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Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals

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Abstract

Classification of bloodstream infections (BSIs) as community-acquired (CA), healthcare-associated (HCA) and hospital-acquired (HA) has been proposed. The epidemiology and clinical features of BSI according to that classification in tertiary-care (TH) and community (CH) hospitals were investigated in a prospective cohort of 821 BSI episodes from 15 hospitals (ten TH and five CH hospitals) in Andalucía, Spain. Eighteen percent were CA, 24% were HCA and 58% were HA. The incidence of CA and HCA BSI was higher in CH than in TH (CA: 3.9 episodes per 1000 admissions vs. 2.2, p <0.01; HCA: 5.0 vs. 2.9, p <0.01), whereas the incidence of HA BSI was lower (7.7 vs. 8.7, p <0.01). In CA and HCA BSI, the respiratory tract was more frequently the source in CH than in TH (CA: 30% vs. 15%; HCA: 20% vs. 9%, p ≤0.03). In HCA BSI, chronic renal insufficiency and tunnelled catheters were less frequent in CH than in TH (11% vs. 26% and 7% vs. 19%, p ≤0.03), although chronic ulcers were more frequent (22% vs. 8%, p 0.008). BSIs as a result of methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* were very rare in CA episodes, although extended-spectrum β-lactamase-producing *Escherichia coli* (ESBLEC) caused a similar proportion of all BSIs in CA, HCA and HA episodes. Multivariate analysis revealed no significant difference in mortality rates in CH and TH. HCA infections should be considered as a separate class of BSI in both TH and CH, although differences between hospitals must be considered. CA BSIs were not caused by multidrug-resistant pathogens, except for ESBLEC.

Keywords: Bloodstream infections, community-acquired infections, extended-spectrum β-lactamases, healthcare-associated infections, methicillin-resistant *Staphylococcus aureus*, multicentre study, nosocomial infections
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Introduction

Bloodstream infections (BSI) are an important cause of morbidity and mortality in hospitalized patients [1–3]. Traditionally, BSI have been divided into community and nosocomial episodes [4]. However, subsequent to the implementation of ambulatory alternatives to inpatient care, significant changes in the epidemiology of BSI have been noted and a proposal was made to further subdivide community-onset BSI into healthcare-associated (HCA) episodes for patients with significant recent healthcare contact and procedures, and strictly community-acquired (CA) episodes for patients without [5].

However, this new classification has been evaluated in only a few studies [5–9], in which HCA episodes were

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shown to be somewhat more similar to hospital-acquired (HA) than to CA BSI in aetiology and predisposing conditions; these studies included retrospective analysis or included cases from a limited number of hospitals, and used different criteria. Its applicability to both tertiary-care hospitals and community hospitals has not been studied specifically, nor is it known whether this classification is helpful in identifying patients with a low risk of acquiring some emergent community-onset infection-causing, antibiotic-resistant pathogens, such as extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* [10]. The present study aimed to investigate the population-based incidence, epidemiology, aetiology and clinical features of BSI according to the epidemiological type of infection, and to evaluate the newly-proposed scheme within a wide sample of hospitals that included both tertiary-care and community settings.

Materials and Methods

Site and design

A multicentre prospective cohort study was conducted in 15 public hospitals (ten tertiary-care and five community hospitals) in Andalucía, Spain. The participating hospitals provide health care to >90% of their catchment areas (>4 million) [11].

All episodes of clinically significant BSI in adult patients (>14 years) between 15 October 2006 and 15 December 2006 were included. Because the aim of the study was to include a significant number of cases from community centres, the study period was extended until 15 March 2007 in these hospitals.

Blood cultures were performed, processed and interpreted in accordance with the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology [12]. Blood cultures (at least two blood draws) were obtained from peripheral veins, except in a few cases where the central venous catheter was the suspected cause, when at least one blood draw was obtained from a peripheral vein and another from the catheter. Susceptibility results were interpreted according to the CLSI recommendations [13]; in this analysis, we focussed on methicillin resistance in *Staphylococcus aureus*, vancomycin-resistance in enterococci, ESBL production in *E. coli* and *Klebsiella* spp., and carbapenem resistance in *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

Cases were detected by daily review of blood culture results. All patients with positive blood cultures were considered eligible. Different episodes occurring in the same patients were included only when caused by different species. For potential contaminants (coagulase-negative staphylococci, diphtheroids), only episodes in which the organism had been isolated from two or more blood draws were included [4,12]. Patients were followed until discharge or death. The study was approved by the Ethics Committees of the participating centres, which waived the need for obtaining informed consent.

Variables and definitions

The data collected included: type of hospital; epidemiologic type of infection (CA, HCA or HA); demographics; type and severity of chronic underlying disease [14]; source of BSI (see below); vascular or urinary catheter and mechanical ventilation at onset, endoscopic procedures performed within the preceding week, and major surgery in the preceding 3 months; antimicrobial use; aetiology; empirical therapy and outcome.

Episodes were classified as HA if the episode occurred more than 48 h after admission [4]; all other episodes were considered community-onset, which were then classified as HCA or CA, according to the criteria used by Friedman *et al.* [5]. In brief, episodes were classified as HCA when any of the following was present: intravenous therapy or specialist nursing care at home, haemodialysis in the 30 days before the BSI; hospitalization for >2 days in an acute care hospital in the 90 days before the BSI; or resident status in a nursing home or long-term care facility.

The BSI source was determined from clinical and laboratory data, using CDC criteria for secondary BSI [4]. Empirical therapy was considered appropriate when an active antimicrobial agent (according to susceptibility data) was administered at recommended doses within the first 24 h after the blood cultures were performed. Crude mortality was recorded at days 14 and 30.

Statistical analysis

Population-based incidence rates were calculated according to the assigned reference population for each centre [15] and extrapolated for 1 year. The reference populations are defined by specific geographic limits; patients needing hospital admission are initially hospitalized in their corresponding centre and are only transferred to reference centres when needed. A comparison of rates was performed using a Poisson regression model. Comparisons between CA and HCA, and between HCA and HA episodes were performed similarly to previously reported methods [5]; variables included in the definitions were not compared. Similar methods were used for comparisons between tertiary-care and community hospitals. Categorical and continuous variables were compared using Fisher's exact test and the the Mann–Whitney *U*-test, respectively. Whenever a significant crude association

was found between the type of hospital and mortality, a multivariate analysis was performed by logistic regression to control for confouders using a stepwise forward method.

Results

Incidence of BSI and epidemiological type of infection

During the study period, 821 BSI episodes in adults were included; 660 (80%) occurred in tertiary-care hospitals and 161 (20%) occurred in community hospitals. Overall, 476 (58%) were classified as HA, 195 (24%) as HCA, and 150 (18%) as CA. The distribution of BSI according to predefined epidemiological types of infection was somewhat different in the two types of hospitals; compared to tertiary hospitals, there was a higher frequency of CA episodes in community centres (25% vs. 17%, p 0.01), a lower frequency of HA episodes (47% vs. 60%, p 0.002) and a similar frequency of HCA episodes (28% vs. 23%, p 0.1). The incidence of BSIs is shown in Table 1. The overall population-based incidence was higher in tertiary-care centres related to the higher incidence of nosocomial episodes; the admissions-based incidence was higher in community hospitals. Because only five patients had been admitted from other centres outside their catchment area, the exclusion of these patients from the analysis did not change the results.

Of patients with HCA episodes, 131 (67%) had been previously admitted, 28 (14%) were residents in long-term care facilities, 28 (14%) were receiving haemodialysis and two (1%) were receiving peritoneal dialysis, 41 (21%) attended a day hospital, four (2%) received home intravenous therapy, and five (3%) were receiving other types of specialized home care (several patients had more than one of these predisposing factors).

Predisposing features, sources and outcome according to epidemiological type of infection

Table 2 shows patient characteristics, clinical features and the outcome of BSI. Chronic renal insufficiency, haematological cancer and neutropenia were more frequent in patients with HCA than in CA BSI. Compared to HA episodes, HCA occurred more frequently in patients with chronic renal insufficiency, liver disease and cutaneous ulcer, whereas previous antibiotic use and invasive procedures (with the exception of tunnelled venous catheters) were more frequent in patients with HA BSI. With regard to the source of infection, urinary tract infection was more frequent in CA episodes than in HCA BSI. Endocarditis was more frequent in HCA than in HA cases, whereas vascular catheter-related infections were more frequent in HA BSI. Inappropriate empirical therapy was more frequent in HA BSI. Although there was a trend toward higher mortality in HCA and HA episodes, these differences were not statistically significant.

TABLE 1. Population-based and admissions-based incidence rates of bloodstream infections

	All hospitals	Tertiary hospitals	Community hospitals
Episodes per 100 000 population/year			
All episodes	109.2	116.4[a]	75.3
CA	19.2	19.2	18.0
HCA	25.2	25.2	27.3
HA	64.8	72.0[a]	30.0
Episodes per 1000 admissions			
All episodes	14.7	13.9[a]	16.8
CA	2.7	2.2[a]	3.9
HCA	3.5	2.9[a]	5.0
HA	8.4	8.7[a]	7.7

CA, community-acquired; HCA, healthcare associated; HA, hospital-acquired.
[a]For comparison with community hospitals, p <0.01

TABLE 2. Patient characteristics, clinical features and mortality of bloodstream infections by epidemiological type of infection

	CA (*n* = 150)	HCA (*n* = 195)	HA (*n* = 476)
Age in years, median (IQ range)	67 (46–77)	69 (56–70)	66 (53–75)
Male gender	80 (53)	116 (60)	286 (60)
Nonfatal underlying disease	106 (71)[a]	91 (47)	326 (68)
Chronic renal insufficiency	5 (3)[a]	33 (17)[b]	42 (9)
Chronic liver disease	17 (11)	26 (13)[b]	31 (7)
Solid cancer	21 (14)	34 (17)	112 (24)
Haematological cancer	4 (3)[a]	24 (12)	43 (9)
HIV infection	6 (4)	5 (3)	5 (1)
Chronic cutaneous ulcer	–[c]	12 (6)[d]	9 (2)
Neutropenia	2 (1)[a]	13 (7)	32 (7)
Nontunnelled central venous catheter	–	4 (2)[b]	182 (38)
Tunnelled venous catheter	–	32 (16)[b]	35 (7)
Urinary catheter	19 (13)	25 (13)[b]	238 (50)
Mechanical ventilation	–	1 (1)[b]	93 (20)
Endoscopic procedure	1 (1)	1 (1)[b]	28 (6)
Surgery	–	9 (5)[b]	106 (22)
Previous antimicrobials	26 (17)[a]	62 (32)[b]	253 (53)
Source			
Unknown	22 (15)	45 (23)	127 (27)
Urinary tract	46 (31)[a]	41 (21)	73 (15)
Respiratory tract	28 (19)	22 (11)	55 (12)
Intra-abdominal infection	15 (10)	22 (11)	44 (9)
Biliary tract	18 (12)	18 (9)	26 (5)
Endocarditis	8 (5)	9 (5)[b]	6 (1)
Skin and skin structures	8 (5)	10 (5)	21 (4)
Vascular catheter	–	24 (12)[b]	116 (24)
Others	5 (3)	4 (2)	8 (2)
Appropriate empirical therapy	115 (77)[b]	141 (72)[b]	296 (62)
Mortality			
14-day	22 (15)	36 (18)	97 (20)
30-day	29 (19)	43 (22)	116 (24)

Data are expressed as the number of cases (%), except where specified. p value for all statistical comparisons ≥0.05, except where specified.
CA, community-acquired. HCA, healthcare-associated. HA, hospital-acquired.
[a] For comparison with healthcare-associated episodes, p <0.01 (Fisher's exact test).
[b]For comparison with hospital-acquired episodes, p ≤0.01 (Fisher's exact test).
[c]For comparison with healthcare-associated episodes, p 0.02 (Fisher's exact test).
[d]For comparison with hospital-acquired episodes, p 0.04 (Fisher's exact test).

Aetiology and antimicrobial susceptibility

The microorganisms causing BSI are shown in Table 3. Overall, Gram-negatives were more frequent in HCA than in CA and HA infections. *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Enterobacter* spp. and *P. aeruginosa* were less frequent in CA infections, whereas *Staphylococcus pneumoniae* and *E. coli* were more frequently associated with this group. None of the CA cases were caused by methicillin-resistant *S. aureus, Stenotrophomonas maltophilia* or *Acinetobacter baumannii,* and only one by *P. aeruginosa.* By contrast, the percentages of isolates producing ESBLs among *E. coli* or *Klebsiella* spp. were similar among CA, HCA and HA BSI. There were no episodes as a result of vancomycin-resistant enterococci or carbapenem-resistant *Enterobactericeae*.

Analysis of BSI by hospital type

Among patients with CA episodes (40 from community hospitals and 110 from tertiary hospitals), there were no significant differences in demographics, underlying conditions, predisposing factors, source, microorganisms or mortality by type of hospital (data not shown), with the following exceptions: the respiratory tract was a more frequent source in community centres (30% vs. 15%, p 0.01), whereas endocarditis was rather less frequent (0 vs. 7%, p 0.07); *E. coli* was less frequent in community centres (23% vs. 44%, p 0.01), whereas *S. pneumoniae* was more frequent (28% vs. 15%, p 0.06).

More differences were found in patients with HCA episodes (45 from community and 150 from tertiary-care hospitals). Chronic renal insufficiency was less frequent in community centres (11% vs. 26%, p 0.03) and chronic cutaneous ulcers were more frequent (22% vs. 8%, p 0.008). Tunnelled venous catheters were more frequent in tertiary-care centres (19% vs. 7%, p 0.04), as was haemodialysis (18% vs. 2%, p 0.008). The respiratory tract was the most frequent source of BSI in community hospitals (20% vs. 9%, p 0.03). Mortality at day 14 was higher in community centres (16% vs. 29%, p 0.03). However, the difference was no longer statistically significant when adjusted for presentation with severe sepsis or septic shock, source of infection and severity of underlying disease (adjusted OR 2.5, 95% CI 0.8–6.9, p 0.1). There was no significant difference in mortality at day 30 (20% vs. 13%, p 0.2).

For patients with HA episodes (76 from community centres and 400 from tertiary hospitals), the following differences were found: haematological cancer and neutropenia were more frequent in tertiary-care centres (11% vs. 1%, p 0.01, and 8% vs. 1%, p 0.04); venous catheters were also more frequent (90% vs. 73%, p <0.001) but previous endoscopic procedures were less frequent (5% vs. 12%, p 0.01). Skin and soft tissue infections were the most frequent source of BSI in tertiary-care hospitals (21% vs. 0, p 0.04), whereas urinary tract and intra-abdominal infections were less frequent (14% vs. 24%, p 0.02, and 7% vs. 20%, p <0.001). There were no significant differences in aetiology or mortality.

TABLE 3. Microorganisms isolated from blood cultures, by epidemiological type of infection

	CA (*n* = 150)	HCA (*n* = 195)	HA (*n* = 476)
Gram-positive	67 (45)	74 (38)[a]	240 (50)
Staphylococcus aureus	10 (7)	22 (11)	67 (14)
Methicillin-resistant *S. aureus*[b]	0[c]	6 (3%)	24 (5%)
Coagulase-negative staphylococci	8 (5)	20 (10)[a]	118 (25)
Enterococcus	5 (3)	8 (4)[a]	47 (10)
Staphylococcus pneumoniae	27 (18)[d]	11 (6)[a]	3 (<1)
Gram-negative	85 (57)	124 (64)[a]	237 (50)
Escherichia coli	57 (38)	72 (37)[a]	96 (20)
ESBL-producing E. coli[e]	5 (3)	6 (3)	18 (4)
Klebsiella spp.	12 (8)	13 (7)	39 (8)
ESBL-producing *Klebsiella* spp.[f]	1 (<1)	1 (<1)	3 (<1)
Enterobacter spp.	1 (<1)	8 (4)	17 (4)
Pseudomonas aeruginosa[g]	1 (<1)[d]	13 (7)	26 (5)
Acinetobacter baumannii	0	2 (1)	23 (5)
Stenotrophomonas maltophilia	0	1 (<1)	5 (1)
Anaerobes	4 (3)	3 (2)	6 (1)
Fungi	0	1 (1)[h]	15 (3)
Polymicrobial bacteraemia	12 (8)	10 (5)	38 (8)

Data are expressed as the number of cases (%), except where specified. The p value for all statistical comparisons ≥0.05, except where specified.
CA, community-acquired; HCA, healthcare associated; HA, hospital-acquired.
[a]For comparison with hospital-acquired episodes, p ≤0.01 (Fisher's exact test).
[b]Methicillin-resistant isolates were 0, 27% and 36% of all *S. aureus* in CA, HCA and HA bloodstream infection (BSI), respectively.The p value for CA vs. HA was 0.02 (Fisher's exact test).
[c]For comparison with healthcare-associated episodes, p 0.03 (Fisher's exact test).
[d]For comparison with healthcare-associated episodes, p ≤0.01 (Fisher's exact test).
[e]Extended-spectrum β-lactamase (ESBL)-producing isolates were 9%, 8% and 19% of all *E. coli* in CA, HCA, and HA BSI, respectively. The p value for HCA vs. HA was 0.05 (Fisher's exact test).
[f]ESBL-producing isolates were 8% of all *Klebsiella* spp. in CA, HCA, and HA BSI.
[g]Carbapenem-resistant isolates were 0, 15% and 12% all *P. aeruginosa* in CA, HCA, and HA BSI, respectively. The p value for HCA vs. HA was 0.05 (Fisher's exact test).
[h]For comparison with hospital-acquired episodes, p 0.04 (Fisher's exact test).

Discussion

The consideration of HCA as a specific category of BSI has been found to be clinically relevant in the few studies addressing the issue that we are aware of [5–9] because it was discovered to be more similar to HA than to CA episodes with respect to underlying conditions and aetiology. We were interested in investigating whether the HCA category was just as relevant in a broader sample of hospitals that included tertiary-care and community hospitals. We used the criteria empirically developed by Friedman *et al.* [5] because they have been shown to be of prognostic importance [5,8] and predictive of ineffective initial therapy [16].

Twenty-four percent of BSI infections reported in this multicentre study including public tertiary-care and community hospitals in Andalucía, Spain, were of the HCA type. This is a similar figure to that reported by Vallés *et al.* [8] in their study performed in two teaching hospitals in Barcelona (24.5%), and lower than that reported by Friedman *et al.* [5] in four hospitals in North Carolina (37%), using similar definitions. Most of our HCA BSI patients had recently been admitted to an acute care hospital, and some were residents in a long-term care facility or receiving haemodialysis. The frequency of BSI in patients with ambulatory intravenous treatment or specialized home care was low, whereas it was much higher in North Carolina [5]. This probably reflects significant differences between the Spanish and US healthcare systems influencing the epidemiology of BSI. We found that the percentage of HCA episodes was similar in community and tertiary-care centres, indicating that this is a category of BSI that should be taken into account in both types of hospitals.

The data obtained in the present study confirm that HCA and CA BSIs show significant differences that physicians attending patients in the emergency room should bear in mind when attending patients with community-onset sepsis [5–9,17]. Beyond the features included in the definition for HCA BSI, patients in this group more frequently showed fatal underlying conditions, chronic renal insufficiency, haematological cancer, previous antimicrobial treatment and an unknown source of infection. More importantly, some typical healthcare-associated antibiotic-resistant organisms, such as *P. aeruginosa* or methicillin-resistant *S. aureus* (MRSA), were not present or rare in CA episodes but should be considered in patients with a suspected HCA BSI (CA MRSA is still anecdotal in Spain) [18]. Curiously, other antibiotic-resistant organisms (such as ESBL producers among *E. coli* or *K. pneumoniae*) were found at similar frequencies in CA, HCA and HA episodes, reflecting the fact that ESBL-producing enterobacteria are now significant causes of CA BSI [10] and that the criteria used to define an HCA episode are not useful for ruling out these organisms in patients with community-onset BSI.

As far as we are aware, the characteristics of patients with HCA BSI episodes by type of hospital have not previously been studied. Significant differences were found between HCA episodes occurring in tertiary-care and community centres, reflecting the type of outpatients cared for in both types of centres. Thus, haemodialysis and tunnelled catheters were more frequent in tertiary-care hospitals, whereas patients with HCA BSI in community hospitals were mainly recently admitted patients with chronic conditions or patients with solid cancer receiving intravenous chemotherapy in a day hospital. There was a higher crude mortality rate for HCA BSI patients treated in community centres compared to tertiary-care hospitals, although the results of the multivariate analysis suggest that the crude association was confounded by other variables.

Although benchmark rates exists for HA BSI and total BSI [1–3], we have provided incidence rates for HCA BSI. Because the most appropriate denominator for HCA BSI (i.e. the number of patients or patient-days at risk) is very difficult to obtain, we opted to provide both population-based and admission-based rates. We consider population-based rates to be more appropriate because not every patient with HCA BSI is admitted to hospital. Because hospitals participating in the study attend >90% of patients in their catchment area needing hospitalization, the population-based rates estimated in the present study should be considered as minimum rates.

The present study has several limitations. The number of cases from community hospitals was lower compared to that from tertiary-care centres, which limits the comparisons between the two types of hospital. Also, the study period was longer in the community hospitals and, because community-onset BSI may show seasonal differences, this may have influenced the results. However, the study periods were chosen aiming to minimize the impact of the different parameters. In addition, even though blood cultures were processed in all centres using standardized protocols [12,13], there may have been some differences among the hospitals. Finally, the results obtained are probably not applicable to areas with different a epidemiology of resistant bacteria (such as endemic CA MRSA) and different healthcare systems.

In summary, HCA BSI should be considered as a distinct class of BSI, in both tertiary-care and community hospitals, although differences in the predisposing conditions of the patients and clinical features should be taken into account.

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Author contributions

JRB and MDLP were the coordinators of the study. JRB, MDLP, MMP and PR are responsible for the study design, which was actively discussed with all authors and modified accordingly. MMP, PR, CN, EN, MH, AA, AM, FT, MTT, AMA, AA, AR, RM, JEC, LL and JAPL coordinated the methodology and data collection in each hospital and verified the databases. JRB, MMP and PR performed the preliminary analysis and wrote the draft of the manuscript, which was discussed with all authors and modified accordingly.

Transparency Declaration

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