Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study

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Background. Infection is a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Our object was to better define the epidemiology and outcomes of infections after HCT.

Methods. This was a prospective, multicenter cohort study of HCT recipients and conducted from 2006 to 2011. The study included 4 US transplant centers and 444 HCT recipients. Data were prospectively collected for up to 30 months after HCT using a standardized data collection tool.

Results. The median age was 53 years, and median follow up was 413 (range, 5–980) days. The most common reason for HCT was hematologic malignancy (87%). The overall crude mortality was 52%. Death was due to underlying disease in 44% cases and infection in 21%. Bacteremia occurred in 231 (52%) cases and occurred early post-transplant (median day 48). Gram-negative bloodstream infections were less frequent than Gram-positive, but it was associated with higher mortality (45% vs 13%, P = .02). Clostridium difficile infection developed in 148 patients (33%) at a median of 27 days post-HCT. There were 53 invasive fungal infections (IFIs) among 48 patients (11%). The median time to IFI was 142 days. Of 155 patients with cytomegalovirus (CMV) infection, 4% had CMV organ involvement. Varicella zoster infection (VZV) occurred in 13 (4%) cases and was disseminated in 2. Infection with respiratory viruses was seen in 49 patients. Pneumocystis jirovecii pneumonia was rare (1%), and there were no documented cases of nocardiosis, toxoplasmosis, endemic mycoses, or mycobacterial infection. This study lacked standardized antifungal and antiviral prophylactic strategies.

Conclusions. Infection remains a significant cause of morbidity and mortality after HCT. Bacteremias and C difficile infection are frequent, particularly in the early post-transplant period. The rate of IFI is approximately 10%. Organ involvement with CMV is infrequent, as are serious infections with VZV and herpes simplex virus, likely reflecting improved prevention strategies.

Keywords. infections; prospective; stem cell; transplant.

More than 8000 allogeneic hematopoietic cell transplants (HCTs) are performed annually in North America. Significant strides have been made in the last few decades to decrease the incidence of serious infections, such as those due to cytomegalovirus (CMV) and varicella zoster virus (VZV), but infection remains a leading cause of morbidity and mortality after HCT [1–5]. The types of patients receiving HCT, as well as the conditioning regimen used, and the source of stem cells and...
Washington University in St. Louis, Cleveland Clinic, University of Pittsburgh, University of Alabama at Birmingham), in collaboration with the Centers for Disease Control and Prevention (CDC). Four centers (University of Michigan, University of Alabama, University of Pennsylvania, and Washington University) contributed patients undergoing HCT to the current study. Data were prospectively collected from each of the centers during 2006–2011. All sites received local institutional review board approval before patient enrollment. Patients were followed for up to 30 months posttransplant. Study visits were performed weekly for the first 4 months and during inpatient stays, and monthly thereafter.

All patients ≥18 years of age who underwent allogeneic HCT at the 4 sites were eligible for enrollment. Data collected at enrollment included demographic information, details about the transplant, graft source (bone marrow, peripheral stem cells, or umbilical cord stem cells), human leukocyte antigen match, conditioning regimen, and immunosuppression as well as recipient comorbidities.

Use of antifungal and antiviral prophylaxis and empiric therapy for neutropenic fever was at the discretion of each center. Antifungal prophylaxis was defined as follows: the use of a systemic antifungal agent for at least 7 days in the absence of a suspected or confirmed invasive fungal infection (IFI). Antiviral prophylaxis was defined as use of an antiviral agent for at least 7 days in the absence of a suspected or confirmed viral infection. Infectious syndromes were defined using Modified National Nosocomial Infection Surveillance System (restructured in 2005 to become National Healthcare Safety Network) definitions [10].

Suspected infections other than CMV or IFI were defined as any clinical syndrome for which antimicrobial treatment was initiated. Cytomegalovirus infection was defined as detection of CMV in the blood by polymerase chain reaction or pp65 antigenemia testing, positive histopathology, or a positive CMV immunostain on a tissue biopsy. Infection onset date was considered to be the date of the first diagnostic culture or test, or if the diagnosis date was unknown, the symptom onset date. An infection was considered new if it occurred at least 2 weeks after the resolution of a previous episode. Invasive fungal infections were defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [11]. An adjudication committee, consisting of 5 study investigators, reviewed each reported IFI and included only those that were proven or probable by the 2008 EORTC/MSG criteria [11].

Statistical Methods
Data collected by the OTIP centers were transmitted to the CDC via an electronic case report form. Categorical variables were analyzed using χ² tests or Fisher’s exact tests, as appropriate. In all analyses, a 2-tailed level of significance was set to α = 0.05. All analyses were done using SAS 9.3 (SAS Institute, Inc., Cary, NC).

Role of the Funding Source
The CDC developed the data collection tool and served as the central unit for data processing and analysis.

RESULTS
During 2006–2011, we enrolled 444 allogeneic HCTs among 431 patients at 4 US transplant centers (153 from University of Michigan Healthcare System, 24 from University of Alabama, 60 from University of Pennsylvania, and 207 from Washington University); 431 patients had 1 transplant, 12 patients had 2 transplants, and 1 patient had 3 transplants. This represents 48% of all patients who received transplants during the enrollment period. Enrollment rates across the 4 different centers ranged from 32% to 57%. The median age was 53 years (range, 18–75), and the median duration of follow up was 413 days (range, 5–980) (Table 1). The most common indication for HCT was hematologic malignancy (87%). Most of the transplants were from matched, unrelated donors (55%) or from matched, related donors (40%) (Table 2). The conditioning regimen was myeloablative in 72%, and the source of hematopoietic cells was peripheral blood in 87%. Relapsed malignancy was present at the time of HCT in 113 (26%) of patients. The median time to engraftment was 12 days (0–101).

Immunosuppression and Antimicrobial Prophylaxis
Most patients received tacrolimus for immunosuppression. Graft-versus-host disease (GVHD) developed in 339 (76%)

Table 1. Organ Transplant Infection Project (2006–2011): Characteristics of 444 Hematopoietic Cell Transplant Patientsa

| Characteristic                      | n   | (Percent or Range) |
|------------------------------------|-----|-------------------|
| Total cases                        | 444 | (100)             |
| Median age, years                   | 53  | (18–75)           |
| Male sex                           | 256 | (58)              |
| White race                         | 421 | (95)              |
| Median days of follow up           | 413 | (5–980)           |
| Indication for Transplant          |     |                   |
| Hematologic malignancy             | 387 | (87)              |
| Acute myelogenous leukemia         | 180 | (41)              |
| Non-Hodgkins lymphoma              | 79  | (18)              |
| Acute lymphocytic leukemia         | 41  | (9)               |
| Chronic myelogenous leukemia       | 24  | (5)               |
| Hodgkin’s disease                  | 9   | (2)               |
| Other hematologic disease          | 57  | (13)              |
| Myelodysplastic syndrome           | 41  | (9)               |
| Other indications                  | 16  | (3)               |
| Comorbidities                      |     |                   |
| Cardiovascular disease             | 112 | (25)              |
| Type 1 diabetes                    | 31  | (7)               |
| Type 2 diabetes                    | 20  | (5)               |
| Pulmonary disease                  | 29  | (7)               |
| Splenectomy                        | 7   | (2)               |
| Chronic kidney disease             | 5   | (1)               |

aA total of 444 transplants in 431 patients.
patients. Use of antiviral prophylaxis at some point after HCT was as follows: acyclovir (70%), valacyclovir (40%), valganciclovir (4%), and ganciclovir (1%). Antifungal prophylaxis was used in 368 patients (83%). Medications used as antifungal prophylaxis during the posttransplant period included the following: fluconazole (53%), voriconazole (35%), caspofungin (5%), posaconazole (3%), and itraconazole (<1%). Trimethoprim-sulfamethoxazole (59%), dapsone (5%), posaconazole (3%), amphotericin B (<1%), and itraconazole (<1%).

**Syndromes and Bacterial Infections**

Infection occurred in 415 (93%) of transplants. Bloodstream infections were the most common site, occurring in 231 (56%) of 410 patients who had an infection (56%). Median time to first bloodstream infection was 48 days (0–847). Bacteremias were caused by Gram-positive bacteria in 244 (56%), Gram-negative bacteria in 93 (21%), and were polymicrobial in 50 (12%). The majority of Gram-positive bacteremias were caused by coagulase-negative staphylococci and enterococci (Table 3). Pseudomonas aeruginosa was the most frequent cause of Gram-negative bacteremia (26%) (Table 3). Anaerobic bloodstream infections were rare, with only 1 case of Bacteroides fragilis bacteremia reported. Mortality within 7 days of bacteremia was significantly higher for Gram-negative pathogens (45%) than Gram-positive pathogens (13%) (P = .02).

Clostridium difficile was the most common bacterial pathogen causing infection. There were 198 episodes of C difficile infection (CDI) in 148 patients (33%). Most patients (110 [74%]) had a single episode, although recurrent CDI developed in 38 (26%). The median time to CDI was 27 days posttransplant. Clostridium difficile infection occurred after 118 (37%) of 319 myeloablative transplants versus 30 (24%) of 125 non-myeloablative transplants (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.1–2.3). Of the 148 patients with CDI, 93 (63%) ultimately died, compared with 138 (47%) of those without CDI infection (OR, 1.9; 95% CI, 1.3–2.9). No infections with Nocardia or mycobacterial species were identified.

Pneumonia developed in 132 (30%) patients. Of the 75 episodes in which a pathogen was identified, 38 (51%) were bacterial, 26 (35%) were fungal, and 11 (15%) were viral. The mortality rate for patients with pneumonia was 62.1% compared with 47.8% for those who never developed pneumonia (OR, 1.79; 95% CI, 1.18–2.72). There were 136 symptomatic urinary tract infections among 89 (20%) patients. Sinusitis occurred in 30 (7%) patients. Only 6 episodes of sinusitis had a microbiologic diagnosis: 2 bacterial and 4 fungal (mucorales n = 2, Alternaria n = 1).

**Viral Infections**

Viral infections are displayed in Table 5. Cytomegalovirus was the most common viral infection (154 patients, 35%). Most episodes were limited to viremia, but organ involvement developed in 6 (4%) patients including the following: 4 with enteritis, 1 with hepatitis, and 1 with pneumonia. Infection with respiratory viruses occurred in 49 (11%) patients. Of 18 patients with parainfluenza infection, there were 8 episodes of pneumonia or other lower respiratory tract infection. Of the 15 patients with influenza infection, 6 had pneumonia or other lower respiratory tract infection. Among 13 patients with respiratory syncytial virus infection, there were 6 episodes of pneumonia or other lower respiratory tract infection. Of the 6 patients with adenovirus infections, 2

### Table 2. Type of Transplant and Conditioning Regimen in 444 Patients

| Characteristic                              | n   | (%) |
|--------------------------------------------|-----|-----|
| Transplant Type                            |     |     |
| Matched, unrelated                         | 245 | (55)|
| Matched, related                           | 177 | (40)|
| Mismatched, unrelated                      | 20  | (5)|
| Mismatched, related                        | 2   | (1)|
| Tandem                                     | 8   | (2)|
| Transplant Source                          |     |     |
| Peripheral blood                           | 386 | (87)|
| Bone marrow                                | 53  | (12)|
| Umbilical cord                             | 5   | (1)|
| T-cell depleted                            | 2   | (<1)|
| Myeloablative conditioning regimen         | 319 | (72)|
| Immunosuppression*                         |     |     |
| Tacrolimus                                 | 388 | (87)|
| Cyclosporine                               | 90  | (20)|

*At any time posttransplant.

### Table 3. Bacterial Bloodstream Infections in 444 Hematopoietic Cell Transplant Recipients

| Characteristic                              | N    | (Percent or Range) |
|--------------------------------------------|------|---------------------|
| Gram positive                             | 244  | (56)                |
| Coagulase-negative staphylococci          | 125  | (51)                |
| Vancomycin-resistant Enterococcus         | 41   | (17)                |
| Enterococcus faecium                      | 31   | (13)                |
| Methicillin-susceptible Staphylococcus aureus | 17   | (7)                 |
| Enterococcus faecalis                     | 8    | (3)                 |
| Methicillin-resistant S aureus            | 7    | (3)                 |
| β-hemolytic streptococci                  | 4    | (2)                 |
| Other                                      | 8    | (3)                 |
| Gram negative                             | 93   | (21)                |
| Pseudomonas aeruginosa                    | 24   | (26)                |
| Escherichia coli                          | 20   | (22)                |
| Klebsiella pneumonia                      | 20   | (22)                |
| Stenotrophomonas maltophilia              | 6    | (7)                 |
| Citrobacter freundii                      | 5    | (5)                 |
| Enterobacter cloacae                      | 5    | (5)                 |
| Acinetobacter baumannii complex           | 3    | (3)                 |
| Burkholderia cepacia                      | 2    | (2)                 |
| Other                                      | 8    | (9)                 |
| Polymicrobialb                            | 50   | (12)                |

*Infection level data (n = 437), some patients had more than 1 infection.

*Gram positive plus Gram negative.
had disseminated infection, 2 had pneumonia, 1 had viremia, and 1 had gastroenteritis. Of the 49 patients with respiratory viral infections, 6 (12%) died within 14 days of infection.

Thirteen patients developed VZV infection, 11 of whom had dermatomal skin lesions. One patient had disseminated disease, and 1 had VZV meningitis. Only 1 of these patients was receiving antiviral prophylaxis at the time of VZV infection. There were 2 documented cases of viral meningitis: the previously mentioned varicella zoster, and 1 due to human-herpesvirus-6.

Fungal Infections
A total of 53 IFI (18 probable and 35 proven) occurred among 48 (11%) patients (Table 4). The median time to the development of IFI was 142 days (range, 14–666). There were 18 infections caused by yeasts (all candidemias), 32 mold infections, and 3 infections with *P jiroveci*. None of the patients with *P jiroveci* pneumonia were receiving prophylaxis at the time of diagnosis. There were no diagnosed cases of cryptococcosis or endemic mycoses.

The median time from the diagnosis of IFI to death was 29 days (0–868), and among the 15 patients with data available, 60% died within 6 weeks of diagnosis. The most common syndromes were as follows: pneumonia (n = 25), candidemia (n = 18), sinusitis (n = 4), and disseminated infection (n = 4) (Table 4). Mucorales infections were uncommon (n = 5). Of the 16 patients with candidemia, there were no cases of disseminated infection.

Outcomes
Of the entire cohort of 444 patients, 113 (26%) had relapse of their underlying disease during the study period and 231 (52%) died (Table 6). The median time from transplant to death was 167 days (range, 5–885). The cause of death was attributed to the underlying disease in 102 (44%) patients, to infection in 49 (21%), and to other or unknown causes in 35%. Transfer to an intensive care unit occurred for 162 (36%) of patients, and, of those, 122 (75%) ultimately died. Most patients (86%) who required mechanical ventilation did not survive. Dialysis occurred in 36 (8%) patients, and 25 (69%) of these patients died.

DISCUSSION
We report results from a large prospective, multicenter study that examined all infectious complications after allogeneic HCT. Infection is a substantial cause of morbidity and mortality and was the second most common cause of death after relapse of the underlying malignancy. Our study reveals suggests that several interventions have been successful in preventing infection after HCT. Only 1% of patients developed a CMV infection with organ involvement, likely attributable to antiviral prophylaxis. Cytomegalovirus pneumonia, which was a major cause of mortality in the era before prophylaxis or early treatment strategies [12], was seen in only 1% of our cohort. Likewise, the frequencies of herpes simplex virus, VZV, and human herpes virus-6 infections were very low, consistent with effective prophylactic strategies, although it should be noted that routine screening for these infections was not part of the study and that less severe infections may have been missed. *Pneumocystis jiroveci* pneumonia was seen in less than 1% of patients and occurred only when prophylaxis was not used. There were no cases of

### Table 4. Proven and Probable Invasive Fungal Infections in 444 Hematopoietic Cell Transplant Recipients*

| Fungal Organisms       | n   | (%)  |
|------------------------|-----|------|
| Candida                | 18  | (34) |
| Aspergillus            | 17  | (32) |
| Mucorales              | 7   | (13) |
| Pneumocystis jiroveci  | 3   | (6)  |
| Exophiala              | 2   | (4)  |
| Alternaria             | 1   | (2)  |
| Mixed                  | 3   | (6)  |
| Syndrome              |
| Pneumonia              | 26  | (49) |
| Bloodstream infection  | 18  | (34) |
| Sinusitis              | 4   | (8)  |
| Disseminated           | 4   | (8)  |
| Central nervous system | 1   | (2)  |

*Fifty-three infections among 48 patients.

### Table 5. Viral Infections in 444 Hematopoietic Cell Transplant Recipients (n = 187)

| Virus                     | N   | (%) |
|---------------------------|-----|-----|
| Cytomegalovirus infection | 154 | (82) |
| Viremia only              | 148 | (86) |
| Organ involvement*        | 6   | (4)  |
| Human herpes virus-6      | 21  | (11) |
| Parainfluenza virus       | 18  | (10) |
| Varicella zoster virus    | 13  | (7)  |
| Respiratory syncytial virus | 13  | (7)  |
| Influenza A virus         | 12  | (6)  |
| Epstein-Barr virus        | 10  | (5)  |
| Herpes simplex virus      | 8   | (4)  |
| Adenovirus                | 6   | (3)  |
| Influenza B virus         | 3   | (2)  |

*One hepatitis, 1 pneumonia, 4 enteritis.
In contrast to lower frequencies of viral and \textit{P jiroveci} infections observed, the rates of bacteremia remain high. Most occurred before engraftment. Consistent with previous studies, Gram-positive bacteremias were more common than Gram-negatives, likely due to the association of Gram-positive organisms with central venous catheters [21–23]. Several recent studies suggest that the ratio of Gram-positive to Gram-negative bacteremias has been decreasing [23–25]. \textit{Pseudomonas aeruginosa} remains the most common etiology of Gram-negative bloodstream infections despite the standard use of anti-pseudomonal \(\beta\)-lactam agents as empiric therapy for neutropenic fever. Others have variably reported \textit{Escherichia coli} as the most common Gram-negative pathogen [3, 23, 26–28], or \textit{Pseudomonas} [1, 24]. This finding is particularly concerning given that the 7-day mortality from Gram-negative bacteremia was approximately 50%, which is more than 3-fold higher than for Gram-positive bacteremia. We were not able to analyze antimicrobial resistance patterns to determine what proportion of these infections represented failure of empiric therapy.

The most common bacterial infectious complication was \textit{C difficile}, which occurred in one third of patients. This rate is higher than that reported in other inpatient populations. A review of US hospital admissions in 2009 found a CDI diagnosis in 0.9% of patients [29]. The overall incidence of CDI in the United States in 2011 was 7.4 per 10,000 patient days and represented 12.1% of all healthcare-associated infections [30, 31]. Others have similarly reported a higher incidence of CDI in the HCT population with incidence rates varying from 4% to 13% [32–36]. \textit{Clostridium difficile} infections most often occurred before engraftment, suggesting that neutropenia, more intense exposure to antimicrobials and immunosuppression, and transmission in the hospital environment are likely to be important risk factors. Another study is underway using this cohort and a parallel cohort of lung transplant recipients from OTIP to provide more detail on risk factors and outcomes for CDI. The association of CDI with GVHD of the gastrointestinal tract was white, and it is unclear whether rates of infection in our population should be examined to help inform prophylactic strategies during different stages of immune reconstitution post-HCT. Further information on the timing and type of environmental exposures that lead to invasive mold infection is needed to prevent these devastating infections. A more individualized and granular understanding of the infectious complications after allogeneic HCT. Although we were not able to examine these risk factors, we believe that our results provide an important snapshot of the incidence of infectious disease events after HCT from diverse geographic settings and prospective data collection. In addition, we lacked data on many important noninfectious complications that may have influenced the risk for infection. The difficulty in ascertaining the cause of death in this population with multiple comorbidities and complications is a recognized problem as well. Because we lacked detailed data on GVHD, it is possible that some patients who died with infection really had GVHD as the cause of death. Finally, it should be noted that 95% of our population was white, and it is unclear whether rates of infection in our centers, which although geographically diverse, are generalizable to other transplant settings.

**CONCLUSIONS**

Several important areas for future investigation are highlighted by our study. Risk factors for bacteremia and \textit{C difficile} infections that occur before engraftment should be examined to help inform prophylactic strategies during different stages of immune reconstitution post-HCT. Further information on the timing and type of environmental exposures that lead to invasive mold infection is needed to prevent these devastating infections. A more individualized and granular understanding of the infections.
state of immunosuppression in an individual patient will allow a finer stratification of risk for infection.

Acknowledgments

We thank Debra Wagner from the Centers for Disease Control and Prevention.

Disclaimer.

The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support.

This work was funded by the Centers for Disease Control and Prevention (Atlanta, GA).

Potential conflicts of interest.

All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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