

by Duygu Uçkan and Nevin Çetin, Hacettepe University-Ankara, Türkiye

Engraftment syndrome (ES) is an early complication of hematopoietic stem cell transplantation (HSCT) that occurs around neutrophil engraftment time and is attributed to the sudden cytokine discharge associated with robust engraftment of transplanted cells. The secreted cytokines cause a clinical picture suggestive of an exaggerated inflammatory response. This complication has been described both in autologous and allogeneic transplantation.

The diagnostic clinical features include the presence of two or more of the following symptoms usually 96 hours before neutrophil engraftment time: 1- fever of unknown origin (38.0-38.5 °C) with no detectable infectious agent or other cause, 2- erythematous skin rash not related to drug reactions or viral infection (usually covering >25% of the body surface), 3- weight gain of 2.5-5% (above baseline of admission) and albumin drop to 90% of pretransplant levels, and 4- pulmonary symptoms with dyspnea, hypoxia and pulmonary infiltrates on a chest X-ray (excluding infection, thromboembolism, pulmonary hemorrhage, fluid overload, or cardiac causes). Though hepatic dysfunction, renal insufficiency and transient encephalopathy have been described in adults, they have not been reported as common findings in pediatric practice.

Risk Factors include; 1. High cell doses infused on day 0, 2. Prompt increase in white blood cell (WBC) counts, 3. Autologous peripheral blood as stem cell source, and 4. Autoimmune disease as an underlying condition.

Differential diagnosis and early recognition are particularly important since corticosteroids have a critical role in the reversal of symptoms and management of the condition.

The prognosis is usually good with early corticosteroid use, and complete resolution is seen in 1-5 days in >80% of cases. Otherwise, this complication occasionally may lead to increased morbidity and mortality if not managed appropriately and timely. ES is associated with increased length of hospitalization. It may be problematic since it can resemble cutaneous acute graft-versus-host disease (aGvHD) or be complicated by capillary leak syndrome and noncardiogenic pulmonary edema. Rarely, ES can mimic aGvHD by affecting the liver and gastrointestinal tract. It has been shown that patients who develop ES receive empirical antifungal therapy more frequently than patients who do not, most likely due to persistent fever. Patients undergoing autologous HSCT for multiple sclerosis who develop ES may experience transient worsening of neurological symptoms. In pediatric patients, ES is also associated with increased transfusion requirements, need for parenteral nutrition and increased risk of critical care requirement

Corticosteroids also have a role in the prevention of ES.

NURSING CARE AND MANAGEMENT IN ES IN HSCT PATIENTS

The initial step in the management of ES is to establish a correct diagnosis.

The following are suggestive of ES:

1. Persistence of fever despite antibiotics
2. Occurrence or recurrence of fever around the time of engraftment
3. Absence of a clear evidence of infection
4. Cutaneous rash around the time of engraftment (not attributable to an allergic reaction or drugs)
5. Sudden rise in WBC count
6. Pulmonary problems (lung infiltrates or hypoxia)
7. Some occasionally observed symptoms, such as weight gain, and liver, kidney or central nervous system (CNS) dysfunction

The HSCT nurse should be aware of the clinical findings suggestive of ES and should monitor the symptoms and findings of patients accordingly.

The presence of any of the aforementioned risk factors should be recorded in the notes.

If the patient's diagnosis is suggestive of ES, then the patient should be managed according to the following steps:

1. **Management of fever:** Non-infectious fever is a common finding seen in ES. The nursing approach to fever management should be applied as indicated in detail in the "Fever" chapter.

The HSCT nurse will take an active role in the exclusion of an infectious etiology. Examinations and evaluations should be done to determine potential sites of infection on the skin and orifices (mouth, perianal region). The patient should be evaluated for a catheter infection by examination of the catheter site and the entirety of the tunnel and by obtaining appropriate cultures as indicated by the physician. The temporal connection of

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fever and catheter use (i.e. administration of fluids and/or medications) should be reviewed by going through nursing notes-flow sheets in order to exclude catheter-related causes of fever. Other risk factors for infection should be considered. The HSCT nurse should manage the patient according to the institutional standard operating procedure (SOP) regarding fever management

1. **Management of skin rash:**

2. The skin of the patient should be examined by a staff nurse during each shift.
3. The characteristics of the rash should be noted and should include details regarding the localization, distribution and character of the rash. The nurse should also record the changes in the rash over time, such as increase or fading or any other changes in the character.

4. The nurse should inform the physician about the rash and especially if worsening occurs.

5. A skin biopsy may be planned by the physician for exclusion of other causes, in which case, the nurse should prepare the necessary set-up.

6. The HSCT nurse will ensure that the patient and/or family is informed about the procedure and that an informed consent is obtained.

7. Appropriate skin care should be provided according to institutional SOP. Prevention of dryness with the use of moisturizers may be needed.

8. **Management of pulmonary symptoms**

9. If present, the character and frequency of cough should be noted and the physician should be notified.

10. Respiratory assessment should include: recording of respiratory rate, character and changes in pattern and signs of dyspnea.

11. Pulse oximetry should be applied.

12. Blood gases may be tested if requested by the HSCT physician.

13. Oxygen may be administered preferably by a reservoir mask.

14. The HSCT nurse should follow in- and output closely, and be careful to avoid fluid overload. A pulmonary X-ray or other radiological tests may be necessary, in which case, the patient and/or the family should be informed and the patient should be prepared according to institutional SOP.

15. The patient should be followed carefully, particularly if respiratory symptoms are worsening, and should be assessed for the need of mechanical ventilator in close interaction with the HSCT physician.

16. The nurse should assess the patient for chest pain, and if present, inform the physician.

17. **Fluid electrolyte balance and fluid overload: :**

18. Close in- and output follow-up is needed.

19. Recording of daily weight is needed since ES is associated with fluid retention in conjunction with cytokine discharge.

20. Adequate hydration is necessary; however, fluid overload should be avoided.

21. Blood chemistry and electrolyte values should be determined, and liver function tests should be obtained (frequency indicated by the physician).

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22. The HSCT nurse should be aware that diuretic administration may be needed as per physician evaluation.
23. Diarrhea may be an accompanying symptom of ES in some patients. Therefore, the nurse should observe the patients' stools regularly.

1. **Corticosteroid administration:**

2. Steroid administration is the mainstay of ES treatment. Steroids may be given by intravenous (iv) or peroral (po) route as per physician orders. A dramatic response of ES to corticosteroid therapy with prompt defervescence in 24 hours is common

3. The HSCT nurse should be aware of the side effects of corticosteroids, including the commonly seen hypertension, hyperglycemia, gastric irritation, fluid retention, and infection.

(Steroid use is usually not prolonged in ES; therefore, late side effects of steroids may not be a real issue; nevertheless, the steroid course is prolonged on rare occasions.)

1. It is also important to know that the risk of cytomegalovirus (CMV) or other viral reactivations is particularly increased with the use of corticosteroids, and the viral surveillance tests (polymerase chain reaction [PCR] or antigenemia) should be followed closely during the period of steroid use.

2. Fungal infection risk is also increased in patients on steroids. Therefore, surveillance tests for fungal agents (i.e. galactomannan) may be needed.

3. Prophylactic use of antimicrobials and/or preemptive use of antifungal and/or antiviral agents may be necessary.

4. Institutional SOP regarding the use of steroids should be followed.

5. **Monitorization of immunosuppressive medications:**

6. Monitoring of blood levels of immunosuppressives (i.e. cyclosporine/tacrolimus) is important since steroids may change their blood levels. The inflammatory state associated with ES may later induce aGVHD. Therefore, it is important to achieve sufficient levels of immunosuppressives to avoid aGVHD, and dose adjustments may be needed. It should be remembered that ES may be confused with hyperacute or aGVHD.

The nurse should send blood samples for monitoring of cyclosporine or tacrolimus levels according to institutional SOPs, and should follow the results and notify the physician when abnormal results are reported.

7. It is critical for the HSCT nurse to administer immunosuppressives at their exact doses and in a timely manner according to the physician's orders.

8. **Other:**

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9. HSCT patients are frequently given granulocyte colony-stimulating factor (G-CSF) to hasten engraftment, which may worsen the clinical course of the patient with ES. Previous reports indicated that G-CSF administration would predispose to ES and to an increased rate of pulmonary complications after HSCT, and the stimulus of endogenous cytokines can be increased by exogenous G-CSF. Therefore, if the patient with ES is already on G-CSF, the nurse should be aware that G-CSF may be discontinued, particularly if the neutrophil count reflects a sudden rise. The nurse should confirm with the physician regarding the necessity of ceasing G-CSF administration.

10. A HSCT patient may have already been receiving granulocyte transfusions due to persistent fever on the assumption of an infectious etiology. If the cause of the fever is not infectious but rather ES, granulocyte transfusion may worsen the clinical picture of ES by inducing cytokine release. However, exclusion of infection may be problematic, particularly if the sudden rise in WBC has not initiated to suggest ES. Therefore, the decision of whether to continue or not should be made by the physician on an individual basis based on the patient's status.

11. The HSCT nurse should bear in mind that, once the diagnosis of ES is made, the physician may request discontinuation of some antibiotics if infection is unlikely. However, due to the difficulty in exclusion of an infectious etiology, antibiotics are continued in most cases throughout the fever course. The decision regarding the use of antimicrobials will be based on each patient's status.

Prevention of ES: It has been shown that steroid prophylaxis decreases the risk of ES; therefore, steroids may be administered to at-risk patients (i.e. autologous peripheral blood [PB]SCT) even if the diagnosis is not fully established. In that case, lower doses, given either as iv or po, have been used between days +4 to +14.

ES in pediatrics: The HSCT nurse working in the pediatric Unit should know that ES is an important cause of increased morbidity/mortality in children, especially in those who received autologous PBSC infusion for solid tumors and in non-hematological conditions.

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- **Internal revision by** Prof. Dr. Petr Sedláček, Charles University, Prague, Czech Republic;

Dr. Jaime Sanz Caballer, La Fe University, Valencia, Spain

- **External revision by** Prof. Dr. Wolfram Ebell, Charite University, Berlin, Germany

- **Edited by** Corinne Can