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Mindy G. Schuster

Angela A. Cleveland

Erik R. Dubberke

Carol A. Kauffman

Robin K. Avery

See next page for additional authors

Authors
Mindy G. Schuster, Angela A. Cleveland, Erik R. Dubberke, Carol A. Kauffman, Robin K. Avery, Shahid Husain, David L. Paterson, Fernanda P. Silveira, Tom M. Chiller, Kaitlin Benedict, Kathleen Murphy, and Peter G. Pappas

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MAJOR ARTICLE

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

Mindy G. Schuster,[1] Angela A. Cleveland,[2] Erik R. Dubberke,[3] Carol A. Kauffman,[4] Robin K. Avery,[5] Shahid Husain,[6] David L. Paterson,[7] Fernanda P. Silveira,[8] Tom M. Chiller,[2] Kaitlin Benedict,[2] Kathleen Murphy,[1] and Peter G. Pappas[9]

[1]University of Pennsylvania, Philadelphia; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Washington University, St. Louis, Missouri; [4]VA Medical Center, University of Michigan, Ann Arbor; [5]Johns Hopkins University, Baltimore, Maryland; [6]University of Toronto, Canada; [7]University of Queensland, Brisbane, Australia; [8]University of Pittsburgh, Pennsylvania; and [9]University of Alabama at Birmingham

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 posttransplant (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 posttransplant 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 immunosuppressive regimens used, differ across institutions and have changed over time. Prospectively collected data from multiple, geographically diverse centers are vital to the understanding of infectious complications and to the development of prophylactic and treatment strategies. No multicenter studies have prospectively evaluated the epidemiology, risk factors, and outcomes of all infectious complications after HCT. Most studies have been from single institutions or have focused on specific types of infections [1–4, 6–9]. We created the Organ Transplant Infection Project (OTIP), a network of 6 collaborating transplant centers, in 2006 to prospectively collect data on all infectious complications and to investigate a variety of potential risk factors and outcomes in a cohort of all allogeneic HCT recipients and lung transplant recipients over a 5-year period. This report examines the HCT population only.

METHODS

The OTIP is a network of 6 collaborating transplant centers (University of Pennsylvania, University of Michigan,

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Correspondence: M. G. Schuster, MD, MSCE, Division of Infectious Disease, University of Pennsylvania, 3 Silverstein, Suite E, Philadelphia, PA 19104 (mindy.schuster2@uphs.upenn.edu).

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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 donor type (related or unrelated), 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 χ^2 tests or Fisher's exact tests, as appropriate. In all analyses, a 2-tailed level of significance was set to $\alpha = 0.05$. 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 recieved 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 Patients[a]

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)

[a]A total of 444 transplants in 431 patients.

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[a]		
Tacrolimus	388	(87)
Cyclosporine	90	(20)

[a]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)
Enterococus 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 baumanii complex	3	(3)
Burkholderia cepacia	2	(2)
Other	8	(9)
Polymicrobial[b]	50	(12)

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

[b]Gram positive plus Gram negative.

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%), amphotericin B (<1%), and itraconazole (<1%). Trimethoprim-sulfamethoxazole (59%), dapsone (29%), and atovaquone (7%) were used for prophylaxis against *Pneumocystis jiroveci*.

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 4. Proven and Probable Invasive Fungal Infections in 444 Hematopoietic Cell Transplant Recipients[a]

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)

[a]Fifty-three infections among 48 patients.

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.

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

Virus	*N*	(%)
Cytomegalovirus infection	154	(82)
Viremia only	148	(96)
Organ involvement[a]	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)

[a]One hepatitis, 1 pneumonia, 4 enteritis.

Table 6. Outcomes in 444 Hematopoietic Cell Transplant Recipients

Characteristic	*n*	(%)
Median time to engraftment, days	12	(0–101)
Graft-versus-host disease requiring treatment	336	(76)
Death	231	(52)
Death from underlying disease	102	(44)
Death from infection	49	(21)
Autopsy performed	24	(5)
Autopsy evidence of fungal infection	4	(1)

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

toxoplasmosis, nocardiosis, endemic mycoses, or mycobacterial infection diagnosed in our cohort, in agreement with low rates of these infections reported previously [13–20].

In contrast to lower frequencies of viral and *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]. *Pseudomonas aeruginosa* remains the most common etiology of Gram-negative bloodstream infections despite the standard use of anti-pseudomonal β-lactam agents as empiric therapy for neutropenic fever. Others have variably reported *Escherichia coli* as the most common Gram-negative pathogen [3, 23, 26–28], or *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 *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]. *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 has been previously reported, and further study is needed in this area [32, 36–38].

Respiratory viral infections were more frequent than expected, which may be a result of increased access to testing in both inpatient and outpatient settings and ease and rapidity of current molecular detection methods. They occurred in 11% of our cohort, compared with previously reported rates of 1.8%–4.3% [9, 39, 40]. Approximately half of patients with these infections developed pneumonia or disseminated disease. It is well known that geographic and seasonal factors are important as well as transmission within the hospital environment [4, 5, 41–47]. Further studies will be important to tease out the effects of these factors.

Current antifungal strategies are relatively effective at preventing candidemia, but rates of invasive mold infection remain constant [4]. Similar to other reports, the median time to an IFI was 142 days, a time when most HCT recipients are outpatients [4, 5, 45, 48]. Death occurred within 6 weeks of IFI in 60%, highlighting the need for early diagnosis and improved prophylaxis and treatment. There have been several reports of a rise in infections with the Mucorales in this population [49–53] and an association with the prophylactic use of triazoles such as voriconazole, which lack activity against these agents [48, 50]. In our cohort, these infections were extremely rare. The difficulty in establishing the diagnosis of invasive mold infection in this population is well recognized, and it is possible that our rates underestimate the true incidence. We found that there were few survivors among patients who required mechanical ventilation or dialysis after hematopoietic stem cell transplant, in keeping with known high mortality rates in patients who require ICU admission or have evidence of multiorgan failure [54–57].

Our study has several limitations. We were able to enroll only 48% of the transplants that were performed at our centers over the study period. Because we did not collect data on the nonparticipants, we do not know how representative our patients were of the total population. Our study was limited by the recognized difficulties in establishing proven infection in this population. We did not collect granular data on GVHD severity, duration, and treatment. Neutropenia and GVHD are well known risk factors for many 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 *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

state of immunosuppression in an individual patient will allow a finer stratification of risk for infection.

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