CHAPTER 13

Graft-versus-host disease

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1. Introduction

Graft-versus-host disease (GvHD) was first recognised in murine models of HSCT, when in the absence of knowledge of the HLA-system, it was termed "secondary" or "runt" disease on the basis of anorexia, reduced weight, diarrhoea, ruffled fur and eventual death. Billingham established the criteria for the occurrence of secondary disease in the 1960s, i.e.:

- The administration of a graft containing immunocompetent cells
- Immunological disparity between host and donor
- The administration of the graft to an immunosuppressed host.

In the human setting we traditionally recognise two forms of GvHD, acute (aGvHD) and chronic (cGvHD). The original distinction of acute from chronic GvHD, namely the occurrence before or after day 100 post stem cell infusion, has become blurred recently due to the development of an aGvHD-like illness beyond day 100 after reduced-intensity conditioning (RIC) regimens and/or after donor lymphocyte infusions (usually given after day 100). Nevertheless the underlying combination of symptoms and signs affecting the skin, liver and gastrointestinal tract form a classical clinical syndrome enabling the diagnosis and a helpful guide to the appropriate terminology is provided in Table 1.

Table 1: **Distinguishing acute and chronic graft-versus-host disease**

Category	Time of symptoms	Acute GvHD features	Chronic GvHD features
Acute GvHD			
Classic acute	≤100 days	Yes	No
Persistent, recurrent or late-onset acute	>100 days	Yes	No
Chronic GvHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

2. Acute graft-versus-host disease

2.1 Definition

aGvHD remains, directly or indirectly, the major cause of short-term (day 100) mortality after allogeneic HSCT. The pathology of aGvHD has been attributed to a three phase process comprising initial tissue damage from the conditioning regimen which in turn leads to activation of host antigen-presenting cells and activation

and proliferation of donor T-cells (afferent phase) and finally to the release of inflammatory cytokines such as interleukin-1 and tissue necrosis factor (TNF)-α that eventually produce tissue necrosis (efferent phase). The action of this pathogenetic process in the induction of aGvHD is modulated in part by the presence of cells capable of inhibiting immune responses, most notably T-regulatory cells (T-regs).

2.2 Risk factors

As aGvHD is a result of an alloimmune effect the major risk for occurrence is the presence of HLA disparity, and increasing degrees of HLA-mismatching increase the probability of more severe disease. Other important and consistent risk factors include older patient age, the use of female donors for male recipients, prior alloimmunisation of the donor and the nature of GvHD prophylaxis. A number of publications have variously reported risk factors such as increasing donor age, increasing intensity of the preparative regimen, the use of peripheral blood stem cells as opposed to bone marrow, and recipient seropositivity for cytomegalovirus. A recent study of 2941 recipients of allogeneic HSCT in Seattle confirmed the importance of the degree of HLA-mismatching, the use of unrelated donors and the administration of total body irradiation in predicting the occurrence of moderate to severe aGvHD. In contrast they found that increasing donor age, cytokine-mobilised stem cells and the use of female donors for male recipients did not impact on the likelihood of aGvHD but were associated with the occurrence of cGvHD (1).

More recently we have begun to appreciate the importance of non-HLA genetic factors in the development of GvHD. Examples include polymorphisms in the genes encoding cytokines such as the tumour necrosis factors, the interleukins (IL-1, IL-6 and IL-10), interferon (IFN)-γ and transforming growth factor (TGF)-β and the expression of the killer cell immunoglobulin-like receptors (KIR) (discussed more extensively in Chapter 5). Interestingly one of the common features of the organs involved in aGvHD is that they are all exposed to microbial pathogens through the intestinal mucosa, epidermis and portal circulation and early murine studies confirmed a reduction in the severity and incidence of GvHD in animals that received antibiotic prophylaxis to "decontaminate" the gastrointestinal tract or those kept in germ-free environments. This has led to the speculation that potential differences within individuals in the interactions of antigens derived from infective organisms and pathogen recognition receptors (PRR) might protect or predispose to the occurrence of GvHD. To date the most extensively studied of these receptors is NOD2 (CARD15) which detects muramyl dipeptide (MDP), a by-product of peptidoglycan, which is itself a cell wall component of most bacteria. Single nucleotide polymorphisms (SNPs) in NOD2 are present in approximately 15% of the population and several investigators have studied their potential association with the occurrence of GvHD. Results are

so far conflicting and further work is required to determine their real significance (reviewed in Penack et al. (2)).

2.3 Diagnosis and scoring

aGvHD is manifested by one or more of the following features: an erythematous skin reaction, cholestatic liver disease and gastrointestinal dysfunction. The variety of presentations in each organ is provided in more detail in Table 2; the syndrome ranges from a mild self-limiting condition to a serious and potentially fatal disorder. Because of the complexity of care of an allogeneic transplant recipient it is often very difficult to distinguish the characteristic features of aGvHD from those of other complications such as veno-occlusive disease, drug toxicity and infection, and consequently to determine the appropriate choice of treatment. For this reason it is essential to establish the diagnosis by biopsy of one or more affected organs and confirmation of the characteristic histopathological features (Table 3). The targets of the immune response in aGvHD are the epithelial cells including basal and suprabasal cells of the epidermis, the intestinal epithelium and the biliary duct epithelium, and the characteristic feature is identical, i.e. the presence of infiltrating immune cells close to apoptotic cells known as "satellite cell necrosis".

The first classification of aGvHD was developed by Glucksberg et al. in 1974. Each organ was staged from 0 to 4 (Table 4) and the resultant stages were combined to provide an overall grade (Table 5) (3). In 1994 Przepiorka et al. described the outcome of a Consensus Workshop to develop an improved scoring system that retained most of the characteristics of Glucksberg but dropped the use of the clinical performance score and included upper intestinal symptoms within the definition of aGvHD (4). Subsequently the IBMTR prospectively evaluated a "severity index" against the

Table 2: **Clinical manifestations of acute graft-versus-host disease**

Organ	Clinical manifestations
Skin	Erythematous maculopapular rash, often initially involving the palms and soles May progress to involve entire body surface May be pruritic and/or painful In severe cases, bullae may form leading to desquamation
Liver	Cholestasis with or without frank jaundice Cholestatic enzymes comparatively more deranged than transaminases
Gastrointestinal tract	Anorexia, nausea and vomiting Diarrhoea, typically green and watery In severe cases diarrhoea contains fresh blood and mucosa and is accompanied by abdominal pain and on occasions followed by paralytic ileus

Table 3: **Histopathological features of acute graft-versus-host disease**	
Organ	**Histopathological features**
Skin	The diagnostic feature is a lichenoid infiltration of the upper dermis and lower epidermis with vacuolation, degeneration and individual cell necrosis of the cells of the basal layer of the epidermis Grade 1: vacuolation of epidermal basal cells Grade 2: presence of individually necrotic keratinocytes Grade 3: confluent areas of keratinocyte necrosis forming bullae Grade 4: sloughing of the epidermis
Liver	The most consistent histological feature is small bile duct damage, which is usually seen in association with cholestasis and is rare in other complications of HSCT. The biliary epithelial cells have enlarged hyperchromatic nuclei or small pyknotic nuclei and vacuolated cytoplasm Periportal and midzone hepatocellular necrosis and minimal lymphocytic infiltrates in the portal tract Although there is a histological grading for liver histology but it has no proven prognostic value
Gastrointestinal tract	"Exploding crypts" within which are necrosis of individual epithelial cells at the periphery of the crypt leaving fragments of nuclear and cytoplasmic debris Grade 1: individual cell necrosis Grade 2: loss of individual crypts Grade 3: loss of two or more adjacent crypts with ulceration Grade 4: denudation of epithelium

Table 4: **Staging of acute graft-versus-host disease**			
Stage	**Skin based on maculopapular rash**	**Liver based on serum bilirubin**	**Gastrointestinal tract based on quantity of diarrhoea**
+	<25% of body surface	34–50 µmol/L	>500 <1000 mL
++	25–50% of body surface	51–102 µmol/L	>1000 <1500 mL
+++	Generalised erythroderma	103–255 µmol/L	>1500 mL
++++	Generalised erythroderma with bullae and desquamation	>255 µmol/L	Severe abdominal pain with or without ileus

Table 5: **Overall grading of acute graft-versus-host disease**

Grade	Organ and stage of involvement
I	Skin + to ++
II	Skin + to +++ Gastrointestinal tract and/or liver + Mild decrease in clinical performance
III	Skin ++ to +++ Gastrointestinal tract and/or liver ++ to +++ Marked decrease in clinical performance
IV	Skin ++ to ++++ Gastrointestinal tract and/or liver ++ to ++++ Extreme decrease in clinical performance

Glucksberg criteria but were unable to identify any particular advantage for the new system (5). In fact the Glucksberg score was a better predictor of survival and remains in regular use.

2.4 Epidemiology

Moderate to severe aGvHD occurs in approximately 40% of all recipients of allogeneic HSCT, but the precise incidence varies considerably depending predominantly on the nature of the donor and the method of GvHD prophylaxis. Without effective prophylaxis it is an almost inevitable complication of unrelated matched donor and mismatched family grafts.

2.5 Prevention

Grade III-IV aGvHD has an extremely poor prognosis despite therapeutic intervention and consequently considerable efforts are made to try and prevent its occurrence (Table 6). The rationale of prophylaxis was originally directed towards prolonged immunosuppression of donor T-cell function through the peri- and post-transplant administration of immunosuppressive agents. Early studies identified the superiority of a combination of the calcineurin inhibitor, cyclosporin, with methotrexate over methotrexate alone. In practice this combination remains the most frequently used method of prophylaxis although some investigators have replaced cyclosporin with tacrolimus since large two phase III randomised studies reported a reduction in the incidence of grade II-IV aGvHD at 32% in recipients of sibling transplants and 56% in those who received unrelated donor grafts in patients who received tacrolimus plus methotrexate compared to 44% (sibling) and 74% (unrelated) in

Table 6: **Agents used in the prevention of acute graft-versus-host disease**

Agent	Mechanism of action	Dose
Cyclosporin	Calcineurin inhibition i.e. blockade of T-cell activation	3 mg/kg iv
Tacrolimus	Calcineurin inhibition i.e. blockade of T-cell activation	0.02 mg/kg iv
Methotrexate	Antimetabolite	15 mg/m^2 day +1, 10 mg/m^2 day +3, 6 and 11
Methylprednisolone	Receptor mediated lympholysis and other unidentified actions	0.5–1.0 mg/kg
Mycophenolate mofetil	Inhibition of DNA synthesis, lymphocyte apoptosis	1.5–3 g/day
Sirolimus	Macrolide antibiotic; blockade of T-and B-cell activations	12 mg day -3 then 4 mg/day
Antithymocyte globulin	Rabbit or equine polyclonal antibodies recognising T-cells	2.5 mg/kg/day x 4
Monoclonal antibodies eg. alemtuzumab (anti-CD52)	Humanised monoclonal antibodies recognising T-cells	10 mg/kg/day, usually for 5 days
Cyclophosphamide	Cytotoxic agent inducing death of proliferating cells	50 mg/kg/day on days +3 and +4

those who were randomised to cyclosporin and methotrexate. However there was no difference in survival that could be attributed to the nature of the GvHD prevention (6, 7). Recently investigators have also reported the efficacy of newer agents such as mycophenolate mofetil (MMF) and sirolimus, and the combination of tacrolimus and sirolimus is currently being compared with that of tacrolimus and methotrexate in a phase III randomised study.

An alternative approach to GvHD prophylaxis is to consider removal of donor T-cells either *ex vivo* prior to infusion or *in vivo* before and/or after infusion using polyclonal (anti-thymocyte globulin, ATG) or monoclonal antibodies. A similar effect can also be achieved by positive selection of CD34$^+$ stem cells. These techniques, collectively known as T-cell depletion, are extremely efficient in preventing acute and chronic GvHD and were in widespread use in the 1980s and 1990s. Unfortunately they were rapidly identified as contributing to an increased risk of infection and disease relapse, and subsequently became confined to situations in which the risk of GvHD is particularly high, e.g. recipients of mismatched and haploidentical transplants where the risk of death from GvHD outweighs the risk of later disease recurrence. In particular ATG contributes substantially to the risk of

developing EBV-related post-transplant lymphoproliferative disease (PTLD) necessitating regular molecular monitoring and prophylaxis or pre-emptive treatment with rituximab.

Other studies have explored alternative methods of acute GvHD prophylaxis including the infusion of an expanded population of T-regulatory cells at the time of stem cell infusion, the use of extracorporeal photophoresis and most recently the administration of high dose cyclophosphamide, particularly in the context of haploidentical transplantation (reviewed in Perez et al. (8)).

2.6 Treatment

Grade I aGvHD, by definition affecting only the skin, can often be effectively treated with topical steroids alone. More advanced grades require systemic therapy and the mainstay of treatment remains high dose methylprednisolone, usually at a dose of 2 mg/kg/day, continued for 7–14 days and followed by a gradual reduction in dose. The chance of response decreases with increasing grade of GvHD but in general approximately 40–50% of patients will demonstrate a response. Reductions in steroid doses are often followed by an exacerbation of symptoms that can sometimes be settled by simply increasing the dose and reducing more slowly on the second occasion. Achieving a balance between the level of immunosuppression required to control aGvHD and retaining a degree of immunocompetence against microbial infection is challenging, and viral and fungal infections are frequent complications of prolonged steroid therapy. Anti-infective prophylaxis should be considered for all such patients. The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) recently completed a randomised phase II study of four agents, etanercept, MMF, denileukin diftitox, or pentostatin, each in combination with methylprednisolone 2 mg/kg/day. The complete remission rates at day 28 after initiation of therapy were 26, 60, 53 and 38% respectively (9). The interpretation of the study was complicated by the fact that many eligible patients had received MMF as GvHD prophylaxis and therefore could not be randomised to the arm containing MMF. Patients randomised to any of the other three arms contained a significant proportion that had previously failed MMF, raising the possibility that the results would be biased in favour of MMF. Nevertheless the combination of steroids and MMF has been taken forward to a phase III study against steroids alone.

Failure to respond to standard steroid doses (defined as progression within 3 days of starting treatment or an incomplete response by 14 days) or refractory recurrence after initial dose reduction will necessitate second line treatment. In this context many agents have been tried alone or in combination with corticosteroid. None have shown convincing long-term efficacy. The most frequent choice of second line therapy involves one or more monoclonal antibodies recognising T-cells, or ATG. Monoclonal

antibodies include alemtuzumab for the pan T-cell marker, CD52, daclizumab, for the alpha sub-unit of the IL-2 receptor expressed on activated T-cells and now no longer available in Europe and infliximab and etanercept for TNF-α. These agents often result in short-term control but durable effects are relatively infrequent and the outcome of refractory aGvHD is dismal with approximately 80% mortality. Newer approaches currently under evaluation include immunotoxin-based agents such as denileukin difitox. Responses have been reported with extracorporeal photopheresis but this is a difficult treatment to deliver at regular intervals (at least twice a week) to individuals who are seriously unwell.
In 2006, Ringden et al. reported the successful use of mesenchymal stromal cells (MSC) in a small group of patients with refractory severe aGvHD (10) and later this group described a response rate of 40% in a larger group of patients (11), MSC exert immunosuppressive effects in a non-HLA restricted manner and like T-regs offer interesting and novel strategies for the management of this potentially fatal complication.

3. Chronic graft-versus-host disease

3.1 Definition and pathology

cGvHD is an immunoregulatory disorder occurring after allogeneic HSCT and shares features of autoimmunity and immunodeficiency. Features of cGVHD resemble other autoimmune diseases such as Sjögren syndrome, scleroderma, primary biliary cirrhosis and immuncytopenias. Similarly to aGVHD, cGVHD is also thought to be induced by the immune cells of the donor but the pathophysiology is even less well understood. Although autoreactive T-lymphocytes are considered to play the key role, recent data revealed the importance of B-cells (12). cGVHD is the main cause of late non-relapse mortality and morbidity after allogeneic HSCT. Mortality is primarily caused by infections either due to the immunodeficiency of cGVHD or its treatment.

3.2 Risk factors

The major risk factors for the development of cGVHD are prior acute GvHD, higher degree of HLA mismatch, older patient age, previous splenectomy, CMV seropositivity, female donor to male recipient and mobilised peripheral blood stem cell graft (Table 7) (1, 13).

3.3 Diagnosis and scoring

The diagnosis of cGvHD is based on its clinical manifestations. The signs and symptoms of cGvHD may occur in any organ but the most frequently affected

Table 7: **Major risk factors for the development of chronic graft-versus-host disease**

Given factors	Variable factors
Older age of recipient	Higher degree of HLA mismatch
CMV seropositivity of recipient	Older age of donor
Previous splenectomy	CMV seropositivity of donor
Prior acute GvHD	Female donor to male recipient
	Mobilised blood stem cell graft

organs/sites are the skin, nails, mouth, eyes, female genitalia, gastrointestinal tract, liver, lungs, muscles, fascia and joints. The disease may be mono-symptomatic, but can also be widespread and leading to debilitating consequences such as end stage lung disease or joint contractures. Since the NIH consensus development project on cGvHD in 2005 new diagnostic and staging criteria has been established (14). The consensus group defined diagnostic signs (any one of these signs itself establishes the diagnosis of cGvHD without further investigation), distinctive signs (should be confirmed by pertinent biopsy or other relevant test, e.g. Schirmer), other features of cGvHD which are not specific, and common signs that occur both in acute and chronic GvHD (Table 8). There is no time limit for setting the diagnosis of cGvHD in contrast to the previous definition when cGvHD could be diagnosed exclusively only after 100 days following the transplant (Table 1).

Until the NIH proposal cGvHD grading was based on a retrospective study of 20 patients (15). This divided cGvHD into limited (only localised skin involvement and/or hepatic dysfunction) and extensive disease. This classification was very easy to use in the daily routine, but was insufficiently robust and reproducible to allow for appropriate comparisons between clinical studies. The NIH global scoring system includes two components. First each organ system (skin, mouth eyes, GI tract, liver, lungs, joints and fascia and female genital tract) receives a score from 0 to 3 precisely described according to the severity of the effected organ. Second, the number of affected sites/organs is calculated and these together establish three categories (mild, moderate and severe) according to the score generated.

Mild cGvHD reflects the involvement of no more than 1 or 2 organs/sites (except for lung) with a maximum score of 1.

Moderate cGvHD involves at least 1 organ/site with a score of 2 or three or more organs/sites with a score of 1 (or lung score 8).

Severe cGvHD is diagnosed when a score of 3 is given to any organ (or score of 2 to lungs) (Table 9).

Table 8: **Signs and symptoms of chronic graft-versus-host disease**

Organ/Site	Diagnostic	Distinctive	Other features*	Common (both acute and chronic)
Skin	Poikiloderma Lichen planus-like features Sclerotic features	Depigmentation	Sweat impairment Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging splitting, or brittle features		
Scalp/hair		Alopecia	Premature gray hair	
Mouth	Lichen planus type features	Xerostomia		Mucositis
Eyes		Dry eyes Keratoconjunctivitis sicca	Photophobia Blepharitis	
Genitalia	Lichen planus type features	Erosions, fissures, ulcers		
Gastrointestinal tract	Esophageal web Stricture or stenosis of the esophagus		Exocrine pancreatic insufficiency	Nausea Vomiting Anorexia, weight loss
Liver				Bilirubin or alkaline phosphatase, ALT or AST >2 x upper limit of normal
Lung	Bronchiolitis obliterans			Bronchiolitis obliterans organising pneumonia (BOOP)
Muscles, fascia, joints	Fasciitis, joint stiffness secondary to sclerosis	Myositis Polymyositis	Oedema Muscle cramps Arthralgia, arthritis	
Haematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies	
Other			Peripheral neuropathy Myasthenia gravis Ascites, pericardial or pleural effusion	

** Can be considered the part of cGvHD symptomatology if the diagnosis is confirmed*

Table 9: **NIH consensus for global grading of chronic graft-versus-host disease**

Number of organs/sites	Mild	Moderate	Severe
1 site	Score 1	Score 2	Score 3
2 sites	Score 1	Score 2	Score 3
3 or more sites		Score 1	Score 3
Lung involvement		Score 1	Score 2

Besides the NIH Global Scoring Akpek et al. established a very simply applicable and useful cGvHD grading in 2001 for assessing prognosis. With the help of the following three risk factors (progressive onset of cGvHD, platelet count lower then 100,000 and more than 50% of body surface involvement of the skin) patients are divided into low risk (no risk factor) intermediate risk (1 or 2 risk factors) and high risk (3 risk factors) categories with significantly different probabilities of long term survival (over 80%, approximately 50%, and less than 20%) respectively (16). Recently, a much more detailed risk score has been proposed by the CIBMTR following a review of 5343 patients with cGvHD. Ten variables (age, prior acute GvHD, time from transplant to cGvHD, donor type, disease status at transplant, GvHD prophylaxis, gender mismatch, serum bilirubin, Karnofsky score and platelet count) were identified resulting in 6 risk groups with significantly different non-relapse mortality and overall survival. This may be a useful tool to precisely identify different risk category patients at the diagnosis of cGvHD and making appropriate decisions regarding further therapy and possible enrolment in clinical trials (17).

3.4 Epidemiology

cGvHD occurs in 40% of HLA identical sibling unmanipulated SCT, more than 50% of HLA- non-identical related SCT and in 70% of matched unrelated SCT. A study from Seattle showed that the higher the degree of HLA disparity, the earlier the onset of symptoms, with a median of 201 days in HLA identical siblings, and 133 days in matched unrelated donors transplanted with bone marrow and after standard conditioning (18). The most frequently involved sites of the clinical manifestations of 324 pts were the mouth (89%), skin (81%), gastrointestinal tract (48%), liver (47%), eyes (47%). The disease started with a quiescent onset (followed acute GvHD with a remission period) in 60%, with a progressive onset (cGvHD transformed from acute) in 13%, and with *de novo* onset (no prior acute GvHD) in 27% of the cases. Symptoms usually start no later than 3 years following transplant.

3.5 Treatment

Limited disease necessitates only local treatment, and this avoids further immuno-

suppression which might result in infectious complications and the other side effects of long term steroids. In the case of extensive disease systemic treatment is necessary and patience and appropriate evaluation of response is very important. Most patients require immunosuppressive treatment for up to 1 year, with more than half of them still on therapy after 2 years.

3.5.1 First line treatment

Standard first line systemic treatment is orally administered prednisolone 1 mg/kg and cyclosporin (CsA) 10 mg/kg with the dose of CSA adjusted to plasma levels. The corticosteroid component is the main part of the therapy while the addition of CsA had the advantage of less avascular necrosis in a prospective randomised study (19, 20). Attempts to add a third immune-suppressive drug (azathioprine, thalidomide or mycophenolate mofetil) to the standard initial treatment did not improve results and should be avoided (21, 22). Because of the significant morbiditiy caused by long-term steroid treatment the dose of prednisolone should be tapered according to response. In practice this usually starts 2 weeks after evidence of improvement of clinical manifestations. The tapering should be very slow with a typical approach starting with 0.25 mg/kg reduction on alternating days reaching no steroid on every second days by 2 months. Then after a 4 months interval an even slower taper may be initiated reaching steroid-free status by the end of the first year but still on CSA treatment (23).

Steroid-refractory cGvHD is defined as progression on prednisolone at 1 mg/kg/day for 2 weeks or stable disease on >0.5 mg/kg/day prednisolone for 4–8 weeks or an inability to taper prednisolone below 0.5 mg/kg/day.

3.5.2 Second line treatment

There is no standard salvage treatment of cGvHD. A large number of options have been tested in rather small phase II clinical trials with different enrolment and response criteria making their comparative evaluation difficult. Possibilities include mycofenolate mofetil, tacrolimus, rapamycin, rituximab, thalidomide, extracorporeal photopheresis, pulsed high dose steroids (10 mg/kg/day for 4 days), total lymphoid irradiation (1 Gy), alemtuzumab, pentostatin, revlimid, anti-IL-2 receptor Ab, anti-TNF receptor Ab, and recently tyrosine kinase (PDGFR, TGF-β) inhibitors such as imatinib, nilotinib, or dasatinib (Table 10) (24).

3.5.3 Ancillary treatment

As the primary cause of death of patients with cGvHD is infection, antimicrobial prophylaxis is of outstanding importance. Prevention from encapsulated bacteria, *Pneumocystis pneumonia*, CMV, *Varicella zoster*, and fungal infections should be

Table 10: **Treatment of steroid-refractory chronic graft-versus-host disease**

Agent	Side effects	Comments
High dose steroids	Osteoporosis, avascular necrosis, diabetes	Important but need to spare steroids because of side effect profile
Extracorporeal photopheresis (ECP)	Venous access required	Spares steroids, excellent safety profile
Sirolimus	Hyperlipidemia, rash, renal dysfunction, infections, thrombotic macroangiopathy (TMA)	Increased risk for TMA in combination with calcineurin inhibitors, lower efficacy in thrombocytopenia, requires frequent monitoring
Tacrolimus	Renal toxicity, hypertension	Spares steroids, should be avoided in renal impairment
Mycophenolate mofetil (MMF)	Nausea Diarrhoea Neutropenia	Increased risk of viral reactivation, spares steroids, GI toxicity may mimic GvHD clinically and histologically
Pentostatin	Cytopenias, infectious risk	Best results in children, caution in presence of impaired marrow function, long-term immunosuppression
MTX	Cytopenias	Best response in mucocutaneous cGvHD, spares steroids
Imatinib	Fluid retention	Best results in sclerotic skin lesions, potentially effective in mild and moderate bronchiolitis obliterans
Thalidomide	Neurotoxicity, sedation, constipation	May be used in concomitant relapse of multiple myeloma
Azathioprine	Cytopenias, infectious risk	Increased risk for oral malignancies
Retinoids	Skin toxicity, hyperlipidemia	Effective in sclerotic skin lesions
Anti-CD20	Infectious risk	Effective in autoantibody-mediated manifestations and cutaneous and musculoskeletal cGvHD
Anti-CD52	Infectious risk	Last choice

considered and adjusted to the actual immunosupressive status. Systemic therapy always should be accompanied with appropriate local treatment of the affected organs and sites accordingly (Table 11) (25).

Table 11: **Ancillary therapy of chronic graft-versus-host disease**

Organ system	Prevention/Treatment
Skin and appendages	Avoidance of sun exposure, topical emollients, steroids, antipruritic agents, topical antimicrobials
Mouth and oral cavity	Topical steroids and analgesics, tacrolimus ointment, cyclosporin/tacrolimus rinses, salivary stimulants (sugar-free gum)
Eyes	Artificial tears, ocular ointments, topical steroids, cyclosporin eye-drops, topical antimicrobials, punctal occlusion
Vulva and vagina	Avoid chemical irritants (eg. soap), clean genital area with warm water. Water-based lubricants, topical estrogens, tacrolimus ointment
GI tract and liver	Dietary modifications, enzyme supplementation for malabsorption, gastroesophageal reflux management, esophageal dilatation, ursodeoxycholic acid
Lungs	Inhaled steroids, bronchodilators, supplementary oxygen, pulmonary rehabilitation, lung transplantation in appropriate candidates
Haematopoietic	Haematopoietic growth factors, immunoglobulin for immune cytopenias
Musculoskeletal	Physical therapy, bisphosphonates for osteopenia and osteoporosis

4. Conclusion

Acute GvHD is a common complication of allo-HSCT and is a leading cause of early morbidity and mortality. First-line therapy is single agent methylprednisolone which is effective in 40–50% of cases. Second line treatment for steroid refractory disease is largely unsatisfactory and therefore major efforts are exerted to prevent the occurrence of aGvHD. The most effective method of prophylaxis is T-cell depletion but in good risk transplants is accompanied by an unacceptable level of infection and relapse of the original disease. The most frequently used regimen for aGvHD prevention remains methotrexate and a calcineurin inhibitor. Manipulation of cellular sub-populations with immunosuppressive properties are promising new strategies for both prevention and treatment.

Chronic GvHD is a common (30 to 70%) complication after allo-HSCT and is a leading cause of late morbidity and mortality. The standard treatment is steroid and a calcineurin inhibitor. Prolonged steroid use is required with fewer than 50% of patients discontinuing immunosuppression by 2 years. There is no standard salvage therapy for cGvHD. cGvHD and its treatment are associated with severe complications including infections, osteoporosis, hypertension, hyperglycemia, hyperlipidemia and renal insufficiency. Infections are the leading cause of death and antimicrobial prophylaxis is necessary. Careful management of complications require multidisciplinary treatment.

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Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/online-training/handbook/

1. Which of the following statements is *untrue*?

a) The incidence and severity of GvHD increases with increasing HLA disparity ☐
b) One of the prerequisites for the occurrence of GvHD is lack of immunocompetence in the patient ☐
c) GvHD can only be diagnosed within the first 100 days of transplant ☐
d) Epithelial tissue damage is modulated through cytokines ☐

2. Which of the following is *not* a feature of acute GvHD?

a) Nausea ☐
b) Raised alkaline phosphatase ☐
c) Lichen planus ☐
d) Bullae ☐

3. Which of the following has *not* been reported as a risk factor for acute GvHD?

a) Older patient age ☐
b) The use of fludarabine in the conditioning regimen ☐
c) CMV seropositivity ☐
d) Gender disparity between donor and recipient ☐

4. Which of the following statements is *untrue*?

a) Keratoconjunctivitis sicca is a feature of chronic GvHD ☐
b) The most frequent cause of mortality in patients with chronic GvHD is infection ☐
c) Prior splenectomy is associated with an increased risk of chronic GvHD ☐
d) The organ demonstrating the best response to imatinib is the mucosa ☐

5. Which of the following features has *not* been used in a scoring system for chronic GvHD?

a) Thrombocytopenia ☐
b) Number of organs involved ☐
c) Time from transplant to occurrence of acute GvHD ☐
d) Extent of skin involvement ☐