ORIGINAL ARTICLE

No Specific Time Window Distinguishes between Community-, Healthcare-, and Hospital-Acquired Bacteremia, but They Are Prognostically Robust

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OBJECTIVE. We examined whether specific time windows after hospital admission reflected a sharp transition between community and hospital acquisition of bacteremia. We further examined whether different time windows to distinguish between community acquisition, healthcare association (HCA), and hospital acquisition influenced the results of prognostic models.

DESIGN. Population-based cohort study.

SETTING. Hospitals in 3 areas of Denmark (2.3 million inhabitants) during 2000–2011.

METHODS. We computed graphs depicting proportions of males, absence of comorbidity, microorganisms, and 30-day mortality pertaining to bacteremia 0, 1, 2, …, 30, and 31 days and later after admission. Next, we assessed whether different admission (0–1, 0–2, 0–3, 0–7 days) and HCA (30, 90 days) time windows were associated with changes in odds ratio (OR) and area under the receiver operating characteristic (ROC) curve for 30-day mortality, adjusting for sex, age, comorbidity, and microorganisms.

RESULTS. For 56,606 bacteremic episodes, no sharp transitions were detected on a specific day after admission. Among the 8 combined time windows, ORs for 30-day mortality varied from 1.30 (95% confidence interval [CI], 1.23–1.37) to 1.99 (95% CI, 1.48–2.67) for HCA and from 1.36 (95% CI, 1.24–1.50) to 2.53 (95% CI, 2.01–3.20) for hospital acquisition compared with community acquisition. Area under the ROC curve changed marginally from 0.684 (95% CI, 0.679–0.689) to 0.700 (95% CI, 0.695–0.705).

CONCLUSIONS. No time transitions unanimously distinguished between community and hospital acquisition with regard to sex, comorbidity, or microorganisms, and no difference in 30-day mortality was seen for HCA patients in relation to a 30- or 90-day time window. ORs decreased consistently in the order of hospital acquisition, HCA, and community acquisition, regardless of time window combination, and differences in area under the ROC curve were immaterial.

Infect Control Hosp Epidemiol 2014;35(12):1474-1482

Bacteremia is a serious infection, with a 30-day mortality of 15%–30%.[1] The infection is usually categorized according to whether it is acquired inside (hospital acquisition) or outside (community acquisition) the hospital setting. In 1975, 1 study defined community acquisition as bacteremia occurring before day 3 after hospital admission and hospital acquisition as occurring thereafter,[2] and a few works from the following years referred to this.[3] However, according to the definitions of acquisition published by the Centers for Disease Control and Prevention in 1988, the distinction between community and hospital acquisition of an infection should be based on individual assessment of all available clinical information and not rely on prespecified time windows.[4] Nevertheless, most of the more than 3,300 studies citing this article have used a 48-hour time window after hospital admission to distinguish between community and hospital acquisition, even though only 1 prior study has assessed whether specific time windows represent biologically plausible transitions between

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Received March 12, 2014; accepted July 25, 2014; electronically published October 31, 2014.

 0899-823X/2014/3512-0006$15.00. DOI: 10.1086/678593

community and hospital acquisition.[5] For the sake of proportions of typical hospital microorganisms, this study showed no evidence of a sharp transition.

Because an increasing number of patients have frequent contacts with hospitals—for example, for hemodialysis or chemotherapy—it may not always be appropriate to categorize their infections as community acquisition. Therefore, a separate healthcare-associated (HCA) group has been proposed to refine the definition of community-acquired infections. HCA is generally defined as home therapy, residence in a nursing home, or hospital contact prior to the infection-related hospitalization, often applying a 30- or 90-day time window.[6,7] Studies have indicated that the prognosis of patients with HCA infections lies between those of patients with community and hospital acquisition.[8,9] However, if the use of different time windows causes only minor changes in the associations between acquisition and other cofactors on the one hand and a poor prognosis on the other, their exact determination may be less important.

We applied 2 hypotheses: (1) specific time windows reflect sharp transitions between community and hospital acquisition pertaining to sex, comorbidity, main types of microorganisms, and 30-day mortality; (2) use of different time windows to distinguish between community acquisition, HCA, and hospital acquisition influences the results of prognostic models. We tested these hypotheses using population-based data from high-quality administrative databases.

METHODS

Setting

The Danish healthcare system is tax financed and provides care free of charge for all residents. The admission of all acutely ill patients to the nearest public hospital in their area of residence and the submission of all the hospitals' blood cultures to a hospital-based department of clinical microbiology (DCM) within that area prompts a population-based coverage. Our data covered 3 demographically well-defined areas (North Denmark Region, Capital Region, Funen County) served by 4 DCMs in hospitals in Aalborg, Herlev, Hvidovre, and Odense (total of 2.3 million inhabitants).[10,11] Blood culture procedures have been described previously.[10-12]

Core Data Set

All microbiological results were recorded in an electronic laboratory information system (Aalborg, Herlev, and Hvidovre: ADBakt; Odense: local patient administrative system in 2000–2005 and MADS system [http://www.madsonline.dk] thereafter). The key data included dates of draw and receipt of blood culture in the DCM and blood culture isolates. We retrieved data on all positive blood cultures and used previously published computer algorithms to exclude likely contaminants and to derive bacteremic episodes.[13] For each episode, we defined the best-estimate baseline date as the date of draw of blood culture; for bacteremic episodes with a missing date of draw (9.3%), we used the never missing date of receipt. We distinguished between incident (first-time) and nonincident (subsequent) episodes, using previously defined criteria.[12]

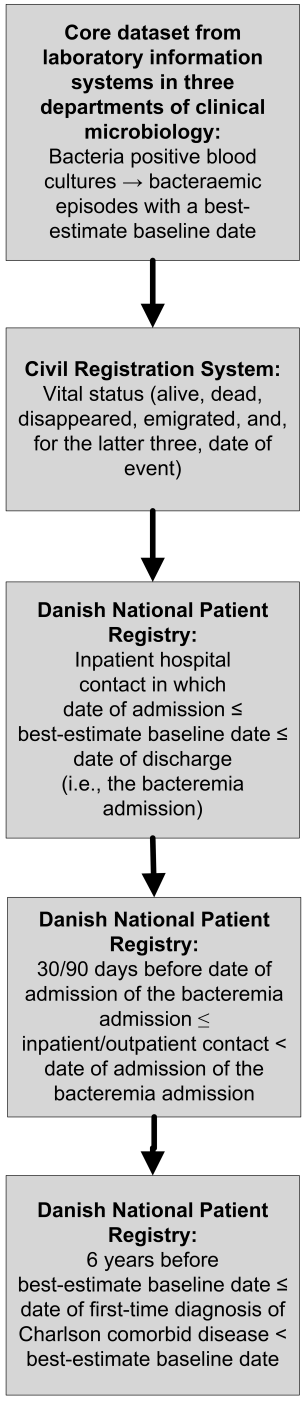

FIGURE 1. Compilation of the study database. Best-estimate baseline date: date of draw of blood culture and, for episodes with missing date of draw, date of receipt of blood culture.

https://doi.org/10.1086/678593 Published online by Cambridge University Press

Linkage to Other Registries

All Danish residents have a unique personal identification number used for all health contacts, which permits unambiguous linkage between health administrative registries.[14] Figure 1 shows the compilation of the study database. By linkage of the core data set to the Danish Civil Registration System,[15] we retrieved data on the patients' vital status.

The Danish National Patient Registry (DNPR) includes all inpatient contacts since 1977 and all hospital outpatient contacts since 1995.[16] We linked to DNPR inpatient data and retrieved the hospital admission, which included the bacteremic episode. We excluded 11 bacteremic episodes (9 patients) that could not be linked to the DNPR. The admission time window (number of days between the hospital admission date [day 0] and the best-estimate baseline date) was subsequently used to compute time windows for community versus hospital acquisition.

We then linked the data set to all the patients' inpatient and outpatient contacts to derive HCA bacteremic episodes. An episode was defined as HCA if the patient had 1 or more outpatient contacts to departments of hematology, oncology, or nephrology or 1 or more hospital admissions, all within either a 30- or a 90-day HCA time window prior to the hospital admission date.

Finally, we relinked to the DNPR to retrieve all first-time diagnoses in the Charlson comorbidity index[17] within a 6-year period prior to the best-estimate baseline date. In this index, 19 major disease categories (eg, malignancy, cardiovascular diseases, and diabetes mellitus) are assigned a score, with higher scores given to prognostically more severe diseases.

Statistical Analyses

We divided each bacteremic episode into 4 overlapping admission time windows (0–1, 0–2, 0–3, and 0–7 days). For episodes defined as community acquisition according to the admission time window, a 30- or 90-day HCA time window was applied.

Initially, we computed graphs depicting days between hospital admission and the best-estimate baseline date (0, 1, …, 30, 31 days or later) on the *X*-axis and proportion of basic characteristics with 95% confidence intervals (CIs) on the *Y*-axis to visually detect possible increases, decreases, and sharp transitions. As basic characteristics, we selected male sex, absence of Charlson comorbidity, certain prominent microorganisms or groups thereof (*Klebsiella* spp., *Pseudomonas aeruginosa*, fungi, polymicrobial, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*), and 30-day mortality.

We used logistic regression with 30-day mortality as the outcome to deduce possible changes of odds ratios (ORs) and 95% CIs according to the admission time windows and combinations of these with the HCA time windows. Models were both crude and adjusted for age, sex, Charlson comorbidity index (0, 1–2, greater than 2), and categories of microorganisms covering almost the entire microbial spectrum (*E. coli*, *Enterobacter*, *Klebsiella* spp., other Enterobacteriaceae, *P. aeruginosa*, anaerobic gram-negative bacteria, other gram-negative bacteria, *S. aureus*, coagulase-negative staphylococci [CNS], *S. pneumoniae*, hemolytic streptococci, enterococci, gram-positive rods, other gram-positive bacteria, fungi, polymicrobial, undetermined [0.4%]).

The high number of bacteremic episodes in the 0–1-day admission time window compared with the number of episodes on days 2, 3, and 4–7 (Table 1) impeded the ability of the latter to alter ORs. We therefore selected the lowest number of episodes on the day(s) that differentiated between the admission time windows (day 3, 1,317 episodes) and randomly drew 1,317 episodes from the 0–1-day admission time window, day 2, and days 4–7, while retaining the remaining

TABLE 1. Days between Admission to Hospital and Best-Estimate Baseline Date

		Bacteremic episodes		
Days	All episodes (n = 56,606)	All, cumulative within periods	Incident (n = 47,285)	Nonincident (n = 9,321)
0	29,520 (52.2)		25,315 (53.5)	4,205 (45.1)
1	7,655 (13.5)	37,175 (65.7)	6,710 (14.2)	945 (10.1)
2	1,895 (3.4)	1,895 (3.4)	1,642 (3.5)	253 (2.7)
3	1,317 (2.3)	1,317 (2.3)	1,131 (2.4)	186 (2.0)
4	1,080 (1.9)		944 (2.0)	136 (1.5)
5	939 (1.7)		794 (1.7)	145 (1.6)
6	809 (1.4)		673 (1.4)	136 (1.5)
7	750 (1.3)	3,578 (6.3)	626 (1.3)	124 (1.3)
8	720 (1.3)		613 (1.3)	107 (1.2)
9	692 (1.2)		576 (1.2)	116 (1.2)
10	590 (1.0)		485 (1.0)	105 (1.1)
11	554 (1.0)		448 (1.0)	106 (1.1)
12	549 (1.0)		450 (1.0)	99 (1.1)
13	511 (0.9)		413 (0.9)	98 (1.1)
14	470 (0.8)		383 (0.8)	87 (0.9)
15	436 (0.8)		362 (0.8)	74 (0.8)
16	400 (0.7)		326 (0.7)	74 (0.8)
17	396 (0.7)		310 (0.7)	86 (0.9)
18	319 (0.6)		257 (0.5)	62 (0.7)
19	367 (0.7)		262 (0.6)	105 (1.1)
20	305 (0.5)		225 (0.5)	80 (0.9)
21	327 (0.6)		257 (0.5)	70 (0.8)
22	255 (0.5)		196 (0.4)	59 (0.6)
23	259 (0.5)		201 (0.4)	58 (0.6)
24	220 (0.4)		170 (0.4)	50 (0.5)
25	232 (0.4)		168 (0.4)	64 (0.7)
26	213 (0.4)		164 (0.4)	49 (0.5)
27	189 (0.3)		145 (0.3)	44 (0.5)
28	193 (0.3)		149 (0.3)	44 (0.5)
29	176 (0.3)		123 (0.3)	53 (0.6)
30	160 (0.3)	8,533 (15.7)	120 (0.3)	40 (0.4)
≥31	4,108 (7.3)	4,108 (7.3)	2,647 (5.6)	1,461 (15.7)

NOTE. Data are no. (%) of episodes. Date of draw of blood culture for 51,354 episodes and, for episodes with missing date of draw, date of receipt of blood culture for 5,252 episodes.

https://doi.org/10.1086/678593 Published online by Cambridge University Press

TABLE 2. Acquisition of Bacteremic Episodes according to Combinations of Admission and Healthcare Association (HCA) Time Windows

Admission time window, days	HCA time window, days	Acquisition		
		Community	HCA	Hospital
0–1	30	25,289 (44.7)	11,886 (21.0)	19,431 (34.3)
0–1	90	20,686 (36.5)	16,489 (29.1)	19,431 (34.3)
0–2	30	26,503 (46.8)	12,567 (22.2)	17,536 (31.0)
0–2	90	21,638 (38.2)	17,432 (30.8)	17,536 (31.0)
0–3	30	27,317 (48.3)	13,070 (23.1)	16,219 (28.7)
0–3	90	22,289 (39.4)	18,098 (32.0)	16,219 (28.7)
0–7	30	29,551 (52.2)	14,414 (25.5)	12,641 (22.3)
0–7	90	24,055 (42.5)	19,910 (35.2)	12,641 (22.3)

NOTE. Data are no. (%) of episodes.

12,641 episodes on day 8 and beyond unaltered, and reiterated the analyses.

To examine the contribution of acquisition to the accuracy of the prognostic models, we computed receiver operating characteristic (ROC) curves and the areas under these.[18,19] The baseline model consisted of the adjustment variables incorporated in the logistic regression analyses. We then added the 4 admission time windows and the combinations of these with the 2 HCA time windows to the baseline model and compared the area under the ROC curve between the models. These analyses were reiterated with the 1,317 episodes on days 0–1, 2, and 4–7. To examine the robustness of our findings, we repeated all analyses in subgroups of incident and nonincident episodes for each DCM and after excluding CNS. The program Stata (release 12; StataCorp) was used for all analyses.

Ethical Considerations

The study was approved by the Danish Data Protection Agency (2007-41-0627, 2008-41-2521, 2008-580035).

RESULTS

Descriptive

In 2000–2011 (North Denmark and Capital regions) and 2000–2008 (Funen), 47,285 patients had 56,606 bacteremic episodes; 40,711 patients (86.1%) had 1 episode, 4,906 (10.4%) had 2 episodes, 1,122 (2.4%) had 3 episodes, 538 (1.1%) had 4–10 episodes, and 8 had 11–19 episodes.

Admission Time Windows

A total of 37,175 bacteremic episodes (65.7%) were encountered on day 0 or 1, 1,895 (3.4%) on day 2, 1,317 (2.3%) on day 3, 3,578 (6.3%) on days 4–7, 8,533 (15.1%) on days 8–30, and 4,108 (7.3%) on day 31 or later (Table 1). Admission time windows were unevenly distributed between incident and nonincident episodes; 67.7% of incident and 55.2% of nonincident episodes occurred on days 0 and 1, while 5.6% of incident and 15.7% of nonincident episodes occurred on day 31 or later.

HCA Time Windows

Table 2 shows the distributions of community acquisition, HCA, and hospital acquisition episodes according to the 8 combinations of admission time windows and HCA time windows. Proportions of community acquisition ranged from 36.5% to 52.2%, HCA from 21.0% to 35.2%, and hospital acquisition from 22.3% to 34.3%.

Proportions of Basic Characteristics in Relation to Days after Hospital Admission

The proportion of males increased from 50%–52% on day 0–1 to 56.2% on day 2 and further to 61.4% on day 3, after which no trend was seen (Figure 2). Sharp transitions were detected between days 1–2 and 2–3. The proportion of patients without diagnosed comorbidities decreased steadily

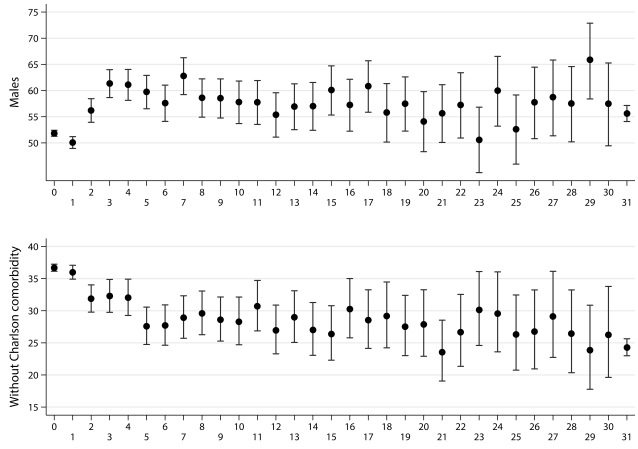

FIGURE 2. Proportion (%) of males and patients without diagnosed comorbidity (Charlson comorbidity index score, 0) among 56,606 bacteremic episodes, according to time of detection after hospital admission (0, 1, …, 30, 31 days and later).

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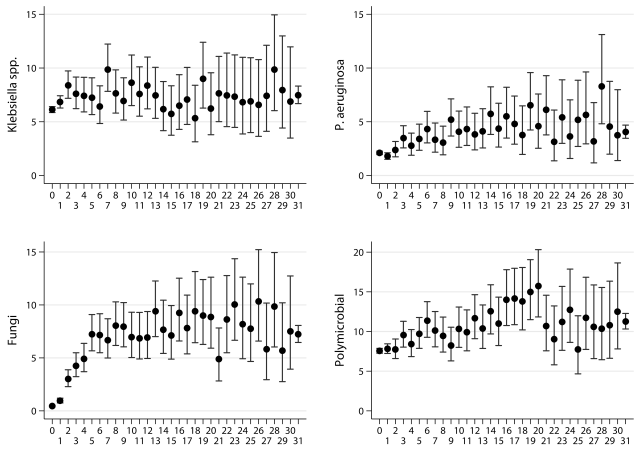

FIGURE 3. Proportion (%) of *Klebsiella* spp., *Pseudomonas aeruginosa*, fungi, and polymicrobial among 56,606 bacteremic episodes according to time of detection after hospital admission (0, 1, …, 30, 31 days and later).

from day 0 (36.7%) to day 5 (27.6%), after which no trend was seen. Sharp transitions occurred between days 1–2 and 4–5.

For proportion of patients with *P. aeruginosa*, fungi, and polymicrobial microorganisms, we noted an increasing trend from day 0 to 10 (*P. aeruginosa*, fungi) or day 20 (polymicrobial), but the only distinct transition was seen for fungi on days 4–5 (Figure 3). For *Klebsiella* spp., no obvious trends or transitions were detected.

The proportion of *E. coli* increased from 31.9% on day 0 to 34.9% on day 1, followed by a steep decline to 24.0% on day 3, with no clear trends thereafter (Figure 4). Several sharp transitions were detected (days 0–1, 1–2, and 2–3). The proportion of *S. aureus* increased steadily from day 0 (10.5%) to day 5 (22.8%), after which it declined until day 20 (12.5%); thus, a sharp transition was detected on days 5–6. The proportion of *S. pneumoniae* was 12.9% on day 0, 8.0% on day 1, and 1%–4% in the remaining period; thus, a sharp decline from day 0 to day 2 was detected, also reflecting sharp transitions on days 0–1 and 1–2.

Thirty-Day Mortality according to Admission Time Windows

The 30-day mortality was 17.1% for patients diagnosed on day 0 and increased steadily to 33.2% for patients diagnosed on day 5, after which no clear trends were seen (Figure 5). For all bacteremic episodes, we saw no material changes in ORs for the greater than 1-, 2-, 3-, or 7-day admission time windows in either crude or adjusted models (Table 3). The analyses with randomly equalized episodes on days 0–1, 2, 3, and 4–7 showed a decline of adjusted ORs from 1.73 (95% CI, 1.49–2.01) in the greater than 1-day admission time window to 1.19 (95% CI, 1.10–1.28) in the greater than 7-day admission time window.

Thirty-Day Mortality according to Admission Time Windows and HCA Time Windows

For all bacteremic episodes, we saw no material changes in ORs for the 0–1-, 0–2-, 0–3-, or 0–7-day admission time windows in combination with the 30- and 90-day HCA time

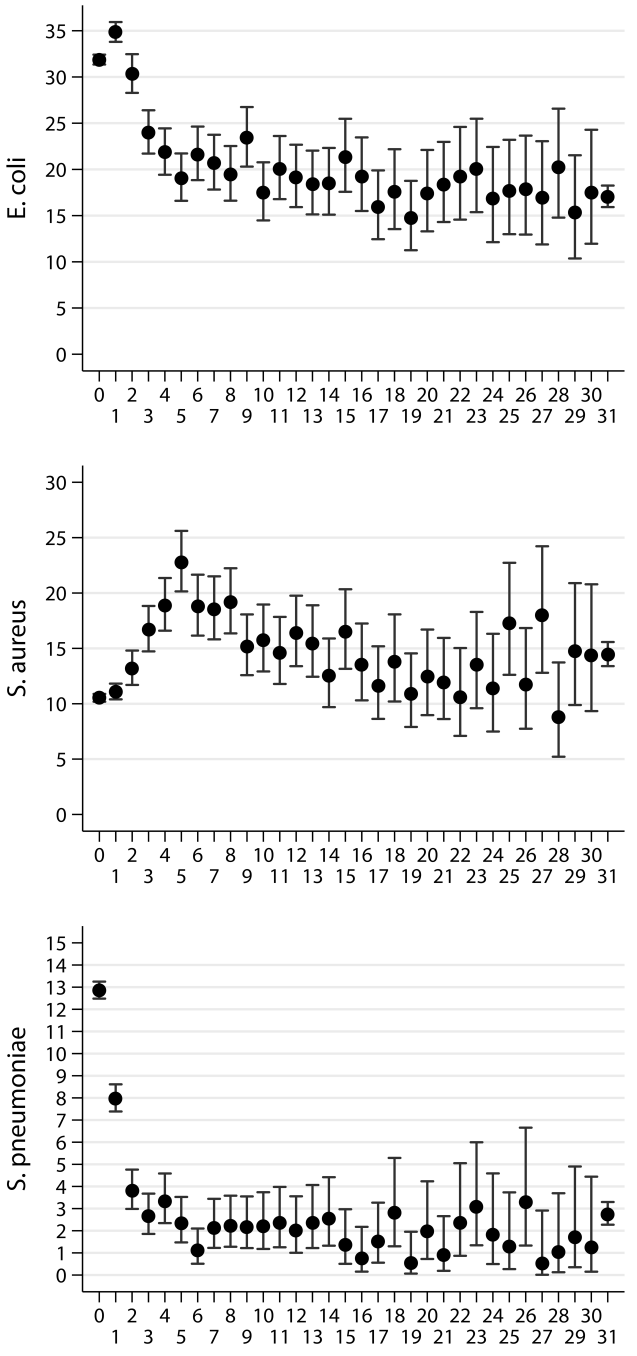

FIGURE 4. Proportion (%) of *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* among 56,606 bacteremic episodes according to time of detection after hospital admission (0, 1, …, 30, 31 days and later).

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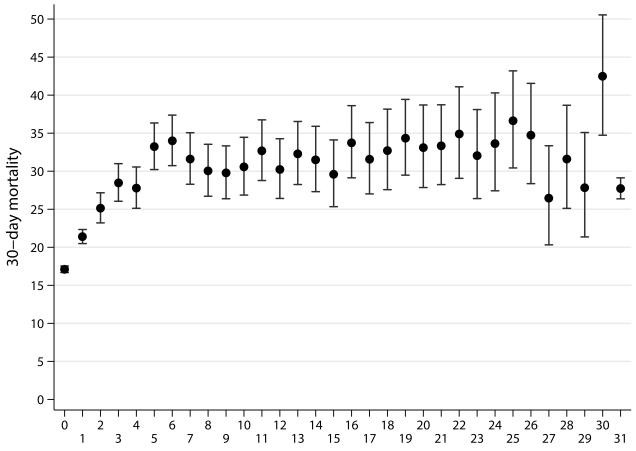

FIGURE 5. Thirty-day mortality (%) among 56,582 bacteremic episodes (follow-up unavailable for 24 episodes) according to time of detection after hospital admission (0, 1, …, 30, 31 days and later).

window or for the greater than 1-, 2-, 3-, or 7-day admission time windows, whether the analyses were crude or adjusted (Table 4). All analyses confirmed that community acquisition had the best prognosis, followed by HCA and hospital acquisition. The analyses with randomly equalized episodes on days 0–1, 2, 3, and 4–7 corroborated the best prognosis of community acquisition, which generally deteriorated by HCA and further by hospital acquisition. The ORs were generally lower than for analyses including all bacteremic episodes, but all ORs were significantly greater than 1. Regardless of model and number of bacteremic episodes, there were only immaterial differences between models with 30- and 90-day HCA time windows.

Receiver Operating Characteristics

Area under the ROC curve (0.684 [95% CI, 0.679–0.689] for all and 0.662 [95% CI, 0.653–0.670] for the randomly selected bacteremic episodes) in the baseline model changed only immaterially when various time window combinations were added (Table 5).

Subgroup Analyses

There were no material differences when incident, nonincident, DCMs, or episodes without CNS were compared with the overall results (data not shown).

DISCUSSION

In this large population-based cohort study comprising more than 50,000 bacteremic episodes, patient characteristics, microorganisms, and 30-day mortality changed with time from hospitalization to occurrence of bacteremia, thereby supporting the use of community acquisition, hospital acquisition, and HCA subgroups. However, we found no sharp time transitions that unanimously distinguished between community acquisition and hospital acquisition in relation to sex, comorbidity, or main groups of microorganisms. Because a 48-hour time window is generally used to distinguish between community acquisition and hospital acquisition, we selected 0–1-, 0–2-, and 0–3-day admission time windows. We further selected the 0–7-day admission time window as an extreme to evaluate the robustness in prognostic models. This was also the reason for randomly equalizing numbers of bacteremic episodes on days 0–1, 2, 3, and 4–7. Regardless of time windows, our prognostic models consistently showed that the prognosis deteriorated from community acquisition to HCA and further to hospital acquisition, which is plausible and in accordance with previous studies.[8,9,20,21] Moreover, the contribution of the acquisition to the area under the ROC curve was minor, indicating that acquisition is mainly useful for explanation rather than for prediction.[22]

To our knowledge, this is the first study that has assessed the robustness of commonly used time windows related to

TABLE 3. Thirty-Day Mortality according to Admission Time Window, with Community Acquisition as Reference Group

		Bacteremic episodes			
		56,582[a]		17,903[b]	
Admission time window, days	Acquisition	Crude model	Adjusted model[c]	Crude model	Adjusted model[c]
>1	Hospital	1.96 (1.88–2.04)	1.78 (1.70–1.86)	1.86 (1.61–2.14)	1.73 (1.49–2.01)
>2	Hospital	1.96 (1.88–2.04)	1.76 (1.68–1.84)	1.58 (1.43–1.75)	1.46 (1.31–1.62)
>3	Hospital	1.93 (1.86–2.02)	1.73 (1.66–1.81)	1.40 (1.29–1.52)	1.31 (1.20–1.42)
>7	Hospital	1.79 (1.72–1.88)	1.59 (1.52–1.67)	1.26 (1.17–1.36)	1.19 (1.10–1.28)

NOTE. Data are odds ratios (95% confidence intervals). Admission time window is defined as days after admission when the bacteremic episode was encountered.

[a] Thirty-day follow-up was unavailable for 24 episodes.

[b] A total of 1,317 episodes randomly drawn on days 0–1, 2, and 4–7, with the remaining 12,641 episodes on day 8 and beyond unaltered; 30-day follow-up was unavailable for 6 episodes.

[c] Adjusted for age, sex, Charlson comorbidity index scores (0, 1–2, greater than 2), and main group of microorganisms.

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TABLE 4. Thirty-Day Mortality according to Admission and Healthcare Association (HCA) Time Windows, with Community Acquisition as Reference Group

			Bacteremic episodes			
			56,582[a]		17,903[b]	
Admission time window, days	HCA time window, days	Acquisition	Crude model	Adjusted model[c]	Crude model	Adjusted model[c]
0–1	30[d]	HCA	1.61 (1.52–1.70)	1.40 (1.32–1.49)	2.01 (1.52–2.66)	1.79 (1.34–2.39)
>1	…[e]	Hospital	2.31 (2.21–2.42)	2.04 (1.94–2.15)	2.43 (2.01–2.93)	2.19 (1.80–2.66)
0–1	90	HCA	1.60 (1.51–1.68)	1.32 (1.24–1.40)	2.30 (1.73–3.06)	1.99 (1.48–2.67)
>1	…	Hospital	2.45 (2.34–2.57)	2.06 (1.95–2.18)	2.90 (2.32–3.62)	2.53 (2.01–3.20)
0–2	30	HCA	1.61 (1.52–1.69)	1.41 (1.33–1.49)	1.73 (1.43–2.09)	1.57 (1.29–1.91)
>2	…	Hospital	2.32 (2.22–2.43)	2.03 (1.92–2.13)	1.95 (1.72–2.22)	1.75 (1.53–2.00)
0–2	90	HCA	1.60 (1.51–1.68)	1.32 (1.25–1.40)	1.75 (1.45–2.11)	1.55 (1.28–1.89)
>2	…	Hospital	2.46 (2.34–2.58)	2.05 (1.94–2.17)	2.13 (1.84–2.46)	1.85 (1.59–2.16)
0–3	30	HCA	1.61 (1.53–1.69)	1.41 (1.33–1.49)	1.65 (1.42–1.91)	1.49 (1.27–1.74)
>3	…	Hospital	2.29 (2.19–2.40)	1.99 (1.89–2.10)	1.71 (1.54–1.89)	1.54 (1.38–1.72)
0–3	90	HCA	1.60 (1.52–1.68)	1.32 (1.25–1.39)	1.64 (1.41–1.90)	1.43 (1.23–1.67)
>3	…	Hospital	2.43 (2.31–2.55)	2.02 (1.91–2.13)	1.82 (1.62–2.05)	1.59 (1.41–1.80)
0–7	30	HCA	1.59 (1.51–1.66)	1.39 (1.32–1.46)	1.55 (1.37–1.76)	1.41 (1.24–1.61)
>7	…	Hospital	2.12 (2.02–2.22)	1.82 (1.73–1.92)	1.50 (1.37–1.64)	1.36 (1.24–1.50)
0–7	90	HCA	1.58 (1.50–1.65)	1.30 (1.23–1.37)	1.50 (1.33–1.70)	1.31 (1.15–1.49)
>7	…	Hospital	2.24 (2.13–2.36)	1.84 (1.74–1.95)	1.56 (1.41–1.72)	1.37 (1.24–1.53)

NOTE. Data are odds ratios (95% confidence intervals). Admission time window is defined as days after admission when the bacteremic episode was encountered. HCA time window is defined as healthcare contact 30 or 90 days prior to admission date. For community association, admission time window is as for HCA but no HCA time windows.

[a] Thirty-day follow-up was unavailable for 24 episodes.

[b] A total of 1,317 episodes randomly drawn on days 0–1, 2, and 4–7, with the remaining 12,641 episodes on day 8 and beyond unaltered; 30-day follow-up was unavailable for 6 episodes.

[c] Adjusted for age, sex, Charlson comorbidity index scores (0, 1–2, greater than 2), and main group of microorganisms.

[d] HCA in 30 or 90 days prior to admission date.

[e] HCA not computed because the bacteremia is hospital acquired, according to the admission time window.

community acquisition versus HCA versus hospital acquisition for any infectious syndrome. A recent literature study evaluated criteria for acquisition among pediatric bacteremia patients.[23] In 23 studies, 13 different criteria were used for community acquisition, 5 for HCA, and 15 for hospital acquisition, though most studies incorporated a 48-hour time window after hospital admission as part of their criteria. This purely descriptive study did not evaluate the different criteria's influence on any clinical or other aspects. To our knowledge, no study has assessed similar criteria for adult bacteremia patients.

We are aware of only 1 study that has evaluated whether distinct time periods could be used to differentiate between community acquisition and hospital acquisition.[5] Among 5,674 isolates, the proportions of *P. aeruginosa*, *Klebsiella* spp., and *Candida* spp. on days 0–25 after hospital admission showed no sharp transitions, except for *Candida* spp., with low proportions until days 7–10, after which it increased. Our study showed a different pattern (Figure 2) for a ×10 higher number of bacteremic episodes, including 1,520 with fungi (1,495 [98.4%] *Candida* spp.). This may also reflect considerable changes in the epidemiology of fungemia in recent years.[24-26] In contrast, the distribution of blood culture isolates, in relation to days 0–25 after hospital admission, resembled ours (Table 1). We are not aware of other studies reporting the time distribution of bacteremic episodes in relation to hospital admission.

The strengths of our study include the population-based design with a high number of bacteremic episodes and complete follow-up for 30-day mortality. Our study also had limitations. First, we had no clinical and paraclinical data that could refine our prognostic models and increase the area under the ROC curve.[11] However, because the main role of clinical/paraclinical variables would be to further adjust for differences between community acquisition, HCA, and hospital acquisition, their ORs would likely decline, but their mutual differences between the models would probably not increase. Second, we had no data on home therapy or nursing home residence, which are often used to define HCA.[6] Because these factors are related to frail patients, this may actually increase the threshold for admission to hospital as a result of many treatments given by the home nurse or a physician attached to a nursing home. Regardless, the lack of these data probably has a minor impact, given the little variations in the results related to a 30- versus 90-day HCA time window. The proportion of HCA in previous studies ranged from 23% to 55%,[9,20,21,27,28] although HCA definitions, cohorts, and settings varied, rendering comparisons difficult.

https://doi.org/10.1086/678593 Published online by Cambridge University Press

TABLE 5. Area under the Receiver Operating Characteristic (ROC) Curve for 30-Day Mortality as Outcome

Admission time window, days	HCA time window, days	Bacteremic episodes	
		56,582[a]	17,903[b]
Baseline[c]		0.684 (0.679–0.689)	0.662 (0.653–0.670)
0–1	Ignored	0.698 (0.693–0.703)	0.665 (0.657–0.674)
0–1	30	0.700 (0.695–0.705)	0.666 (0.657–0.674)
0–1	90	0.699 (0.694–0.704)	0.666 (0.658–0.675)
0–2	Ignored	0.697 (0.692–0.702)	0.665 (0.657–0.674)
0–2	30	0.700 (0.695–0.705)	0.666 (0.658–0.675)
0–2	90	0.699 (0.694–0.704)	0.666 (0.658–0.675)
0–3	Ignored	0.696 (0.691–0.701)	0.665 (0.656–0.673)
0–3	30	0.699 (0.694–0.704)	0.666 (0.658–0.675)
0–3	90	0.698 (0.693–0.703)	0.666 (0.658–0.675)
0–7	Ignored	0.692 (0.687–0.697)	0.663 (0.655–0.672)
0–7	30	0.695 (0.690–0.700)	0.665 (0.657–0.674)
0–7	90	0.694 (0.689–0.699)	0.665 (0.656–0.673)

NOTE. Data are areas under the ROC curve (95% confidence intervals). Admission time window is defined as days after admission when the bacteremic episode was encountered.

[a] Thirty-day follow-up was unavailable for 24 episodes.

[b] A total of 1,317 episodes randomly drawn on days 0–1, 2, and 4–7, with the remaining 12,641 episodes on day 8 and beyond unaltered; 30-day follow-up was unavailable for 6 episodes.

[c] Adjusted for age, sex, Charlson comorbidity index scores (0, 1–2, greater than 2), and main group of microorganisms.

Curiously, the study with 55% HCA did not include home therapy or nursing home residence in their HCA definition either.[27] Third, because some patients were included more than once, the observations were not independent. Nevertheless, we selected all episodes to evaluate the clinical assessments, which are principally performed for all patients with positive blood cultures deemed to be clinically important. Our subgroup analyses did not reveal any material differences between incident and nonincident episodes. Fourth, we met difficulties when applying uniform criteria for bacteremic episodes with CNS because blood culture practices differed among the 4 DCMs in terms of both numbers of bottles per set (2–4) and recommendations for repeat sampling.[12] This was probably the main reason for the differences between proportions of CNS for DCMs in Aalborg, Herlev, and Hvidovre (1.4%–2.2%) and Odense (10.3%), since the algorithm for bacteremia with regard to possible skin contaminants includes their detection in 2 or more blood culture sets.[13] Subgroup analyses for each DCM and the exclusion of CNS were, however, very consistent with the overall results. No other major group of microorganisms differed between the 4 DCMs (data not shown).

In conclusion, patient characteristics, microbiology, and 30-day mortality changed with time from hospital admission to occurrence of bacteremia. However, we found no time transitions that unanimously distinguished between community acquisition and hospital acquisition in relation to sex, comorbidity, or main groups of microorganisms, and we found no difference in 30-day mortality for HCA patients regardless of whether a 30- or 90-day time window was used. The robustness of these results have implications for future prognostic studies of infectious syndromes with acquisition as a cofactor, in particular if they comprise databases derived retrospectively from administrative data, which may be less valid than prospective data.

ACKNOWLEDGMENTS

Contributing members of the Danish Collaborative Bacteraemia Network: Christian Østergaard (Department of Clinical Microbiology, Copenhagen University Hospital, Hvidovre Hospital, Copenhagen, Denmark), Magnus Arpi (Department of Clinical Microbiology, Copenhagen University Hospital, Herlev Hospital, Copenhagen, Denmark), Kim Oren Gradel (Center for National Clinical Databases–South, Odense University Hospital, Odense, Denmark), Ulrich Stab Jensen (Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark), Sara Thønnings (Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark), Jenny Dahl Knudsen (Department of Clinical Microbiology, Copenhagen University Hospital, Hvidovre Hospital, Copenhagen, Denmark), Kristoffer Koch (Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark), Mette Pinholt (Department of Clinical Microbiology, Copenhagen University Hospital, Herlev Hospital, Copenhagen, Denmark), Jesper Smit (Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark), Henrik Carl Schønheyder (Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark), Mette Søgaard (Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark).

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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REFERENCES

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;19:501–509.
2. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972), with special reference to hospital-acquired cases. *J Infect Dis* 1975;132:316–335.
3. Brenner ER, Bryan CS. Nosocomial bacteremia in perspective: a community-wide study. *Infect Control* 1981;2:219–226.
4. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128–140.
5. Leibovici L, Schønheyder HC, Pitlik SD, Samra Z, Moller JK. Bacteraemia caused by hospital-type micro-organisms during hospital stay. *J Hosp Infect* 2000;44:31–36.
6. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791–797.
7. Pedersen G, Schønheyder HC, Sørensen HT. Source of infection and other factors associated with case fatality in community-acquired bacteremia: a Danish population-based cohort study from 1992 to 1997. *Clin Microbiol Infect* 2003;9:793–802.
8. Al-Hasan MN, Eckel-Passow JE, Baddour LM. Impact of healthcare-associated acquisition on community-onset gram-negative bloodstream infection: a population-based study: healthcare-associated gram-negative BSI. *Eur J Clin Microbiol Infect Dis* 2012;31:1163–1171.
9. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. *BMC Infect Dis* 2012;12:85.
10. Pinholt M, Østergaard C, Arpi M, et al. Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006–2009: a population-based cohort study. *Clin Microbiol Infect* 2014;20:145–151.
11. Gradel KO, Jensen TG, Kolmos HJ, Pedersen C, Vinholt PJ, Lassen AT. Does C-reactive protein independently predict mortality in adult community-acquired bacteremia patients with known sepsis severity? *APMIS* 2013;121:835–842.
12. Gradel KO, Knudsen JD, Arpi M, Østergaard C, Schønheyder HC, Søgaard M. Classification of positive blood cultures: computer algorithms versus physicians' assessment: development of tools for surveillance of bloodstream infection prognosis using population-based laboratory databases. *BMC Med Res Methodol* 2012;12:139.
13. Trick WE, Zagorski BM, Tokars JI, et al. Computer algorithms to detect bloodstream infections. *Emerg Infect Dis* 2004;10:1612–1620.
14. Frank L. Epidemiology: when an entire country is a cohort. *Science* 2000;287:2398–2399.
15. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–25.
16. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–33.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
18. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. *Crit Care* 2004;8:508–512.
19. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993;39:561–577.
20. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, et al. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis* 2002;34:1431–1439.
21. Rodriguez-Bano J, Lopez-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect* 2010;16:1408–1413.
22. Clayton D, Hills M. Choice and interpretation of models. In: Clayton D, Hills M, eds. *Statistical Models in Epidemiology*. Oxford: Oxford Science, 1993:271–281.
23. Henderson KL, Muller-Pebody B, Johnson AP, Wade A, Sharland M, Gilbert R. Community-acquired, healthcare-associated and hospital-acquired bloodstream infection definitions in children: a systematic review demonstrating inconsistent criteria. *J Hosp Infect* 2013;85:94–105.
24. Arendrup MC, Bruun B, Christensen JJ, et al. National surveillance of fungemia in Denmark (2004 to 2009). *J Clin Microbiol* 2011;49:325–334.
25. Morgan J. Global trends in candidemia: review of reports from 1995–2005. *Curr Infect Dis Rep* 2005;7:429–439.
26. Cleveland AA, Farley MM, Harrison LH, et al. Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011. *Clin Infect Dis* 2012;55:1352–1361.
27. Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: a distinct entity? insights from a large U.S. database. *Crit Care Med* 2006;34:2588–2595.
28. Valles J, Calbo E, Anoro E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. *J Infect* 2008;56:27–34.