



## REVIEW

# Chronic graft-versus-host disease

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### KEYWORDS

Chronic graft versus host disease;  
Hematopoietic stem cell transplantation;  
Cyclosporine;  
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**Summary** Chronic graft versus host disease (GVHD) remains today one of the most vexing late complications of allogeneic stem cell transplantation. Occurring a minimum of 100 days following stem cell transplantation, approximately 50% of patients will experience some degree of chronic GVHD. Host-reactive lymphocytes of donor origin are the cells responsible for the “alloimmune” attack. The increased use of hematopoietic stem cells collected from the peripheral blood instead of bone marrow and the increasing age of stem cell transplant recipients has led to a higher incidence of chronic GVHD. Chronic GVHD most commonly affects the skin, liver, eyes or the mouth, however multiple other sites may also be affected. Chronic GVHD and the medications used to treat it result in a profoundly immunocompromised state. Death due to severe chronic GVHD is usually a consequence of infectious complications. Standard treatment for severe chronic GVHD is a combination of cyclosporine and prednisone. An alternating day regimen of these two agents prolongs survival and reduces drug-related adverse events. Topical therapy to affected areas is preferred for patients with mild disease. The 10-year survival of patients with mild chronic GVHD is approximately 80%, but is less than 5% for patients affected by severe chronic GVHD.

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## Background

Due to a poor understanding of the human leukocyte antigen (HLA) system, early human transplants of allogeneic marrow were often complicated by graft versus host disease (GVHD).

Features were remarkably similar to those seen in animal studies of GVHD<sup>1</sup> and to reports of GVHD developing in immunodeficient children who received blood transfusions.<sup>2</sup> The term *acute* GVHD describes a distinctive syndrome of dermatitis, hepatitis, and enteritis developing within 100 days of allogeneic hematopoietic stem cell transplantation. The term *chronic GVHD* describes a more pleiotropic syndrome that develops after day 100. This review will focus on the syndrome of chronic GVHD.

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## Pathophysiology

Alloreactivity forms the basis for the pathogenesis of chronic GVHD, however the exact phenotype and origination of the alloreactive cells remains somewhat ambiguous. Mature, donor-derived alloreactive T-cells that are transplanted with the hematopoietic stem cells play a key role in both acute and chronic GVHD. In both experimental and clinical studies of chronic GVHD, thymic atrophy, lymphocyte depletion, and loss of thymic epithelial secretory function are observed.<sup>3–6</sup> Thus, aberrant thymopoiesis resulting in retention of autoreactive clones may occur. The current animal models of chronic GVHD implicate the T-helper 2 (Th2) cell as the primary offending cell type. In human chronic GVHD, however, CD4+ cells with both Th2 and Th1 polarity have alloreactive properties.<sup>7</sup> Similarities of clinical features of chronic GVHD and several autoimmune diseases have been commonly observed. Autoantibody formation has been noted in experimental models of chronic GVHD<sup>8</sup> and clinical studies also report these findings.<sup>9–11</sup> Occurrence of antinuclear, anti-double-stranded DNA, and anti-smooth muscle autoantibodies ranges in frequency from 11% to 62% of patients with chronic GVHD, while anticytoskeletal and antinucleolar antibodies have also been detected.<sup>12,13</sup> Although specific nucleolar phosphoproteins have been identified as targets of GVHD,<sup>14</sup> the pathogenetic role for antibodies in chronic GVHD is still poorly defined.<sup>15</sup>

## Incidence and predictive factors

### Donor–recipient factors

Among patients who survived 150 days after allogeneic BMT, chronic GVHD was observed in 33% of HLA-identical sibling transplants, in 49% of HLA-non-identical related transplants, and in 64% of matched unrelated donor transplants.<sup>16</sup> Data from single-institution and registry studies indicate that the incidence of chronic GVHD may be as high as 80% in one-antigen HLA-non-identical unrelated transplants. Among more homogeneous ethnic populations sharing minor histocompatibility antigens, rates of chronic GVHD are lower.<sup>17</sup> In addition to HLA disparity, prior acute GVHD and increasing patient age are independent factors associated with an increased risk of developing chronic GVHD.<sup>18,19</sup> Among recipients of HLA-identical marrow who survived beyond day 150, the probability for development of chronic

GVHD was 13% in children less than 10 years old, 28% in adolescents 10–19 years old, and 42–46% in adults over age 20.<sup>16</sup> In contrast, there appeared to be little reduction in GVHD in young patients given HLA-non-identical and unrelated marrow. However, among recipients of unrelated marrow, increasing donor age is associated with an increased incidence of chronic GVHD.<sup>20,21</sup>

There have been conflicting reports regarding the relationship between hematopoietic growth factor use (G-CSF and GM-CSF) following bone marrow stem cell transplantation and GVHD. A meta-analysis of 18 studies and 1198 patients failed to reveal a difference in incidence of acute or chronic GVHD in patients who did or did not receive hematopoietic growth factors.<sup>22</sup> In contrast, Ringden and colleagues retrospectively sampled registry data from the European Group for Blood and Marrow Transplantation and found that for recipients of bone marrow stem cell grafts, the incidence of acute and chronic GVHD was increased for those treated with hematopoietic growth factors (relative risk 1.33;  $P = 0.007$  and 1.29;  $P = 0.03$ , respectively). This study found no relationship between growth factor use and GVHD in patients who received a peripheral blood stem cell graft.<sup>23</sup>

### Source and dose of hematopoietic cells

Cord blood HCT is associated with low rates of chronic GVHD.<sup>24</sup> Among allogeneic peripheral blood stem cell transplant recipients, higher CD34+ cell doses ( $>8.0 \times 10^5$ /kg) were associated with significantly increased risk (RR 2.3) of clinical extensive chronic GVHD.<sup>25</sup> Initial reports suggested that no increased incidence of chronic GVHD when stem cells are harvested from cytokine mobilized peripheral blood instead of the bone marrow<sup>26,27</sup>, but subsequent studies revealed more frequent chronic GVHD in patients receiving peripheral blood stem cell grafts.<sup>28–33</sup> Meta-analysis indicates the magnitude to be 1.66 RR ( $P = 0.001$ ) of developing chronic GVHD with peripheral blood stem cell grafts.<sup>34</sup>

## Clinical features

### Dermal

Two types of cutaneous involvement have been described. An early phase resembles lichen planus. Lesions may be scanty or evanescent, ranging from polygonal papules to more typical lesions. During later phases, poikiloderma is observed. In patients

with the localized type of histology, epidermal atrophy and dense focal dermal fibrosis are noted in the absence of significant inflammation. In other patients, a generalized type of histology is noted, with inflammation in eccrine coils and pilar units resulting in fibrosis throughout the dermis and adnexal structures. Generalized scleroderma may lead to joint contractures and severe debility.

The tempo of dermal abnormalities may show wide variation. In some patients, erythema, hyperkeratosis, and desquamation develop rapidly, sometimes after solar exposure. Erythema may begin in the malar area and resemble lupus erythematosus but soon spreads to sun-exposed and sun-shielded areas. In others, the onset is insidious, with patchy hypo- and hyperpigmentation, reticular mottling, perifollicular papules, and papulosquamous plaques. Total leukoderma has also been observed.<sup>35</sup> Guttate lesions appear on the trunk as shiny indurated areas, or can be localized to areas of pressure-point trauma, prior irritation, injury, zoster, or irradiation. Rarely, vesicles, bullae, or bullous pemphigoid lesions have been reported.<sup>36</sup> Alopecia and nail loss are common, and regrowth of body hair and return of sweat gland function usually herald disease improvement.

## Hepatic

Liver function tests manifest predominantly cholestatic abnormalities. The degree of hyperbilirubinemia correlates less closely with clinical outcome than in patients with acute GVHD.<sup>37</sup> Although reported, development of portal hypertension, cirrhosis, and death from hepatic failure are surprisingly rare despite years of hepatic abnormalities.<sup>38</sup> The differential diagnosis of late hepatic abnormalities is broad and includes viral infection, hepatotoxic drug reactions, gallstones, and infiltrative hepatic abnormalities, including fungal infection and neoplastic disease. Liver biopsies are helpful in establishing a diagnosis. Naturally occurring primary biliary cirrhosis and chronic GVHD show similarities in bile duct damage, ocular and oral sicca syndrome.<sup>39</sup>

## Ocular

Ophthalmic symptoms of keratoconjunctivitis sicca include burning, irritation, photophobia, and pain. Tear function is evaluated by Schirmer's testing and fluorescein biomicroscopy of the cornea. Punctate keratopathy can range from minimal stippling to massive erosions. Even in the absence of symp-

toms, patients should be screened for ocular sicca and started on artificial tear replacement if indicated. Ligation of the lacrimal puncti may be of benefit to conserve corneal wetting in the severely dry eye. A more common cause of impaired vision acuity is the development of cataracts following BMT.<sup>40</sup> Analyses found that use of prednisone after day 100 to treat chronic GVHD and use of TBI in conditioning promote cataract formation. Fortunately, cataract repair can be performed safely even in the presence of ocular sicca.

## Oral

Oral dryness, sensitivity to acidic or spicy foods, and increasing pain after day 100 strongly suggest the development of chronic GVHD.<sup>41</sup> In a prospective study of 60 long-term survivors after allogeneic BMT, oral atrophy, erythema, and lichenoid lesions of the buccal and labial mucosa were significantly correlated with development of chronic GVHD.<sup>41</sup> A common clinical error is to confuse lichen planus-like lesions of chronic GVHD with oral candidiasis. Lichenoid reactions range from fine white reticular striae on buccal surfaces to large plaques on the buccal surface or the lateral tongue. Oral herpes simplex can exacerbate the pain associated with chronic GVHD and serial viral cultures may be required to establish the diagnosis and direct appropriate antiviral therapy.

## Pulmonary

Several non-infectious pulmonary complications can be associated with chronic GVHD.<sup>42,43</sup> Bronchodilator-resistant obstructive lung disease can be a clinical feature of chronic GVHD<sup>44,45</sup> and histopathology reveals characteristic lesions of obliterative bronchiolitis. Patients with chronic GVHD and hypogammaglobulinemia or IgG subclass deficiencies appear to be at increased risk for late obstructive airway disease.<sup>46</sup> In a large retrospective survey of bronchiolitis obliterans following stem cell transplantation, the five-year survival was only 10% in affected patients, compared to 40% in those who were unaffected by bronchiolitis.<sup>47</sup>

## Gastrointestinal

Intestinal involvement is uncommon in chronic GVHD. Dysphagia, pain, and insidious weight loss may be presenting symptoms of chronic GVHD of the esophagus.<sup>48</sup> Manometric studies demonstrate poor acid clearance, and motor abnormalities range from aperistalsis to high-amplitude

contractions. Radiographic findings feature web formation, ring-like narrowings, and tapering of structures in the mid and upper esophagus.<sup>49</sup> It was possible to distinguish esophageal involvement of chronic GVHD from that of naturally occurring progressive systemic sclerosis in a coded review of autopsy material.<sup>48</sup> Nerve fibers and silver stains of the myenteric plexus were of normal appearance in all patients with chronic GVHD, in contrast to findings in patients with scleroderma.

### Other manifestations of chronic GVHD

Vaginitis and vaginal strictures have been noted in women with chronic GVHD.<sup>50</sup> In a study of women examined 1 year after allogeneic BMT, the gynecological effects of chronic GVHD could be distinguished from those of primary ovarian failure due to TBI.<sup>51</sup> Recurrent sterile effusions have also been reported in patients with chronic GVHD.<sup>52</sup> Less easy to attribute to chronic GVHD were the effects on renal and marrow function in long-term survivors.<sup>53–55</sup> In one study, chronic GVHD was associated with poor growth of hematopoietic progenitor cells.<sup>56</sup> In other reports, autoimmune-like thrombocytopenia and anemia have been described.<sup>57–59</sup> Hypogammaglobulinemia and factor VIII inhibitors have also been noted in patients developing GVHD.<sup>60,61</sup> The treatment of chronic GVHD with long-term corticosteroids in turn increases the risk of cataract formation, avascular necrosis, and osteoporosis.<sup>60,62,63</sup> In children, weight loss and growth arrest (runting) are observed during active GVHD, and growth and development abnormalities improve when the disease resolves and corticosteroid therapy is withdrawn.<sup>64</sup>

## Diagnosis and grading

### Staging

Clinicians rely on histological review of oral and skin biopsies to diagnose disease and gauge response to therapy.<sup>65</sup> Table 1 presents a summary of the clinicopathological classification of chronic GVHD.<sup>66</sup> Patients with *limited* disease involving the skin or liver have a favorable course, even if untreated.<sup>37</sup> In contrast, patients with *extensive* disease involving multiple organs have an adverse natural course. This staging system is easily derived and highly reproducible when tested in an international survey.<sup>67</sup>

**Table 1** Classification of GVHD.

Limited chronic GVHD	
Either or both:	
1.	Localized skin involvement
2.	Hepatic dysfunction due to chronic GVHD
Extensive chronic GVHD	
Either:	
1.	Generalized skin involvement, or
2.	Localized skin involvement and/or hepatic dysfunction due to chronic GVHD
Plus:	
3a.	Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or
b.	Involvement of eye (Schirmer test with <5-mm wetting), or
c.	Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or
d.	Involvement of any other target organ

### Grading

Morbidity and mortality are highest in patients with *progressive* onset of chronic GVHD directly following acute GVHD, intermediate in those with a *quiescent* onset following resolution of acute GVHD, and lowest in patients with a *de novo* onset.<sup>37</sup> Approximately 20% of patients with chronic GVHD have a *de novo* onset without prior acute GVHD. Since the classification in Table 1 does not capture prognostic outcome based on organ involvement or type of chronic GVHD onset, investigators have proposed additional classifications. The Baltimore group found that non-relapse mortality after the diagnosis of chronic GVHD was independently associated with extensive skin involvement (>50% body surface area), thrombocytopenia and progressive-type of onset.<sup>68</sup> Using these three risk factors, a prognostic model was created. This new prognostic model successfully predicted GVHD-specific survival when applied retrospectively to 4 separate, large datasets.<sup>69</sup> In another study which was validated with International Bone Marrow Transplant Registry and National Marrow Donor Program datasets, Karnofsky performance score (KPS), weight loss, chronic diarrhea, and skin or oral involvement were found to be key prognostic variables.<sup>70</sup>

### Diagnosis

The median time to diagnosis of chronic GVHD in HLA-identical sibling recipients is 201 days after transplant; in contrast, HLA-non-identical related and unrelated donor marrow recipients have an

earlier diagnosis and onset (159 and 133 days, respectively).<sup>16</sup> Few patients develop chronic GVHD beyond day 500. Screening studies to detect early clinical chronic GVHD are routinely conducted on all allogeneic HCT recipients 100 days after transplantation.<sup>71</sup> Even in the absence of active signs or symptoms of chronic GVHD, a positive random skin biopsy or a history of prior acute GVHD independently predicts a threefold increase in the relative risk of subsequent chronic GVHD. Analysis of day 100 screening studies in patients who received methotrexate/cyclosporine prophylaxis showed that corticosteroid-dependent acute GVHD (i.e., patients unable to taper successfully and discontinue prednisone by day 100) was the most significant factor for development of subsequent chronic GVHD.<sup>72</sup> To establish an early diagnosis of chronic GVHD, real-time monitoring of patients leaving the transplant center is of critical importance for preventing late complications and disability. Similarly, establishing an early and correct diagnosis is essential. In a referral cohort of 123 patients thought to have chronic GVHD, 7% had other disorders and 20% were found to have inactive chronic GVHD.<sup>73</sup>

## Prevention

### T-cell depletion

The risk of chronic GVHD was found to be reduced by more than 50% after T-cell depletion of HLA-identical marrow.<sup>74</sup> Overall survival, however, was not improved. Moreover, chronic GVHD was still noted in 85% of long-term survivors who received T-cell depleted marrow from unrelated donors.<sup>75</sup>

### Antibody prophylaxis

Weekly administration of IVIg through day 90 post-transplant reduced the incidence and mortality of acute GVHD.<sup>76</sup> When the same dose of 500 mg/kg IVIg was given on a monthly schedule from day 90 to day 360 post-transplant, median serum IgG levels decreased from 1600 to 900 mg/dL, and the cumulative incidence of chronic GVHD was not different from that of patients randomized not to receive IVIg.<sup>77</sup> A controlled trial performed in 109 unrelated donor BMT recipients found that individuals randomized to receive anti-thymocyte globulin in the preparative regimen had a significant reduction in grades III–IV acute GVHD.<sup>78</sup> This study also showed a reduction in chronic GVHD in those who

received ATG conditioning compared with those not who did not (39% versus 62%, respectively). Overall survival and non-relapse mortality, however, did not improve. Recently, Campath 1-H has been used by a number of investigators for both in vivo and in vitro purging of donor T-cells. The incidence of chronic GVHD was 4.4% in 24 such patients, compared to 56.3% in a historical control population.<sup>79</sup>

### Immunosuppressive drugs

In a retrospective registry review of the effect of GVHD prophylaxis on transplant outcome in patients with aplastic anemia, 5-year survivals were shown to be improved in recipients of cyclosporine or cyclosporine/methotrexate prophylaxis ( $n = 341$ ) compared with those given methotrexate alone ( $n = 254$ ).<sup>80</sup> In this non-randomized study, patients who received a cyclosporine containing regimen had a decreased risk of developing chronic GVHD. However, several other prospective trials failed to demonstrate a difference in the incidence of chronic GVHD when cyclosporine was part of the GVHD prophylactic regimen.<sup>81,82</sup> This is in marked contrast to the clear reduction in incidence of acute GVHD with cyclosporine treatment.

### Prolonged immunosuppression

Several pilot studies suggest that the incidence of chronic GVHD may be reduced when an extended course of cyclosporine prophylaxis is administered.<sup>83–85</sup> These findings are further supported by the observation that chronic GVHD usually develops during or shortly after the routine 6-month taper of cyclosporine. Additional insights were provided by a trial of 103 patients given cyclosporine/methotrexate prophylaxis: Those who had no active acute GVHD at day 60 were randomized to stop cyclosporine at day 60 ( $n = 52$ ) or day 180 ( $n = 51$ ) post-transplant.<sup>86</sup> In the former group, the onset of chronic GVHD was significantly more rapid in onset, but not significantly greater in incidence than that of the day 180 control group. Among those with no prior acute GVHD, non-relapse mortality was similar in the two groups; however, among those with prior acute GVHD, mortality was 38% in the day 60 cohort and 17% in the day 180 group. In another controlled study to test whether prolonged administration was of value in preventing chronic GVHD, individuals without clinical manifestations of GVHD on day 80 post-transplant were randomized to receive 24 months (89 patients) or to complete 6 months (73 patients)

of cyclosporine prophylaxis.<sup>87</sup> Clinical extensive chronic GVHD developed, respectively, in 39% and 51% of the patients (RR 0.76,  $P = 0.25$ ). Moreover, there were no significant differences in non-relapse mortality or survival. Thus, the need for an effective regimen to prevent chronic GVHD remains an unmet challenge to the field.

## Treatment

### Primary systemic treatment

Corticosteroid therapy has been the mainstay of therapy since chronic GVHD was first described. Table 2 lists the major trials of immunosuppressive medications for the treatment of chronic GVHD. In the pre-cyclosporine era, multiple agents such as low dose oral cyclophosphamide, procarbazine, anti-thymocyte globulin and azathioprine were tested in combination with prednisone in an attempt to improve response. None of these combinations improved non-relapse mortality. Conversely, the addition of oral cyclosporine (6 mg/kg every 12 h every other day) in patients with GVHD and thrombocytopenia (high-risk disease) appeared to improve survival.<sup>88</sup> However, infections remained a frequent cause of morbidity and contributed to transplant-related mortality in patients with high-risk chronic GVHD. The value of initial

treatment with cyclosporine + prednisone in standard-risk (platelets > 100,000/ $\mu$ L) chronic GVHD was prospectively compared to prednisone alone.<sup>89</sup> Although the combination may reduce steroid-related toxicity, there was no beneficial effect on non-relapse mortality on survival.

A report from the Baltimore group described the use of thalidomide in high-risk patients.<sup>90</sup> The three-year survival was 48% in 21 patients who received primary treatment and infections seemed to be diminished in the long-term survivors. Part of the benefit of this therapy may be due to modulation of TNF production.<sup>91</sup> The value of thalidomide has been studied in two-controlled trials of initial treatment of chronic GVHD. In one trial of standard and high-risk patients, prednisone + cyclosporine was compared with prednisone + cyclosporine + thalidomide and no clinical benefit for the addition of thalidomide was found.<sup>92</sup> Poorer outcome was seen in individuals with thrombocytopenia, progressive-type onset of chronic GVHD, unrelated and sex mismatch donors. In a placebo-controlled study enrolling high-risk patients with thrombocytopenia or progressive-type onset of chronic GVHD, administration of thalidomide (200 mg/day increasing to 800 mg/day) was associated with neutropenia and neurologic toxicity.<sup>93</sup> In that study, 92% of thalidomide and 65% of placebo patients had study drug stopped before resolution of GVHD ( $P = 0.02$ ).

**Table 2** Trials of medical management of chronic GVHD.

Sullivan et al. (1988, 395) (Standard risk)	63	PSE + Placebo vs PSE + AZ	62% (NS)	21% ( $P = 0.003$ )	61% ( $P = 0.03$ )
Koc et al. (2002, 420) (Standard risk)	145	PSE vs PSE + CSP	53% (NS)	13% (NS)	54% (NS)
Arora et al. (2001, 423) (Standard & high risk)	27	PSE + CSP vs PSE + CSP + Thal	73% (NS)		72% (NS)
Sullivan et al. (1988, 395) (High risk)	38	PSE (Placed) (thombocytopenia)	32%	58%	26%
Sullivan et al. (1988, 416) & (High Risk)	40	PSE + CSP	56%	40%	52%
Koc et al. (2000, 424) (High Risk)	26	PSE + [CSP or TACR] + Placebo vs PSE + [CSP or TACR] + Thal	23% (NS)		47% (NS)
	26		39%		49%

AZ, azathioprine; CSP, cyclosporine; GVHD, graft-versus-host disease; PSE, prednisone; TACR, tacrolimus; Thal, thalidomide. Reproduced by kind permission of Blackwell Publishing from Sullivan K. *Graft-versus-host disease*. In Blume et al., editors. *Thomas' hematopoietic cell transplantation*. 3rd ed. Oxford, UK.

## Primary topical treatment

When possible, limited chronic GVHD should be treated with topical agents since the adverse effects of systemic immunosuppressive medications may be more harmful than the GVHD. If the skin disease is localized, topical corticosteroids of varying potencies or topical tacrolimus can be beneficial. Vaginal GVHD can be managed with topical or systemic estrogen therapy with addition of topical cyclosporine for patients who continue to have vaginal pain or scarring.<sup>94</sup> Oral GVHD refractory to topical steroids was treated with tacrolimus ointment which, in one study, resulted in a 14% complete response rate and an 80% partial response rate.<sup>95</sup> Ophthalmic preparations of both prednisone and cyclosporine are available and have been successfully used to treat ocular manifestations of chronic GVHD.<sup>96</sup>

## Secondary treatment

As with acute GVHD, to date there is no clear standard salvage regimen for chronic GVHD treatment. Azathioprine, alternating cyclosporine/prednisone, high-dose pulse MP, tacrolimus and thalidomide give surprisingly similar 2–3-year survival rates (approximately 75%) for patients failing initial steroid therapy.<sup>97–100</sup> As with the primary treatment studies, significant side effects were noted with thalidomide.<sup>101</sup> For several of these regimens, approximately 30% of patients can successfully discontinue treatment after 2–3 years of salvage therapy without return of active GVHD.<sup>1</sup> Similar to thalidomide, clofazimine is used in treating leprosy and immune-mediated skin disorders. It also has activity in the cutaneous and oral lesions of chronic GVHD.<sup>102</sup> Side effects and infectious complications appear minimal and this agent may be useful as adjunctive, steroid-sparing therapy.

Other investigations have explored the use of PUVA in treating patients with refractory cutaneous chronic GVHD.<sup>103–105</sup> Dermal responses were observed in 31 of 40 patients, and some improvement was noted at extracutaneous sites.<sup>104,106</sup> Extracorporeal photopheresis has demonstrated benefit in reversing cardiac allograft rejection<sup>107</sup> and has been reported to improve oral manifestations, sclerodermatous involvement, and joint contractures in patients with refractory chronic GVHD.<sup>108–112</sup> Secondary treatment of cutaneous chronic GVHD has shown some benefit with halofuginone (an inhibitor of collagen) and etretinate (a synthetic retinoid).<sup>113–115</sup> Apparent activity in ste-

roid refractory chronic GVHD has also been reported with daclizumab (an anti-IL-2 receptor MAB) and etanercept (anti-TNF antibody).<sup>116,117</sup> Other clinical trials found responses with MMF and hydroxychloroquine.<sup>118–120</sup>

## Supportive care

Given the multitude of organs affected by both chronic GVHD and the medicines used to treat it, a multidisciplinary approach to treatment is ideal. Since it is a rare disorder, it is helpful to establish a select cadre of subspecialist who, with repeated referrals, will become more familiar with the treatment options. Severe dermal involvement of chronic GVHD may benefit from burn care management to speed re-epithelialization and closure of portals of infection. Ocular sicca may respond to retinoic acid and oral sicca to pilocarpine.<sup>121,122</sup> Neuromuscular manifestations of chronic GVHD (muscular aches, cramping, and carpal spasm) have improved with clonazepam treatment.<sup>123</sup> Liver function abnormalities in patients with refractory hepatic chronic GVHD have improved by approximately 30% following bile acid displacement therapy with ursodiol.<sup>124</sup> For patients who are receiving long-term corticosteroid therapy, estrogen replacement in women, calcium supplements, and antiosteoporosis agents should be considered for individuals at risk for bone loss and fracture.<sup>125,126</sup> The relationships between immunodeficiency, GVHD-associated immunosuppression, and infection are complex interactions which are of critical importance in the management of patients with GVHD.

## Late infections

### Spectrum of infection

Extensive chronic GVHD and the immunomodulatory medications used for treatment result in a profoundly immunocompromised state. Bacteremia and sinopulmonary infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* are common. The probability of developing pneumococcal sepsis by 10-years in patients with chronic GVHD is estimated at 14%.<sup>127</sup> Of note, none of the patients with fatal infections were taking prophylaxis for *Pneumococcus*. Late infections appear to be particularly increased in mismatched and unrelated marrow recipients. The probability of bacteremia or septicemia after

day 100 was 22% in 364 HLA-identical sibling transplant recipients and 38% in 38 unrelated transplant recipients ( $P = 0.008$ ).<sup>16</sup> Chronic GVHD and HLA non-identity contribute to this increased rate of infection in unrelated marrow recipients, as does the frequent presence of hypogammaglobulinemia.<sup>97</sup>

### Antimicrobial prophylaxis

Most BMT patients receive *Pneumocystis carinii* prophylaxis through day 120 following transplantation or for as long as they continue on chronic GVHD therapy with corticosteroids. Prophylaxis with TMP-SMX significantly reduced the incidence of late interstitial pneumonia from 28% to 8% in patients with chronic GVHD.<sup>128</sup> Given the risk for infection with encapsulated organisms, penicillin prophylaxis is recommended for at least 6 months after all immunosuppressive therapy for chronic GVHD has been discontinued.<sup>129</sup>

### Immunizations

One year following stem cell transplantation, healthy patients free of chronic GVHD are likely to respond to influenza, pneumococcal polysaccharide, inactivated poliovirus, diphtheria, pertussis, tetanus toxoid, and *H. influenzae* type b conjugate vaccines. Patients being treated for chronic GVHD who are receiving immunosuppressive therapy may or may not form an adequate antibody response.<sup>130,131</sup> Live virus vaccines such as measles, mumps, rubella (MMR); oral poliovirus; oral typhoid; and bacillus Calmette-Guerin carry risk in the immunocompromised host.<sup>129</sup> Clinical studies suggest that MMR can be given safely after the second year after transplantation in individuals who are free of chronic GVHD.<sup>132</sup>

### Prognosis

As previously noted, mortality is increased in patients with extensive disease, progressive-type onset, thrombocytopenia, impaired performance status, weight loss, and HLA-non-identical marrow donors.<sup>37,70</sup> The Baltimore Team reviewed 151 patients with chronic GVHD, outcome, and relation to 23 variables at diagnosis of chronic GVHD.<sup>68</sup> Survival 10 years after diagnosis is listed in Table 3.

**Table 3** Prognostic model for chronic GVHD.

Prognostic factors <sup>a</sup>	Survival 10 years after Dx of chronic GVHD (%)
None	82
1 or 2 + 3	68
1 + 2 or 3	34
1 + 2 + 3	3

BSA, body surface area; Dx, Diagnosis; GVHD, graft-versus-host disease. (Adapted from Ref. [69]).

<sup>a</sup> Factor 1: Extensive skin involvement (>50% BSA), Factor 2: Thrombocytopenia (<100,000/ $\mu$ S L), Factor 3: Progressive – type onset of chronic GVHD.

### Quality of life

Chronic GVHD remains the prime determinant of late transplant-related morbidity, including abnormalities of growth and development in children,<sup>64,133</sup> sexual satisfaction and employment in adults,<sup>51</sup> and functional performance status. Symptoms resulting from chronic GVHD have been studied in relation to self-assessed severity, and recently reported as a 30-item measure of GVHD manifestations.<sup>134</sup>

### Practice points

- Chronic GVHD is a consequence of alloreactive T-cells of donor origin. It occurs a minimum of 100 days following allogeneic stem cell transplantation.
- Chronic GVHD is more common when the donor stem cells are harvested from cytokine mobilized peripheral blood compared to bone marrow.
- Chronic GVHD affects multiple organs, but the most commonly affected sites are the skin and underlying fascia, liver, mouth and eyes.
- Patients affected by chronic GVHD have a reduced chance for disease recurrence as a consequence of an immune attack against the tumor.
- Thrombocytopenia (<100,000) is an important poor prognostic feature of chronic GVHD.
- A regimen of alternate day cyclosporine and prednisone improves survival of patients with chronic GVHD.
- All patients with chronic GVHD should receive prophylaxis for pneumococcal infections with penicillin V 250 mg by mouth twice daily.
- Live virus vaccines must be avoided in patients with active chronic GVHD.

## Research points

- Pathophysiology of chronic GVHD.
- Development of more effective prophylactic and treatment regimens for chronic GVHD.
- Improved methods of diagnosis and staging of chronic GVHD.
- Establishment of biological markers of chronic GVHD.

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Excerpts of Sullivan, K; Graft-versus-Host Disease, In Blume et al. Thomas' Hematopoietic Cell Transplantation, 3rd ed. were reproduced with kind permission from Blackwell Publishing, Oxford, UK.

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