Historical outcomes of pediatric hematopoietic stem cell transplantation patients requiring critical care

Janet R. Hume*, Sameer Gupta and Marie E. Steiner

Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, USA

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Abstract. Hematopoietic stem cell transplantation (HSCT) is being used to treat numerous malignant and non-malignant medical conditions in pediatric patients, but frequently is associated with severe medical complications. We review the outcomes of HSCT patients who developed complications requiring pediatric intensive care unit (PICU) care. The earliest reported patient cohorts, who were transplanted prior to 1990, had high PICU mortality rates, exceeding 80%. Patients transplanted from the 1980s–1990s varied more widely in mortality rates, with mortalities of 56–88% reported for mechanically ventilated patients and rates of 44–50% reported for studies including both mechanically ventilated and non-mechanically ventilated patients in PICU. The patient group transplanted from the 1990s to the early 2000s had reported mortalities of 46–60%. For patients transplanted after 2000, mortality rates were reported ranging from 37–69%. Two centers reported a significant improvement in mortality over time at their centers, although other institutions did not find similar changes. Factors associated with increased mortality included the need for mechanical ventilation, pulmonary pathology as a cause for intubation, severity of lung disease, multiorgan failure, and severe graft versus host disease. The Pediatric Risk of Mortality scoring system has not been consistently predictive of mortality; the modified Oncological Pediatric Risk of Mortality system was more predictive of mortality in several studies. Overall, the mortality of pediatric HSCT patients requiring PICU care has decreased, but remains substantial. Further study is needed to define clinical factors that affect outcome, so that treatments might be modified to improve survival.

Keywords: Hematopoietic stem cell transplant, intensive care, bone marrow transplant, mechanical ventilation, pediatric, sepsis, mortality

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is an increasingly common treatment for a wide range of pediatric illnesses, including malignancies, genetic immunodeficiencies, bone marrow failure syndromes, and inborn errors of metabolism. In recent case series of pediatric HSCT patients, 14–35%

developed complications that required intensive care support modalities such as mechanical ventilation, inotrope/vasopressor infusion, or renal replacement therapies post-transplantation [1–3]. Early reports of dismal survival for pediatric HSCT patients requiring intensive care unit level care have been followed up by a number of case series suggesting an improvement in outcomes, as described in previous reviews and a meta-regression analysis of published case series [4–7].

The objective of this review is to provide a comprehensive summary of the published outcomes as well as factors associated with mortality for pediatric

*Corresponding author: Dr. Janet R. Hume, University of Minnesota Medical School, Department of Pediatrics, Division of Pediatric Critical Care Medicine, MB530 East Building, 2450 Riverside Avenue, Minneapolis, MN 55454, USA. Tel.: +1 612 626 7158; Fax: +1 612 626 0413; E-mail: jrhume@umn.edu.

HSCT patients requiring pediatric intensive care unit (PICU) care. We searched PubMed using the phrases “outcome HSCT intensive care” and “outcome bone marrow transplant intensive care.” Of the identified publications, we excluded those focusing exclusively on adults greater than 18 years, as well as papers including both adults and children where the pediatric data were not reported separately from the adult data. Other papers were identified via references in publications found in the PubMed search. After reviewing our publication list, we included 40 reports of pediatric HSCT patients requiring PICU care. Most studies, with three exceptions, were retrospective single center studies representing patients transplanted from 1973 to 2010.

2. Indications for PICU care

Intubation and mechanical ventilation was the most commonly reported indication for critical care in pediatric HSCT patients. Many publications divided patients requiring invasive ventilation into those requiring intubation for pulmonary disease, including etiologies such as pulmonary infection, diffuse alveolar hemorrhage (DAH), and idiopathic pneumonia syndrome; and those requiring intubation for non-pulmonary disease, including upper airway obstruction, mucositis, sepsis/shock, and airway protection due to seizures or altered mental status. Other indications for PICU care, not necessarily requiring intubation, included sepsis/septic shock, renal failure, multiorgan failure, and neurological dysfunction. In reviewing the reported mortality of HSCT patients requiring PICU care, published reports can be divided into four time periods based on the years when most or all of the reported patients were transplanted: primarily before 1990, before 2000 (1980s–1990s), from the 1990s to early 2000s, and all transplanted after 2000.

3. Mortality and survival in the beginning (pre-1990)

The primarily pre-1990 reports are described in five papers; one paper included patients transplanted until 1992, but the bulk of reported patients were transplanted in the 1970s–1980s [8–12]. In addition, these publications describe only intubated and mechanically ventilated patients. The four earliest reports, discussing

only patients transplanted prior to 1990 [8–11], are notable for a mortality rate of 80–95% in mechanically ventilated HSCT patients in the PICU. However, the study by Warwick et al. [12], which included patients from 1976 to 1992, reported a lower rate of 60% mortality in mechanically ventilated patients. The paper of Warwick et al. [12] examined a larger patient population ($n = 196$) than the other papers ($n = 5–54$), which might have contributed to the difference in mortality rate [8–12].

4. Mortality and survival in the middle (1980s–1990s)

Unlike the reports from the pre-1990 period, the 1980s–1990s era demonstrated a greater variation in published outcomes for HSCT PICU patients and also described a broader range in patients beyond those intubated and mechanically ventilated. In series from this period where all patients were mechanically ventilated, the reported PICU mortality was 56–88% [11, 13–16]. Hagen reported a PICU mortality rate of 59% that rose to 72% by the time of hospital discharge [14], suggesting that PICU survival did not predict hospital survival. A study by Eikenberry et al. [17] demonstrated the impact of respiratory pathophysiology on mortality: HSCT patients with pulmonary complications (96% of whom required intubation and mechanical ventilation) had a mortality rate of 64%, while HSCT patients without pulmonary complications had a mortality rate of 45%.

The reports from this era described HSCT patients who required other types of PICU cares besides mechanical ventilation, reflecting advances in PICU support modalities. In a group of four papers [18–21], mortality for HSCT PICU patients was reported between 44–50%, with an outlier publication by Hayes et al. [22] with a reported mortality of 73%. Of note, two of these papers [18, 20] described a higher mortality rate in the subset of PICU patients requiring mechanical ventilation: Díaz de Heredia et al. [18] reported mortality among mechanically ventilated patients of 54% versus 45% for HSCT PICU patients as a whole group, and Schneider et al. [20] described mortality among intubated HSCT patients of 64% versus 50% for all HSCT patients in the PICU. Only one study included a comparison of mortality to a control group: Schneider et al. [20] reported 3 yr mortality in HSCT patients not requiring transfer to the PICU as

30%, compared to 71% of HSCT patients requiring PICU care.

Outcomes for specific subsets of HSCT patients requiring PICU care were also published. The mortality rate for HSCT patients with septic shock admitted to the PICU was 38.5%, compared to 5.5% for non-HSCT oncologic patients with septic shock in the PICU [23]. With regard to renal failure, Bunchman et al. [24] reported on a cohort of 226 patients requiring renal replacement therapy for acute renal failure and noted a mortality rate of 58% for the subset of HSCT patients, in contrast to the 46% rate found in the cohort as a whole.

5. Mortality and survival more recently (1990s-early 2000s)

Studies covering transplants in the next time period, from the 1990s to early 2000s, described HSCT patients admitted to the PICU for a wide variety of causes. Five publications of this time period reported a mortality range from 46–60% [25–29] that included all HSCT PICU admissions, not just those requiring mechanical ventilation. Several papers reported higher mortalities, however. Lamas et al. [30] reported a PICU mortality of 70%, which may have been influenced by the high rate of mortality associated with mechanical ventilation in that study (76.5% mortality in 34 mechanically ventilated patients versus 50% mortality in 10 non-mechanically ventilated patients). Another outlier was a report from Heggen et al. [31], who focused on patients with DAH but also described a mortality rate of 89% in 18 HSCT patients without DAH who developed respiratory failure requiring mechanical ventilation [31]. Finally, Kache et al. [32] reported mean 100 days mortality of 77% (82% for mechanically ventilated patients) for HSCT PICU patients transplanted from 1992–1999.

Two studies included only mechanically ventilated patients: one study reported a short-term mortality of 55% (75% at 6 mo), compared to 25% for non-HSCT hematologic and oncologic patients (40% at 6 mo) [33]; the second reported a short-term mortality of 42%, with no control group for comparison [34]. Kaya et al. [35] reported 70% mortality in allogeneic HSCT patients with pulmonary complications requiring mechanical ventilation. In addition, a retrospective analysis of patients with HSCT-associated codes listed in the Kids Inpatient Database for the years of 1997,

2000, and 2003 reported an in-hospital mortality rate of 64% for mechanically ventilated HSCT patients [36].

Analysis of specific subgroups in the 1990s–2000s included reports on HSCT patients with sepsis, renal failure, and specific pathologies including those patients with DAH and hemophagocytic lymphohistiocytosis (HLH). Fiser et al. [37] described a PICU mortality rate of 30% for the HSCT subgroup admitted for management of sepsis compared to 12% for non-HSCT oncology patients. Those patients requiring mechanical ventilation and inotropic support had substantially worse mortality of 74% for HSCT patients versus 56% for non-transplant oncology patients [37]. Another subgroup, that of HSCT patients with renal failure (defined as doubling of baseline serum creatinine) had a reported mortality rate of 58% for all HSCT patients with renal failure and 71% in patients requiring renal replacement therapy [38]. Two papers reported primarily on patients with DAH [31, 39], describing mortality rates of 43% and 83% for small groups of patients, numbering seven and eight respectively. Naithani et al. [40] reported on a group of nine patients undergoing HSCT for HLH who required PICU care and had a mortality rate of 66%; the calculated 3 yr actuarial survival for all HLH patients receiving HSCT was 61%.

6. Mortality and survival in the present era

In studies including only patients transplanted after 2000, reported mortalities for HSCT patients requiring intensive care ranged from 37% to 69%, with higher mortality rates associated with mechanical ventilation, especially if needed for longer than 24 hr [1–3, 41–44]. Mortality in these studies continued to rise to 75–79% at 6 mo post-HSCT [1, 3]. A *post hoc* analysis of mortality in immunocompromised children included in a multicenter prospective randomized study of calfactant versus placebo in acute lung injury described the mortality in the HSCT subgroup ($n=27$) as 67% in-hospital mortality as opposed to 44% for non-HSCT immunocompromised patients [41].

The lowest reported PICU mortality for this period was 37% [2] in a group of 155 patients; their mortality increased to 49% at 100 days and then to 55% at long-term follow-up (median 2.5 yr post HSCT). This mortality contrasted with only 2% mortality at 100 days for HSCT patients not admitted to the PICU,

rising to 12% at 1 yr [2]. Another report of lower mortality came from a multicenter retrospective study examining the outcomes of HSCT patients requiring intensive care support that was published by Duncan et al. [44] in conjunction with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network. This study examined all pediatric HSCT patients requiring intensive cardiopulmonary support, as defined by at least one of following: continuous positive pressure ventilation (invasive or non-invasive), dopamine infusion $\geq 10 \mu\text{g/kg/min}$, or the use of any other vasoactive infusion at any dose [44]. They reported an overall mortality of 38% for all intensive cardiopulmonary support patients, which increased to 42% for patients requiring invasive ventilatory support [44]. Of the patients receiving intensive cardiopulmonary support, 50% died before hospital discharge, compared to only one percent in-hospital mortality for HSCT patients not requiring intensive cardiopulmonary support [44]. This study also investigated long-term outcome of survivors and found that there was no significant difference at 1 yr post-HSCT between survivors of intensive cardiopulmonary support and those who did not require intensive support in survival, relapse, or a number of indicators of cardiopulmonary function [44].

Analysis of specific subgroups showed that mortality for HSCT patients who required continuous renal replacement therapy while in the PICU remained high, with an in-PICU mortality of 66% that increased to 97% at greater than 6 mo post-HSCT [43]. Also, Cole et al. [42] described outcomes in a group of pediatric patients who all received HSCT for primary immunodeficiencies or other non-malignant disorders. In this unique population, the HSCT patients requiring transfer to the ICU had a recorded mortality rate of 54% in the ICU, versus a mortality rate of 24% for all patients receiving HSCT.

7. Trends over time

Looking at mortality rates over time, the overall trend has been improving since the earliest papers on pediatric HSCT patients requiring intensive care [8–11], where mortality rates were reported to be greater than 80%. Fig. 1 shows the trend in improved survival for mechanically ventilated HSCT patients over time. The majority of more recent publications report mortality rates ranging from 40 to 70%, likely reflecting the year of HSCT, the number of patients

studied, the underlying primary diagnoses, the donor type, the indications for PICU care, and the treatment practices of individual institutions.

One method of partially controlling for this variability is to examine the trends in mortality within a single institution over time. The group from the University of California at Los Angeles reported a marked improvement in mortality over time: Kache et al. [32] divided the 1992–2004 period into two subgroups, 1992–1999 and 2000–2004. In the earlier time period, mortality for all HSCT patients requiring PICU care was 77% at 100 days, but in the later time period mortality had dropped to 36% at 100 days. The difference was statistically significant for the mechanically ventilated subgroup, with mortality improving from 82% at 100 days from 1992–1999 to 41% in the 2000–2004 era [32]. Two reports from the Fred Hutchinson Cancer Research Center also demonstrated improved survival over time. In the first study, Keenan et al. [15] reported a mortality rate at Fred Hutchinson Cancer Research Center of 84%, rising to 93% in the long-term, for patients transplanted from 1983–1996 and requiring intubation and ventilation. In a later report, Aspesberro et al. [1] reported a statistically significant survival improvement in patients transplanted from 2000–2004 and requiring mechanical ventilation, with a 6 mo odds ratio for mortality relative to the earlier transplant period of 0.25 (95% confidence interval 0.09–0.72, $P=0.01$).

Conversely, some studies found no significant change in mortality of critically ill HSCT patients over time in their institutions. Hagen et al. [14] found no difference in survival between patients receiving transplants in the years 1990–1995 and 1996–1999. Although Tamburro et al. [33] described improved mortality for non-HSCT oncology patients requiring PICU admission and mechanical ventilation in the years 2002–2004 relative to 1996–1998 and 1999–2001, there was a non-statistically significant trend toward improved mortality for HSCT patients. The analysis of Bratton et al. [36] using the Kids Inpatient Database did not find in a change in mortality of HSCT recipients requiring mechanical ventilation over the 3 yr analyzed, although overall hospital mortality significantly decreased from 1997 to 2003. Therefore, although a universal improvement in survival over the last two decades cannot be demonstrated, clearly an overall trend towards decreased mortality appears to be occurring, most notably during more recent years (Fig. 1).

Fig. 1. Published short-term survival of mechanically ventilated pediatric hematopoietic stem cell transplantation patients. Data points represent short-term survival of mechanically ventilated hematopoietic stem cell transplantation patients. Definitions of short-term survival varied between publications but most commonly represented successful extubation and discharge from pediatric intensive care unit, while other definitions included extubation and discharge from hospital, successful extubation for ≥ 30 days, survival at hospital discharge, or survival to discontinuation of intensive cardiopulmonary support. Each survival point was graphed versus the final year included in the published study. All studies reviewed in this paper were included in this graph except for those in which survival of the mechanically ventilated subset alone could not be determined, the specific short term mortality could not be determined, or all the patients reported had a single specific disease process (diffuse alveolar hemorrhage). The number of patients in reported studies (except one where the number of ventilated patients could not be determined) ranged from 13 to 434 (median 37, inter-quartile range 26–87.5).

8. Contributors to survival

The factors associated with increased mortality in these studies provide insight into the prognostication of outcomes as well as offering potential therapeutic targets. The most consistent correlation with increased mortality was the need for intubation and mechanical ventilation in those reports that included both intubated and non-intubated patients [18, 20–22, 26–28, 30, 32, 36, 38]. Aspesberro et al. [1] reported increased mortality only with mechanical ventilation for greater than or equal to 7 days. Among intubated patients, the reason for intubation was correlated repeatedly with mortality, with patients suffering respiratory failure due to pulmonary disease having significantly higher risks of mortality than patients intubated for other reasons, such as upper airway obstruction and mucositis, sepsis and septic shock, or neurological alterations [10, 12, 14, 15, 18, 22, 30]. Specifically, indicators of worsened pulmonary parenchymal disease were asso-

ciated with increased mortality. Rowan et al. [3] and Rossi et al. [16] reported that increased maximum oxygenation index correlated with increased mortality. Similarly, Kache et al. [32] reported a correlation between P_aO_2/F_iO_2 ratio <300 and requiring positive end expiratory pressure >8 and mortality. Several studies described high frequency oscillatory ventilation as being associated with very high rates of mortality most likely reflecting the use of this technology for a greater severity of pulmonary disease [3, 14, 21, 34].

Increasing severity of multiorgan failure has also been recurrently associated with increased mortality [2, 10, 15, 16, 18, 20, 21, 26, 27, 30, 34, 42]. With regard to donor type, Tamburro et al. [33] found an increased risk of mortality with allogeneic HSCT relative to autologous HSCT (odds ratio 4.52). An earlier study found no difference in mortality between mechanically ventilated patients who received umbilical cord blood HSCT versus those who received bone marrow HSCT [14]. The presence of graft versus host disease (GVHD), particularly severe grade III–IV disease, has generally been associated with increased mortality [10, 20, 30], except in one report which described reduced mortality in grade III–IV disease [12]. The authors could not offer an explanation for this disparate finding and suggested that perhaps it was related to a beneficial effect of steroids started for the GVHD on overall pulmonary inflammation. A later study from the same institution identified advanced GVHD as a risk factor for pulmonary complications associated with higher mortality, in agreement with other reports [17].

A number of investigators have applied standardized scoring systems in an attempt to develop a uniform method of prognostication for HSCT patients requiring intensive care. The most widely used scoring system has been the Pediatric Risk of Mortality system (PRISM) or the further modifications PRISM II or PRISM III. The majority of studies using PRISM scoring did not find that PRISM scores were significantly different between survivors and non-survivors [1, 20–22, 34]. However, Rossi et al. [16] reported that the median PRISM score was significantly higher in non-survivors, while Cheuk et al. [28] also reported a significant correlation between PRISM score and mortality by univariate and multivariate analysis. Using the PRISM II scoring system, Chima et al. [2] reported a significantly lower PRISM II score in patients surviving to PICU discharge than in non-survivors. When using the PRISM III scoring system, Tamburro et al. [33] described a significant correlation between

increased PRISM III scores on day of intubation with mortality for HSCT patients in PICU. In contrast, other authors found no significant difference between PRISM III scores in survivors versus non-survivors [32, 43].

Schneider et al. [20] developed a new scoring system, the oncological PRISM (O-PRISM) score, which added to the original PRISM score additional HSCT-specific factors: C-reactive protein, presence of GVHD, and macroscopic hemorrhage. The original authors, as well as several other centers, have applied this scoring to HSCT patients and found a correlation between increased O-PRISM scores and mortality [20, 25, 27, 28]. One group found no significant difference in O-PRISM scores between survivors and non-survivors [1]. A potential problem with O-PRISM scores is that they would be expected to be biased towards a higher score for allogeneic transplants given the presence of GVHD as part of the score [20].

9. Unanswered questions

There remain a number of unanswered questions in the literature on this subject. The heterogeneity of these studies, with almost all single center studies with relatively small number of patients, makes a clear definition of trends in mortality over time difficult. The retrospective nature of these reports results in outcomes being confounded by significant changes in clinical practice over time. In addition, there is wide reported variability in the initiation of intensive support on the ward versus transfer to the PICU, indications for transfer to the PICU, and treatment strategies in the PICU [45]. Thus, pre-PICU and PICU care may be significantly different between institutions and this is not addressed in the reported studies. Best practice guidelines are lacking and urgently required.

None of the publications we reviewed above reported any HSCT patients requiring support with extracorporeal membrane oxygenation (ECMO). Published reviews of patients in the extracorporeal life support organization registry found overall poor outcomes for pediatric HSCT patients receiving ECMO support [46, 47]. However, there are isolated case reports describing successful use of ECMO and survival in pediatric patients undergoing HSCT for various non-malignant diagnoses [48–50]. Ongoing improvements in ECMO technology, including advances in cannula development, circuit technology

and homeostasis management, along with refinement in patient selection, raise the possibility of ECMO successes in selected HSCT populations [46]. Since the number of HSCT patients amenable to ECMO is likely to be small, collaborative efforts are warranted for ongoing studies to optimize implementation of ECMO following HSCT.

Another unanswered question is whether use of non-invasive ventilation (NIV) in pediatric HSCT affects outcomes. While several studies reported on NIV use in small numbers of patients, the most detailed analysis of NIV is from Duncan et al. [44], who reported that 43% of patients requiring intensive cardiopulmonary support received noninvasive ventilation [29, 31]. Most (69%) of patients receiving NIV were transitioned to invasive ventilation, with 24% transitioning off NIV and 7% dying on NIV support, though there was no statistical analysis of association between NIV and mortality [44]. The requirement for invasive mechanical ventilation has consistently been associated with an increased risk of mortality over time [6, 18, 20–22, 26–28, 30, 32, 36]. Moreover, two studies have found decreases in the number of mechanically ventilated HSCT patients over time in conjunction with overall increased survival for all HSCT patients; only one of these studies described NIV use, and almost all of NIV patients in that study required eventual invasive ventilation [4, 36]. As more modalities for NIV in different age groups become available, it is plausible to hypothesize that NIV use might decrease the number of HSCT patients requiring intubation and thereby decrease mortality, though this requires further study.

10. Conclusions and future

Overall, the literature suggests improvement over time in survival of pediatric HSCT patients requiring intensive care, particularly when the most recent series are compared to the earliest published series (Fig. 1). There are a number of possible reasons to account for this improvement. First, the practice of critical care medicine has changed substantially in the last several decades, with a movement towards low tidal volume/lung protective ventilation strategies, early and aggressive goal-directed therapy in sepsis, and more varied modalities for renal replacement therapy [6]. HSCT protocols have changed as well, incorporating aspects such as reduced intensity conditioning and broad spectrum antimicrobial prophylaxis, depending

on the patient and institution [5, 6]. In addition, perhaps clinicians have become progressively more willing to transfer patients to the PICU given increasing evidence that such care is not universally futile [5]. Finally, the field of pediatric palliative care has expanded, and perhaps, patients with the poorest prognoses are being transitioned to limitations of support prior to transfer to the PICU.

Future directions in studying outcomes of critically ill pediatric HSCT patients would ideally include multicenter, prospective clinical studies associated with standardized scoring systems. In addition, studying the timing of the initiation of intensive support, even if it is prior to PICU transfer, would provide useful information on whether earlier introduction is associated with decreased mortality. Close collaboration between medical teams, particularly, but not limited to the HSCT service, the pediatric critical care team and their accompanying nursing staff and other support service providers, is critical to the successful development and performance of clinical research to define practices, which may produce improvement in the outcomes of critically ill pediatric HSCT patients.

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