (0.9%)*	12/76 (15.8%)	4/60 (6.7%)	0.281
Central IV line	7/165 (4.2%)	7/323 (2.2%)	5/55 (9.1%)	4/109 (3.7%)	6/76 (7.9%)	4/59 (6.8%)	0.709
Source of infection							
Lower respiratory	16/170 (9.4%)	33/323 (10.2%)	6/55 (10.9%)	12/109 (11.0%)	9/76 (11.8%)	11/60 (18.3%)	0.722
UTI	62/170 (36.5%)*	161/323 (49.8%)*	19/55 (34.5%)	44/109 (40.4%)	24/76 (31.6%)	20/60 (33.3%)	0.465
Abdominal	11/170 (6.5%)	23/323 (7.1%)	8/55 (14.5%)	6/109 (5.5%)	3/76 (3.9%)	2/60 (3.3%)	0.216
Skin/soft tissue	19/170 (11.2%)	21/323 (6.5%)	3/55 (5.5%)	8/109 (7.3%)	7/76 (9.2%)	2/60 (3.3%)	0.364
Primary/unknown	64/170 (37.6%)*	85/323 (26.3%)*	19/55 (34.5%)	39/109 (35.8%)	33/76 (43.4%)	25/60 (41.7%)	0.259
Resistance profile							
Extended-spectrum beta-lactamase	18/170 (10.6%)*	5/323 (1.5%)*	15/55 (27.3%)*	1/109 (0.9%)*	12/76 (15.8%)*	2/60 (3.3%)*	0.227
Multidrug-resistant *Acinetobacter baumannii*	9/170 (5.3%)*	4/323 (1.2%)*	8/55 (14.5%)*	4/109 (3.7%)*	11/76 (14.5%)*	0/60 (0.0%)*	0.307
Methicillin-resistant *Staphylococcus aureus*	22/170 (12.9%)*	14/323 (4.3%)*	13/55 (23.6%)*	4/109 (3.7%)*	10/76 (13.2%)*	2/60 (3.3%)*	0.000
Carbapenem-resistant Enterobacteriaceae	1/170 (0.6%)	1/323 (0.3%)	10/55 (18.2%)*	5/109 (4.6%)*	11/76 (14.5%)*	1/60 (1.7%)*	0.605
Vancomycin-resistant *Enterococcus*	1/170 (0.6%)	0/323 (0.0%)	0/55 (0.0%)	0/109 (0.0%)	1/76 (0.0%)	0/60 (0.0%)	0.255

A significant difference between the subgroups is marked by *; 18 patients (approximately 2% of all patients) had no information about appropriateness of empirical treatment

Table 3 Univariate analysis to detect variables associated with inappropriate empirical treatment in all patients

Characteristic	Inappropriate empirical treatment [*n*/*N* (%)]	Appropriate empirical treatment [*n*/*N* (%)]	*p*-Value
Previous use of antibiotics	85/301 (28.2%)	77/492 (15.7%)	0.000
Septic shock	31/294 (10.5%)	43/481 (8.9%)	0.461
Demographics			
Age (mean ± SD)	71.85 ± 15.39	70.88 ± 16.20	0.387
Gender (male)	173/301 (57.5%)	223/491 (45.4%)	0.001
Place of acquisition			
Hospital	75/300 (25.0%)	81/492 (16.5%)	0.003
Nursing home	59/298 (19.8%)	75/491 (15.3%)	0.101
Background conditions			
Bedridden patient	29/301 (9.6%)	24/492 (4.9%)	0.009
Congestive heart failure	54/301 (17.9%)	59/492 (12.0%)	0.020
Diabetes mellitus	96/301 (31.9%)	109/492 (22.2%)	0.002
Liver cirrhosis	8/301 (2.7%)	14/492 (2.8%)	0.876
Chronic renal failure	52/301 (17.3%)	57/492 (11.6%)	0.024
Devices			
Mechanical ventilation	16/301 (5.3%)	6/492 (1.2%)	0.001
Central IV line	18/301 (6.0%)	15/492 (3.0%)	0.045
Source of infection			
Lower respiratory	31/301 (10.3%)	56/492 (11.4%)	0.636
UTI	105/301 (34.9%)	225/492 (45.7%)	0.003
Abdominal	22/301 (7.3%)	31/492 (6.3%)	0.581
Skin/soft tissue	29/301 (9.6%)	31/492 (6.3%)	0.085
Primary/unknown	116/301 (38.5%)	149/492 (30.3%)	0.017
Resistance profile			
Extended-spectrum beta-lactamase	45/301 (15.0%)	8/492 (1.6%)	0.000
Multidrug-resistant *Acinetobacter baumannii*	28/301 (9.3%)	8/492 (1.6%)	0.000
Methicillin-resistant *Staphylococcus aureus*	27/301 (9.0%)	36/492 (7.3%	0.404
Carbapenem-resistant Enterobacteriaceae	22/301 (7.3%)	7/492 (1.4%)	0.000
Vancomycin-resistant *Enterococcus*	1/29 (3.4%)	0/11 (0.0%)	0.533

Descriptive epidemiology

The baseline characteristics of bacteremic patients in each period and the results of the χ^2 test for trends are presented in Table 1. A significant downward trend has been seen in hospital-acquired infections [from 21.9% (108/493) to 14.3% (21/147), $p = 0.023$] and urinary tract infections (UTI) [from 45.2% (223/493) to 32.7% (48/147), $p = 0.004$]. A significant upward trend has been seen in infections of a primary/unknown source [from 30.2% (149/493) to 43.5%

Table 4 Logistic regression analysis of independent risk factors for inappropriate empirical antibiotic treatment

Risk factor	OR (95% CI)	*p*-Value
Gender (male)	1.511 (1.014–2.253)	0.043
Last study period	2.766 (1.655–4.625)	0.000
Extended-spectrum beta-lactamase	10.426 (4.688–23.187)	0.000
Multidrug-resistant *Acinetobacter baumannii*	5.428 (2.181–13.513)	0.000
Skin/soft tissue infection	3.23 (1.148–9.084)	0.026

$N = 786$; Hosmer–Lemeshow goodness of fit test: $p = 0.690$; constant: $\beta = -1.301$; risk for inappropriate empirical antibiotic treatment: OR > 1

(64/147), $p = 0.002$], presence of central line [from 2.9% (14/488) to 8.2% (12/146), $p = 0.003$], and rate of mechanical ventilation [from 0.2% (1/493) to 12.9% (19/147), $p = 0.000$]. The most common Gram-negative bacteria in all three periods were *Escherichia coli*. Three Gram-negative pathogens have shown a significant upward trend: *Acinetobacter* sp. [from 2.6% (13/493) to 10.2% (15/147), $p = 0.000$], *Klebsiella* sp. [from 11.4% (56/493) to 20.4% (30/147), $p = 0.003$], and *Pseudomonas* sp. [from 9.1% (45/493) to 22.4% (33/147), $p = 0.000$]. The most common Gram-positive bacterium in all three periods was *Staphylococcus aureus*. *Enterococcus* sp. showed a significant upward trend [from 4.7% (23/493) to 13.6% (20/147), $p = 0.000$]. Resistance to antibiotics increased significantly in all three periods.

Subgroup differences according to appropriateness of empirical treatment throughout the study periods

We looked for factors associated with inappropriate empirical antibiotic treatment in each of the three periods (Table 2). It is interesting to note that septic shock, old age, nursing home residence, and diabetes mellitus were more closely related to inappropriate treatment in the third period. The mortality rate was significantly higher in the inappropriate treatment subgroup in all three periods (an absolute difference of 14.5–19.9%).

Risk factors for inappropriate empirical treatment

The univariate analysis for appropriateness of empirical treatment is displayed in Table 3. UTI was excluded from the multivariate analysis due to significant correlation with primary/unknown source of infection ($r = -0.599$, $p = 0.000$).

The following risk factors for inappropriate empirical treatment were included in the final logistic model: study period (third period) [OR = 2.766 (1.655–4.625)], gender (male) [OR = 1.511 (1.014–2.253)], pathogen carrying extended-spectrum beta-lactamases (ESBLs) [OR = 10.426 (4.688–23.187)], multidrug-resistant (MDR) *Acinetobacter baumannii* [OR = 5.428 (2.181–13.513)], and skin/soft infections [OR = 3.23 (1.148–9.084)] (Table 4).

In order to assess risk factors that were associated with clinical decision-making, we analyzed the same variables excluding microbiological data. The final model of the multivariate analysis included: gender (male) [OR = 1.648 (1.216–2.234)], study period (third period) [OR = 2.446 (1.653–3.620)], hospital-acquired infection [OR = 1.551 (1.060–2.270)], previous use of antibiotics [OR = 1.815 (1.247–2.642)], bedridden patient [OR = 2.019 (1.114–3.658)], and diabetes mellitus [OR = 1.620 (1.154–2.274)] (Table 5).

Table 5 Logistic regression analysis of non-bacteriological risk factors for inappropriate empirical antibiotic treatment

Risk factor	OR (95% CI)	*p*-Value
Gender (male)	1.648 (1.216–2.234)	0.001
Study period	2.446 (1.653–3.620)	0.000
Hospital-acquired infections	1.551 (1.060–2.270)	0.024
Previous use of antibiotics	1.815 (1.247–2.642)	0.002
Bedridden patient	2.019 (1.114–3.658)	0.021
Diabetes mellitus	1.620 (1.154–2.274)	0.005

$N = 786$; Hosmer–Lemeshow goodness of fit test: $p = 0.262$; constant: $\beta = -1.386$; risk for inappropriate empirical antibiotic treatment: OR > 1

Discussion

The prescription of inappropriate empirical antibiotic treatment has risen by more than 20% (up to 55.9% in 2010–2011) in the last 20 years, along with a significant increase in resistant bacteria.

We observed trends over time in patients with bacteremia. The ratio of hospital-acquired to community-onset episodes has decreased over the years. The marked rise in mechanical ventilation and the increased use of central catheters as underlying conditions are consistent with previous reports [9, 10]. A major concern is the rise in infections that are defined as primary or unknown due to the difficulty of defining the source of infection, found to be a risk factor of mortality [11–13]. Almost all antibiotics showed an upward trend in resistance. The most prominent trend was of carbapenem-resistant Enterobacteriaceae (CRE), which was barely present in the late 1980s and reached 9.5% of patients in 2010–2011. The increased prevalence of MDR *A. baumannii* came in tandem with the increase in prevalence of *Acinetobacter* sp.

In a stratified analysis, we assessed whether the association of risk factors with inappropriate treatment changed over time. Nursing home residents were increasingly given inappropriate treatment: the odds for inappropriate treatment increased from 0.93 in the first period to 4.3 in the third, probably reflecting the prevalence of resistant bacteria in nursing home residents [14], the increasing use of antibiotics in these institutions [15], and the inability of physicians to take that into account. We observed the same trend over time in diabetic patients: while the percentage of diabetes mellitus among patients given appropriate antibiotic treatment remained stable over time, the percentage of patients with diabetes among patients given inappropriate treatment increased from 23% in the first period to 32% in the second period and 43% in the third period.

The strong risk factors for inappropriate treatment were stable over the years: patients infected with ESBL-carrying Enterobacteriaceae, MDR *A. baumannii*, and methicillin-resistant *Staphylococcus aureus* were at high risk for inappropriate early antibiotic treatment. Carbapenem resistance joined these risk factors in the third period.

In the multivariate regression for the risk of inappropriate empirical treatment including all patients, ESBL-producing bacteria had the highest impact (OR = 10.426). In our study, a marked increase in the incidence of infections due to ESBLs was observed over the years (from 4.7% up to 10.2%) [16–20]. A possible association with the surge in ESBLs is the increase over time in the use of third-generation cephalosporins. The study period was entered in our final model and was not explained by the other risk factors. This might be explained by a general rise in antibiotic resistance that was not fully accounted for by the variables we have used. A second explanation might be stricter restrictions on the use of broad-spectrum antibiotics over the years.

In conclusion, we have observed a worrisome increase in the rate of inappropriate empirical treatment of bacteremia, a trend similar to that observed in the published literature [21] (and unpublished data). Of special interest was the role of long-term care facilities as risk factors for inappropriate treatment; interventions to prevent the spread of resistant bacteria and avoid abuse of antibiotics should target these institutions [22]. We need tools that will allow us better prediction of the pathogen and its susceptibilities during the first hours of managing a patient suspected of a severe bacterial infection. This can be done by better use of the patient's data [23, 24] or by rapid, point-of-care, culture-free tests. These tools should focus on the main culprits: ESBL-carrying bacteria, *A. baumannii*, methicillin-resistant *Staphylococcus aureus*, and carbapenem-resistant Enterobacteriaceae.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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