Engraftment Syndrome after Autologous Stem Cell Transplantation: An Update Unifying the Definition and Management Approach

Robert Frank Cornell1,*, Parameswaran Hari2, William R. Drobyski2

1 Division of Hematology and Oncology, Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee
2 Division of Hematology and Oncology, Department of Internal Medicine, The Medical College of Wisconsin, Milwaukee, Wisconsin

ABSTRACT
Engraftment syndrome (ES) encompasses a continuum of perengraftment complications after autologous hematopoietic stem cell transplantation. ES may include noninfectious fever, skin rash, diarrhea, hepatic dysfunction, renal dysfunction, transient encephalopathy, and capillary leak features, such as noncardiogenic pulmonary infiltrates, hypoxia, and weight gain with no alternative etiologic basis other than engraftment. Given its pleiotropic clinical presentation, the transplant field has struggled to clearly define ES and related syndromes. Here, we present a comprehensive review of ES in all documented disease settings. Furthermore, we discuss the proposed risk factors, etiology, and clinical relevance of ES. Finally, our current approach to ES is included along with a proposed treatment algorithm for the management of this complication.

INTRODUCTION
Engraftment syndrome (ES) was first defined by Lee et al. [1] in a retrospective analysis of 248 patients with cancer undergoing autologous stem cell transplantation (ASCT). Fifty-nine percent of patients developed a skin rash and noninfectious fever, with a median onset at 7 days post-ASCT. Capillary leak, pulmonary infiltration, and hypoxia were also commonly observed. ES has been documented in patients undergoing ASCT or syngeneic SCT for multiple myeloma, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin abnormalities) syndrome, light chain amyloidosis, lymphoma, breast cancer, and multiple sclerosis.

ES is now considered to be a formidable complication after ASCT [2-4]. Although most cases of ES are mild and resolve spontaneously or with corticosteroid therapy, ES can occasionally be fatal. Although ES has been documented in the transplant literature for more than 45 years, the etiology of this syndrome remains incompletely understood. Updated diagnostic criteria are necessary to standardize future research in ES. Here, we review the literature on ES and related syndromes and discuss potential risk factors, underlying mechanisms, and clinical relevance of ES. Furthermore, we include our current management approach for the diagnosis and treatment of ES.

DIFFERENTIAL DIAGNOSIS OF ES
The clinical features of ES have been defined according to diagnostic criteria of and Maiolino et al. [5] and Spitzer [6]. The Spitzer criteria were developed from a broad literature review of ES-like syndromes in patients who had undergone autologous, syngeneic, and allogeneic SCT. According to Spitzer, the major criteria for ES were fever (≥101°F), erythrodermatous rash over more than 25% of the body not linked to medication, and noncardiogenic pulmonary edema. Secondarily, ES is characterized by hepatic dysfunction (ie, bilirubin ≥ 2 mg/dL or a 2-fold increase in transaminase over baseline), renal insufficiency (ie, 2-fold increase in serum creatinine over baseline), weight gain (ie, 2.5% increase), and unexplained transient encephalopathy. A diagnosis of ES requires the presence of all 3 major criteria or 2 major and 1 or more minor criteria within 96 hours of neutrophil engraftment (Table 1). The Maiolino criteria were developed from a single-center review of 125 patients who had undergone autologous SCT. According to Maiolino et al., ES is defined as the development of a noninfectious fever in combination with diarrhea, rash, or pulmonary infiltrates within 24 hours of engraftment (Table 1).
Other studies have described more liberal timing for the development of ES. Capizzi et al. [7] retrospectively assessed signs of ES in ASCT patients who developed periengraftment respiratory distress syndrome and found that symptoms occurred within 5 days before or 4 days after engraftment. Dispensieri et al. [8] and Carreras et al. [2] found that symptoms of ES were evident within 7 days of neutrophil engraftment. Our group has found that symptoms most commonly occur from 3 days before to 7 days after engraftment [9].

Although no definitive biomarkers of ES have been identified, elevated levels of C-reactive protein have been associated with ES [2,10]. A fairly recent case report suggested that expression of elafin, a protein secreted by epithelial cells in response to IL-1 and tumor necrosis factor-α, may be an early biomarker of ES [11]. In more severe cases of ES, the diagnosis can be confirmed using a skin or colonic biopsy to assess histology and mononuclear cell infiltrates [12-16].

### ES: A SPECTRUM OF DISEASE SEVERITIES

Use of multiple nomenclatures in the ES literature has complicated the field. ES has been used synonymously with capillary leak syndrome, autoagression syndrome, periengraftment respiratory distress syndrome, and autologous graft-versus-host disease (AGVHD) [7,17-19]. Each of these syndromes encompasses all, or a subset, of symptoms that have been attributed to ES (Figure 1). Although the ES nomenclature appears to be widely accepted, the use of the term "AGVHD" and the relationship between AGVHD and ES is still debated.

Rappeport et al. [19] first described evidence of an acute cutaneous graft-versus-host–like disorder after syngeneic bone marrow transplants between identical twins for leukemia. Hood et al. [20] reported a similar response in patients undergoing either autologous or syngeneic bone marrow transplant for leukemia or lymphoma. Skin biopsies, taken 6 to 62 days post-transplant, showed histologic signs of GVHD with features of altered polarity, dyskeratosis, and basal vacuolization, with or without mononuclear cell infiltration [19-21]. Although AGVHD cases involving only the skin are typically self-limiting or managed with corticosteroids, more severe cases of AGVHD may affect the gastrointestinal (GI) tract and liver [12,13,20,22-24]. In 1 study, GI AGVHD occurred in 13% of ASCT patients and was defined by persistent symptoms, mucosal abnormalities, and the presence of apoptotic crypt cells, with or without lymphoid infiltrates, upon histologic examination [23]. In a subset of these studies, rash and/or fever were noted in conjunction with GI and liver involvement [13,22,24].

Despite overlapping symptoms observed in ES and AGVHD, some investigators view AGVHD and ES as distinct syndromes. For example, in a recent review of ES in the context of both autologous and allogeneic transplantation, Spitzer [25] suggested that ES be defined as noninfectious fever, capillary leak, and rash in the absence of histologic evidence of GVHD. The diagnosis of ES, rather than AGVHD, in past literature may be due to the lack of a tissue biopsy confirming classic GVHD pathology. In an attempt to unify the field, we propose that all forms of AGVHD (ie, cutaneous, GI, and liver) be included under the umbrella of “engraftment syndrome” (Figure 1). We encourage investigators and clinicians, henceforth, to note the severity of ES based on clinical symptoms and histologic evidence of immune involvement.

### ES IN MULTIPLE MYELOMA

In a retrospective analysis by Katz et al. [26] of 90 patients with multiple myeloma who received ASCT after melphalan therapy, 10% of patients developed ES according to the Spitzer or Maiolino criteria. All patients developed a noninfectious fever, and 8 of 9 had diarrhea. A skin rash was evident in 4 patients, whereas pulmonary infiltrates were seen in 6 patients. Three of 4 patients who developed hypoxia responded to high-dose steroids, whereas the remaining patient died of multisystem failure. This patient did not receive steroid therapy until day 17. The incidence of ES reached 29% (13/45) in Maiolino et al.’s cohort of patients with myeloma [5].

Giralt et al. [27] reported 14 patients with myeloma who developed varied degrees of ES/AGVHD after ASCT and cyclosporine (CsA) treatment. Specifically, 10 patients developed mucositis, 8 patients developed kidney or liver complications, and 4 developed cardiac problems. Histologic signs of acute GVHD were evident in 7 patients. One patient was diagnosed with clinically and histologically evident GVHD and was responsive to steroid therapy. In our
ES AND POEMS SYNDROME

In a retrospective analysis of 30 POEMS patients who underwent ASCT, fever, diarrhea, weight gain, and rash were observed in 93%, 77%, 53%, and 43% of patients, respectively [8]. ES was found to occur in 27% to 47% of patients depending on the criteria used [8]. The onset of ES symptoms occurred at a median of 9 days. When the required time to engraftment, based on Maiolino and Spitzer criteria, was broadened, the rate of ES surpassed 50%. The authors suggested that these patients might be highly susceptible to ES because of a pre-existing aberrant cytokine milieu (vascular endothelial growth factor, tumor necrosis factor-α, IL-1β) that is exaggerated by ASCT [8].

Jimenez-Zepeda et al. [28] reported the outcome of 8 patients with POEMS who had undergone ASCT. In contrast to the previous study, only 37.5%, 12.5%, 25%, and 50% of patients developed fever, diarrhea, weight gain, and rash, respectively. Here, none of the patients developed ES. The onset of ES symptoms was 5 to 13 days post-transplant. This syndrome was defined by the development of a skin rash that presented 5 to 13 days post-transplant. This ASCT-related skin rash was more frequently observed in patients with breast cancer (20/30; 67%) compared with patients with lymphoma (3/12; 25%). Fever was evident in 18 patients and was more prevalent in the breast cancer cohort (57% versus 8%). Six of 10 patients showed evidence of grades I to II GVHD by skin biopsy [18].

In a large retrospectively analysis of 452 lymphoma patients, Keung et al. [31] found evidence of ES or AGVHD in 40 of 452 patients (9%) after ASCT. We observed a frequency of 10% in our retrospective analysis of 170 patients with lymphoma [9]. ES has also been documented in patients undergoing ASCT for multiple sclerosis. Carreras et al. [32] noted the development of ES, characterized by noninfectious fever, skin rash, and weight gain, in 3 of 15 patients (20%) undergoing ASCT for multiple sclerosis. ES symptoms were readily resolved with corticosteroid therapy in these patients. Although ASCT is commonly used in cases of autoimmune disease, corticosteroids are regularly used as a maintenance therapy in these patients and may prophylactically reduce the risk of ES.

RISK FACTORS FOR ES

Elucidation of the risk factors for ES has been hindered by variations in patient populations, subject number, pretreatment regimens, and lack of clearly defined disease criteria. Numerous risk factors for ES have been suggested in the literature. A correlation with female gender has been suggested but has not been consistent in all reports [2,33]. In their initial definition of ES, Lee et al. [1] noted a positive correlation between post-transplant granulocyte colony-stimulating factor (CSF) therapy and development of ES; however, this association has not been confirmed in more recent studies [18]. Akesheh et al. [34] found that ES was more common in breast cancer patients who received granulocyte-macrophage CSF (8/10) compared with granulocyte CSF (4/9). Similarly, a recent presentation at the American Society for Blood and Marrow Transplantation tandem meetings in San Diego regarding patients undergoing ASCT for myeloma suggested that granulocyte-macrophage CSF treatment was associated with a higher risk of ES (28% versus 3%; odds ratio, 12.5; P = .001) [35]. Conflicting reports have been published assessing the role of CD34+ cell number and engraftment rate in development of ES [9,33,34,36]. Of note, a comparison of CD34+ donor cells from patients who developed ES/AGVHD (n = 9) versus those who did not (n = 42) revealed increased expression of GATA-2 and CD130 and decreased expression of CXCR4, suggesting the phenotype of donor cells may play a role [37].

A number of studies have attempted to link the development of ES with various pretreatment regimens. Although Ravoet et al. [36] showed a correlation with the use of busulfan, González-Vicent et al. [38] found the opposite to be true. Jimenez-Zepeda et al. [28] suggested that...
cyclophosphamide pretreatment was responsible for the reduced incidence of ES in patients with POEMS. The interpretation of these results was complicated by the fact that all patients also received prednisone before ASCT [28]. However, in support of their findings, our assessment of pre-treatment regimens in patients with myeloma or lymphoma revealed that cyclophosphamide exposure was associated with reduced risk for ES [9]. Of interest, Carreras et al. [2] showed in a broad spectrum of patients that a less aggressive history of chemotherapy was associated with a higher risk of ES. In line with this theory, Moreb et al. [18] found that patients undergoing ASCT for breast cancer were more likely to develop ES if they had previously undergone only a single round of chemotherapy or radiotherapy. Furthermore, in patients with myeloma, previous exposure to bortezomib or lenalidomide, rather than broad cytotoxic chemotherapies, was linked to a higher risk of ES [9]. Future large, multicenter studies using the current criteria are necessary to more accurately define the risk factors for ES across the broad spectrum of patients undergoing ASCT.

MECHANISMS OF ES

The mechanisms responsible for ES/AGVHD development are poorly understood. Although a number of studies suggest that ES can be reversed by corticosteroid therapy, controlled trials have not been performed to directly assess the benefit of corticosteroids [39]. Nevertheless, a number of studies in animal models and humans suggest that the immune system plays a role in the development of ES, despite the absence of HLA and minor histocompatibility antigen mismatch.

Early work in the Lewis rat model showed that a GVHD-like syndrome occurred after transplantation of syngeneic bone marrow into irradiated recipients that received CsA post-transplant. Specifically, irradiated rats received a bone marrow graft and were treated with CsA for 20 to 40 days post-transplant after engraftment was complete. Syngeneic GVHD (SGVHD) developed 12 to 40 days after the last CsA treatment [40-42]. In this model, SGVHD was delayed in the absence of CD4+ T cells and completely inhibited in the absence of CD8+ T cells [43,44]. Furthermore, the authors showed that MHC-II-specific antibodies significantly delayed the development of SGVHD [44]. Analysis of the TCR repertoire in this model revealed that Vβ8.5 T cells were predominant in SGVHD lesions and more frequent in rats treated with CsA, suggesting that T cell selection is skewed in the presence of CsA [45]. In support of this hypothesis, CsA is known to alter T cell development and selection in the thymus [46]. Induction of SGVHD required that the recipient undergo high-dose irradiation and CsA treatment, and transfer of the disease required an irradiated recipient. Of interest, SGVHD was abrogated if the disease-promoting T cells were transferred with CD4+ T cells from untreated normal littermates [47]. These studies suggest that a radiation-sensitive CD4+ T cell is necessary for controlling the development of SGVHD.

A number of clinical trials were designed based on the knowledge gained from the Lewis rat model. In an early study by Jones et al. [48], CsA appeared to induce cutaneous GVHD in 5 patients after autologous transplant. Of interest, peripheral blood lymphocytes isolated post-transplant displayed cytotoxic capacity against autologous lymphocytes that were recovered from peripheral blood before the start of treatment. This autoreactivity was not observed in lymphocytes isolated from peripheral blood after resolution of AGVHD or in patients not induced with CsA. Blocking antibodies specific for MHC-II and the invariant chain (Call II-associated invariant chain [CLIP]) inhibited T cell cytotoxicity ex vivo [48,49]. Thus, in agreement with the rat model, CsA-induced AGVHD depends on recognition of MHC-II, presumably by T cells that hold a relatively high affinity for self-MHC and have escaped negative selection. To further investigate the role of the T cell response in AGVHD, Massumoto et al. [50] compared the incidence of AGVHD in patients before or after treatment with IL-2. IL-2 treatment was given for 5 consecutive days 25 to 58 days post-transplant. The incidence of AGVHD increased from 30% (3/10) at baseline to 79% (11/14) after treatment with IL-2. In this scenario IL-2 may have enhanced an ensuing autoreactive T cell response or encouraged a break in tolerance. Importantly, in the absence of a control group, it is difficult to determine whether this delayed presentation of AGVHD was mediated by IL-2 [50]. Although CsA induction studies of SGVHD/AGVHD provided valuable insight into the mechanisms of the disorder, the penetration of CsA-induced AGVHD is highly variable in humans, suggesting that genetic variability and disease history in patients play an important role.

In line with the Lewis rat model, Rappeport et al. [19] hypothesized that suppressive T cells, perhaps analogous to regulatory T cells (Tregs), would be eliminated by irradiation and prior chemotherapy in patients undergoing syngeneic or ASCT. In the absence of these suppressive T cells, autoreactive T cells would be free to target “self” in the immune-ablated graft recipient [19,51]. Of interest, mobilization of stem cells with cyclophosphamide is known to enrich for Tregs, whereas lenalidomide has been shown to inhibit Treg proliferation and suppressive function in vitro [52,53]. The immune-modulatory effects of these pretreatment regimens may explain the respective negative and positive associations with risk of ES. A detailed analysis of in vivo immune modulatory effects of broad cytotoxic regimens and more targeted therapies (ie, bortezomib and lenalidomide) may shed light on the role of immune ablation in ES.

Engraftment of neutrophils and other myeloid derived cells generally occurs within 2 weeks, whereas T cell engraftment is not complete until 2 months after autologous transplant with CD34+ peripheral blood stem cells [54]. ES is defined, in part, by early presentation of symptoms that coincide with neutrophil engraftment. Surprisingly, the presence of neutrophils and other innate immune cells in skin grafts has rarely been assessed. Kennedy et al. [55] noted that AGVHD was evident in their CsA-treated patients before the appearance of leukocytes in the blood. This is in sharp contrast to the rat model of SGVHD where T cells are fully reconstituted before CsA treatment. Lymphocytic infiltrates have been noted in biopsies from patients with more aggressive AGVHD. In the study by Goddard et al. [22], the biopsy was taken 41 days post-transplant when T cells reconstitution would be nearly complete. Our group has also noted lymphocytic infiltrates at 26 days post-transplant [13]. Lee et al. [1] performed immunohistochemistry to characterize infiltrating immune cells in skin biopsies from patients who developed ES after bone marrow or peripheral stem cell transplants. Perivascular mononuclear cells infiltrates were composed primarily of cells expressing CD2 (natural killer [NK] and T cells), CD4 and CD3 (T cells), and CD5 (B and T cells), and showed low levels of CD8 (T, NK, and dendritic cells), CD16 (neutrophils and NK cells), and CD56 (NK cells). Importantly, the presence of contaminating lymphocytes in the transplant was not assessed and the time of biopsy acquisition was not reported [1]. A prospective, detailed
analysis of the cellular infiltrate in skin biopsies following ASCT with purified CD34+ cells would shed light on the role of both the innate and adaptive immune response in ES development and progression.

Overall, mechanistic studies of ES in humans have been sparse. We suggest that, even in the absence of HLA mismatch, the principles of allogeneic GVHD may be applicable to ES [56] (Figure 2). Proinflammatory cytokines (ie, IL-1, tumor necrosis factor-α, and IFN-γ) and innate immune cells likely play a role in the initial stages of ES [6,57]. These cytokines predispose patients to heightened antigen presentation and T cell activation in the allogeneic setting and may contribute to a break in peripheral tolerance in the autologous setting. Spontaneous resolution in mild cases of ES likely coincides with tissue repair and completion of engraftment. More aggressive presentations of ES may occur in patients with a predisposition to self-reactivity as the lymphocytes are reconstituted. In these patients T cells that recognize self-MHC and self-peptide may evade central tolerance and become cytotoxic in the absence of effective peripheral regulation. At later stages of engraftment, peripheral regulatory mechanisms are restored, allowing spontaneous remission of symptoms. Those patients who succumb to ES may fail to generate these regulatory mechanisms. Of note, efficient Treg reconstitution has been associated with reduced risk of allogeneic GVHD [58]. Future characterization of the cytokines milieu, immune infiltrate, and Tregs in patients with ES is necessary to validate this hypothetical model.

CLINICAL IMPLICATIONS OF ES

It has been postulated that an ES-associated graft-versus-tumor effect may ensue in patients undergoing ASCT, contributing to improved survival in cancer patients [59]. Survival outcomes are rarely reported in the ES literature. In a single case report, Byrne et al. [60] reported a possible graft-versus-myeloma effect, as evidenced by a reduction in Bence-Jones protein excretion to .08 g/dL and <2% plasma cell infiltration in a bone marrow aspirate. In sharp contrast to this case, a review of 461 lymphoma patients by Keung et al. [31] failed to show improved survival in patients who developed ES and instead revealed an association between ES/GVHD and the development of a secondary myelodysplastic syndrome. Similarly, Khan et al. [61] studied the association between disease outcome and ES in 85 patients with breast cancer and reported that disease-related mortality was higher in relapsed patients who developed ES during ASCT. Our review of 591 patients undergoing ASCT for myeloma or lymphoma found no association between development of ES and mortality, relapse, or survival [9].

Early studies, performed shortly after the discovery of AGVHD and SGVHD, attempted to augment this phenomenon to generate an antitumor effect [47]. As seen in the rat models of CsA-induced AGVHD, Yeager et al. [62] reported that 15 of 19 patients (79%) undergoing SCT for chronic myelogenous leukemia developed ES/GVHD after post-transplant treatment with 1 mg/kg CsA. Kennedy et al. [55] found that CsA induced ES/GVHD in a dose-dependent manner in patients with breast cancer. One of 7 (14%), 21 of 31 (68%), and 12 of 13 (92%) patients developed ES/GVHD when treated with 1 mg/kg, 2.5 mg/kg, or 3.75 mg/kg CsA, respectively. Although the rate of ES/GVHD induction with 2.5 mg/kg CsA was not increased with the addition of IFN-γ (56%), a larger proportion of patients developed a more severe rash (grades 2 and 3) [63].

A small study (n = 17) by Ratanatharathorn et al. [64] suggested that IFN-α treatment could enhance CsA-induced ES/GVHD. Specifically, the incidence of grades II/III GVHD increased from 50% (2/4) in CsA-induced patients to 100% (8/8) in those receiving CsA in combination with IFN-α. Of note, all 4 patients who received IFN-α alone also developed grades II/III GVHD [64]. Bolanos-Meade et al. [65] reported the first controlled trial comparing untreated or CsA-induced patients. Fifty-one patients with lymphoma were evaluated in a prospective trial for any benefit of CsA-induced AGVHD. Unfortunately, only 4 of the 24 patients who received CsA developed AGVHD, and no conclusions could be drawn from such a small population.

Figure 2. Hypothetical mechanisms of ES. Proposed stages and severities of ES after ASCT are modeled. Predicted cytokine and leukocyte involvement is shown for each stage. Neutrophil and T cell engraftments are complete by days 14 and 56, respectively. TNF indicates tumor necrosis factor; Mac, macrophage; N, neutrophil; DC, dendritic cell; CD4, helper T cell; CD8, cytotoxic T cell; B, B cell; NE, normal epithelium.
CONTROVERSY OVER THE EXISTENCE OF ES

Investigators who question the premise that ES is a true clinical entity have introduced additional controversy in the field. The major arguments for this stance are that ES is an artifact of nontransplant-related complications (ie, infection and pretreatment toxicity), that the features of ES and AGVHD overlap, and that the incidence of ES is not uniform among the disease subtypes [66]. Although it is possible that some cases of ES may be explained by post-transplant complications, in the most stereotypical cases of ES, the onset of fever, rash, and diarrhea invariably occurs during or after neutrophil engraftment when the risk of infection is actually decreased. In our experience many of these patients failed to exhibit evidence of infection before or concurrent with the development of ES. Furthermore, ES does not occur during bone marrow recovery in a nontransplant setting (ie, chemotherapy), suggesting that stem cell transplant is required. Second, in those patients for whom biopsies are performed for evaluation of diarrhea, the pathologic findings are typically indistinguishable from what is observed with allogeneic GVHD. As discussed above, we believe ES encompasses a continuum of disease severities, including more severe, sometimes fatal, cases with histologic evidence of GVHD. We suggest that the overlap of symptoms with AGVHD, on the contrary, proves the existence of ES. This controversy is rooted in semantics of nomenclature rather than in evidence of clinical relevance. Third, the lack of a uniform incidence across disease subtypes can be explained by differences in the underlying disease, prior therapy, and inherent patient susceptibility. We would concur with others that the pathophysiology of ES requires further elucidation. Our view remains that ES is a complication that occurs in a significant percentage of ASCT recipients. Appropriate awareness and management of this problem is essential to reduce patient morbidity and, in some cases, mortality.

OUR MANAGEMENT APPROACH TO ES

The most important aspect in management of ES is early recognition of the defined clinical features according to the Spitzer and Maiolino criteria (Table 1). It is important to recognize that a subset of patients, including those with POEMS, may have ES up to 7 days before engraftment and thus not follow these criteria [8]. Also, in patients who present with more severe symptoms, early signs of ES at the time of neutrophil engraftment may have been overlooked. In these cases a diagnosis of ES should be suspected based on the clinical criteria regardless of the timing of symptoms relative to engraftment. In our study approximately 95% of patients developed symptoms consistent with ES between 3 days before and 7 days after engraftment.

Our first step in management of suspected ES is to exclude alternative causes (Figure 3). Patients should be treated with broad-spectrum antibiotics while ruling out infection. In addition, the potential etiology for drug-induced rash should be assessed. Causes for medication-and infection-induced diarrhea should be evaluated. Features of capillary leak and fluid overload should be confirmed to be independent of i.v. fluid administration. Brain natriuretic peptide assessment can be helpful to evaluate for possible cardiac etiology. In many cases clinical features of ES will resolve spontaneously.

Figure 3. Our management approach to ES. IST indicates immunosuppressive therapy.
If symptoms are not improved after 48 to 72 hours, a diagnosis of ES should be considered. The decision to treat is based on the severity of symptoms and judgment of the treatment provider that other etiologies are excluded and treatment is warranted.

When treatment is indicated, we suggest initiation of methylprednisolone 1 to -1.5 mg/kg/day until symptoms begin to resolve, which typically occurs within 2 to 3 days, followed by a reduction to 40 to 50 mg p.o. prednisone a day for 2 to 3 days. Oral prednisone can then be tapered 10 mg every 2 to 3 days as long as symptoms continue to resolve. Alternatively, methylprednisolone may be reduced to .5 mg/kg/day, followed by a slower taper of 10 mg/day. We find that early intervention with corticosteroids is sufficient to mitigate progression to more severe manifestations [9]. If clinical features have not improved 72 hours after initiation of corticosteroids, further evaluation is warranted. In corticosteroid-refractory cases, we recommend biopsy of the site of end-organ damage: skin biopsy for skin rash, colon biopsy for severe diarrhea, and/or liver biopsy for liver function test abnormalities. If the diagnosis of ES is confirmed histologically, additional immune suppressants should be administered until symptoms subside. If an alternative etiology is found, patients should be managed accordingly.

FUTURE DIRECTIONS

Future studies are required to better characterize the risk factors and underlying mechanisms in ES. Development of a grading system, such as that for National Institutes of Health criteria for acute and chronic GVHD, would be a useful guide for determination of management decisions for ES. Basic immunohistochemistry studies are necessary to identify the specific leukocyte populations (eg, myeloid lineage, NK cells, Tregs, CD4+ T cells, and CD8+ T cells) contributing to early and late stages of ES. Larger prospective analyses of elafin and inflammatory cytokines in peripheral blood may confirm the role of such biomarkers in predicting ES. New biomarkers may be identified through molecular profiling of archived hematopoietic stem cells from ES-positive and ES-negative patients. Collectively, these studies will improve diagnosis and treatment of ES.

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