Central venous catheter-related bloodstream infections in patients with haematological malignancies during the SARS-CoV-2 pandemic

Patients with haematological malignancies are at increased risk for infectious complications. This also applies to infections due to central venous catheters (CVC), which account for a significant proportion of morbidity and mortality in these high-risk patients. Therefore, implementation of infection prevention bundles is important. Maximal sterile barrier precautions during CVC insertion or guidewire exchange are strongly recommended including wearing a mask. Furthermore, surveillance of patients with a CVC is encouraged to determine and monitor trends in infection rates and to assist in identifying lapses in infection control practice.

To date, the SARS-CoV-2 pandemic has changed our awareness of infection control measures.

We therefore hypothesize, that CVC-related bloodstream infections (CRBSI) in patients with haematological malignancies might be less common during the SARS-CoV-2 pandemic due to more stringently applied hygiene measures are not only followed during CVC insertion but potentially throughout the whole patient stay by hospital staff, patients and visitors. Thus, CRBSI surveillance data before and during the SARS-CoV-2 pandemic were compared.

We used data from the SECRECY registry, an ongoing, clinical CRBSI registry established in March 2013, currently active in six German sites. Surveillance data are documented on CRBSI of non-selected, consecutive patients with short-term, non-tunnelled jugular, subclavian or femoral vein CVCs inserted for routine clinical use. All CVCs were inserted according to local standard operating procedures following current guidelines. CRBSI were classified according to the 2012 Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO) definition. No changes were made regarding CVC insertion procedures or care by the sites over time.

For the present analysis, of all cases documented registry data on jugular and subclavian CVC with CVC in situ at least one day were used. Only CRBSI cases classified as definite CRBSI (dCRBSI) and the combination of definite and probable (dpCRBSI) were considered. The primary end-point was dCRBSI incidence. Definite CRBSI is subject to the strictest diagnostic criteria, and seemed to yield more consistent epidemiological parameters. For epidemiological studies, it is recommended to use CRBSI incidence (incidence density; calculated per 1000 CVC days).

All of the six currently active sites are documenting patients with CVC cases since the third quarter of 2018 (3q2018). As the WHO has declared the SARS-CoV-2 outbreak a global pandemic at the end of the first quarter of 2020 (1q2020), on 11 March 2020, we have chosen the time from the beginning of the second quarter of 2020 (2q2020) to the end of the fourth quarter of 2021 (4q2021) as ‘during’ the pandemic. The time from 3q2018 to 1q2020 was defined as ‘before’ the pandemic, so that both time periods are made up of seven quarters each.

Statistical analysis was performed using OpenEpi, version 3.01 (https://www.openepi.com), and IBM® SPSS® Statistics, version 28 (IBM Corp., Armonk, NY, USA). Two-sided p values <0.05 were considered statistically significant. Statistical tests used are detailed in Table 1.

We identified a total of 2553 CVC with 1474 CVC inserted before and 1079 during the pandemic (Table 1). Most patients suffered from haematological malignancies [2357 (92.3%)]. The great majority of patients were neutropenic at the time of CRBSI diagnosis and rates of neutropenia at the time of dCRBSI and dpCRBSI during both time periods were not different (p = 0.121 for dCRBSI, and p = 0.144 for dpCRBSI).

Looking at the primary end-point, the dCRBSI incidence was significantly lower during as compared to before the pandemic (1.9 vs 3.9 per 1000 CVC days; p < 0.001), and the same is true for the incidence of dpCRBSI (3.5 vs 6.1 per 1000 CVC days; p < 0.001), the dCRBSI rate (2.9% vs 6.0%; p < 0.001) and the dpCRBSI rate (5.4% vs 9.4%; p < 0.001) (Table 1). In a time-to-event analysis there were also fewer dCRBSI [hazard ratio (HR) 0.47, 95% confidence interval (95% CI) 0.31–0.70; p < 0.001] and dpCRBSI (HR 0.56, 95% CI 0.41–0.76; p < 0.001) during the pandemic compared to before (Figure 1).

In summary, we found about 50% fewer CRBSI cases during the pandemic as compared to the equivalent time period before. This is somewhat unexpected, as there were no changes regarding CVC insertion procedures or care by the participating sites during the time periods. Also, there were no differences in terms of underlying diseases or most CVC characteristics.
TABLE 1  Comparison of characteristics of patients, CVC and CRBSI of both periods

|                              | Before pandemic $n = 1474$ | During pandemic $n = 1079$ | $p$ value |
|------------------------------|-----------------------------|----------------------------|-----------|
| **Patients**                 |                             |                            |           |
| Median age, years (IQR)      | 59 (49–66)                  | 60 (51–66)                 | 0.010     |
| Men, $n$ (%)                 | 827 (56.1)                  | 656 (60.8)                 | 0.019     |
| Underlying disease, $n$ (%)  |                             |                            |           |
| Acute myeloid leukaemia      | 532 (36.1)                  | 383 (35.5)                 | 0.160     |
| Acute lymphoblastic leukaemia| 117 (7.9)                   | 78 (7.2)                   |           |
| Non-Hodgkin lymphoma         | 285 (19.3)                  | 236 (21.9)                 |           |
| Multiple myeloma             | 321 (21.8)                  | 229 (21.2)                 |           |
| Hodgkin lymphoma             | 41 (2.8)                    | 26 (2.4)                   |           |
| MDS/MPN                      | 71 (4.8)                    | 38 (3.5)                   |           |
| Cytopenia                    | 28 (1.9)                    | 10 (0.9)                   |           |
| Germ cell tumour             | 26 (1.8)                    | 20 (1.9)                   |           |
| Carcinoma                    | 25 (1.7)                    | 23 (2.1)                   |           |
| Sarcoma                      | 19 (1.3)                    | 23 (2.1)                   |           |
| Infection                    | 3 (0.2)                     | 6 (0.6)                    |           |
| Others*                      | 6 (0.4)                     | 7 (0.6)                    |           |
| **CVC**                      |                             |                            |           |
| Median CVC time, days (95% CI)| 15 (14.4–15.6)               | 15 (14.3–15.7)             | 0.576     |
| Internal jugular vein, $n$ (%)| 1306 (88.6)                 | 1048 (97.1)                | <0.001    |
| Antimicrobial-coated, $n$ (%)| 231 (15.7)                  | 187 (17.3)                 | 0.279     |
| CHG-coated dressings, $n$ (%)| 463 (31.4)                  | 309 (28.6)                 | 0.138     |
| Neutropenia at insertion, $n$ (%)| 261 (17.7)               | 177 (16.4)                 | 0.396     |
| Neutropenia at dCRBSI diagnosis, $n/N$ (%)| 68/89 (76.4) | 28/31 (90.3)               | 0.121     |
| Neutropenia at dpCRBSI diagnosis, $n/N$ (%)| 111/138 (80.4) | 52/58 (89.7)               | 0.144     |
| Neutropenia at removal, $n$ (%)| 476 (32.3)                  | 319 (29.6)                 | 0.153     |
| High-risk CVC for CRBSI, $n$ (%)| 681 (46.2)                  | 541 (51.1)                 | 0.050     |
| **CRBSI**                    |                             |                            |           |
| Incidence, $x/1000$ CVC days (95% CI) |                       |                            |           |
| dCRBSI                       | 3.9 (3.2–4.9)               | 1.9 (1.3–2.6)              | <0.001    |
| dpCRBSI                      | 6.1 (5.1–7.2)               | 3.5 (2.6–4.5)              | <0.001    |
| Cumulative incidence, % (95% CI) |                       |                            |           |
| dCRBSI                       | 41.6 (81–75.1)              | 9.1 (3.4–14.8)             | <0.001    |
| dpCRBSI                      | 49.3 (19.1–79.5)            | 15.0 (8.9–21.1)            | <0.001    |
| Rate, $n$ (%) [95% CI)       |                             |                            |           |
| dCRBSI                       | 89 (6.0 [4.9–7.4])          | 31 (2.9 [2.0–4.0])         | <0.001    |
| dpCRBSI                      | 138 (9.4 [8.0–11.0])        | 58 (5.4 [4.2–6.9])         | <0.001    |
| Causative pathogens, $n/N$ (%)|                             |                            |           |
| dCRBSI                       |                             |                            |           |
| CoNS                         | 63/89 (70.8)                | 25/31 (80.6)               | 0.770     |
| Enterobacteriaceae           | 6/89 (6.7)                  | 1/31 (3.2)                 |           |
| Other Gram-negative bacteria | 5/89 (5.6)                  | 0                          |           |
| Other Gram-positive bacteria | 9/89 (10.1)                 | 3/31 (9.7)                 |           |
| Candida spp.                 | 3/89 (3.4)                  | 1/31 (3.2)                 |           |
| Multimicrobial               | 3/89 (3.4)                  | 1/31 (3.2)                 |           |
As previously shown, male sex, complicated CVC insertion, diagnosis of acute myeloid leukaemia, multiple myeloma or non-Hodgkin lymphoma are independent risk factors for CRBSI at time of CVC insertion (HR 1.59; p = 0.02). In the present analysis the number of high-risk CVCs was numerically higher during the pandemic than before the pandemic (51.1% vs 46.2%; p = 0.050) so that even more cases of CRBSI should have been expected. Furthermore, although there were numerically more patients neutropenic during the pandemic, this did not translate into more CRBSI. As stated in Table S1, one centre had a markedly reduced CVC insertion/documentation rate during the pandemic, and the six centres had no similar CRBSI incidences/rates. Therefore, a centre effect cannot be ruled out. However, we found an equal (numerical) reduction of dCRBSI incidence/rate at each centre. Due to fewer CVC insertions/documentation during the pandemic, one might assume this may have influenced the result of our study. Therefore, we have compared the data before and during the pandemic without the mentioned centre. Even without this centre we found a significant decrease in dCRBSI incidence (3.7 vs 1.8/1000 CVC days; p < 0.001) and dCRBSI rate (5.5% vs 2.7%; p = 0.001). Therefore, we think that the change in CVC insertion/documentation rate would not be an explanation for the fewer CRBSIs during the pandemic.

Potential reasons for the lower CRBSI incidence during the pandemic are unclear at the moment. At this point in time we can only speculate that rigorous and stringent hygiene measurements (beyond our standard CVC-related procedures) during the pandemic might have resulted in lower rates of CRBSI.
wearing face masks, which may have had an impact on the CRBSI incidence during the pandemic. In addition, contact restrictions during the pandemic reduced the number of visits to the patients by relatives and other non-healthcare professionals. This might have been associated with less CVC manipulations (fewer disconnections of long-running infusions for walks outside the hospital ward, etc.) which in turn may have resulted in a lower CRBSI risk. Intensified hand hygiene/disinfection during the pandemic\textsuperscript{3,4,10} may also have had an impact on the CRBSI risk.\textsuperscript{1,2}

In conclusion, our data provide some evidence that the incidence of CRBSI in patients with haematological malignancies was reduced during the SARS-CoV-2 pandemic, probably as a result of stricter overall hygiene measures\textsuperscript{10} which may also have contributed to a general lower incidence of infectious diseases.\textsuperscript{11,12} However, not only hygiene, but also thorough surveillance, including awareness, may have contributed to the significant reduction in CRBSI.

**ETHICS APPROVAL STATEMENT**
The study was approved by the central ethics committee (Magdeburg University Hospital, approval no. 84/14) as well as by respective local ethics committees.

**PATIENT CONSENT STATEMENT**
Given the nature of routine clinical data and the anonymization of patient data, written informed consent was not required within the study.

**CLINICAL TRIAL REGISTRATION**
SECRECY (Study to Evaluate Central Venous Catheter-related Infections in Haematology and Oncology) was registered in the German Clinical Trial Register (DRKS, no. DRKS00006551).

**PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES**
Not applicable.

**AUTHOR CONTRIBUTIONS**
Enrico Schalk designed the study, collected and analysed the data and wrote the manuscript. Timo Schmitt collected the data, interpreted the data and revised the manuscript. Jens Panse interpreted the data and revised the manuscript. Eva Fiegle collected the data, interpreted the data and revised the manuscript. Jan-Hendrik Naendrup collected the data, interpreted the data and revised the manuscript. Martin Schmidt-Hieber interpreted the data and revised the manuscript. Boris Böll interpreted the data and revised the manuscript. Marcus Hentrich interpreted the data and revised the manuscript. Daniel Teschner interpreted the data, and revised the manuscript. Dimitrios Mougiakakos interpreted the data, and revised the manuscript. All authors were involved in patient management and approved the final version of the manuscript.

**KEYWORDS**
central venous catheter, central venous catheter-related bloodstream infection, epidemiology, haematological malignancies, pandemic, SARS-CoV-2

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**CONFLICTS OF INTEREST**
All authors have no competing interests to declare that are relevant to the content of this article.

**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available from the corresponding author upon reasonable request.
LETTER TO THE EDITOR

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