Surveillance of Nosocomial Sepsis and Pneumonia in Patients with a Bone Marrow or Peripheral Blood Stem Cell Transplant: A Multicenter Project

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Background. For surveillance of nosocomial bloodstream infections (BSIs) and pneumonia during neutropenia in adult patients who have undergone bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT), a multicenter study—the Hospital Infection Surveillance System for Patients with Hematologic/Oncologic Malignancies (ONKO-KISS)—was initiated in Germany in 2000.

Methods. Nosocomial infections were identified in neutropenic patients by means of Centers for Disease Control and Prevention definitions for laboratory-confirmed BSI and modified criteria for pneumonia.

Results. During the first 38-month period of the study (i.e., through December 2003), a total of 1899 patients associated with 28,273 neutropenic days were investigated. Of these, 1173 (62%) had undergone allogeneic and 726 (38%) had undergone autologous BMT or PBSCT. The mean duration of neutropenia was 14.9 days (9.6 and 18.1 days after autologous and allogeneic transplantation, respectively). Overall, 395 BSIs and 168 cases of pneumonia were identified. The pooled mean site-specific incidence density per 1000 neutropenic days was 14.0 for BSI (12.4 and 18.9 for the allogeneic and autologous transplantation groups, respectively) and 5.9 for pneumonia (6.1 and 5.6 in the allogeneic and autologous transplantation groups, respectively). After allogeneic transplantation, 22.4 BSIs per 100 patients and 11.0 cases of pneumonia per 100 patients occurred, whereas 18.2 BSIs per 100 patients and 5.4 cases of pneumonia per 100 patients occurred after autologous transplantation. The majority (57%) of pathogens associated with BSI were coagulase-negative staphylococci.

Conclusions. The ongoing ONKO-KISS project provides unprecedented reference data about the incidence of pneumonia and sepsis among BMT recipients and PBSCT recipients in Germany. These data will be used for further evaluation of the impact of hygiene measures and therapeutic regimens for these patients.

Nosocomial infection rates among patients mainly depend on the severity of illness, the therapeutic interventions undertaken, and the exposure to invasive devices or procedures (i.e., use of central venous catheters, mechanical ventilation, and urinary catheters). In addition, after allogeneic and autologous bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT), patients are at increased risk for acquiring ≥1 potentially life-threatening nosocomial infection [1]. This risk is especially high during the neutropenic phase of their therapeutic course, as recently confirmed in the case of 351 adult hematopoietic stem cell transplant (HSCT) recipients treated in one of the hematology wards at University Hospital of Freiburg (Freiburg, Germany) [2].

Hospital infection-control programs include surveillance, which involves the systematic collection, tabulation, and analysis of and feedback on data about the occurrence of nosocomial infections. Data useful for identifying infected patients, determining the site of infection, and identifying factors that contribute to the
The Hospital Infection Surveillance System for Patients with Hematologic/Oncologic Malignancies (ONKO-KISS) study was initiated in 2000 as part of the surveillance program of the German National Reference Center for Surveillance of Nosocomial Infections (KISS—German Hospital Infection Surveillance System) to provide ongoing surveillance of neutropenic patients for nosocomial bloodstream infections (BSIs) and pneumonia, which are the most frequent and most important nosocomial infections in adult patients who have recently undergone BMT or PBSC [2]. Despite the fact that endogenous infections play an important role in such patients, there are striking differences in the hygiene and therapeutic measures employed to treat these infections. Thus, to support improvement of the quality of care, it is reasonable to compare infection rates in different hospitals [3]. This requires standardized definitions and methods. It was for this purpose that ONKO-KISS was initiated. The establishment of a surveillance system has been proven to lead to a decrease in infection rates, known as the Hawthorne effect. Apart from reducing nosocomial infection rates and reliably identifying epidemics, a surveillance system is essential for determining how the infection rate endemic to one’s own hospital compares with that in other hospitals. Altogether, surveillance of nosocomial infections helps to reduce the rate of these infections among critically ill patients [5].

PATIENTS AND METHODS

Study population. Eighteen hospitals in Germany, Switzerland, and Austria participated in this project during the first 38-month period of the study (i.e., through December 2003). Of these, 12 (67%) are university hospitals, 5 (28%) are teaching hospitals, and 1 (6%) is a district hospital. Name, location, and other data about the study centers are strictly confidential. Fourteen of the participating hospitals perform allogeneic and autologous BMT or PBSC, whereas 4 hospitals perform autologous transplantations only. The participating hospitals reported data for 21–306 patients each, depending on the size of the hospital and the duration of participation in the study. All adult patients (age, ≥16 years) with an allogeneic or autologous BMT or PBSC were evaluated during neutropenia.

Surveillance. Trained infection-control practitioners visited the wards involved in the study once per week. General data collected about participating patients included name, age, sex, diagnosis, type of central venous catheter, and antimicrobial treatment. Nursing notes, medical notes, microbiology reports, temperature charts, and antibiotic treatment charts were reviewed to determine whether a patient had any signs or symptoms of infection. In addition, the nursing and medical staff were consulted about any queries regarding signs and symptoms.

A worksheet was completed for every patient who became neutropenic (regardless of infection status). A special postdischarge follow-up examination was not performed. The time required to collect and analyze the data was assessed in 2002.

Definitions. Nosocomial BSIs and cases of pneumonia were categorized according to Centers for Disease Control and Prevention (CDC) definitions that include clinical and laboratory criteria [4]. However, a few modifications have been introduced, as proposed and described in detail by Carlisle et al. [6], because of the absence of a clinical manifestation of focal infections and leukocyte response.

In line with these definitions, the diagnosis of nosocomial pneumonia was made on the basis of several criteria, which included fever and new or worsening infiltrates (revealed by chest radiography or, if necessary, a thoracic CT) or fulfillment of at least 2 of the following: production of sputum, cough, dyspnea, rhonchi, or rales; polymorphonuclear leukocytes on a sputum gram stain; and pleural rub. Primary BSIs were defined as isolation of a recognized pathogen from ≥1 blood culture that was unrelated to an infection at another site; and/or: fever, shivering, or hypotension; and 1 of the following: isolation of a common skin contaminant from 2 separate blood cultures that was unrelated to an infection at another site, isolation of a common skin contaminant from 1 blood culture for patients with an intravascular device for whom a physician initiated appropriate antimicrobial therapy, or a blood test result positive for an antigen of a pathogen that was unrelated to an infection at another site.

Classification of an infection as nosocomial was made only if evidence showing that the infection was active or incubating at the time of admission to the ward was absent. Infections occurring at ≥1 site in the same patient were reported as separate infections, with the exception of secondary BSIs caused by pneumonia.

Only nosocomial infections that occurred during the neutropenic phase were recorded. This phase was shown to be the period of highest risk for acquiring a nosocomial infection [2]. Neutropenia was defined as an absolute WBC count <1 × 10^9 cells/L. The neutropenic phase was declared to be over once the patient had a neutrophil count >1 × 10^9 cells/L for ≥2 days. An infection was considered to be nosocomial if symptoms appeared at any time on or after the second day after the onset of neutropenia up to 2 days after the end of neutropenia.

Statistics. Rates (episodes per 100 patients) and incidences of site-specific infections per 1000 days at risk (i.e., the neutropenic phase) were calculated [3].

RESULTS

Over the first 38-month period, 1899 patients associated with 28,273 neutropenic days were investigated. Of these patients, 1142 were men, and 757 were women. The mean age of the patients was 46 years (range, 16–76 years). A total of 1173 (62%) underwent allogeneic and 726 (38%) underwent autologous transplantations only. The participating hospitals reported data for 21–306 patients each, depending on the size of the hospital and the duration of participation in the study. All adult patients (age, ≥16 years) with an allogeneic or autologous BMT or PBSC were evaluated during neutropenia.

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Table 1. Primary diagnoses received by 1899 patients who underwent allogeneic or autologous bone marrow or peripheral blood stem cell transplantation.

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Overall (n = 1899)</th>
<th>Autologous (n = 726)</th>
<th>Allogeneic (n = 1173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>539 (28)</td>
<td>69 (10)</td>
<td>470 (40)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>208 (11)</td>
<td>10 (1)</td>
<td>198 (17)</td>
</tr>
<tr>
<td>Acute lymphocyte leukemia</td>
<td>185 (10)</td>
<td>8 (1)</td>
<td>177 (15)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>315 (17)</td>
<td>221 (30)</td>
<td>94 (8)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>80 (4)</td>
<td>3 (&lt;1)</td>
<td>77 (7)</td>
</tr>
<tr>
<td>Plasmocytoma</td>
<td>199 (10)</td>
<td>172 (24)</td>
<td>27 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>374 (20)</td>
<td>243 (33)</td>
<td>130 (11)</td>
</tr>
</tbody>
</table>

The mean duration of neutropenia was 14.9 days, for a total of 28,273 neutropenic days (21,271 and 7002 of which were after allogeneic and autologous transplantation, respectively). The mean duration of neutropenia was 9.6 days for autologous transplant recipients (median, 9 days; range, 3–64 days) and 18.1 days for allogeneic transplant recipients (median, 17 days; range, 2–99 days). The mean duration of neutropenia at the different centers was 7.7–20.7 days.

Nosocomial infections. Overall, 395 BSIs and 168 cases of pneumonia were identified during the neutropenic phase. Forty-five patients contracted 2 infections each, whereas 3 patients contracted 3 infections each. Pooled mean site-specific incidence densities for BSIs and cases of pneumonia per 1000 neutropenic days were 14.0 and 5.9, respectively.

There were 7.1–35.2 BSIs per 1000 neutropenic days (median [interquartile range (IQR)], 17.7 [11.8–20.3] BSIs per 1000 neutropenic days) (figure 1). There were 0–11.8 cases of pneumonia per 1000 neutropenic days (median [IQR], 5.1 [3.6–7.8] cases of pneumonia per 1000 neutropenic days) (figure 1).

Table 2 summarizes the infection rates (means) according to transplant source (i.e., allogeneic vs. autologous). A greater number of BSIs developed in neutropenic patients who received an autologous transplant than in neutropenic patients who received an allogeneic transplant (18.9 vs. 12.4 per 1000 days of...
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center surveillance project that involves ongoing collection and
analysis of data about nosocomial sepsis and pneumonia in
patients with hematologic disease. At the same time, the project
places reference data at the disposal of hospitals that are and
aren’t participating in the project.

In recent decades, allogeneic and autologous HSCTs have
become of great importance in the therapeutic management of
patients with hematologic disease [7–12]. However, apart from
reports about outbreaks of nosocomial infection [13–16], in-

neutropenia). The BSI rate was higher among allogeneic trans-
plant recipients than among autologous transplant recipients
(22.4% vs. 18.2%). The incidence of pneumonia was com-
parable for both transplant sources (6.1 and 5.6 cases of pneu-
monia per 1000 neutropenic days for recipients of allogeneic
and autologous transplants, respectively). However, the rate of
pneumonia among allogeneic transplant recipients was higher
than that among autologous transplant recipients (11.0% vs.
5.4%).

**Time required for data collection.** By use of the surveil-
ance method described above, the mean time required to col-
lect, document, and analyze data from the HSCT units was
reported to be 3.5 h per 10 beds per week (range, 2.1–5.0 h
per 10 beds per week).

**Microbiological analysis.** A total of 460 analyzable path-
ogenic microorganisms are classified in table 3 by descending
order of frequency. The main pathogens were coagulase-neg-
ative staphylococci (262 [57%] of 460 isolates), streptococci
(37 [8%]), *Escherichia coli* (35 [8%]), enterococci (30 [7%]),
and *Candida* species (20 [4%]). Fourteen (3%) of 460 isolates
were *Staphylococcus aureus*, of which 5 were resistant to meth-
illin (MRSA).

In 119 (71%) of 168 cases of pneumonia, no pathogen could
be isolated. Only 63 (pathogenic) microorganisms were isolated
in 49 cases. Of these 63 isolates, 14 (22%) were *Candida* species,
14 (22%) were coagulase-negative staphylococci, 10 (19%) were
*Aspergillus* species, and 7 (11%) were enterococci.

**DISCUSSION**

To our knowledge, the ONKO-KISS project is the first multi-
center surveillance project that involves ongoing collection and
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become of great importance in the therapeutic management of
patients with hematologic disease [7–12]. However, apart from
reports about outbreaks of nosocomial infection [13–16], in-

formation on the endemic occurrence of nosocomial infection
among these patients is limited [6, 17–20]. In a previous study
performed in one of the wards of the Hematologic Stem Cell
Transplantation Unit of the University Hospital of Freiburg, all
nosocomial infections acquired by 351 patients with hemat-
ologic and/or oncologic diseases during their entire hospital stay
were recorded [2]. This study found that 72% of infections
occurred during neutropenia. Neutropenia is without doubt
one of the main risk factors for infection in these patients. An
additional finding was that approximately two-thirds (68%) of
the infectious episodes were BSI or pneumonia. These infec-
tions are of great importance because they are associated with
high morbidity and mortality. Thus, because of restricted hos-
pital personnel resources, targeted surveillance of these 2 types
of infection is reasonable.

The Freiburg study served as a basis for the ONKO-KISS
surveillance project, which was initiated to provide reference
data about the incidence of nosocomial sepsis and pneumonia
among neutropenic patients undergoing BMT or PBSCT and
to use these data as a basis for improving the quality of care.
In this study, we have shown that the mean time required for
surveillance (i.e., collection, documentation, and analysis of
data) was 3.5 h per 10 beds per week. However, there was quite

<table>
<thead>
<tr>
<th>Transplant source</th>
<th>Incidence density, episodes per 1000 neutropenic days</th>
<th>Rate, episodes per 100 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>BSI 14.0 Pneumonia 5.9</td>
<td>BSI 20.8 Pneumonia 8.8</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>12.4 6.1</td>
<td>22.4 11.0</td>
</tr>
<tr>
<td>Autologous</td>
<td>18.9 5.6</td>
<td>18.2 5.4</td>
</tr>
</tbody>
</table>

**Table 3.** Classification of 460 analyzable pathogenic microorganisms recovered from 395 episodes of bloodstream infection in patients who underwent bone marrow transplantation or peripheral blood stem cell transplantation.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>No. (%) of isolates (n = 460)</th>
</tr>
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<tbody>
<tr>
<td><strong>Gram-positive cocci</strong></td>
<td>343 (75)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>262 (57)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin susceptible</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Methicillin resistant</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>37 (8)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Other cocci</td>
<td>19 (4)</td>
</tr>
<tr>
<td><strong>Gram-negative rods</strong></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>35 (8)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>12 (3)</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>5 (1)</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Other gram-negative rods</td>
<td>9 (2)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>67 (15)</td>
</tr>
<tr>
<td><strong>Yeasts</strong></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Non-<em>Candida</em> species</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Gram-positive rods</strong></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
a wide difference in surveillance requirements (range, 2.1–5.0 h per 10 beds per week) between the participating hospitals. This might depend on the experience of the infection-control practitioner or on the number of different wards in which the hematologic transplant recipients are placed. In the previous study, 5 h per 10 beds per week were needed to perform surveillance for all infections during the entire hospital stay [2]. Targeted surveillance was therefore shown to have saved time.

We used the modified definitions for nosocomial pneumonia described by Carlisle et al. [6], rather than the definitions offered by the CDC, because the symptoms of pneumonia are often subtle in severely immunocompromised patients, and chest radiography is seldom performed twice to verify a new or worsening infiltrate. On the other hand, because only few criteria are required for diagnosis, this might lead to overestimation in some cases. Thus, there is a risk of underreporting the number of pneumonia cases. This is also underlined by the fact that, in 70% of the pneumonia cases, no pathogen could be isolated. In addition, the majority of the microorganisms isolated, such as Candida species, coagulase-negative staphylococci, and enterococci, were probably only contaminants and were thus unlikely to cause pneumonia. Attention, therefore, must focus on findings of chest radiography or thoracic CT and on clinical symptoms.

The vast majority of pathogens associated with BSI (343 [75%] of 460) were gram-positive cocci, primarily coagulase-negative staphylococci (262 [57%]). This generally reflects the expected frequencies among the infecting pathogens, with gram-positive isolates predominating. However, the high percentage of gram-positive cocci, especially coagulase-negative staphylococci, is rarely observed in other studies. In 2000, the Surveillance and Control of Pathogens of Epidemiologic Importance study, for example, reported that 487 (61%) of all BSIs were caused by gram-positive organisms but that only 252 (32%) were caused by coagulase-negative staphylococci [21]. S. aureus was isolated in 14 (3%) of 460 BSI episodes. Five (36%) of these 14 isolates were MRSA. This exceeds the ~21% proportion of BSI-associated S. aureus isolates that were resistant to methicillin (compared with MSSA) in intensive care units in Germany [22, 23]. Because of the low overall number of S. aureus isolates recovered, it is not possible to draw conclusions about the higher proportion of MRSA in this patient population.

Two-thirds of HSCTs were allogeneic, and one-third were autologous. The mean duration of neutropenia for recipients of autologous transplants was one-half that for allogeneic transplant recipients (9.6 vs. 18.1 days, respectively). It is remarkable that, during the neutropenic phase, the incidence density of BSIs among autologous HSCT recipients was higher than that among allogeneic HSCT recipients (18.9 vs. 12.4 nosocomial infections per 1000 neutropenic days, respectively), whereas the numbers for pneumonia were nearly identical (5.6 vs. 6.1 cases of pneumonia per 1000 neutropenic days).

In a study by Engels et al. [24], allogeneic transplant recipients were significantly more likely to develop infection than were autologous transplant recipients (55% vs. 30%, respectively [P = .01]; all infections were recorded, and surveillance was not standardized on the basis of CDC definitions). According to the authors, this was due to prolonged and more-severe neutropenia and possibly also to severe mucositis and use of immunosuppressive medications [24]. These investigators collected data about patients until discharge or death and did not relate the infection rate to the number of neutropenic days. Similar to the results of our study, allogeneic transplant recipients had more neutropenic days than did autologous transplant recipients. Our study likewise shows a lower rate of BSIs among autologous transplant recipients, compared with allogeneic transplant recipients. The relatively high BSI rate among autologous transplant recipients may possibly be due to the fact that many BSIs appear during the early phase of neutropenia after transplantation.

The incidence of BSI and pneumonia shows clear differences between the participating hospitals. The infection rate for one of the hospitals in particular is markedly higher than that for the others. Infection rates between the 25th and 75th percentile are considered to be within the normal range. When infection rates are less than the 25th percentile, a distinction has to be made about whether the rates were underreported, the patient population was unique, or other factors were present. When infection rates are very high (i.e., greater than the 75th percentile), there may be additional underlying reasons, other than poor hygiene or therapeutic management.

Continuation of surveillance and additional studies, such as those involving hygiene measures and antibiotic use in hematologic stem cell transplantation units, are needed to further evaluate the risk factors that lead to severe infection in this group of patients. Furthermore, to permit evaluation of the influence of the antibiotic regimen on the incidence of infection, it would be desirable to record data about antibiotic prophylaxis and the use of granulocyte colony-stimulating factor at the participating centers.

Acknowledgments

We thank the medical staff and study nurses at all participating centers as well as other people involved in this project for their invaluable support throughout the study. We also thank Matthias Albert, and we are grateful to Deborah Lawrie for her help in preparing the manuscript.

Financial support. Federal Ministry of Health and Social Security, Germany.

Potential conflicts of interest. All authors: no conflicts.
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