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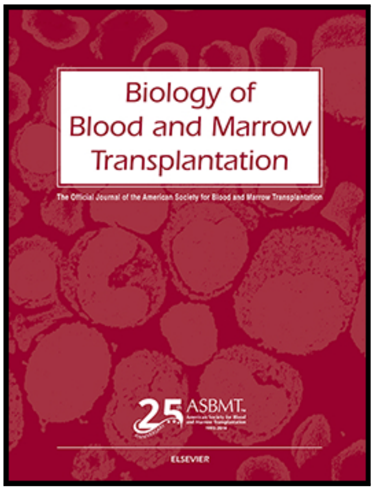

Utility of Autopsy among Pediatric Allogeneic Hematopoietic Stem Cell Transplant Recipients: One Last Chance to Learn?

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Highlights

- Autopsy rate for pediatric stem cell transplant recipients declined >50% from 1990s
- Infectious diagnoses that may have changed outcome are now less frequent on autopsy
- Overall utility of autopsy remains high; 1 unexpected diagnosis for every 7 autopsies

Utility of Autopsy among Pediatric Allogeneic Hematopoietic Stem Cell Transplant Recipients: One Last Chance to Learn?

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Abstract

Background: Autopsy may confirm clinical diagnoses or identify conditions that were not suspected prior to a patient's death. Previous studies evaluating the utility of autopsy in hematopoietic stem cell transplant (HSCT) recipients yielded conflicting results.

Methods: We conducted a retrospective cohort study of children (<18 years of age) undergoing allogeneic HSCT at Duke University who died of any cause between January 1, 1995 and December 31, 2016. We evaluated associations between patient characteristics and autopsy performance using Chi-square or Fisher's exact tests. We reviewed autopsy reports to determine the concordance between pre-autopsy causes of death and pathological diagnoses identified on autopsy. We classified unexpected diagnoses on autopsy using criteria developed by Goldman et al. We evaluated for temporal changes in the autopsy consent rate and the frequency of unexpected diagnoses on autopsy using Cochran-Armitage tests.

Results: During the 22-year study period, 475 patients died and had data available on autopsy performance, and 130 (27%) of these patients underwent autopsy. The autopsy consent rate declined over time (P<0.0001), with autopsies being performed for 40% of deaths in 1995-1999 and 17% of deaths in 2009-2016. White patients were more likely to undergo autopsy than non-white patients (P=0.03). There were no associations between autopsy performance and patient age, sex, HSCT indication, or HSCT donor. Unexpected diagnoses were identified in 31 (24%) autopsies. The proportion of autopsies with an unexpected diagnosis did not change during the study period (*P*=0.45). However, infectious diagnoses that would have led to a change in management were more frequently identified on autopsies in 1995-2003 than in 2004-2016 (20% vs. 0%; *P*=0.001).

Conclusions: The autopsy consent rate for pediatric HSCT recipients at our institution declined substantially over the past several decades. The utility of autopsy in this patient population remains high despite a reduction in the identification of unexpected infections.

Introduction

Autopsies may give comfort to the families of deceased patients and provide insight into the clinical circumstances surrounding a patient's death.[1-4] Families may benefit from autopsy through the recognition that they are helping to further medical knowledge or through reassurance that appropriate medical care was provided.[3] Autopsies may also confirm clinical diagnoses, clarify the cause of death, or identify conditions that were not suspected by the clinical team prior to the patient's death.[5] The identification of unexpected diagnoses on autopsy in patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) may differ from other patient populations. Allogeneic HSCT recipients are at risk for specific post-transplant conditions, including graft-versus-host disease and veno-occlusive disease, and opportunistic infections related to prolonged impaired immunity. However, prior studies evaluating the utility of autopsy in HSCT recipients yielded conflicting results.[6-8] Moreover, no studies were published in the past decade, during which there were significant advances in the diagnosis, prevention, and treatment of infectious and noninfectious post-transplant complications.

In this study, we evaluated if the autopsy consent rate and the frequency of unexpected diagnoses identified on autopsy changed among children undergoing allogeneic HSCT at our institution over more than two decades. As secondary objectives, we sought to evaluate associations between patient characteristics and autopsy performance and to identify the most frequent unexpected diagnoses on autopsy in this patient population.

Methods

Study Population

We performed a retrospective cohort study of children less than 18 years of age who underwent an allogeneic HSCT through the Duke University Pediatric Blood and Marrow Transplantation (PBMT) Program and died of any cause between January 1, 1995 and December 31, 2016. The study protocol was approved by the Duke University Institutional Review Board.

Data Sources and Measures

We identified patient deaths using a secure database maintained by the Duke University PBMT program. We determined pre-autopsy causes of death through review of the PBMT database and patient electronic medical records, including physician notes, laboratory testing, and diagnostic imaging. Additional patient data were obtained from the Duke Enterprise Data Unified Content Explorer (DEDUCE) research portal.[9] To determine if an autopsy was performed, we reviewed documentation contained within the PBMT database and a registry of autopsy reports maintained by the Duke University Department of Pathology. When possible, autopsy reports from deaths occurring at other medical facilities were obtained. Patients for whom we were unable to determine if an autopsy was performed were excluded from analyses. An autopsy diagnosis was considered to have been made clinically if the diagnosis was: 1) recorded in physician notes prior to the patient's death, 2) confirmed based upon laboratory testing sent prior to death, or 3) considered to be sufficiently likely that specific treatment was initiated. We used criteria proposed by Goldman et al. to classify autopsy diagnoses that were not made clinically as Class I or Class II major diagnoses.[10] Class I major diagnoses were those for which identification before death would likely have led to a change in management and may have resulted in cure or prolonged survival. Class II major diagnoses were those for which identification before death would probably not have led to a change in management or patient outcome.

Review Process

A board-certified pediatric infectious diseases physician (MSK) reviewed the PBMT database, electronic medical record, and autopsy report for all children and assessed for unexpected diagnoses using the aforementioned criteria. All autopsies for which this first reviewer identified an unexpected diagnosis were reviewed by a board-certified pediatric bone marrow transplant physician (PLM). For any diagnoses for which these first two reviewers disagreed, a third independent review was performed by a board-certified pathologist (ADP), and the diagnosis was classified based upon a consensus of the three reviewers.

Statistical Methods

We subdivided the 22-year period from 1995 to 2016 into four time periods such that the number of deaths occurring during each time period was approximately equivalent: 1995-1999 (n=130), 2000-2003 (n=136), 2004-2008 (n=141), 2009-2016 (n=129). We evaluated associations between patient characteristics and the performance of a diagnostic autopsy using Chi-square or Fisher's exact tests. We examined temporal trends in the autopsy consent rate and the proportion of autopsies that yielded unexpected major diagnoses using Cochran-Armitage tests. Data analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and R version 3.3.1.

Results

Of 536 patients who died during the study period, 475 (89%) had available data on autopsy performance, and 130 (27%) of these patients underwent diagnostic autopsy. The overwhelming majority (92%) of these autopsies were performed at Duke University. The proportion of deaths for which an autopsy was obtained declined over time during the study period (P<0.0001; Figure 1). The autopsy consent rate was 40% in 1995-1999, 30% in 2000-2003, 23% in 2004-2008, and 17% in 2009-2016. A slight majority (52%) of autopsies were full autopsies, but autopsies became increasingly likely to be limited to specific organs over time during the study period (P=0.06). The most frequent partial autopsies performed were limited to the lungs (n=28, 41%), chest and abdomen (n=17, 25%), and liver (n=5, 7%).

Patient Characteristics

Table 1 presents characteristics of the study population. A diagnostic autopsy was more likely to be performed on white than non-white patients (P=0.03). Among non-white racial minorities, autopsies were performed on 19 of 75 (25%) black patients, 10 of 35 (29%) Hispanic patients, 3 of 22 (14%) Asian patients, and 1 of 19 (5%) Middle-Eastern patients. Compared with white patients, Asian and Middle-Eastern patients were less likely to undergo autopsy (30% vs. 10%; P=0.01). Patients who died during the first 100 days after HSCT were also more likely to undergo autopsy than patients who died more than 100 days after HSCT (P=0.04). Finally, pre-autopsy cause of death was strongly associated with autopsy performance. Specifically, patients with a pre-autopsy cause of death of malignancy were less likely to undergo autopsy than patients with a non-malignant pre-autopsy cause of death (P<0.0001). Moreover, patients with a pre-autopsy cause of death of organ failure were more likely to undergo autopsy than patients with other pre-autopsy causes of death (*P*<0.0001). There were no significant associations between autopsy performance and patient age, sex, HSCT indication, or HSCT donor.

Autopsy Diagnoses

The most frequent primary causes of death in the 130 patients who underwent diagnostic autopsy were infection (n=46; 35%), graft-versus-host disease (n=34; 26%), veno-occlusive disease (n=10; 8%), organ failure (n=8; 6%), and hemorrhage (n=8; 6%). A total of 35 unexpected major diagnoses, including 22 Class I major diagnoses, were identified in 31 (24%) patients who underwent autopsy. The proportion of autopsies that yielded an unexpected major diagnosis did not change during the study period (*P*=0.45; Figure 2). However, the proportion of autopsies in which a Class I major diagnosis was identified declined over time (*P*=0.03). Table 2 shows the specific Class I and Class II major diagnoses identified on autopsy. Infections accounted for the majority (78%) of Class I major diagnoses. These infectious Class I major diagnoses were more frequently identified on autopsies performed in 1995-2003 than in 2004-2016 (20% vs. 0%, *P*=0.001). Deaths caused by infections and the identification of infections unexpectedly on autopsy both declined during the study period. The proportion of deaths caused by infections fell from 65% in 1993-2003 to 46% in 2004-2016 (*P*=0.03). In total, 62 infections contributed to the deaths of 52 patients who underwent autopsy in 1995-2003 and 27 infections contributed to the deaths of 23 patients who underwent autopsy in 2004-2016. In addition, fewer of these infections were identified unexpectedly on autopsy in 2004-2016 than in 1995-2003. Most notably, 17 of 62 (27%) infectious causes of death in 1995-2003 and 0 of 27 (0%) infectious causes of death in 2004-2016 were classified as Class I major diagnoses (*P*=0.001). The infectious Class I major diagnoses identified between 1995 and 2003 were *Aspergillus* species (n=8), adenovirus (n=7), and *Toxoplasma gondii* (n=2). The most frequent Class II major diagnosis over the entire study period was parainfluenza virus infection.

Given that the yield for unexpected diagnoses may differ between complete and partial autopsies, we performed sensitivity analyses limited to patients who underwent complete autopsy (n=68). Our primary findings were substantively unchanged in these analyses; specifically, the proportion of autopsies that yielded an unexpected major diagnosis did not change during the study period (P=0.30) and the proportion of infections that were categorized as Class I major diagnoses declined between 1995-2003 and 2004-2016 (P=0.02).

The pre-autopsy causes of death for which autopsy had the highest yield were multisystem organ failure and respiratory failure. However, the utility of autopsy in these clinical scenarios differed markedly by time period. Between 1995 and 2003, Class I major diagnoses were identified on autopsy in 9 of 13 (69%) children who died of multisystem organ failure and 5 of 18 (28%) children who died of respiratory failure. The most frequent Class I diagnoses in these patients were *Aspergillus* species (n=5) and adenovirus (n=4). In contrast, a Class I major diagnosis was identified in only 1 of 25 (4%) children dying of multisystem organ failure or respiratory failure between 2004 and 2016.

Discussion

During a 22-year period at our institution, the autopsy rate among pediatric allogeneic HSCT recipients declined from 40% to 17%. Moreover, when an autopsy was performed, it was increasingly likely that it was limited to specific organs. Although the proportion of autopsies that identified an unexpected major diagnosis was stable during the study period, we observed a sharp decline in the identification of infections that would have led to a change in management and the possibility of cure or prolonged survival.

The autopsy rate has fallen substantially in the United States over the past half-century. In the 1960s, an autopsy was performed in approximately 40% of hospital deaths.[11] Data from the National Vital Statistics System indicate that an autopsy was performed in only 19.3% of deaths in 1972, with a further decline in the autopsy rate to 8.5% in 2007.[5] Similar trends have been seen in European countries and in Australia.[12-15] Our results indicate that, consistent with this worldwide trend, the autopsy consent rate for pediatric HSCT recipients in our program declined over the past several decades. We were only able to identify a single prior study that evaluated the autopsy rate over time in HSCT recipients. Allan et al. reported a relatively stable autopsy rate (32%) within the HSCT program at their Canadian institution between 1992 and 2002 despite a fall in the overall hospital autopsy rate.[7] Notably, this study did not include patients who died at home or at other institutions, in whom the autopsy rate likely differs. Moreover, this study only included data through 2002, and the autopsy rate among pediatric HSCT recipients at our institution did not fall below 30% until after 2003. We also noted a trend toward the performance of limited autopsies when consent for an autopsy was provided. This may be the result of increasing apprehension toward full autopsies among parents. Alternatively, this may reflect clinicians' perceptions that a request for a biopsy through a modest incision might be more acceptable to families.

Several explanations have been proposed for the global decline in autopsy rates, including medicolegal concerns, preconceptions by physicians that families will decline autopsy for religious or cultural reasons, and a lack of reimbursement for autopsy performance by pathologists.[16-18] Certainly in the United States, there was less of an incentive for hospitals to perform autopsies once the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) removed a minimum autopsy rate from the requirements for accreditation in 1970 and after Medicare stopped paying for autopsies in 1986.[2] However, in a survey of hospital administrators, the factor that was perceived to have contributed most to the decline in the autopsy rate was the impression that autopsy was of little value with current diagnostic imaging modalities and laboratory testing.[19] Regardless of the antecedent causes, an unfortunate result is that fewer young pathologists are trained in autopsy techniques and are capable of interpreting gross pathological findings.[20] Few strategies have been proposed to preserve the role of autopsy in modern medicine. Perhaps the most promising strategy is the establishment of regional autopsy centers that are funded to maintain a high autopsy rate and to perform autopsies for other institutions.[2,20] While it is unlikely that this approach would reverse the fall in autopsy performance that occurred over the past several decades, it could lower costs and ensure that autopsy training and quality is maintained in the setting of a continued low autopsy rate.[2] Other potential strategies include educating clinicians on the continued value of autopsy despite current diagnostic testing and having specific trained personnel discuss autopsy performance with families.

Our findings indicate that an autopsy was less likely to be performed for children of racial minorities. Prior studies did not find an association between race and parental consent for autopsy, although these studies were conducted primarily in neonates.[21,22] Racial differences in pediatric autopsy rates could reflect the cultural, religious, or spiritual beliefs of parents, or provider preconceptions about these parental beliefs. Data from a study of pediatric health professionals indicate that white and black providers perceive autopsy more favorably than providers of Indian, Asian, or Middle-Eastern descent.[23] Consistent with the results from this study, we found that the autopsy rate was lower for Asian and Middle-Eastern patients than for white patients. Although data on religion were not available for children in our cohort, autopsy has historically been viewed particularly unfavorably in Islam, and many of the Asian and Middle-Eastern patients in our study were from countries with large Muslim populations.[24,25]

In a landmark paper published by Goldman et al., an unexpected major diagnosis was identified in more than 20% of autopsies performed at a single institution in 1960, 1970, and 1980.[10] In a systematic review that included data from 42 autopsy series published between 1966 and 2002, unexpected major diagnoses were identified in a median of 23.5% autopsies.[26] Moreover, although the identification of major diagnoses on autopsy declined by nearly 20% per decade in this review, the authors concluded that unexpected major diagnoses would still be anticipated in approximately 24% of autopsies conducted in 2003.[26] Relatively few prior studies evaluated the utility of autopsy in HSCT recipients. Hofmeister et al. reported disagreement between the pre-autopsy and pathological cause of death in 29 of 111 (26%) HSCT recipients dying between 1986 and 2003.[6] However, the authors concluded that management would have been altered in only four cases and speculated that none of these diagnoses would have been missed with current diagnostics.[6] Similarly, unexpected diagnoses were identified in 10 of 28 (36%) critically ill HSCT patients who died between 1994 and 1999, but in each case the authors deemed that earlier knowledge of the diagnosis would not have impacted the patient's outcome.[8] Finally, among pediatric and adult HSCT recipients dying between 1992 and 2002, Allan et al. reported disagreement with the pre-autopsy cause of death in 17 of 61 (28%) autopsies.[7] Consistent with these prior studies, we found that unexpected major diagnoses were identified in 24% of 130 autopsies performed in pediatric HSCT recipients between 1995 and 2016. Moreover, unexpected major diagnoses were found in seven of 50 (14%) autopsies performed between 2004 and 2016. This suggests that, in the era of current diagnostic testing, one unexpected major diagnosis would be identified for every seven autopsies performed in this patient population.

Our results indicate that the likelihood of autopsies identifying infectious Class I diagnoses – infections that would result in a change in management and the possibility of cure or prolonged survival – has declined over the past two decades in pediatric HSCT recipients. This trend was accounted for both by a decline in the proportion of deaths caused by infections and a reduction in the identification of infections unexpectedly on autopsy. In particular, *Aspergillus* and adenovirus infections were the most common infectious Class I diagnoses identified on autopsy between 1995 and 2003, but these diagnoses were not detected unexpectedly on any autopsies conducted between 2004 and 2016. Possible explanations for this decline include the routine use of sensitive and specific polymerase chain reaction assays for adenovirus, serum antigen tests for *Aspergillus*, and the availability of extended-spectrum triazoles for the prevention and treatment of invasive aspergillosis.[27-31]

This study has several limitations. First, it was conducted at a single academic hospital, and the autopsy consent rate and the value of autopsy may differ from other medical centers. Moreover, it is unclear how the decline in the autopsy consent rate during the study period might have influenced the frequency of unexpected diagnoses found on autopsy. It is certainly possible that the declining autopsy rate reflected an increase in patients for which there was confidence in the pre-autopsy cause of death. In addition, although we used established criteria for the identification of unexpected major diagnoses on autopsy, the process of applying these criteria remained somewhat subjective. Thus, all unexpected major diagnoses were reviewed independently by a pediatric infectious diseases physician, a pediatric bone marrow transplant physician and, for diagnoses for which there was disagreement, a pathologist. Although this is to our knowledge the largest autopsy study of HSCT recipients conducted to date, our conclusions are limited by the relatively small number of autopsies performed in this study, particularly during more recent time periods. Finally, our study did not evaluate other potential benefits of autopsy, including the reassurance of families that appropriate care had been provided and the advancement of medical knowledge.

In summary, the autopsy consent rate for pediatric HSCT recipients at our institution declined substantially over the past several decades. During this time, autopsies in this patient population became less likely to yield information that would have changed clinical management or outcomes, a trend that is likely related to advances in the diagnosis and treatment of infections. However, the overall utility of autopsy for the identification of unexpected diagnoses did not change during the study period, demonstrating the continued value of autopsy in pediatric HSCT recipients.

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Disclosure of Conflicts of Interest

The authors have no conflicts of interest to declare.

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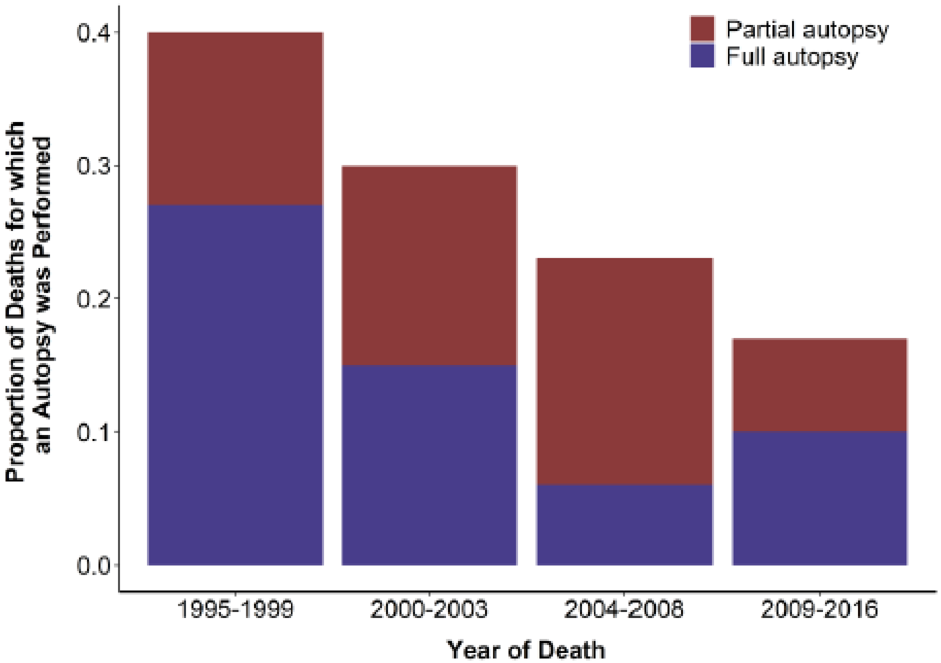

Figure 1. Proportion of deaths for which a diagnostic autopsy was performed by year of death. The performance of a diagnostic autopsy declined over time during the study period (*P*<0.0001). Moreover, when a diagnostic autopsy was performed, it became increasingly likely that the autopsy was limited to specific organs (*P*=0.06).

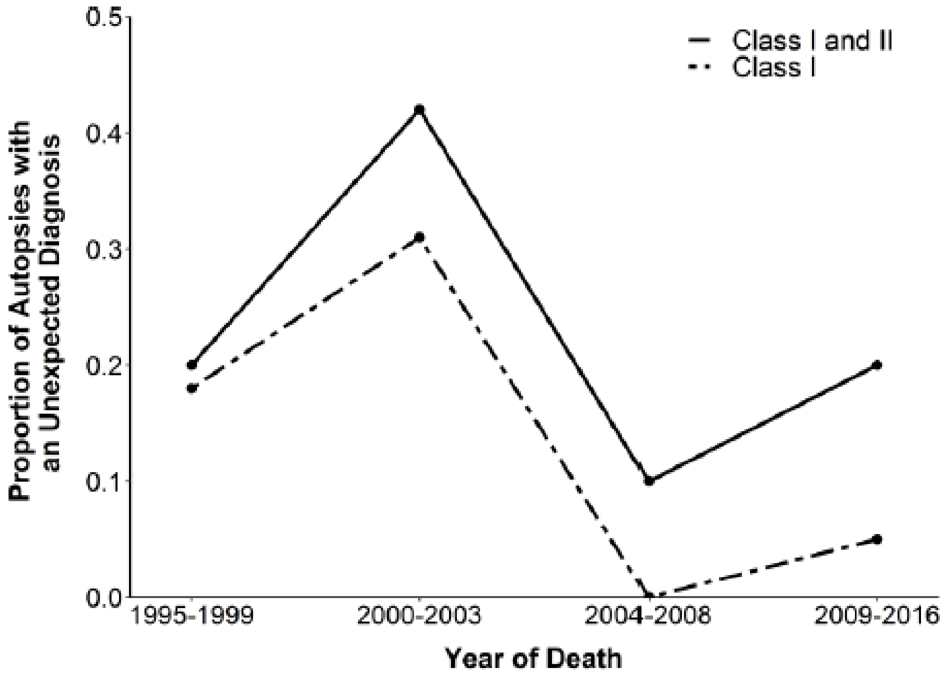

Figure 2. Unexpected diagnoses on autopsy by year of death. The proportion of autopsies that identified an unexpected cause of death did not change over time during the study period (*P*=0.45). However, when only Class I unexpected diagnoses were considered, the utility of autopsy declined during the study period (*P*=0.03).

Table 1. Characteristics of the study population by performance of a diagnostic autopsy

	Autopsy (n=130)		No Autopsy (n=345)		*P*
	n	%	n	%	
Age					0.20
<5 years	61	47	131	38	
5 to <12 years	36	28	116	34	
≥12 years	33	25	98	28	
Sex					0.29
Female	48	37	146	42	
Male	82	63	199	58	
Race					0.03
Non-white	33	25	123	36	
White	97	75	222	64	
HSCT indication					0.17
Genetic or metabolic disorder	33	25	72	21	
Immunodeficiency	20	15	37	11	
Malignancy	70	54	201	58	
Non-malignant hematological	7	5	34	10	
HSCT donor					0.20
Matched related bone marrow	18	14	49	14	
Matched unrelated bone marrow	3	2	22	6	
Umbilical cord blood	109	84	274	79	
Timing of death in relation to HSCT					0.04
≤100 days	63	48	132	38	
>100 days	67	52	213	62	
Pre-autopsy cause of death					
Graft-versus-host disease	29	22	70	20	0.63
Hemorrhage	7	5	19	6	0.96
Infection	34	26	107	31	0.30
Malignancy	1	1	88	26	<0.000
Organ failure	37	28	25	7	<0.000
Veno-occlusive disease	10	8	12	3	0.05

HSCT, hematopoietic stem cell transplantation

Table 2. Unexpected diagnoses identified on autopsy by time period

	1995-2003 (80	2004-2016 (50
	n	n
Class I		
Infectious	17	0
Aspergillus species	8	0
Adenoviruses	7	0
Toxoplasma gondii	2	0
Noninfectious[a]	4	1
Class II		
Infectious	5	4
Parainfluenza viruses	2	3
Polyomaviruses	2	0
Non-*aspergillus* molds	1	0
Respiratory syncytial virus	0	1
Noninfectious[b]	2	2

One subject had three Class I major diagnoses and two subjects had one Class I and one Class II major diagnoses.

[a]Noninfectious Class I major diagnoses included bowel perforation (n=1), cholecystitis (n=1), post-transplant lymphoproliferative disorder (n=2), and veno-occlusive disease (n=1).

[b]Noninfectious Class II major diagnoses included busulfan-induced pulmonary injury (n=1), liver fibrosis (n=1), pulmonary hemorrhage (n=1), and veno-occlusive disease (n=1).