Central venous catheter–related bloodstream infections in patients with hematological malignancies: Comparison of data from a clinical registry and a randomized controlled trial

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To the Editor—Central venous catheter (CVC)–related bloodstream infections (CRBSIs) are clinically important healthcare-associated infections.[1,2] To reduce the burden of CRBSIs, many countries have implemented national surveillance programs.[3,4] Reliable epidemiological data are provided not only by cohort studies but also by randomized controlled trials (RCTs),[5–7] which are considered the gold standard for assessment of clinically relevant questions.[8] However, patient populations included in RCTs are often highly selected, limiting the generalizability of study results. In contrast, clinical registries can provide useful data on rare conditions in the daily routine that may also be helpful in assessing quality of care. On the other hand, they are limited by substantial confounders and bias.[8]

Our aim was to compare epidemiological data on CRBSIs in patients with hematological malignancies derived from a RCT (COAT,[6] ClinicalTrials.gov, no. NCT01544686) with data from a prospective registry (SECRECY,[9] German Clinical Trial Register, no. DRKS00006551). We hypothesized that patients included in a CVC RCT profit from improved CVC care compared to patients under standard clinical care conditions, possibly resulting in different CRBSI rates. Thus, the primary aim of the present analysis was to compare the CRBSI incidences between these groups.

The COAT trial was a RCT carried out from February 2012 to September 2014 in 10 hematology/oncology departments in Germany to compare 2 different types of CVC dressings with respect to the associated CRBSI incidence in neutropenic patients.[6] The SECRECY registry began in March 2013 and is an ongoing CRBSI registry,[9] now in 6 hematology/oncology departments in Germany.[10] In the present analysis, we included data from patients with nontunneled jugular and subclavian vein CVCs placed ≥1 day in situ. For CRBSI diagnosis, we used the 2012 definitions of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO), considering only definite or probable CRBSIs.[7] Because the end points in the COAT trial referred to the 2008 AGIHO/DGHO definitions,[11] the underlying data were reassessed, and the more recent definitions were applied to ensure the comparability of the 2 data sets.

According to the aforementioned inclusion criteria, we found 610 cases in the completed COAT trial data set and, as of May 2019, 2,390 cases in the SECRECY registry. In this entire cohort of 3,000 CVCs with 49,542 CVC days, underlying diseases were hematological malignancies and solid tumors in 2,719 (90.6%) and 158 (5.3%) cases, respectively. For a matched-pair analysis, the 610 patients from the COAT trial were matched with those patients from the SECRECY registry with regard to the use of chlorhexidine-coated CVC dressings, sex, and underlying disease with a high risk for CRBSI (ie, acute myeloid leukemia [AML], multiple myeloma, or non-Hodgkin lymphoma[10]).

Comparison of continuous variables was conducted using the Mann-Whitney U test, and categorical variables were compared using the Pearson χ^2 test or the Fisher exact test, when possible. CRBSI incidences were compared by χ^2 test. The Kaplan-Meier method was used for calculating the CRBSI probability over time, and the comparison between both groups was performed using the log-rank test and Cox regression. Two-sided *P* values <.05 were considered statistically significant. Statistical analyses were carried out using SPSS version 24 statistical software (IBM, Armonk, NY).

Patient and CVC characteristics as well as CRBSI features are shown in Table 1. Patients from the COAT cohort were younger than those from the SECRECY cohort (median, 58 vs 60 years; *P* < .001). There was a slight male predominance in both groups. COAT included fewer cases of AML than SECRECY (243 of 610 [39.8%] vs 300 of 610 [49.2%]; *P* = .001) but more cases of multiple myeloma (170 of 610 [27.9%] vs 123 of 610 [20.2%]; *P* = .002). In the COAT cohort, significantly fewer CVCs were inserted into the jugular vein, compared to the matched SECRECY cohort (41.8% vs 94.3%; *P* < .001). Although the median duration of CVC placement was significantly longer in the COAT trial than in the SECRECY registry (18 vs 15 days; *P* < .001), the median time to CRBSI onset was significantly shorter in the COAT cohort (12 vs 14 days; *P* = .040). We found no difference in the CRBSI rate between the COAT group and the SECRECY group (79 of 610 [13.0%] vs 71 of 610 [11.6%]; *P* = .542). Furthermore, the proportion of definite and probable CRBSIs was similar in both cohorts (*P* = .744). Regarding the primary aim of this analysis, the incidence of CRBSIs did not differ significantly with 7.0 CRBSIs per 1,000 CVC days in the COAT trial and 7.3 CRBSIs per 1,000 CVC days in the SECRECY registry (*P* = .794). Analyzing the CRBSI probability over time (ie,

Table 1. Patient/CVC Characteristics and CRBSI Features

Parameter	Whole Cohort (n = 3,000)	COAT Trial (n = 610)	SECRECY Registry (n = 610)	P Value[a]
Median age, years (IQR)	59 (48–66)	58 (48–66)	60 (53–68)	<.001[b]
Males, n/N (%)	1,759/3,000 (58.6)	361/610 (59.2)	361/610 (59.2)	1.000[c]
Underlying disease, n/N (%)				<.001[d]
Acute myeloid leukemia	1,194/3,000 (39.8)	243/610 (39.8)	300/610 (49.2)	
Multiple myeloma	658/3,000 (21.9)	170/610 (27.9)	123/610 (20.2)	
Non-Hodgkin lymphoma	529/3,000 (17.6)	115/610 (18.9)	105/610 (17.2)	
Acute lymphoblastic leukemia	271/3,000 (9.1)	34/610 (5.6)	12/610 (3.1)	
Hodgkin lymphoma	86/3,000 (2.9)	24/610 (3.9)	6/610 (1.0)	
Other	316/3,000 (10.5)	24/610 (3.9)	57/610 (9.3)	
High-risk disease, n/N (%)[e]	2,381/3,000 (79.4)	528/610 (86.6)	528/610 (86.6)	1.000[c]
Chlorhexidine-coated CVC dressing, n/N (%)	1,271/3,000 (42.4)	306/610 (50.2)	306/610 (50.2)	1.000[c]
Jugular vein CVC, n/N (%)	2,509/3,000 (83.6)	255/610 (41.8)	575/610 (94.3)	<.001[c]
CVC days, total	49,542	11,221	9,664	
CVC days, median (IQR)	16 (9–23)	18 (14–24)	15 (7–23)	<.001[f]
Median time to CRBSI onset, d (IQR)	14 (11–20)	12 (10–16)	14 (11–20)	.040[b]
CRBSI, n/N (%)	335/3,000 (11.2)	79/610 (13.0)	71/610 (11.6)	.542[c]
Definitive, n/N (%)	175/335 (52.2)	37/79 (46.8)	36/71 (50.7)	.744[c]
Probable, n/N (%)	160/335 (47.8)	42/79 (53.2)	35/71 (49.3)	
CRBSI incidence, x/1,000 CVC days	6.8	7.0	7.3	.794[g]
CRBSI14, % (95% CI)	8.5 (7.3–9.7)	10.4 (7.7–13.1)	9.6 (6.7–12.5)	.580[f]
Causative pathogens, n/N (%)				.142[d]
Coagulase-negative staphylococci	241/335 (71.9)	49/79 (62.0)	51/71 (71.8)	
Other Gram-positive bacteria	34/335 (10.1)	10/79 (12.7)	3/71 (4.2)	
Enterobacteriaceae	20/335 (6.0)	8/79 (10.1)	4/71 (5.6)	
Other Gram-negative bacteria	12/335 (6.6)	2/79 (2.5)	6/71 (8.5)	
Candida spp	10/335 (3.0)	2/79 (2.5)	3/71 (4.2)	
Multibacterial	18/335 (5.4)	8/79 (10.1)	4/71 (5.6)	

Note. CVC, central venous catheter; CRBSI, central venous catheter-related bloodstream infection; IQR, interquartile range; CRBSI14, cumulative CRBSI probability at day 14; 95% CI, 95% confidence interval.
[a]Comparison COAT trial data vs matched-pair data from SECRECY registry; all P values are 2-sided.
[b]Mann-Whitney U test.
[c]Fisher's exact test.
[d]Pearson's χ^2 test.
[e]Underlying disease with high risk for CRBSI: acute myeloid leukemia, multiple myeloma or non-Hodgkin lymphoma.[10]
[f]log-rank test.
[g]χ^2 test.

cumulative CRBSI incidence), we also found no significant differences at day 14 between these groups (10.4% in the COAT trail vs 9.6% in the SECRECY registry: hazard ratio, 1.12; 95% confidence interval, 0.74–1.71; *P* = .583). Finally, we detected no differences in the distribution of pathogen subgroups (*P* = .142), and coagulase-negative staphylococci were the most common causative pathogens for CRBSIs in both groups.

To the best of our knowledge, the present analysis is the first to provide comparative epidemiological data on CRBSIs from a RCT and a registry study in high-risk patients with hematological malignancies. Although limited by some differences in patient and CVC characteristics between both groups, this large matched-pair analysis did not show a reduced CRBSI incidence in patients treated in a RCT compared to patients in routine clinical care implicating a comparable quality of CVC care. Thus, epidemiological data on

CRBSIs derived from RCTs may reliably be transferred to real-world settings.

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A pseudo-outbreak of Legionnaires' disease in an acute-care hospital

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To the Editor—Epidemics of Legionnaires' disease (legionellosis) may involve large numbers of cases, with case-fatality rates of about 10% overall, and 25% in healthcare-associated cases.[1] The sources of legionellosis outbreaks are usually building water systems and devices, including potable water and cooling towers; therefore, any suspicion of a legionellosis outbreak must prompt efforts to identify the source and to stop further transmission.

This is a report on a suspected healthcare-associated legionellosis outbreak in an acute-care hospital involving 10 inpatients who tested positive for urinary antigen of Legionella pneumophila serogroup 1 between January and April 2017. Of 160 urinary antigen tests performed during this time period, 10 yielded positive results (positivity rate, 6.3%). In the previous year, only 1 of 76 tests had yielded a positive result (positivity rate, 1.3%).

The public health authority was notified and extensive testing of water samples for Legionellae was ordered. These tests only yielded L. pneumophila of a serogroup other than 1. Patient data showed that 5 patients had signs of pneumonia on admission:

1 patient had nonrespiratory signs consistent with legionellosis on admission, and 4 patients did not present any signs of pneumonia during their hospital stay. At the time of intervention, all but 1 patient had been discharged. A urine sample of the last patient was divided into 2 portions. One portion was sent to laboratory A, which had issued the positive test results, and the other portion was sent to laboratory B. In laboratory A, the urine sample again tested positive, whereas in laboratory B, the sample tested negative. Confronted with these findings, laboratory A reported having switched to a new urinary antigen test early in 2017, which later turned out to be of poor specificity. After a healthcare-associated outbreak had been ruled out, public health officials ruled out an outbreak altogether, either because legionellosis was not confirmed in the patients presenting signs of pneumonia or because no epidemiological link was found.

In conclusion, the presumptive healthcare-associated legionellosis outbreak caused considerable unrest within the hospital and among the public health authorities, but it proved to be a pseudo-outbreak. Pseudo-outbreaks (or pseudo-epidemics) are real clusters of false infections or artifactual clusters of real infections.[2] The pseudo-outbreak described here was caused by false-positive urinary-antigen test results. Community pseudo-outbreaks of this kind have been reported previously.[3,4] In our case, the pseudo-outbreak was complicated by assuming healthcare

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