Engraftment Syndrome in Hematopoietic Stem Cell Transplantations

Kelli Thoele, MSN, RN, ACNS-BC, BMTCN, OCN®

Hematopoietic stem cell transplantation (HSCT) is an increasingly common treatment option for malignant and nonmalignant diseases, but it has significant associated morbidity and mortality. Nurses caring for HSCT recipients must be aware of all potential complications, including engraftment syndrome (ES). Previous nursing literature has included little information on this syndrome, which often presents with noninfectious fever, skin rash, and pulmonary infiltrates, and ES may be fatal if left unidentified and treatment is not initiated promptly. Reports of the risk factors, incidence, clinical manifestations, diagnosis, treatment, and outcomes have much variation, likely from a lack of definite diagnostic criteria and inconsistency in the terminology associated with ES. The purpose of this article is to provide an overview of ES and the implications for nursing practice and research.

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Each year, more than 50,000 hematopoietic stem cell transplantations (HSCTs) occur worldwide (Gratwohl et al., 2010), and about 15,000 bone marrow or umbilical cord blood transplantations occur in the United States (Pasquini & Wang, 2011). HSCTs are used to cure or treat malignancies (e.g., multiple myeloma, lymphoma, leukemia, neuroblastoma, germ cell cancer) as well as nonmalignant disorders (e.g., aplastic anemia, immune deficiencies) (Gratwohl et al., 2010; Pasquini & Wang, 2011). Stem cells for the transplantation may be harvested from the patient (autologous), an identical twin (syngeneic), or a related or unrelated donor (allogeneic) and may be extracted from bone marrow, peripheral blood, or cord blood. For the purposes of the current article, HSCT will be used to describe allogeneic or autologous transplantations from bone marrow, peripheral blood, or cord blood.

HSCTs are complex and have significant associated morbidity and mortality. Complications of HSCT may occur because of treatment-related toxicity, immunosuppression, donor-mediated toxicity, recipient-mediated toxicity, or relapse of the malignancy (Scott, Morgan, Durrant, & Boots, 2002). Although the majority of transplantation recipients are monitored at an outpatient facility or inpatient oncology unit, life-threatening complications may necessitate admission to an intensive care unit. The overall rate of admission to intensive care units is 16% in all HSCT recipients (Afessa & Azoulay, 2010), but the rate is as high as 57% in adult recipients of allogeneic cord blood transplantations (Naeem et al., 2006). HSCT recipients are at risk of death from the primary malignancy, but many deaths are caused by complications of the transplantation. In patients who received HSCT in the United States in 2008 and 2009, 27% of deaths in autologous recipients and 67% of deaths in unrelated donor allogeneic recipients were caused by complications of the transplantation, such as graft-versus-host disease (GVHD), infection, and organ failure (Pasquini & Wang, 2011).

To provide high-quality care to HSCT recipients, nurses must be aware of the pathophysiology, clinical manifestations, and treatment of complications associated with transplantations. Nurses must be vigilant about assessing for signs and symptoms associated with complications and intervene as appropriate to ensure optimal clinical outcomes. GVHD and infection are common complications of HSCT that may result in morbidity and mortality (Pasquini & Wang, 2011), and resources are available for nurses to learn about those complications. In contrast, very
few resources are available for nurses regarding engraftment syndrome (ES), another common complication of HSCT.

Background

ES is a poorly defined and poorly understood complication of HSCT that occurs during neutrophil recovery and often is characterized by noninfectious fever, skin rash, and pulmonary infiltrates (Maiolino et al., 2003; Spitzer, 2001). Because of a lack of definitive diagnostic criteria, reports on the incidence of ES vary from 10%–77% (Gorak et al., 2005; Hong et al., 2013; Kanda et al., 2013; Lee, Lim, Kim, Kim, & Lee, 2008; Schmid, Stachel, Pagel, & Albert, 2008). The presence of ES has been linked to increased mortality and longer length of hospitalization (Gorak et al., 2005; Maiolino et al., 2003), and early identification and treatment has been shown to result in improved clinical outcomes (Capizzi et al., 2001; Carreras et al., 2010; Gorak et al., 2005; Maiolino et al., 2003; Spitzer, 2001).

Although oncology nurses are able to assess for clinical manifestations of ES and intervene to enhance symptom management, nursing literature regarding ES is scarce. This article aims to summarize incidence, pathophysiology, risk factors, and clinical manifestations of ES; discuss assessment, diagnosis, and treatment of ES; and determine nursing implications for practice and future research.

Definitions

Rimkus (2009) described five phases of HSCT (i.e., conditioning, transplantation, recovery, engraftment, and postengraftment). In the conditioning phase, chemotherapy, radiation and/or immunotherapy are given to eliminate residual disease and create space for donor hematopoietic stem cells. The second phase of HSCT, the transplantation phase, is the administration of autologous, syngeneic, or allogeneic stem cells. In the recovery phase, the donated stem cells have not yet differentiated into mature hematopoietic cells, and HSCT recipients are vulnerable to complications related to myelosuppression and toxicities related to the conditioning. Engraftment is the fourth phase, in which transplanted stem cells begin to differentiate into mature hematopoietic cells. Engraftment is complete in the postengraftment phase, the final stage of HSCT. Each phase of HSCT has unique associated complications.

In the context of ES, engraftment is usually defined by neutrophil engraftment because the clinical manifestations of ES often occur when neutrophils appear in the peripheral blood (Spitzer, 2001). During recovery, HSCT recipients are pancytopenic because of the conditioning treatment, and have little to no neutrophils present. As the transplanted stem cells differentiate and mature, neutrophils begin to appear in peripheral blood and the absolute neutrophil count (ANC) increases. One author defined engraftment as “the first appearance of neutrophils the peripheral blood” (Maiolino et al., 2003, p. 394), and other authors defined engraftment as an elevated number of neutrophils over an extended period of time. Kanda et al. (2013) defined engraftment as an ANC count of greater than or equal to 500 mcl for three consecutive days, some authors defined it as an ANC count of greater than 500 mcl for three consecutive days (Hong et al., 2013; González-Vicent et al., 2004; Schmid et al., 2008), and others defined it as an ANC count of greater than 500 mcl for two consecutive days (Capizzi et al., 2001; Carreras et al., 2010; Lee et al., 2008). Some authors particularly noted that engraftment begins on the first day of the consecutive days of specific ANC counts (Carreras et al., 2010; Hong et al., 2013; Kanda et al., 2013; Schmid et al., 2008). Spitzer (2001) defined engraftment as an ANC count of greater than or equal to 500 mcl for two consecutive days, and Gorak et al. (2005) defined it as an ANC count of greater than 100 mcl.

Although ES is the term most often used to describe the HSCT complication, other terms have been used as well. Pre-ES (Kanda et al., 2013; Lee et al., 2008) and peri-ES (Hong et al., 2013) describe the syndrome in relationship to its timing with neutrophil engraftment. Peri-engraftment respiratory distress syndrome also has been used to emphasize the respiratory aspect of ES (Capizzi et al., 2001). Other terms used include capillary leak syndrome (Cahill, Spitzer, & Mazumder, 1996), auto-aggression syndrome (Capizzi et al., 2001; Moreb et al., 1997), and auto-aggression graft-versus-host-like syndrome (Schmid et al., 2008).

Pathophysiology and Clinical Manifestations

The exact cause of ES is unknown, but the most likely cause is a pro-inflammatory reaction. Palomo et al. (2009) found that endothelial cells are damaged in autologous and allogeneic HSCT, resulting in a pro-inflammatory state. The endothelial damage may result from the conditioning regimen, administration of granulocyte-colony-stimulating factor (G-CSF), alloseactivity, or engraftment (Carreras & Díaz-Ricart, 2011; Palomo et al., 2009). In addition, the degranulation and oxidative metabolism of neutrophils may cause the release of cytokines and other products that lead to local and systemic injury to tissue (Spitzer, 2001; Varani & Ward, 1994). The movement of neutrophils across the endothelial tissue from the marrow to the peripheral vascular system may cause the release of pro-inflammatory cytokines related to ES (Carreras & Diaz-Ricart, 2011). Although the exact cytokine profile of ES is unknown, pro-inflammatory cytokines related to ES may include interleukin-1, tumor necrosis factor-alpha, and interferon gamma (Spitzer, 2001).

Evidence exists that C-reactive protein (CRP) levels significantly correlate with an ES diagnosis. CRP is an acute phase reactant and a marker of systemic inflammation (Gabay & Kushner, 1999; Kushner, 2013). Carreras et al. (2010) measured serum CRP in 328 autologous HSCT recipients. All patients with neutropenic fever had moderate elevation of CRP levels. Although the level of CRP decreased after resolution of the neutropenic fever in patients without ES, CRP levels continued to increase in patients with ES to an average of three times the CRP level of patients without ES. According to Carreras et al. (2010), serum CRP greater than 6 mg per 100 ml has a sensitivity and specificity of 90% for discerning patients with ES. Another study of 265 autologous HSCT recipients supported those findings. In a study by Lopes da Silva, Costa, Ferreira, and de Sousa (2012), elevated CRP levels correlated with a diagnosis of ES.

Noninfectious fever is the most common clinical manifestation associated with ES (see Table 1). Other common manifestations include skin rash, pulmonary infiltrates, weight gain,
hypoxia, hepatic dysfunction, and renal dysfunction (Carreras et al., 2010; Gorak et al., 2005; Hong et al., 2013; Maiolino et al., 2003; Patel et al., 2010; Schmid et al., 2008). The median onset of ES has ranged from 9–13 days post-transplantation (Capizzi et al., 2001; Gorak et al., 2005; Hong et al., 2013; Kanda et al., 2013; Patel et al., 2010), but has occurred as early as three days (Gorak et al., 2005) and as late as 22 days (Kanda et al., 2013) post-transplantation.

**Diagnostic Criteria**

Because of inconsistencies in the definition of engraftment and uncertainty about the pathophysiology, diagnosis is unreliable. Spitzer (2001) and Maiolino et al. (2003) have proposed diagnostic criteria for ES (see Table 2). The diagnostic criteria proposed by Spitzer (2001) included major and minor criteria. ES is diagnosed if the HSCT recipient has all three major criteria or two major criteria with at least one minor criterion. In addition, the signs and symptoms must occur within a certain time frame of neutrophil engraftment. Maiolino et al. (2003) also proposed criteria for the diagnosis of ES. According to Maiolino et al.’s (2003) diagnostic criteria, ES is present if the HSCT recipient has a noninfectious fever, plus at least one of three other clinical manifestations. However, the signs and symptoms must occur within a certain time frame of neutrophil engraftment.

Carreras et al. (2010) analyzed the diagnostic criteria in autologous HSCT recipients proposed by Spitzer (2001) and Maiolino et al. (2003). Of 328 patients reviewed, the authors identified 43 patients with probable ES. Of the 43 identified patients, 22 were diagnosed with ES using Spitzer (2001) criteria, and 41 were diagnosed with ES using the Maiolino et al. (2003) criteria. Carreras et al. (2010) found the Maiolino et al. (2003) criteria to be the best tool for identifying HSCT recipients with ES. Lopes da Silva et al. (2012) compared the criteria with similar results. In that study, 18 of 265 autologous HSCT recipients were identified as having signs and symptoms indicative of ES. Of the 18 identified patients, eight were diagnosed with ES using Spitzer (2001) criteria, and 13 were diagnosed with ES using the Maiolino et al. (2003) criteria. Lopes da Silva et al. (2012) stated that the Spitzer (2001) criteria were more stringent, but less sensitive than the Maiolino et al. (2003).

Dispenzieri et al. (2008) studied 30 patients receiving peripheral autologous blood stem cell transplantations for polineuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. Because neutrophil engraftment is delayed in HSCT recipients with POEMS syndrome, Dispenzieri et al. (2008) used modified criteria, where the clinical

### TABLE 1. Incidence and Clinical Manifestations of ES

<table>
<thead>
<tr>
<th>Study</th>
<th>Population and Setting</th>
<th>ES Incidence</th>
<th>Clinical Manifestations</th>
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<tbody>
<tr>
<td>Carreras et al., 2010</td>
<td>328 adult patients with autologous HSCT and a variety of diagnoses, disease stages, mobilization, and conditioning</td>
<td>13% overall; n = 43</td>
<td>Elevated C-reactive protein (100%), noninfectious fever (98%), rash (65%), diarrhea (40%), pulmonary infiltrates (37%), hypoxemia (33%), renal dysfunction (26%), hepatic dysfunction (21%), weight gain (19%), transient encephalopathy (3%)</td>
</tr>
<tr>
<td>Gorak et al., 2005</td>
<td>149 adult patients who received allogeneic HSCT with a variety of diagnoses, as well as a condition regimen that included cyclophosphamide and fludarabine</td>
<td>10% overall; n = 15</td>
<td>Noninfectious fever (100%), room air hypoxia (87%), pulmonary infiltrates (100%), cough (53%), wheezing (26%), weight gain (53%), skin rash (13%)</td>
</tr>
<tr>
<td>Hong et al., 2013</td>
<td>176 pediatric patients who received allogeneic HSCT with a variety of diagnoses, stem cell sources, and conditioning regimens</td>
<td>17% overall; n = 30, n = 15 receiving DUCBT</td>
<td>Fever (100%), maculopapular rash (100%), pulmonary infiltrates (57%), renal dysfunction (10%), encephalopathy (20%), weight gain (50%), hepatic dysfunction (23%)</td>
</tr>
<tr>
<td>Kanda et al., 2013</td>
<td>57 adult and pediatric patients who received DUCBT, total body irradiation, and myeloablative conditioning</td>
<td>77% overall; n = 44</td>
<td>Body weight gain greater than 10% (23%), diarrhea (32%), hyperbilirubinemia (14%)</td>
</tr>
<tr>
<td>Maiolino et al., 2003</td>
<td>125 pediatric and adult patients who received autologous HSCT with a variety of diagnoses, stem cell sources, and conditioning regimens</td>
<td>7%; 20%; overall; n = 9</td>
<td>Hypoalbuminemia (78%), weight gain (67%), pulmonary infiltrates (56%), diarrhea (56%)</td>
</tr>
<tr>
<td>Patel et al., 2010</td>
<td>52 pediatric and adult patients who received allogeneic HSCT and DUCBT with hematologic malignancies</td>
<td>31% overall; n = 16</td>
<td>Fever (94%), skin rash (81%)</td>
</tr>
<tr>
<td>Schmid et al., 2008</td>
<td>61 pediatric patients who received allogeneic HSCT with a variety of graft sources, conditioning regimens, and diseases</td>
<td>48% overall; n = 29</td>
<td>Fever (90%), skin rash (72%), weight gain and albumin drop (66%), pulmonary symptoms (24%)</td>
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</table>

DUCBT—double-unit cord blood transplantation; ES—engraftment syndrome; HSCT—hematopoietic stem cell transplantation

* ES was defined as noninfectious fever and/or rash prior to engraftment.
* Diagnostic criteria included fever and skin rash.
* Noninfectious fever and skin rash during peri-engraftment.
* Maiolino et al.’s (2003) criteria used to define ES
manifestations of ES were uncoupled with the timing of neutrophil engraftment. Using Spitzer (2001), Maiolino et al. (2003), and modified criteria, the authors found that the incidence of ES ranged from 27%–57%, depending on the diagnostic criteria used. In that study, ES rates were 27% (n = 8) using Spitzer (2001) criteria, 50% (n = 15) using the modified Spitzer (2001) criteria, 47% (n = 14) using Maiolino et al. (2003) criteria, and 57% (n = 17) using the modified Maiolino et al. (2003) criteria. Dispenzieri et al. (2008) noted that the modified Spitzer (2001) criteria most accurately reflected an ES diagnosis.

Incidence

Reports on the incidence of ES in HSCT vary. Although diagnostic criteria have been proposed, investigators continue to use varying criteria in studies. For example, Hong et al. (2013) used Spitzer’s (2001) criteria but uncoupled the timing between the symptoms and neutrophil engraftment. Gorak et al. (2005) defined ES as having two or more of a set of symptoms (i.e., noninfectious fever, weight gain, rash, and hypoxia or pulmonary infiltrates) within 96 hours of the beginning of neutrophil recovery. Kanda et al. (2013) only diagnosed HSCT recipients with ES if they had a noninfectious fever plus a rash prior to neutrophil recovery. Definitions of neutrophil engraftment also vary and may affect diagnosis and the incidence of ES. Other factors, such as variation in patient age, conditioning regimens, sources of stem cells, and diagnoses, may affect the incidence of ES in the HSCT recipients studied. Overall incidence varies from as low as 10% to as high as 77% (Gorak et al., 2005; Kanda et al., 2013).

Treatment and Prevention

No guidelines exist for the treatment of ES; however, treatment with corticosteroids has been shown to result in rapid reduction in the clinical manifestations of ES. Although dosages vary, treatment commonly includes IV methylprednisolone 1–3 mg/kg per day (Carreras et al., 2010; Gorak et al., 2005; Hong et al., 2013; Maiolino et al., 2003; Patel et al., 2010). After treatment with IV corticosteroids, fever usually resolved within 24–48 hours of initiation of treatment (Hong et al., 2013; Patel et al., 2010), pulmonary symptoms resolved about 24 hours later (Gorak et al., 2005), and skin rash improved within three days (Kanda et al., 2013). Some HSCT recipients required prolonged or repeated steroid treatment to achieve complete resolution of ES (Carreras et al., 2010; Hong et al., 2013).

Evidence also exists that steroids may prevent ES. In one study of allogeneic HSCT recipients, patients received various GVHD prophylactic regimens, including cyclosporine plus mycophenolate mofetil, cyclosporine plus steroid, cyclosporine plus methotrexate, and tacrolimus plus methotrexate (Hong et al., 2013). Overall incidence of ES in this study was 17%, but none of the 31 recipients who received a steroid regimen for GVHD prophylaxis developed ES.

In another study of 194 consecutive autologous HSCT recipients, the first 111 HSCT recipients (Group A) did not receive any ES prophylaxis, and the final 83 HSCT recipients (Group B) received steroid ES prophylaxis from day 4 to day 14 post-transplantation. Group B had significantly lower rates of ES (6% versus 57%) and significantly shorter length of hospital stay (21 versus 23 days). Hospital readmission rates and infection rates were similar in both groups (Mossad et al., 2005).

Risk Factors and Outcomes

Various risk factors have been associated with ES, and they may be related to disease, conditioning treatment, stem cell source, patient characteristics (e.g., gender, age), and supportive treatment. Risk factors may include double-unit cord blood transplantation (Hong et al., 2013), total body irradiation (Hong et al., 2013), female gender (Carreras et al., 2010; Gorak et al., 2005), amyloidosis (Carreras et al., 2010), recipients who did not receive prior chemotherapy (Carreras et al., 2010), treatment with amphotericin (Gorak et al., 2005; Schmid et al., 2008), treatment with G-CSF (Schmid et al., 2008), increased age (Gorak et al., 2005; Koreth et al., 2011), high mononuclear

### TABLE 2. Diagnostic Criteria for Engraftment Syndrome

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**Diagnosis:** All three major criteria or two major criteria and at least one minor criterion within 96 hours of engraftment

**Diagnosis:** Fever plus at least one other criterion 24 hours before the first measured neutrophils in peripheral blood or anytime after the appearance of neutrophils

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increased risk of ES.

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**Greater than or equal to twice normal**

**Greater than or equal to 38.3°C; infectious etiology must be ruled out by obtaining appropriate cultures.**

**Greater than 25% of body surface area; erythrodermatous**

**Greater than equal to 2 mg/dl or transaminase greater than or equal to twice normal**

**Greater than or equal to 38.3°C; infectious etiology must be ruled out by obtaining appropriate cultures.**

**Greater than or equal to 2.5% baseline**

**Greater than or equal to 38°C; does not respond to antimicrobials; infectious etiology must be ruled out by obtaining appropriate cultures.**

**Greater than or equal to 38°C; does not respond to antimicrobials; infectious etiology must be ruled out by obtaining appropriate cultures.**

**Two or more episodes of diarrhea per day; noninfectious**

**Absolute neutrophil count greater than or equal to 500 mcl for two consecutive days**

cell count (Schmid et al., 2008), and cyclosporine administration (Kanda et al., 2013).

ES has been shown to be associated with increased transplantation-related mortality (Gorak et al., 2005), decreased overall survival (Gorak et al., 2005), and increased length of hospitalization (González-Vicent et al., 2004; Maiolino et al., 2003). In the Gorak et al. (2005) study, 14 of 15 patients with ES received steroids. In contrast, other researchers did not find a significant relationship between ES and overall survival (Kanda et al., 2013; Schmid et al., 2008) or treatment-related mortality (Schmid et al., 2008). In the Kanda et al. (2013) study, 22 of 44 patients with ES received steroids, and in the Schmid et al. (2008) study, 18 of 29 patients received steroids.

Discussion

The purpose of the current article is to summarize current research on ES and discuss nursing implications for practice and research. Because of the potentially devastating outcomes associated with ES, nurses caring for HSCT recipients must be aware of ES and its symptoms to intervene quickly and appropriately. Risk factors, incidence, clinical manifestations, and outcomes of ES are variable and uncertain, in part, because of varying definitions of neutrophil engraftment and lack of consistent ES diagnostic criteria, as well as variations in conditioning regimens, stem cell source, diagnosis, and patient characteristics. Once ES is identified, treatment with corticosteroids has proven to result in rapid resolution of symptoms. Awareness of ES is an important first step in understanding the problem, but much work needs to be done.

Nursing Implications

A thorough nursing assessment must include assessment for the clinical manifestations associated with ES, with anticipated presentation 9–13 days post-transplantation. The patient’s temperature should be monitored frequently. In addition, a thorough skin assessment should be performed routinely, noting any rashes or abnormalities. Mental status, oxygenation, and lung sounds should be assessed regularly, and nurses should note changes. Nurses must monitor frequency and consistency of stool, trends in weight, ANC, total bilirubin, transaminase, and serum creatinine.

The lack of definitive diagnostic criteria presents challenges in diagnosing ES. Diagnostic criteria have been proposed, but those criteria have limited sensitivity and specificity. Infectious etiology should be ruled out when diagnosing ES, which may include obtaining blood and urine cultures. If the HSCT recipient is having diarrhea, a stool culture and a test for *Clostridium difficile* also may be necessary to rule out infection. A chest x-ray or computed tomography scan may be performed to assess for pulmonary infiltrates.

Interventions for ES should address treating the cause of ES, as well as the symptoms. If steroids are given to treat ES, the nurse should assess for possible adverse effects of steroids, including hyperglycemia and insomnia. Fevers should be managed to keep the patient comfortable, and oxygen therapy should be given, if necessary, to ensure adequate oxygenation.

Implications for Practice

- Assess for signs and symptoms of engraftment syndrome (ES) with anticipated presentation 9–13 days post-transplantation.
- Educate patients who receive hematopoietic stem cell transplantations and their families about the identification and reporting of signs and symptoms of ES.
- Obtain necessary tests to rule out infectious etiology.

Patient and family education also is essential, and nurses should educate all HSCT recipients about the signs and symptoms, treatment, and symptom management of ES.

Conclusion

Definitive diagnostic criteria for the identification of ES have not been developed, but researchers have noted specific symptoms associated with this side effect of HSCT. Oncology nurses should be educated on the signs and symptoms of ES to monitor patients who receive HSCT. Many opportunities for future research of ES in HSCT recipients. One possible area of research is in nurse knowledge of ES. Identification of gaps in knowledge can lead to interventions to increase knowledge. Future research may focus on definitive diagnostic criteria, prevention of ES, as well as related risk factors, incidence, and outcomes.

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