PEDIATRIC STEM CELL TRANSPLANTATION AND CRITICAL CARE (AN OUTCOME EVALUATION)

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1. ABSTRACT

This paper reviews eight published studies of children who required critical care following a stem cell transplant. Approximately 14% of children required mechanical ventilation following stem cell transplant. Sixteen percent of these children survived. Eleven percent of children who had primary lung injury secondary to either infectious or non-infectious causes survived. Patients with respiratory failure induced by disease in organ systems other than the lungs had much better survival (33-39%). Children reported to have a non-bacterial infectious lung disease had very poor survival. Children who developed multi-organ system failure (MOSF) in addition to lung disease also had poor survival. The majority of children died of MOSF or pulmonary failure.

2. INTRODUCTION

Stem cell transplantation (SCT) is a high-risk procedure with potential for high morbidity and mortality. Patients may have complications related to the underlying disease, previous therapy, preparative regimen, and/or prolonged immune- incompetence. Some patients suffer complications necessitating pediatric critical care intervention. Adult patients undergoing stem cell transplant (SCT) who require mechanical ventilation (MV) have a dismal prognosis (1-10). The survival to hospital discharge ranges from 0 –8%. Data on pediatric patients requiring critical care following SCT is limited by the small numbers of patients at any individual institution.

This paper is a review of the current English literature regarding the outcome of pediatric patients requiring critical care and/or MV following SCT. The goals of this review are to determine the reasons for initiation of critical care, determine which patients have a reasonable chance of long-term survival (LTS), and to determine if a subset of patients can be defined for whom aggressive critical care should not be instituted and/or be terminated.

Each study was analyzed for the following data.
   Total number of SCT patients
   Number of patients requiring MV
   Survival of mechanically ventilated patients
   Reasons for MV and/or critical care.
      Primary pulmonary failure
      Non primary pulmonary failure
   Etiology of pulmonary failure
   Duration of MV
   Possible risk factors for requiring MV and/or critical care and for survival

2.1. Studies

Six studies dealt with pediatric SCT patients who required MV (11-16). Two studies dealt with patients who required pediatric critical care with or without MV (17, 18) (Table 1). The seven studies included 3445 patients who had stem cell transplants, of which, 492(14%) required MV. The eighth study included 43 patients who required
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Table 1. Incidence and Long Term Survival of Patients Requiring Mechanical Ventilation

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Total Patients</th>
<th>Mechanical Ventilation</th>
<th>LTS &gt; 6 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nichols</td>
<td>1986-88</td>
<td>318</td>
<td>23 (7%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Rossi</td>
<td>1986-88</td>
<td>355</td>
<td>39 (11%)</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Todd</td>
<td>1973-90</td>
<td>285</td>
<td>54 (18%)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Warwick</td>
<td>1976-92</td>
<td>869</td>
<td>196 (23%)</td>
<td>33 (16%)</td>
</tr>
<tr>
<td>Hayes</td>
<td>1987-97</td>
<td>367</td>
<td>33 (9%)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Diaz de Heredia</td>
<td>1991-95</td>
<td>176</td>
<td>26 (15%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Keenan</td>
<td>1983-96</td>
<td>1075</td>
<td>121 (11%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3445</td>
<td>492 (14%)</td>
<td>83 (16%)</td>
</tr>
</tbody>
</table>

Bojko         | 1986-93 | nr             | 43                     | 1 (2%)      |

NR – not reported; LTS – long term survival * > 30 days

Table 2. Diagnosis and Stem Cell Source of Patients Requiring MV or PICU Admission

<table>
<thead>
<tr>
<th>Study</th>
<th>Leukemia</th>
<th>Lymphoma</th>
<th>Solid Tumors</th>
<th>Non Malignant</th>
<th>Allogeneic</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nichols</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Rossi</td>
<td>19</td>
<td>3</td>
<td>17</td>
<td>33</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Todd</td>
<td>33</td>
<td>10</td>
<td>11</td>
<td>46</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Warwick</td>
<td>92</td>
<td>21</td>
<td>83</td>
<td>154</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Hayes</td>
<td>35</td>
<td>0</td>
<td>9</td>
<td>43</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diaz de Heredia</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>20</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bojko</td>
<td>19</td>
<td>13</td>
<td>11</td>
<td>30</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Keenan</td>
<td>59</td>
<td>nr</td>
<td>nr</td>
<td>112</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

NR – not reported

MV, but the total number of SCT patients in that series was not reported (12). The diseases and transplant type are depicted in Table 2. The majority of patients underwent an allogeneic SCT. More patients had leukemia than solid tumors or non-malignant conditions (aplastic anemia, immunodeficiency, or metabolic disorders). The most common reasons for admission to the Pediatric Intensive Care Unit (PICU) were pulmonary failure, sepsis/sepsis syndrome, and neurologic events. Other less common reasons for PICU admission were cardiac dysfunction, renal dysfunction, hemodynamic instability from hemorrhage or GI losses, and/or hepatic insufficiency.

2.1.2. Outcomes

2.1.2.1. Primary Pulmonary Disease

Of the 492 patients who required MV, 281 had respiratory failure secondary to primary lung injury (Table 3). The overall survival of these patients was 11%. Only 148 of these patients had data reported as to the etiology of the primary lung injury. Overall, infectious causes were diagnosed in 87 patients. The method of diagnosis was not always evident. Viral infections were diagnosed in 47 children (CMV 20 pts, RSV 5 pts, parainfluenza 3 pts, rubella 1 pt, unspecified 18 pts). Fungal organisms were found in 29 patients (aspergillus 5 pts, candida 4 pts, unspecified 20 pts). Pneumocystis carinii (PCP) was found in 7 patients. One out of 39 children with a viral etiology of pulmonary failure for whom data was reported survived. No children with reported fungal or pneumocystis carinii pulmonary failure survived (Table 4). Bojko (12) reviewed pathologic specimens in 21 patients. Nine patients had an infectious etiology identified (4 viral, 5 fungal). Nine patients had specimens obtained by bronchoalveolar lavage, which identified pathogens in 5. Two of these pathogens correlated with the pathologic findings. Interestingly four children had non-diagnostic bronchoalveolar lavages (BAL) and one child had PCP on BAL but fungal organisms were found in their lung tissue. Non-infectious causes of primary pulmonary failure (interstitial pneumonitis, hemorrhage, capillary leak, pulmonary edema, and bronchiolitis obliterans) affected 54 children. The overall survival of these children was <5%.

2.1.2.2. Secondary Pulmonary failure

Overall, 153 patients required MV secondary to non-primary pulmonary disease. Sepsis and/or cardiovascular collapse (16/33 pts survived), cardiac arrest (1/28 pts survived), airway protection for severe mucositis (18/61 pts survived) and mental status changes (13/27 pts survived) accounted for the majority of the children. Other causes were cardiac dysfunction, anaphylaxis, hemorrhage, and veno-occlusive disease of the liver. The overall long-term survival for this group of patients was 33%. If the group of patients who suffered a cardiac arrest were excluded, the survival was 39%.

2.1.3. Cause of Death

The cause of death was defined in 409 patients. Multi-organ system failure (47%) defined as two or more non-hematopoietic organ systems failing and primary pulmonary failure (33%) were the most common causes of mortality. Rossi (11) described 4 out of 20 patients surviving with 4 or more organ systems failing. Of 21 patients with up to 3 organ systems failing, 14 survived. Hayes (17) documented poor survival in children with 2 or more organ systems failing, particularly if associated with hepatic or...
2.1.4. Timing and Duration of MV

The median time from transplant to requiring MV ranged from 15.5-47 days post stem cell infusion (range day –12 to day +4798). The duration of mechanical ventilation for survivors and non-survivors were compared in 3 studies. (Table 5) (11, 14, 18) The mean time for successfully extubated patients to require MV was < 1 week. Some patients survived following prolonged intubations. It is not clear if patients with primary lung injury were among the survivors of prolonged intubations. Nicholls’ (15) paper described 2 patients with primary lung disease that survived MV courses of 7 and 12 days. This data is in contrast to a statement in an adult series (6) that MV for more than 4 days is futile. Indeed, the mean times of survivors requiring MV in two series (11, 18) were greater than 4 days.

2.1.5. Risk Factors

Predictors of the need for MV were GVHD, HLA mismatched marrow transplants, and the underlying diagnosis (immune deficiency, metabolic disorders, and neuroblastoma) (13). An elevated serum creatinine and/or a serum bilirubin predicted a shortened time to the onset of respiratory failure (15). Warwick found that patients with metabolic disorders were more likely to be successfully extubated (13). Paradoxically patients described by Warwick with high grade GVHD were also more likely to be successfully extubated in contrast to the patients described by Diaz de Heredia (18) who found that patients with high grade GVHD were more likely to die. However, Rossi did not find the underlying disease, type of transplant or degree of GVHD to be significantly associated with survival (11).

In studies that compared patients with autologous SCT or allogeneic SCT who required critical care, 8 out of 37 (22%) autologous SCT patients survived compared to 15 out of 94 (16%) allogeneic transplant patients (13, 14, 18).

Two studies compared Pediatric Risk of Mortality (PRISM) scores in survivors and non-survivors (11, 17). In a general pediatric intensive care unit, a PRISM score of less than 10 had a mortality risk of less than 1% (19). The surviving patients in one study (11) had a median score of 7. The non-survivors median score was 14 (p<.05). However, there was a large amount of overlap between the two groups. The other study found a mean score of 21 in survivors and 34 in non-survivors (p=. 21) (17).

2.1.6. Dialysis

Lane et al. reviewed their experience with 30 SCT children who required dialysis (20). Sixteen children had a hypotensive episode prior to development of renal failure. Two patients had urinary tract obstruction secondary to hemorrhagic cystitis. The etiology of renal failure in the other 12 patients was unknown. The indications for dialysis were hypervolemia, hyperkalemia, acidosis, hyperphosphatemia, and uremia. Twenty-three patients died without recovery of renal function. Seven patients were able to have dialysis discontinued. Three children survived to be discharged from the hospital. Rossi described 8 patients who required dialysis.11 One patient survived to be discharged. Therefore, only 4 out of 38(10%) children who required renal replacement therapy survived.

3. DISCUSSION

Children undergoing SCT are at risk for complications requiring critical care intervention. The overall experience in adult SCT patients who require MV has been dismal with less than 5 % LTS (2). The LTS is even worse when lung injury is associated with liver and renal failure and the need for vasopressors (2). The poor prognosis of these adult SCT patients raises the question of whether aggressive interventional care is warranted in patients undergoing SCT. When children develop complications that require critical care, decisions must be
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made regarding the utility and futility of aggressive PICU intervention. PICU care is expensive, utilizes limited resources (blood products), is invasive, and is painful. It also carries a tremendous emotional burden for families and health care workers. Knowing which patients have virtually no chance of survival with current therapeutic supportive and diagnostic measures would be helpful in reaching decisions regarding the institution and/or termination of critical care.

An analysis of eight series of pediatric SCT patients reveals that approximately 14% of SCT children require MV at some time during their transplant course. The overall survival of these patients is approximately 16%. Children who suffer a non-bacterial infectious or non-infectious primary lung injury fare worse (11% survive) than SCT patients requiring MV for non-pulmonary injury without a cardiac arrest (39% survive). Children reported with non-bacterial infectious lung injury have a dismal prognosis (<2% survive). The onset of MOSF with increasing amounts of organ dysfunction and/or the need for dialysis is associated with poor survival.

There are major difficulties in drawing any firm conclusions regarding the data from these studies. The criteria for admission to the PICU are not universal. Some institutions may admit less sick children to the critical care unit than others. The PICU care regarding ventilator management, vasopressor use and diagnostics may alter the outcome data. Most of the institutions report on relatively small numbers of patients. Only one study has data tracking the progress of the children from the time of intubation until day +7. The deterioration in organ function over a one-week period markedly lessens the chance for survival. Tracking serial changes in oxygenation index, alveolar-arterial oxygen gradient, and other measures of lung function may help predict the outcome of these children. Collecting more serial data might be helpful when deciding to terminate or continue care. Data is also needed to determine which children might benefit from earlier intervention, aggressive diagnostic procedures, new supportive therapies and/or discontinuation of aggressive management. Each clinical situation needs to be assessed and reevaluated frequently regarding the feasibility of continued aggressive management. It is not always in the child’s or family’s best interest to initiate or continue aggressive critical care when care is futile.

Pulmonary disease predominates as the reason for critical care intervention. Some studies suggest that perhaps earlier intervention or more aggressive diagnostic procedures would improve the prognosis in SCT patients with pulmonary failure (11, 12). Data from adult patients suggest that prolonged ventilatory support is futile (6). However, some pediatric patients are survivors following prolonged ventilatory support (11, 15, 18). Patients with a predictably poor prognosis with current therapeutic modalities may be candidates for studies involving other means of supportive care such as extracorporeal membrane oxygenation, surfactant, or liquid ventilation in an investigational study (21, 24). Because of the small numbers of patients at any given institution, multi -institutional data needs to be collected to assess the efficacy of new therapies in pediatric stem cell transplant patients who require critical care intervention.

When respiratory failure occurs, attempts should be made to determine the cause of the illness, assess other organ system function and determine whether intervention is appropriate. While an initial attempt at MV may be appropriate while evaluating the problem, frank discussions with family members regarding the likelihood of reversibility of the condition and the appropriateness of continued care need to be done frequently. Children who have primary lung injury and deteriorating organ function during their PICU course should be reevaluated frequently as to the utility versus futility of continued aggressive management. Everything that can be done must be distinguished from everything that should be done (25).

4. ACKNOWLEDGMENTS

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5. REFERENCES


4. Torrecilla C; Cortes JL; Chamorro C; Rubio JJ; Galdos P; Dominguez de Villota E: Prognostic assessment of the acute complications of BMT requiring intensive therapy. Intensive Care Med 14, 393-398 (1988)


Critical care following stem cell transplant


13. Warwick AB; Mertens AC; Shu XO; Ramsay NK; Neglia JP: Outcomes following mechanical ventilation in children undergoing BMT. Bone Marrow Transpl 22, 787-784 (1998)

14. Todd K; Wiley F; Landaw E; Gajewski J; Bellamy PE; Harrison RE; Brill JE; Feig SA: Survival outcome among 54 intubated pediatric BMT patients. Crit Care Med 22, 171-76 (1994)


17. Diaz de Heredia C; Moreno A; Olive T; Iglesias J; Ortega JJ: Role of the intensive care unit in children undergoing BMT with life-threatening complications. Bone Marrow Transpl 24, 163-168 (1999)


20. Lane PH; Mauer SM; Blazar BR; Ramsay NK; Kashtan CE: Outcome of dialysis for acute renal failure in pediatric BMT patients. Bone Marrow Transpl 13, 613-617 (1994)


22. Gauger PG; Pranikoff T; Schreiner RJ; Moler FW; Hirschl RB: Initial experience with partial liquid ventilation in pediatric patients with ARDS. Crit Care Med 24, 16-22 (1996)


25. Schuster DP. Everything that should be done- not everything that can be done. Am Rev Respir Dis 145, 508-509 (1992)

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