

Organ-specific management and supportive care in chronic graft-versus-host disease

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Summary

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation has reviewed the available literature and made recommendations for the supportive care and management of organ-specific complications of chronic graft-versus-host disease (cGvHD). This guideline includes recommendations for the specific therapy of skin, oral, liver, gut, lung, ocular and genital manifestations of cGvHD and for the supportive care of these patients, including vaccinations and prophylaxis against infection. The goal of treatment should be effective control of GvHD while minimizing the risk of toxicity and relapse.

Keywords: chronic, graft-versus-host disease, supportive care, transplant.

Summary of Recommendations

General

- 1 Patients with chronic graft-versus-host disease (GvHD) should be reviewed by a team experienced in managing transplant-related complications. (1C)

- 2 Transplant centres should establish a clinical network of specialists with an interest in GvHD to allow for multidisciplinary management. (1C)
- 3 Assessment of quality of life is recommended in all patients with GvHD. (1C)
- 4 Systemic treatment is the mainstay of therapy in patients with moderate or severe GvHD. (1A)

Cutaneous

- 1 Referral to a dermatologist with experience in transplant dermatology should be considered in patients with moderate or severe cutaneous GvHD (1C).
- 2 All patients with cGvHD on prolonged immunosuppression should have an annual skin check by a dermatologist in view of the increased risk of cutaneous malignancy (1C).
- 3 All growing/non healing skin lesions should be referred within 2 weeks to a dermatologist (1C).
- 4 Emollients should be used for symptom control in skin GvHD (1C).
- 5 Topical therapy, including steroids or topical calcineurin inhibitors, is recommended as first line therapy (1B).
- 6 ECP is recommended as a second line systemic therapy for steroid-refractory skin GvHD (1B).
- 7 Physiotherapy is recommended in patients with scleroderoid disease (1C).

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Gastrointestinal

- 1 Referral to a gastroenterologist should be considered in patients with suspected gastrointestinal GvHD. (1C)
- 2 In view of the wide differential diagnosis, patients with diarrhoea without associated jaundice or rash suggestive of GvHD should be investigated by both upper (with duodenal aspirate and biopsies) and lower (flexible sigmoidoscopy and biopsy) gastrointestinal endoscopy in preference to colonoscopy alone. (1C)
- 3 All patients should be assessed and reviewed by a dietician with experience of managing patients with gut GvHD and each unit should have an agreed protocol for nutritional issues. (1C)

Genital

- 1 All patients should be actively questioned about genital tract symptoms. (1C)
- 2 Referral for specialist advice should be considered in all patients with genital symptoms that are difficult to manage. (1C)
- 3 High potency topical steroids (+/– topical calcineurin inhibitors) are recommended as first line therapy. (1C)

Liver

- 1 Referral for specialist hepatology opinion should be considered in patients with significant liver GvHD. (1C)

Ocular

- 1 Patients with symptoms suggestive of significant ocular involvement should be reviewed by an ophthalmologist preferably with an interest in ocular GvHD. (1C)
- 2 Patients on prolonged systemic steroids for chronic GvHD should be aware that their vision may be reduced if they develop cataracts and should seek ophthalmic advice if this occurs. (2C)
- 3 Supportive care with artificial tears and topical anti-inflammatory/antibiotic treatment may be helpful as first line treatment. (2C)

Oral

- 1 Referral to Oral Medicine should be considered in patients with significant oral symptoms. (1C)
- 2 Topical therapies including steroid mouthwashes are recommended as first line treatment. (2C)
- 3 ECP is recommended as a second line systemic therapy for steroid-refractory GvHD. (1B)

Pulmonary

- 1 Referral to a respiratory physician should be considered in all patients with suspected pulmonary GvHD. (1C)

- 2 All patients with chronic GvHD should be screened using pulmonary function tests regardless of symptoms. (1A)
- 3 Systemic steroids are recommended in patients with pulmonary GvHD at a dose of 1 mg/kg of prednisolone; for those not responding, consider pulsed steroids or imatinib. (2C)
- 4 Supportive care, including intravenous immunoglobulin, vaccinations and azithromycin, is also recommended. (2C)

Infection

- 1 Prophylaxis against viral, fungal, *Pneumocystis jiroveci* and *Streptococcus pneumoniae* infection should be considered in all patients receiving immunosuppressive agents for chronic GvHD. (1A)
- 2 The prophylactic and/or pre-emptive strategy for prevention of cytomegalovirus (CMV) infection including regular monitoring of CMV polymerase chain reaction adopted for haematopoietic stem cell transplantation recipients should be continued throughout the period of acute and/or chronic GvHD. (1B)
- 3 A mould-active azole is recommended for prophylaxis in patients undergoing treatment for GvHD (1A); suitable agents include posaconazole and voriconazole (1A) or itraconazole with regular monitoring of levels. (2B)

Vaccinations

- 1 Live vaccines must not be administered in patients with chronic GvHD. (1A)
- 2 All patients with chronic GvHD should receive vaccination against pneumococcus, influenza and *Haemophilus influenzae*. (1B)

Long Term Steroid Use

- 1 All patients on long-term steroid treatment should have blood pressure and glucose monitored at clinic visits and should receive gastric protection. (1A)

Introduction

Chronic graft-versus-host disease (cGvHD) remains a major complication of allogeneic stem cell transplantation and is the leading cause of late non-relapse death (Lee *et al*, 2002a). cGvHD is a complex disorder which can affect every organ system. The most commonly affected organs are the skin, eyes, mouth, lungs, liver, gut and genitalia. There is a lack of evidence-based data of the management of these complications and there is wide variation in practice. In the United States, the National Institutes of Health (NIH) consensus development project has tried to address this issue by developing criteria for clinical trials in cGvHD, which include a report on

ancillary therapy and supportive care recommendations (Couriel *et al*, 2006). Similarly, the German-Austrian-Swiss working party on bone marrow and blood stem cell transplantation held a consensus conference to define clinical management of cGvHD in 2009 and have recently published several papers, some of which focus on organ-specific complications (Hildebrandt *et al*, 2011; Marks *et al*, 2011a; Meier *et al*, 2011).

There are currently no UK guidelines outlining the management of cGvHD. This guideline aims to include practical recommendations for the specific therapy of the more common manifestations of cGvHD and for the supportive care of these patients. This guideline benefits from the expertise of both experienced transplant physicians as well as specialist physicians experienced in managing the organ-specific complications of cGvHD. The management of patients with cGvHD is known to vary widely between countries but this guideline aims to reflect national practice in the UK. A discussion of all possible late effects of allogeneic transplantation is beyond the scope of this document and this guideline will focus on specific management of patients with cGvHD. Some of the recommendations in this guideline, e.g. those related to management of skin, liver and gut GvHD may be equally applicable to those patients with acute GvHD. The systemic treatment of acute and chronic GvHD is discussed in two separate documents (Dignan *et al*, 2012a,b). These guidelines are designed to be used together and to complement each other in order to provide an evidence-based approach to managing this complex disorder.

Methodology

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation and specialists in managing GvHD from the following specialities: dermatology, oral medicine, hepatology, gastroenterology, ophthalmology, respiratory, endocrinology, microbiology.
- Literature review to 17th June 2011 including Medline, internet searches and major conference reports.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The GRADE nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guideline pack and the GRADE working group website. See Appendix 1. Further information is available from the following websites:
 - http://www.bcsghguidelines.com/4_HAEMATOLOGY_GUIDELINES.html
 - <http://www.gradeworkinggroup.org/index.htm>

- Review by the BCSH committees, British Society of Blood and Marrow Transplantation (BSBMT) executive committee, the UK Photopheresis Society and the UK Paediatric Bone Marrow Transplant Group.
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK

Principles of GvHD management

The NIH has classified cGvHD as mild, moderate or severe using a global scoring system (Filipovich *et al*, 2005). Mild cGvHD may respond to local treatments without the need for systemic therapy. Local, organ-specific therapies can also be a useful adjunct in the management of moderate and severe cGvHD. The diagnosis, staging and systemic management of cGvHD is detailed in a separate document (Dignan *et al*, 2012b). Systemic treatment is likely to be the mainstay of treatment in patients with moderate or severe cGvHD.

A multidisciplinary approach is vital in the management of cGvHD. The multidisciplinary team should include input from physiotherapists, microbiology, occupational therapists, dieticians, pharmacists and psychologists from the transplant centre. In addition, referral to specialist physicians may be helpful in patients with organ-specific complications that are difficult to manage. Each transplant centre should try to establish a network of specialists with an interest in GvHD to facilitate the referral pathway.

Patients should be cared for by physicians with experience in managing transplant-related complications. Transplant centres may find that it is helpful to have a dedicated late effects or GvHD clinic. Response to treatment should be documented at each clinic visit and formal staging by NIH criteria (Filipovich *et al*, 2005) should be recorded every 3 months. It has been shown that quality of life can be severely affected in patients with cGvHD and it is important to make a formal assessment of quality of life using a validated questionnaire (Pidala *et al*, 2011). Suitable questionnaires for adult patients include the FACT-BMT, SF-36 questionnaire, EORTC QLQ-C30 and the Lee cGvHD symptom scale (McQuellon *et al*, 1997; Kopp *et al*, 2000; Lee *et al*, 2002b; Pidala *et al*, 2011).

Recommendations

- **Patients with cGvHD should be reviewed by a team experienced in managing transplant-related complications (1C).**
- **Transplant centres should establish a clinical network of specialists with an interest in GvHD to allow for multidisciplinary management (1C).**
- **Assessment of quality of life is recommended in all patients with GvHD (1C).**
- **Systemic treatment is the mainstay of therapy in patients with moderate or severe GvHD (1A).**

Cutaneous GvHD

Diagnosis and management of cutaneous GvHD

The diagnosis of cutaneous cGvHD requires diagnostic clinical signs and/or consistent skin histology. Cutaneous pathology is frequent following bone marrow transplantation and may be caused by infection, vasculitis, drug reactions, dermatitis or skin cancer. In cGvHD the skin integrity is damaged and this results in loss of skin function. The role of the skin as a barrier and in temperature regulation may be impaired. It is therefore imperative that following transplants all patients receive good skin care. Skin-directed therapies are less toxic than their systemic counterpart and may lead to improvement in cutaneous lesions without systemic toxicities and can provide relief from cutaneous symptoms such as pain, swelling and itch. Skin-directed therapies are adjuvant or palliative in all but the mildest cases of cGvHD. There are no randomized controlled trials in this supportive approach but these therapies are used widely and regarded as best medical practice worldwide (Couriel *et al*, 2006; Häusermann *et al*, 2008; Chavan & el-Azhary, 2011; Marks *et al*, 2011a).

Cutaneous involvement with cGvHD may respond to skin-directed therapy. In patients with moderate/severe involvement or involvement of other organs, skin-directed therapies may be used as adjuvant treatments to systemic immunosuppression and/or extracorporeal photopheresis (ECP). Patients with mild skin disease may be treated with skin-directed therapy alone without the toxicities of systemic immunosuppression or loss of graft-versus-malignancy effect (Lee *et al*, 2002a). When using skin-directed therapy alone care must be taken to monitor for onset of GvHD in other organs. Referral to a dermatologist with experience in transplant dermatology should be considered in patients with moderate or severe GvHD. An annual skin check by a dermatologist is also recommended in patients with cGvHD on prolonged immunosuppression due to the increased risk of cutaneous malignancy in this group. In addition, urgent dermatology review is recommended in all patients with growing or non-healing skin lesions.

Emollients may be helpful for xerosis and both sclerodermoid and lichenoid skin may respond to topical corticosteroids, which are recommended as first line treatment. Potent or very potent strength should be prescribed and massaged into affected areas twice per day. Improvements in lichenoid disease, particularly erythema, may occur within days whilst sclerodermoid disease is typically slower to respond (Couriel *et al*, 2006). Care should be taken in flexural areas where skin thinning and striae may occur with prolonged steroid use. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have also been shown to improve skin GvHD with erythema and pruritus responding first (Choi & Nghiem, 2001; Elad *et al*, 2003a; Ziemer *et al*, 2004a; Schmook *et al*, 2005). Whilst there is no risk from skin atrophy, patients may report a burning sensation on application and there is an increased risk of cutaneous infection.

There is a potential increased risk of skin malignancies and exposure to ultraviolet (UV) light during therapy should be minimized.

Phototherapy may be of benefit although the increased risk of skin malignancies in this group is significant, as these patients have typically received chemotherapy prior to bone marrow transplantation and subsequently immunosuppression with ciclosporin.

UV-B (290–320 nm) may be useful in the treatment of lichenoid skin disease and is now more frequently given as narrowband (311 nm) (Enk *et al*, 1998). UV-A may be used, traditionally as psoralen plus ultraviolet A (PUVA; 320–400 nm) (Atkinson *et al*, 1986; Eppinger *et al*, 1990; Jampel *et al*, 1991; Vogelsang *et al*, 1996; Leiter *et al*, 2002; Ghoreschi *et al*, 2008) but UVA-1 (340–400 nm) is now used in a variety of sclerotic skin diseases, including sclerodermoid GvHD. Response to phototherapy may take weeks and a course typically lasts 2–3 months (Grundmann-Kollmann *et al*, 2000; Calzavara *et al*, 2003; Ziemer *et al*, 2004b; Wetzig *et al*, 2005).

ECP provides response rates of up to 80% in patients with skin GvHD and is a useful second line treatment. ECP is discussed in detail in the guideline on systemic management of cGvHD and is recommended as a second line treatment option (Dignan *et al*, 2012b). The role of supportive therapies in cutaneous GvHD is reviewed in Table I. Physiotherapy may be a useful adjunctive treatment in patients with contractures due to sclerodermoid disease.

Recommendations

- **Referral to a dermatologist with experience in transplant dermatology should be considered in patients with moderate or severe cutaneous GvHD (1C).**
- **All patients with cGvHD on prolonged immunosuppression should have an annual skin check by a dermatologist in view of the increased risk of cutaneous malignancy (1C).**
- **All growing/non healing skin lesions should be referred within 2 weeks to a dermatologist (1C).**
- **Emollients should be used for symptom control in skin GvHD (1C).**
- **Topical therapy, including steroids or topical calcineurin inhibitors, is recommended as first line therapy (1B).**
- **ECP is recommended as a second line systemic therapy for steroid-refractory skin GvHD (1B).**
- **Physiotherapy is recommended in patients with sclerodermoid disease (1C).**

Gastrointestinal GvHD

Introduction

There are no typical symptoms that are diagnostic of gastrointestinal (GI) GvHD although the GI tract is commonly

Table I. The role of supportive therapies in cutaneous graft-versus-host disease.

Problem	Supportive therapy
Xerosis	<ul style="list-style-type: none"> • Regular moisturisers • Substitute creams for soaps
Pruritus	<ul style="list-style-type: none"> • Advise tepid water rather than hot water for bathing • Advise patients to rub rather than scratch skin • Consider occlusion of affected areas • Topical corticosteroids • Oral antihistamines • Doxepin 25–50 mg nocte • Gabapentin
Erythema and oedema	<ul style="list-style-type: none"> • Topical corticosteroids • Elevation • Compression bandaging if adequate arterial blood flow and no cutaneous infection
Cutaneous malignancy	<ul style="list-style-type: none"> • Advise patients regarding self-checking skin for tumours • Annual dermatology review for patients on immunosuppression • Advise on sun protection
Cutaneous infection	<ul style="list-style-type: none"> • Monitor for development of cutaneous bacterial infection, viral infections (<i>Herpes simplex</i>, <i>Varicella zoster</i>, <i>Molluscum contagiosum</i> and papilloma virus), fungal infections
Dyspigmentation	<ul style="list-style-type: none"> • May not resolve • Trial of depigmenting creams containing hydroquinone • Combination with topical tretinoin and corticosteroids may be helpful • Camouflage creams
Leg ulcers	<ul style="list-style-type: none"> • Establish cause (squamous cell carcinoma, infection, arterial or venous insufficiency, sclerodermoid disease) • Wound management • Compression if good arterial supply • Consider referral to plastic surgeon
Dermatopathic contractures	<ul style="list-style-type: none"> • Physiotherapy • Massage of very potent topical steroids and topical calcineurin inhibitors may soften skin
Dystrophic nails	<ul style="list-style-type: none"> • Massage of very potent steroids/or topical calcineurin inhibitors into nail cuticles • Artificial nails
Hair loss	<ul style="list-style-type: none"> • Early stage disease may be reversible • Dermatology review, scalp biopsy and culture to exclude infection • Dermovate scalp lotion once or twice daily • Ensure adequate iron, vitamin B12, folate, zinc and vitamin D • Artificial hair pieces

involved in acute GvHD. The only diagnostic feature of chronic GI GvHD is the presence of oesophageal strictures (Filipovich *et al*, 2005). Clinical experience shows that it is not uncommon to have multiple causes at the same time for GI symptoms, therefore if empirical treatment for suspected

GvHD is not rapidly effective, systematic investigation is required and referral to a gastroenterologist should be considered.

Upper GI symptoms: dysphagia, nausea, vomiting and anorexia

GvHD may lead to a number of upper GI symptoms but other conditions should be considered, including acid reflux, metabolic causes and infection. Bile reflux is a commonly forgotten cause of intractable nausea (often responsive to sucralfate suspension) and small bowel bacterial overgrowth may cause any upper (or lower) GI symptom including reflux, nausea, anorexia, epigastric discomfort, bloating and wind.

Oesophageal or duodenal strictures occur rarely following stem cell transplantation. Guidelines for their management has been published by the British Society of Gastroenterology (Riley & Attwood, 2004) and early advice from experienced endoscopists must be sought as endoscopic intervention in immunosuppressed and thrombocytopenic patients is a high risk procedure.

If no obvious cause for persistent nausea, vomiting or anorexia is found after endoscopy ± radiology and trials of routine therapy have not helped, occult biliary sepsis or neurological disease should be considered.

Many endoscopists are not familiar with the spectrum of problems developed after stem cell transplantation and often appreciate guidance. Consider asking the endoscopist specifically to comment on the presence or absence of gastric bile reflux and specifically request that distal duodenal aspirates are taken and sent for microbiological culture as well as biopsies for histology. Figure 1 provides an overview of the management of upper GI symptoms.

Management of loose stool

The systemic management of GI luminal GvHD is discussed in the guideline on diagnosis and management of acute GvHD (Dignan *et al*, 2012a). Clinical experience suggests that other diagnoses not infrequently coexist. The cardinal clinical issue to differentiate is whether patients have diarrhoea or steatorrhoea. Causes for diarrhoea and steatorrhoea (Table II) require specific investigations. Patients with diarrhoea without associated jaundice or rash suggestive of GvHD should initially be investigated by upper GI endoscopy and flexible sigmoidoscopy and biopsy of the lower GI tract in preference to colonoscopy alone.

It is also imperative to exclude infectious causes for diarrhoea as infection may co-exist in patients with GvHD. The two most important treatable pathogens are cytomegalovirus (CMV) and *Clostridium difficile* infection (10% are toxin-negative) however, many other pathogens – amoebae, giardia, viruses such as herpes simplex virus (HSV), rotavirus or adenovirus, bacterial pathogens and fungi – can cause symptoms.

Table II. Physiological causes for diarrhoea and steatorrhoea following stem cell transplantation, which, if identified correctly, may respond well to treatment even if the gastrointestinal tract is also affected by graft-versus-host disease.

Common causes of diarrhoea	Useful/diagnostic investigations
GvHD	OGD and flexible sigmoidoscopy with duodenal and colonic biopsies Colonoscopy may be required as a second line test
Bile acid malabsorption	SeHCAT scan (nuclear medicine)
Carbohydrate malabsorption	Lactose/sucrose/fructose hydrogen methane breath test
Constipation with overflow	Plain abdominal X-ray
Dietary problems (e.g. excess/inadequate fibre)	Dietetic review
Drug side effects (e.g. mycophenolate mofetil, lansoprazole)	Drug levels/stop drug
Endocrine abnormalities	TFTs, Synacthen test
Infection	Stool culture/endoscopy
Rapid intestinal transit	Correct anti-diarrhoeal usage
Small intestinal bacterial overgrowth	Glucose hydrogen methane breath test/distal duodenal aspirate
<i>Common causes of steatorrhoea</i>	
Bile acid malabsorption	SeHCAT scan (nuclear medicine)
Intestinal lymphangiectasia	Time limited trial of a low fat diet (c 50 g/day)
Pancreatic insufficiency	Faecal elastase
Small intestinal bacterial overgrowth	Glucose hydrogen methane breath test/Small intestine aspirate

GvHD, graft-versus-host disease; OGD, oesophagogastroduodenoscopy; SeHCAT, selenium homocholic acid taurine; TFTs, thyroid function tests.

One single stool specimen is sufficient for the detection of bacteria or toxins, however three separate specimens are required to exclude parasitological causes with sufficient diagnostic sensitivity. Early endoscopic assessment is also mandatory, as stool culture may not detect viral infection, toxin-negative *clostridium difficile* or drug-induced colitis. The endoscopist must be specifically asked to take biopsies even if the endoscopic appearance is normal as the typical appearance of these conditions may be altered in people with reduced neutrophil counts. Occult anorectal sepsis may be an overlooked cause of morbidity. Clinical assessment by an experienced colorectal surgeon supplemented by magnetic resonance imaging scanning can often be helpful.

In patients with established GvHD in whom other causes of diarrhoea have been excluded, supportive care with anti-diarrhoeal agents including loperamide, codeine or octreotide may be helpful in addition to systemic immunosuppression.

Nutritional issues

Malnutrition and an elevated body mass index (BMI) are both risk factors for adverse outcome after stem cell transplantation. A BMI of more than 25 may be associated with an increased risk of GvHD (Deeg *et al*, 1995; Fuji *et al*, 2009). Malnutrition is associated with decreased overall survival and increased infection risk. Trained dietetic support is a standard for units performing transplantation. Pre-transplant patients should be assessed nutritionally as soon as possible and all patients with gut GvHD should be assessed by a dietician with experience of managing patients with gut GvHD.

Nutritional requirements will vary with age, gender, weight and severity of GvHD. Maintaining nutritional status may be very demanding. Acutely ill patients receiving parenteral nutrition need, as a minimum, twice-weekly monitoring of phosphate, calcium, magnesium, bicarbonate and monthly assessment of selenium, copper and zinc. Supplemental vitamin D, E and B12 should be considered if parenteral nutrition is continued for several months.

Enteral nutrition is always to be preferred if possible to parenteral nutrition. Maintaining oral intake may be difficult. However, data from allogeneic transplant patients treated at home suggest that they maintain their oral intake better than patients in a hospital setting, strongly suggesting that environmental factors, e.g., quality, presentation, timing and temperature of the meal, is critically important (Svahn *et al*, 2008).

Nasogastric feeding is more likely to be effective if started early before mucositis is established. The advantage of nasojejunal feeding is not established and many jejunal placed tubes will rapidly displace into the stomach. Nasogastric feeding is significantly less likely to be associated with systemic infection than parenteral nutritional and small but challenging studies have suggested that enteral feeding is associated with significantly less GvHD (Seguy *et al*, 2006). Unless there is severe intestinal failure, when parenteral nutrition with added glutamine should be used, oral nutrition with or without intravenous fluids is the best way to manage patients (Murray & Pindoria, 2009).

Recommendations

- Referral to a gastroenterologist should be considered in patients with suspected GI GvHD (1C).
- In view of the wide differential diagnosis, patients with diarrhoea without associated jaundice or rash suggestive of GvHD should be investigated by both upper (with duodenal aspirate and biopsies) and lower (flexible sigmoidoscopy and biopsy) GI endoscopy in preference to colonoscopy alone (1C).
- All patients should be assessed and reviewed by a dietician with experience of managing patients with gut GvHD and each unit should have an agreed protocol for nutritional issues (1C).

<p>Step 1: Metabolic profile (including CRP, U&Es, LFTs) Screen for sepsis</p>
<p>Step 2: Trial of full dose proton pump inhibitor Add sucralfate suspension (1 g qds) if no response</p>
<p>Step 3: Early upper GI tract endoscopy</p> <ul style="list-style-type: none"> • Oesophageal brushings if evidence of possible fungal infection • Multiple biopsies if any ulceration with specific request for viral stains including CMV and HSV • Comment on presence or absence of bile in the stomach • Send duodenal biopsies and distal duodenal aspirate for microbiology
<p>Step 4: If biopsies confirm GvHD, commence systemic immunosuppressive treatment if not already started Initiate treatment for any associated infection If more distal small bowel pathology is suspected, consider barium follow through/enteroscopy or capsule endoscopy If extra-luminal disease or sepsis is possible, consider cross sectional imaging with ultrasound or CT scanning</p>

Fig 1. A management approach to unexplained nausea, retching, vomiting or anorexia. CRP, C-reactive protein; U&Es, urea and electrolytes; LFTs, liver function tests; GI, gastrointestinal; CMV, cytomegalovirus; HSV, herpes simplex virus, GvHD, graft-versus-host disease; CT, computerized tomography.

Genital cGvHD

Chronic GvHD of the vulva and vagina are well recognized. The incidence varies widely between published reports, with rates from 2% to 49%. It is likely that the incidence is underestimated in some reports where only those patients who reported symptoms were included. Stratton *et al* (2007) reported an incidence of 11% in a cohort of 266 female patients, while Spiryda *et al* (2003) reported an incidence of only 2% in 501 female patients. In contrast, a prospective surveillance programme of 61 female patients reported an incidence of 35% at 1 year and 49% at 2 years (Zantomio *et al*, 2006). Spinelli *et al* (2003) reported an incidence of 25%. In both of the latter studies, the incidence of systemic cGvHD overall was very high (>80%). The association of cGvHD in other organs with genital GvHD is well recognized, in particular with sclerodermatous skin disease (Zantomio *et al*, 2006; Stratton *et al*, 2007). Some, but not all, studies suggest that genital GvHD is more common following transplants that use peripheral blood stem cells as the source compared to bone marrow (Flowers *et al*, 2002; Mohy *et al*, 2002).

Symptoms include pain, dryness, dysuria and dyspareunia. Clinical features include: erythematous patches, redness, mucosal erosions/fissures, retiform leukokeratosis (lichen planus-like lesions), vaginal synechiae and adhesions, complete vaginal closure or shortening and architectural changes due to sclerosis. Systems for grading GvHD into minimal, moderate and severe have been proposed (Spinelli *et al*, 2003; Stratton *et al*, 2007). The grade of genital GvHD does not necessarily correlate with the severity of the systemic GvHD.

The diagnosis of cGvHD may be easily made in the presence of characteristic features and evidence of systemic GvHD, however, histological diagnosis is strongly recom-

mended in the absence of systemic features, particularly as the pathological features will distinguish GvHD from a hypo-oestrogenic state, an important differential diagnosis. Infections should also be actively excluded in all cases (Couriel *et al*, 2006).

Female patients, particularly those with systemic cGvHD, should be actively questioned about vulvovaginal symptoms. Genital cGvHD is reported to occur late and thus may be completely avoided by preventive strategy and education in those with systemic cGvHD. Those with difficult-to-manage symptoms should be referred to a gynaecology service. Treatment strategies have been outlined in the NIH ancillary therapy and supportive care guidelines (Couriel *et al*, 2006). These guidelines are predominantly based on evidence from non-randomized clinical studies or opinion, or from evidence in analogous disease. Simple preventative measures, such as avoidance of irritants, should be advised. Emollients applied to the external genitalia may relieve symptoms. Replens or other gels may be used in the vagina for comfort. Topical therapy with high or ultrahigh potency steroids (clobetasol/beclomethasone) or with immunosuppressive agents (e.g. tacrolimus ointment) is associated with a high success rate and is recommended as first line treatment; Zantomio *et al* (2006) reported improvement in 23/28 patients, while Stratton *et al* (2007) reported response rates of 27/29 after 4–8 weeks of therapy. More rapid healing has been reported with the addition of hormone-replacement therapy (Stratton *et al*, 2007). Although surgery may be indicated for those with severe signs, such as complete vaginal closure, the most recent reports suggest that surgery is completely avoidable using simpler measures such as dilators and/or oestrogen rings. Stratton *et al* (2007) reported that 11/12 women with vaginal synechiae responded to these interventions. In a minority of patients the symptoms of vulvovaginal GvHD may not be resolved by topical therapies and in such cases systemic immunosuppression may be required (Stratton *et al*, 2007).

GvHD involving the male genito-urinary tract or penis is far less commonly reported and the incidence is not well known. The literature consists predominantly of case reports. cGvHD may involve the glans penis and foreskin. Inflammation may lead to scarring and fibrosis (causing phimosis) and features may resemble lichen planus (Marks *et al*, 2011a). Topical steroids form the mainstay of therapy and surgery may be required for advanced cases (Au *et al*, 2008).

Referral to a specialist with appropriately experience in genital GvHD is recommended. Assessment and advice should include treatment of symptoms and signs, consideration of hormone replacement, screening for secondary malignancies and advice related to sexual health and function. It is recommended that links with local services (e.g. individual practitioners, sexual health clinics) are formed and that shared treatment pathways are agreed. The management of genital GvHD is summarized in Fig 2.

<p>Prevention: Genital hygiene Consideration of oestrogen replacement</p>
<p>Symptomatic treatment (mild): Emollients (external)/lubricants (vaginal)</p>
<p>First line treatment: High and ultra-high potency corticosteroids e.g. clobetasol gel 0.05%, betamethasone gel 0.05% Consider topical calcineurin inhibitors e.g. tacrolimus 0.1%</p>
<p>Second line/resistant disease: Systemic therapy Dilator therapy Surgery for strictures</p>

Fig 2. A flow chart to summarize management of genital graft-versus-host disease (GvHD).

Recommendations

- All patients should be actively questioned about genital tract symptoms (1C).
- Referral for specialist advice should be considered in all patients with difficult-to-manage genital symptoms (1C).
- High potency topical steroids (+/- topical calcineurin inhibitors) are recommended as first line therapy (1C).

Liver GvHD

Liver involvement is very common in acute GvHD with around 50% of patients affected. It is estimated that 40–55% of patients with cGvHD have liver involvement although this is usually asymptomatic (Lee *et al*, 2002b). The diagnosis and systemic management of liver GvHD is discussed in the accompanying guideline on acute GvHD (Dignan *et al*, 2012a).

Patients with liver involvement with GvHD should be reviewed by a hepatologist with an interest in GvHD wherever possible. The management includes augmentation of immunosuppression with high-dose corticosteroids (methylprednisolone 2 mg/kg/day or equivalent) still representing the main treatment. High-dose ursodeoxycholic acid (UDCA) (30–40 mg/kg/day) is helpful to stimulate choleresis and alleviate cholestasis and itching. Many centres now use UDCA on a pre-emptive basis due to its virtual complete lack of side effects (Ruutu *et al*, 2002). Standard supportive measures for management of liver failure, such as intravenous vitamin K, spironolactone and albumin infusions, with careful fluid balance planning should be in place. Liver transplantation has been described in hepatic aGvHD (Rhodes *et al*, 1990) for worsening coagulopathy, jaundice and development of encephalopathy.

Recommendation

- Referral for specialist hepatology opinion should be considered in patients with significant liver GvHD (1C).

Ocular GvHD

The eyes can be involved in both acute and cGvHD but much more commonly in the latter. In addition, patients may have ocular side effects from the drugs used to treat systemic GvHD or the immunosuppression caused by them. Diagnosis is largely made on clinical symptoms and signs, with tests such as Schirmer's test and tear break up time (which identify reduced amounts and quality of tears), being useful in early disease.

The eyes become involved in 25–45% of patients with cGvHD (Lee *et al*, 2002b). Ocular cGvHD is particularly common in those with cutaneous or oral involvement but may also be the initial manifestation of the disease. No obvious associations have been found between the source of the stem cells and ocular disease. All parts of the eye may be affected. The commonest symptoms at onset are dry, gritty and painful eyes, which are caused by inflammatory destruction of the conjunctiva and lacrimal glands causing tear deficiency and ocular surface damage. Secondary involvement of the meibomian glands leads to further reduced tear film quality and the possibility of superimposed infection. Conjunctival and corneal damage with scarring and subsequent permanent visual loss may result (reviewed in Kim, 2006). Patients with symptoms suggestive of significant ocular involvement should be reviewed by an ophthalmologist who preferably has an interest in ocular GvHD.

Uveitis (intraocular inflammation) is less common and predominantly occurs during exacerbations of systemic GvHD (Wertheim & Rosenbaum, 2005). Cataracts may occur especially if systemic corticosteroids are required or local radiation given. Patients should be made aware of this complication and advised to seek ophthalmic advice if they notice a reduction in vision. A variety of complications may occur in the retina, such as cotton wool spots, haemorrhages and optic disc swelling. Systemic use of ciclosporin may also contribute to these findings. Infectious retinitis from CMV, HSV or *Varicella zoster* virus (VZV) may also be seen if the patient becomes profoundly immunosuppressed from systemic medication.

There are no controlled trials of therapy for ocular GvHD and current treatment options are often unsatisfactory in patients with more than mild ocular surface dryness. Therapy consists of symptomatic medication, such as artificial tears and topical anti-inflammatory/antibiotic therapy as required. Autologous serum tears may also be useful in some patients (Chiang *et al*, 2007; Kojima *et al*, 2008). Topical ciclosporin has been used successfully in small numbers of patients. If ocular lubricants are insufficient or are being used extremely frequently, lacrimal duct punctal occlusion (Ervin *et al*, 2010; Westeneng *et al*, 2010) may help. Attention is paid to the eyelids, keeping them clean and preventing eyelashes from abraded the cornea if there is entropion from conjunctival scarring. Moisture chambers,

Eye Symptoms: Refer to ophthalmologist to identify cause of symptoms and establish if any visual loss
Dry Eyes: Lubricants Treat any associated eyelid disease
If lubricants effective but need to be used frequently: Try punctal plugs
If lubricants not effective: Topical ciclosporin and autologous serum eye drops

Fig 3. A flow chart summarizing the management of ocular graft-versus-host disease (GvHD).

retinoic acid, collagen shields and limbal cell transplantation have all been tried and, in severe cases, amniotic membrane grafts and corneal transplantation may be required but they may not be effective in an eye which is very dry. Systemic immunosuppression may have an additional role in some patients (Westeneng *et al*, 2010). The management of ocular GvHD is summarized in Fig 3.

Recommendations

- Patients with symptoms suggestive of significant ocular involvement should be reviewed by an ophthalmologist preferably with an interest in ocular GvHD (1C).
- Patients on prolonged systemic steroids for cGvHD should be aware that their vision may be reduced if they develop cataracts and should seek ophthalmic advice if this occurs (2C).
- Supportive care with artificial tears and topical anti-inflammatory/antibiotic treatment may be helpful as first line treatment (2C).

Oral GvHD

The oral cavity is frequently involved in cGvHD and is the second most common site involved after skin following peripheral blood stem cell transplantation (Flowers *et al*, 2002). Diagnostic clinical features include lichenoid features, hyperkeratotic plaques and restriction of mouth opening from fibrotic bands (Filipovich *et al*, 2005). Distinctive features include xerostomia, mucocelles, mucosal atrophy, mucosal erosion and ulcers. In patients with these features, the diagnosis can be made if cGvHD has already been confirmed in another organ without the need for a further biopsy. Alternatively, if no other organs are involved or an alternative diagnosis is suspected, biopsy of the oral mucosa should be performed (Meier *et al*, 2011). Shulman *et al* (2006) summarized the minimal histopathological diagnostic criteria.

All patients with significant oral GvHD should be referred to a specialist in Oral Medicine. The treatment of oral cGvHD has recently been summarized following the Ger-

Prevention: Oral hygiene instruction Dental and oral health review every 6 months Infection prophylaxis only when specific fungal, bacterial or viral agent is demonstrated Awareness of the risk of oral malignancies
Symptomatic treatment (mild): Taste disturbance: sodium bicarbonate solution or BioXtra® mouthwash Use toothpaste for sensitive teeth Dry mouth: BioXtra® gel and Biotene moisturising drops® Analgesia: Difflam® mouthwash or lidocaine before meals
First line treatment: Betamethasone 0.5 mg in 10 mL water used as a mouthwash for 2 min then expectorated three times daily. No food or drink to be taken for a minimum of 1 h after mouthwash Consider topical calcineurin inhibitors e.g. tacrolimus 0.1%
Second line/resistant disease: Systemic therapy ECP

Fig 4. A flow chart summarizing management of oral GvHD. GvHD, graft-versus-host disease; ECP, Extracorporeal photopheresis.

man-Austrian-Swiss working party conference (reviewed in Meier *et al*, 2011). Topical steroids have been used in several studies and are recommended as first line therapy. Budesonide, at a dose of 3 mg dissolved in 5–10 ml of saline, has been found to be beneficial (Elad *et al*, 2003b; Sari *et al*, 2007). Response to topical dexamethasone was observed in a retrospective study of 16 patients (Wolff *et al*, 2004) and betamethasone rinse was beneficial in a case report when combined with systemic agents (França *et al*, 2001). Both budesonide and dexamethasone have significant systemic absorption whereas betamethasone 0.5% has mainly local effects in the oral cavity. Topical tacrolimus and ciclosporin have also been used in small series with some positive results (Epstein & Reece, 1994; Eckardt *et al*, 2004; Sánchez *et al*, 2004; Albert *et al*, 2007; Fricain *et al*, 2007). A combination protocol using dexamethasone and tacrolimus was assessed retrospectively in 14 patients and was reported to reduce symptoms due to cGvHD (Mawardi *et al*, 2010). ECP has been reported to be beneficial in the management of oral GvHD and is discussed in the guideline on cGvHD diagnosis and management (Dignan *et al*, 2012b).

Supportive care for patients with cGvHD includes twice-yearly dental assessments, oral care protocols, infection prophylaxis and monitoring for the development of osteonecrosis of the jaw in patients receiving intravenous or prolonged oral bisphosphonates. Patients should be warned about the increased risk of oral malignancies and re-referred to an Oral Medicine specialist if malignancy is suspected. Artificial saliva or the administration of parasympathetic agents e.g. pilocarpine may be beneficial for patients with hyposalivation (Singhal *et al*, 1997; Nagler & Nagler, 1999). BioXtra gel® is symptomatically helpful especially for use before sleeping and Biotene® moisturising drops during the day to facilitate talking and swallowing. Local anaesthetics may be helpful for pain control (reviewed in Meier *et al*, 2011). Both local anaesthetics and analgesics may include lidocaine or Difflam®

mouthwash. Patients who experience pain while brushing their teeth may benefit from using toothpastes designed for sensitive teeth. Taste disturbance may be helped by sodium bicarbonate and water mouthwash or BioXtra[®] mouthwash. The management of oral GvHD is summarized in Fig 4.

Recommendations

- **Referral to Oral Medicine should be considered in patients with significant oral symptoms (1C).**
- **Topical therapies including steroid mouthwashes are recommended as first line treatment (2C).**
- **ECP is recommended as a second line systemic therapy for steroid-refractory GvHD (1B).**

Pulmonary GvHD

It is likely that the bronchiolitis obliterans syndrome is under-diagnosed as it has been shown that 26% of allogeneic transplant patients and 30% of those with cGvHD developed airflow decline post-transplant (Chien *et al*, 2003). The onset of pulmonary GvHD can be insidious with slowly progressive dyspnoea and cough and may occur as other manifestations of cGvHD are improving and immunosuppression is being tapered. The differential diagnosis includes infection of the respiratory tract and cryptogenic organizing pneumonia, which often presents with fever, cough and consolidated infiltrates on chest X-ray and responds to steroid therapy (Chien *et al*, 2003). Referral to a respiratory physician should be considered in all patients with suspected pulmonary GvHD.

Diagnostic investigations include pulmonary function tests, chest X-ray, high-resolution expiratory chest computerized tomography (CT) scan and bronchoscopy to exclude infection. Pulmonary function tests demonstrate the features of air flow obstruction with a reduction in FEV₁ (forced expiration volume at 1 s), FVC (forced vital capacity) and also in the FEV₁/FVC ratio. FEV₁ is the most sensitive marker for early obstructive changes and is likely to be the best way of identifying patients at risk of developing clinically significant disease (Dudek *et al*, 2003; Chien *et al*, 2010). A FEV₁ of < 45% appears strongly predictive of poor outcome (Schwarer *et al*, 1992). Regular FEV₁ monitoring is recommended with formal pulmonary function testing or home monitoring of spirometry to allow early detection of problems. Chest radiographs may be normal but can demonstrate a range of changes, from focal shadowing to more diffuse changes. High-resolution expiratory chest CT scan can show evidence of air trapping, small airway thickening or bronchiectasis and may help in the distinction of bronchiolitis obliterans (BO) from bronchiolitis obliterans with organizing pneumonia (BOOP), which has prognostic relevance. Bronchoscopy with broncho-alveolar lavage is an

important tool to exclude infection in patients with symptoms suggestive of infection. Lung biopsies have a high complication rate (White *et al*, 2000) and may be best reserved for patients where there is uncertainty about the diagnosis.

First line treatment consists of augmentation or re-institution of systemic immunosuppression, usually 1 mg/kg of oral prednisolone, but is unsatisfactory with a 5-year survival rate as low as 10%, as considerable damage may have occurred prior to the onset of clinical symptoms (Dudek *et al*, 2003). BOOP tends to be more steroid-responsive than BO. A small study suggested that monthly-pulsed methylprednisolone (10 mg/kg for 3 days) may stabilize lung function in children who develop BO as a manifestation of cGvHD and this approach may be a useful second line option (Ratjen *et al*, 2005). Lung transplantation may be appropriate in selected patients. A recent report also described a response to ECP in 6/9 patients with refractory disease (Lucid *et al*, 2011).

The role of imatinib in the systemic treatment of cGvHD is outlined in the guideline on cGvHD diagnosis and management (Dignan *et al*, 2012b). It may be particularly helpful in patients with pulmonary GvHD. Complete or partial responses were observed in 7/11 patients with mild pulmonary cGvHD after 6 months of treatment (Olivieri *et al*, 2009). The initial dose used was 100 mg once daily, which was increased to 200 mg after 1 month in the absence of toxicities. A small pilot study suggested that imatinib shows best responses in those with mild pulmonary cGvHD and is not effective in severe disease (Stadler *et al*, 2009). A 6-month trial of imatinib is recommended in patients with pulmonary GvHD who do not respond to 1 mg/kg of prednisolone. The initial recommended starting dose is 100 mg once daily.

Macrolides, inhaled steroids and leucotriene inhibitors may be helpful adjunctive therapies. Khalid *et al* (2005) used azithromycin in 8 patients with an obstructive defect on pulmonary function tests and reported improvements in FVC and FEV₁. These results were not replicated in a recent small randomized controlled trial (Lam *et al*, 2011). A retrospective study of 17 patients reported a benefit of high-dose inhaled corticosteroids in patients with new onset air-flow obstruction (Bashoura *et al*, 2008). A pilot study of montelukast showed improvement in 3/5 patients with BO syndrome (Or *et al*, 2007). A recent report described a steroid-sparing effect of using fluticasone, azithromycin and montelukast therapy in 8 patients (Norman *et al*, 2011). Supportive care to prevent superadded infection is critical (see below). In this regard, intravenous immunoglobulin may be helpful in this group who are particularly susceptible to infection if immunoglobulin levels are low (Bass *et al*, 1993). In addition, vaccination against pneumococcus and seasonal influenza is recommended (see vaccination section).

Recommendations

- Referral to a respiratory physician should be considered in all patients with suspected pulmonary GvHD (1C).
- All patients with cGvHD should be screened using pulmonary function tests regardless of symptoms (1A).
- Systemic steroids are recommended in patients with pulmonary GvHD at a dose of 1 mg/kg of prednisolone and, for those not responding, consider pulsed steroids or imatinib (2C).
- Supportive care including intravenous immunoglobulin, vaccinations and azithromycin is also recommended (2C).

Antimicrobial prophylaxis for infections in GvHD

Patients with cGvHD are highly immunocompromised and infection is the single most important non-relapse cause of mortality in such patients. Infection during acute and chronic GvHD following haematopoietic stem cell transplantation (HSCT) is primarily the consequence of T-cell dysfunction. Hence intra-cellular pathogens, such as the herpes viruses, opportunistic fungi and parasites, such as *Toxoplasma gondii* and *Cryptosporidium parvum*, are the main causes of sepsis. In addition, defective antibody production (particularly of opsonic antibodies) gives rise to an increased risk of infection with encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. There are very few studies of antimicrobial prophylaxis in the setting of cGvHD so much of the information below is derived from studies undertaken in the general post-transplant setting.

Antibacterial prophylaxis

In the post-engraftment period the major risk is from encapsulated organisms. Whilst there are no randomized controlled trials to support this, guidelines recommend prophylaxis for *S. pneumoniae* (Engelhard *et al*, 2009), given that the risk of infection is more than double that of patients without GvHD (Engelhard *et al*, 2002). Phenoxymethyl penicillin has been shown to prevent infection in other patient groups and may be suitable. Choice should be based on local antibiotic susceptibility data.

Antifungal prophylaxis

There are fewer reports of antifungal prophylaxis specifically in patients with GvHD. In retrospective series, itraconazole and weekly liposomal amphotericin B have been reported to have some benefit in reducing the incidence of invasive fungal infections (Grigg *et al*, 2004; El Cheikh *et al*, 2010). In a randomized, double-blind trial, in patients with acute or cGvHD on steroids, posaconazole was as least as effective as

fluconazole in preventing all fungal infections at the end of 112 days but superior in preventing invasive aspergillosis (2.3% vs. 7%) (Ullmann *et al*, 2007). In a retrospective review, Gergis *et al* (2010) reported that voriconazole may be more effective than fluconazole or itraconazole in preventing invasive fungal infection in patients receiving glucocorticoids post-transplant. In addition, Marks *et al* (2011b) compared voriconazole to itraconazole in patients with acute or cGvHD. Both agents were effective in preventing invasive fungal infection but voriconazole was tolerated for a significantly longer mean duration (Marks *et al*, 2011b). Prophylaxis with mould active azoles is recommended for patients on high doses of steroids for cGvHD but these studies do not include patients on low doses of steroids (<15 mg) and there is no evidence that antifungal prophylaxis is of benefit in this group.

There are no studies of *Pneumocystis* prophylaxis specifically during GvHD, but the risk of infection is increased in cGvHD and prophylaxis should be considered (Chen *et al*, 2003).

Antiviral prophylaxis

GvHD is a significant risk factor for a number of herpes virus infections but randomized controlled trials have not been limited to this post-transplant phase alone.

Aciclovir and valaciclovir have been shown to reduce the incidence of CMV reactivation, but not CMV disease, post-transplant (Prentice *et al*, 1994; Ljungman *et al*, 2002). IV ganciclovir reduces the risk of CMV disease but has no survival advantage over placebo, because of secondary neutropenia and associated infection (Goodrich *et al*, 1993; Winston *et al*, 1993, 2003; Boeckh *et al*, 1996).

Monitoring of CMV viral load allows prediction of disease and subsequent early pre-emptive therapy and has been shown to prevent CMV disease post-transplant. Ganciclovir and foscarnet are equally effective and cidofovir also prevents disease but is associated with renal toxicity (Lengerke *et al*, 2006; Winston *et al*, 2006; Einsele *et al*, 2006; Volin *et al*, 2008; van der Heiden *et al*, 2006; Ayala *et al*, 2006; Busca *et al*, 2007; Reusser *et al*, 2002; Ljungman *et al*, 2001; Platzbecker *et al*, 2001; Cesaro *et al*, 2005; Bacigalupo *et al*, 1996; Mattes *et al*, 2004).

Aciclovir prophylaxis has not been specifically studied in the setting of cGvHD but there is evidence that the drug is effective in preventing HSV and VZV disease in the post-transplant setting and therefore may also be beneficial in the setting of cGvHD (Sara *et al*, 1981; Gluckman *et al*, 1983; Hann *et al*, 1983; Ljungman *et al*, 1986; Shepp *et al*, 1987; Perren *et al*, 1988; Bergmann *et al*, 1995; Boeckh *et al*, 2006).

It may also be helpful to monitor patients with cGvHD for Epstein-Barr virus reactivation as this may lead to the development of post-transplant lymphoproliferative disorder (Omar *et al*, 2009).

Antiparasitic prophylaxis

The incidence of toxoplasmosis is around 0.8% post-HSCT (Martino *et al*, 2000a). It almost always occurs in seropositive patients (Martino *et al*, 2000b; Mele *et al*, 2002) and, in a 5-year European Group for Blood and Marrow Transplantation survey, 77% had prior acute or cGvHD (Martino *et al*, 2000b). The majority of cases also occur in patients who are not currently receiving cotrimoxazole for *pneumocystis* pneumonia (PCP) prophylaxis. There is insufficient evidence to make a recommendation for toxoplasmosis prophylaxis in this setting, but the recommendations for PCP prophylaxis with cotrimoxazole will provide a potential protective benefit.

Recommendations

- Prophylaxis against viral, fungal, *Pneumocystis jiroveci* and *streptococcus pneumoniae* infection should be considered in all patients receiving immunosuppressive agents for cGvHD (1A).
- The prophylactic and/or pre-emptive strategy for prevention of CMV infection including regular monitoring of CMV polymerase chain reaction adopted for HSCT recipients should be continued throughout the period of acute and/or cGvHD (1B).
- A mould-active azole is recommended for prophylaxis in patients undergoing treatment for GvHD (1A); suitable agents include posaconazole and voriconazole (1A) or itraconazole with regular monitoring of levels (2B).

Vaccination

Several guidelines on vaccinations have previously been published (Ljungman *et al*, 2005, 2009) and a recent report focussed on recommendations in patients with cGvHD (Hilgendorf *et al*, 2011). Previous studies have shown that patients with cGvHD are able to mount a response to vaccination and there is likely to be little benefit to postponing vaccination in these patients until their GvHD has resolved and they have stopped immunosuppression. Hilgendorf *et al* (2011) suggested that it may be helpful to wait until patients are receiving < 0.5 mg/kg of prednisolone and dual agent, rather than triple agent, immunosuppression as responses may be higher. The main exception is the administration of live vaccines, which are contraindicated in cGvHD patients.

The measurement of antibody levels before and after vaccination may be helpful to establish the level of protection and guide the need for further booster immunizations (Ljungman *et al*, 2009). In view of the significant risk of infection in this population, vaccination against pneumococcus, influenza and *Haemophilus influenzae* is particularly prudent. Inactivated influenza vaccine can be given 4–

6 months post-transplant and should be repeated on an annual basis. The pneumococcal conjugate vaccination can be administered 3–6 months post-transplant and the *Haemophilus influenzae* conjugate at 6–12 months post-transplant. A full re-vaccination schedule is described in Ljungman *et al* (2009). Household contacts should also receive routine vaccinations plus the seasonal influenza vaccine (reviewed in Hilgendorf *et al*, 2011).

Recommendations

- Live vaccines must not be administered in patients with cGvHD (1A).
- All patients with cGvHD should receive vaccination against pneumococcus, influenza and *Haemophilus influenzae* (1B).

Complications associated with long-term steroid use

Many patients with cGvHD require long-term treatment with corticosteroids. Regular monitoring of blood pressure and checking blood or urine for glucose is recommended at clinic visits. All patients should receive gastric protection with either ranitidine or a proton pump inhibitor. A dual-emission X-ray absorptiometry (DEXA) scan may be considered in patients who are expected to receive steroid treatment for more than 3 months. DEXA interpretation in children and adolescents should be according to the guidelines published by the International Society for Clinical Densitometry (<http://www.iscd.org/Visitors/pdfs/ISCD2007OfficialPositions-Combined-AdultandPediatric.pdf>). All symptoms of back pain should be investigated for vertebral collapse. Correction of deficiency/insufficiency in vitamin D and calcium and mobilization are recommended. Use of bisphosphonates in children with secondary osteoporosis remains controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend that the use of these agents should be limited to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass (Bachrach & Ward, 2009). Measurement of 9 a.m. cortisol can be helpful during the withdrawal of steroids doses. Morning cortisol values of 400 nmol/l or more indicate that the dose of steroids can be reduced safely. Recovery of the hypothalamo-pituitary-adrenal axis can also be monitored by performing a short Synacthen® test. If cortisol peak response to the short Synacthen® test is suboptimal, emergency steroid cover should be provided for acute illness and surgical stress. Adrenal failure should be suspected if there are symptoms such as lethargy, malaise, anorexia, headache, nausea and fever. Children should have growth monitored and be referred to an endocrinologist for specialist review.

Recommendation

- All patients on long-term steroid treatment should have blood pressure and glucose monitored at clinic visits and should receive gastric protection (1A).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, the British Society of Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.

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Author contributions

FLD reviewed the literature, wrote sections of the initial draft of the manuscript and redrafted and compiled the final version. BES co-chaired the writing group, wrote sections of the initial draft and redrafted and compiled the final version. MNP co-chaired the writing group, reviewed the literature and revised the manuscript. AC represented BCSH, reviewed the literature and revised the manuscript. GJ represented BSBMT, reviewed the literature and revised the manuscript. JS, PS, FF, JA, SL, AA, CK, NH reviewed the literature, wrote sections of the initial draft of the manuscript and revised the final draft. JC, PA, PT and PM reviewed the literature and revised the manuscript.

Conflicts of interest

All authors have declared any potential conflicts of interest to BCSH. FLD and BES have received research funding, honoraria and speaker's fees from Therakos, a Johnson and Johnson company. PCT has received honoraria from Therakos, a Johnson and Johnson company. None of the other authors have declared any conflicts of interest.

References

Albert, M.H., Becker, B., Schuster, F.R., Klein, B., Binder, V., Adam, K., Nienhoff, C., Führer, M. & Borkhardt, A. (2007) Oral graft vs. host disease in children—treatment with topical tacrolimus ointment. *Pediatric Transplantation*, **11**, 306–311.

Atkinson, K., Weller, P., Ryman, W. & Biggs, J. (1986) PUVA therapy for drug-resistant graft-versus-host disease. *Bone Marrow Transplantation*, **1**, 227–236.

Au, W.Y., Yeung, C.K., Cheung, M.C. & Trendell-Smith, N.J. (2008) Penile lichen sclerosus after allogeneic stem cell transplantation. *British Journal of Dermatology*, **159**, 470–472.

Ayala, E., Greene, J., Sandin, R., Perkins, J., Field, T., Tate, C., Fields, K.K. & Goldstein, S. (2006) Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **37**, 851–856.

Bachrach, L.K. & Ward, L.M. (2009) Clinical review 1: Bisphosphonate use in childhood oste-

oporosis. *Journal of Clinical Endocrinology and Metabolism*, **94**, 400–409.

Bacigalupo, A., Bregante, S., Tedone, E., Isaza, A., Van Lint, M.T., Trespi, G., Occhini, D., Gualandi, F., Lamparelli, T. & Marmont, A.M. (1996) Combined foscarnet-ganciclovir treatment for cytomegalovirus infections after allogeneic hemopoietic stem cell transplantation. *Transplantation*, **62**, 376–380.

Bashoura, L., Gupta, S., Jain, A., Couriel, D.R., Komanduri, K.V., Eapen, G.A., Safdar, A., Broglio, K.R., Adachi, R. & Dickey, B.F. (2008)

Appendix GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines

Strength of recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) *High*: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) *Moderate*: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) *Low*: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

- Inhaled corticosteroids stabilize constrictive bronchiolitis after hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **41**, 63–67.
- Bass, E.B., Powe, N.R., Goodman, S.N., Graziano, S.L., Griffiths, R.I., Kickler, T.S. & Wingard, J.R. (1993) Efficacy of immune globulin in preventing complications of bone marrow transplantation: a meta-analysis. *Bone Marrow Transplantation*, **12**, 273–282.
- Bergmann, O.J., Ellermann-Eriksen, S., Mogensen, S.C. & Ellegaard, J. (1995) Acyclovir given as prophylaxis against oral ulcers in acute myeloid leukaemia: randomised, double blind, placebo controlled trial. *British Medical Journal*, **310**, 1169–1172.
- Boeckh, M., Gooley, T.A., Myerson, D., Cunningham, T., Schoch, G. & Bowden, R.A. (1996) Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood*, **88**, 4063–4071.
- Boeckh, M., Kim, H.W., Flowers, M.E., Meyers, J.D. & Bowden, R.A. (2006) Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation – a randomized double-blind placebo-controlled study. *Blood*, **107**, 1800–1805.
- Busca, A., de Fabritiis, P., Ghisetti, V., Alice, T., Mirabile, M., Gentile, G., Locatelli, F. & Falda, M. (2007) Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. *Transplant Infectious Disease*, **9**, 102–107.
- Calzavara, P.P., Porta, F., Izzi, T., Venturini, M., Capezzer, R., Zane, C. & Notarangelo, L.D. (2003) Prospects for ultraviolet A1 phototherapy as a treatment for chronic cutaneous graft-versus-host disease. *Haematologica*, **88**, 1169–1175.
- Cesaro, S., Zhou, X., Manzardo, C., Buonfrate, D., Cusinato, R., Tridello, G., Mengoli, C., Palù, G. & Messina, C. (2005) Cidofovir for cytomegalovirus reactivation in pediatric patients after hematopoietic stem cell transplantation. *Journal of Clinical Virology*, **34**, 129–132.
- Chavan, R. & el-Azhary, R. (2011) Cutaneous graft-versus-host disease: rationales and treatment options. *Dermatologic Therapy*, **24**, 219–228.
- Chen, C.S., Boeckh, M., Seidel, K., Clark, J.G., Kansu, E., Madtes, D.K., Wagner, J.L., Witherspoon, R.P., Anasetti, C., Appelbaum, F.R., Bensing, W.I., Deeg, H.J., Martin, P.J., Sanders, J.E., Storb, R., Storek, J., Wade, J., Siadak, M., Flowers, M.E. & Sullivan, K.M. (2003) Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **32**, 515–522.
- Chiang, C.C., Lin, J.M., Chen, W.L. & Tsai, Y.Y. (2007) Allogeneic serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Cornea*, **26**, 861–863.
- Chien, J.W., Martin, P.J., Gooley, T.A., Flowers, M.E., Heckbert, S.R., Nichols, W.G. & Clark, J.G. (2003) Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *American Journal of Respiratory and Critical Care Medicine*, **168**, 208–214.
- Chien, J.W., Duncan, S., Williams, K.M. & Pavletic, S.Z. (2010) Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation—an increasingly recognized manifestation of chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **16**(1 Suppl): S106–S114.
- Choi, C.J. & Nghiem, P. (2001) Tacrolimus ointment in the treatment of chronic cutaneous graft-vs-host disease: a case series of 18 patients. *Archives of Dermatology*, **137**, 1202–1206.
- Couriel, D., Carpenter, P.A., Cutler, C., Bolaños-Meade, J., Treister, N.S., Gea-Banacloche, J., Shaughnessy, P., Hymes, S., Kim, S., Wayne, A.S., Chien, J.W., Neumann, J., Mitchell, S., Syrjala, K., Moravec, C.K., Abramovitz, L., Liebermann, J., Berger, A., Gerber, L., Schubert, M., Filipovich, A.H., Weisdorf, D., Schubert, M.M., Shulman, H., Schultz, K., Mittelman, B., Pavletic, S., Vogelsang, G.B., Martin, P.J., Lee, S.J. & Flowers, M.E. (2006) Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group report. *Biology of Blood and Marrow Transplantation*, **12**, 375–396.
- Deeg, H.J., Seidel, K., Bruemmer, B., Pepe, M.S. & Appelbaum, F.R. (1995) Impact of patient weight on non-relapse mortality after marrow transplantation. *Bone Marrow Transplantation*, **15**, 461–468.
- Dignan, F.L., Clark, A., Amrolia, P., Cornish, J., Jackson, G., Mahendra, P., Scarisbrick, J.J., Taylor, P.C., Hadzic, N., Shaw, B.E., Potter, M.N. & on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (2012a) Diagnosis and management of acute graft-versus-host disease. *British Journal of Haematology*, **158**, 30–45.
- Dignan, F.L., Amrolia, P., Clark, A., Cornish, J., Jackson, G., Mahendra, P., Scarisbrick, J.J., Taylor, P.C., Shaw, B.E., Potter, M.N. & on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (2012b) Diagnosis and management of chronic graft-versus-host disease. *British Journal of Haematology*, **158**, 46–61.
- Dudek, A.Z., Mahaseth, H., De For, T.E. & Weisdorf, D.J. (2003) Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biology of Blood and Marrow Transplantation*, **9**, 657–66.
- Eckardt, A., Starke, O., Stadler, M., Reuter, C. & Hertenstein, B. (2004) Severe oral chronic graft-versus-host disease following allogeneic bone marrow transplantation: highly effective treatment with topical tacrolimus. *Oral Oncology*, **40**, 811–814.
- Einsele, H., Reusser, P., Bornhauser, M., Kalhs, P., Ehninger, G., Hebart Chalandon, H.Y., Kröger, N., Hertenstein, B. & Rohde, F. (2006) Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood*, **107**, 3002–3008.
- El Cheikh, J., Castagna, L., Wang, L., Esterni, B., Faucher, C., Furst, S., Duran, S., Berger, P., Ranque, S., Mohty, M. & Blaise, D. (2010) Once-weekly liposomal amphotericin B for prophylaxis of invasive fungal infection after graft-versus-host disease in allogeneic hematopoietic stem cell transplantation: a comparative retrospective single-center study. *Hematology/Oncology Stem Cell Therapy*, **3**, 167–173.
- Elad, S., Or, R., Resnick, I. & Shapira, M.Y. (2003a) Topical tacrolimus: a novel treatment alternative for cutaneous chronic graft-versus-host disease. *Transplant International*, **16**, 665–670.
- Elad, S., Or, R., Garfunkel, A.A. & Shapira, M.Y. (2003b) Budesonide: a novel treatment for oral chronic graft versus host disease. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, Endodontology*, **95**, 308–311.
- Engelhard, D., Cordonnier, C., Shaw, P.J., Parkalli, T., Guenther, C., Martino, R., Dekker, A.W., Prentice, H.G., Gustavsson, A., Nurnberger, W., Ljungman, P. & Infectious Disease Working Party of the European Bone Marrow Transplantation (IDWP-EBMT). (2002) Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *British Journal of Haematology*, **117**, 444–450.
- Engelhard, D., Akova, M., Boeckh, M.J., Freifeld, A., Sepkowitz, K., Viscoli, C., Wade, J., Raad, I. & Center for International Blood and Marrow Transplant Research; National Marrow Donor Program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Disease Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Diseases Canada; Centers for Disease Control and Prevention (2009) Bacterial infection prevention after hematopoietic cell transplantation. *Bone Marrow Transplantation*, **44**, 467–470.
- Enk, C.D., Elad, S., Vexler, A., Kapelushnik, J., Gorodetsky, R. & Kirschbaum, M. (1998) Chronic graft-versus-host disease treated with UVB phototherapy. *Bone Marrow Transplantation*, **22**, 1179–1183.
- Eppinger, T., Ehninger, G., Steinert, M., Niethammer, D. & Dopfer, R. (1990) 8-Methoxypsoralen

- and ultraviolet A therapy for cutaneous manifestations of graft-versus-host disease. *Transplantation*, **50**, 807–811.
- Epstein, J.B. & Reece, D.E. (1994) Topical ciclosporin A for treatment of oral chronic graft-versus-host disease. *Bone Marrow Transplantation*, **13**, 81–86.
- Ervin, A.M., Wojciechowski, R. & Schein, O. (2010) Punctal occlusion for dry eye syndrome. *Cochrane Database of Systematic Reviews*, **8**(9), CD006775.
- Filipovich, A.H., Weisdorf, D., Pavletic, S., Socie, G., Wingard, J.R., Lee, S.J., Martin, P., Chien, J., Przepiorka, D., Couriel, D., Cowen, E.W., Dinnendorf, P., Farrell, A., Hartzman, R., Henslee-Downey, J., Jacobsohn, D., McDonald, G., Mittleman, B., Rizzo, J.D., Robinson, M., Schubert, M., Schultz, K., Shulman, H., Turner, M., Vogelsang, G. & Flowers, M.E. (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biology of Blood and Marrow Transplantation*, **11**, 945–956.
- Flowers, M.E., Parker, P.M., Johnston, L.J., Matos, A.V., Storer, B., Singsing, W.I., Storb, R., Appelbaum, F.R., Forman, S.J., Blume, K.G. & Martin, P.J. (2002) Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood*, **100**, 415–419.
- França, C.M., Domingues-Martins, M., Volpe, A., Pallotta Filho, R.S. & Soares de Araújo, N. (2001) Severe oral manifestations of chronic graft-vs.-host disease. *Journal of the American Dental Association*, **132**, 1124–1127.
- Fricain, J.C., Sibaud, V., Swetyenga, N., Tabrizi, R., Campana, F. & Taieb, A. (2007) Long-term efficacy of topical tacrolimus on oral lesions of chronic graft-versus-host disease. *British Journal of Dermatology*, **156**, 588–590.
- Fuji, S., Kim, S.W., Yoshimura, K., Akiyama, H., Okamoto, S., Sao, H., Takita, J., Kobayashi, N., Mori, S. & Japan Marrow Donor Program. (2009) Possible association between obesity and posttransplantation complications including infectious diseases and acute graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **15**, 73–82.
- Gergis, U., Markey, K., Greene, J., Kharfan-Dabaja, M., Field, T., Wetzstein, G., Schell, M.J., Huang, Y., Anasetti, C. & Perkins, J. (2010) Voriconazole provides effective prophylaxis for invasive fungal infection in patients receiving glucocorticoid therapy for GVHD. *Bone Marrow Transplantation*, **45**, 662–667.
- Ghoreschi, K., Thomas, P., Penovici, M., Ullmann, J., Sander, C.A., Ledderose, G., Plewig, G., Kolb, H.J. & Röcken, M. (2008) PUVA-bath photochemotherapy and isotretinoin in scleroderma-tous graft-versus-host disease. *European Journal of Dermatology*, **18**, 667–670.
- Gluckman, E., Lotsberg, J., Devergie, A., Zhao, X.M., Melo, R., Gomez-Morales, M., Nebout, T., Mazon, M.C. & Perol, Y. (1983) Prophylaxis of herpes infections after bone-marrow transplantation by oral acyclovir. *Lancet*, **2**, 706–708.
- Goodrich, J.M., Bowden, R.A., Fisher, L., Keller, C., Schoch, G. & Meyers, J.D. (1993) Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Annals of Internal Medicine*, **118**, 173–178.
- Grigg, A.P., Brown, M., Roberts, A.W., Szer, J. & Slavin, M.A. (2004) A pilot study of targeted itraconazole prophylaxis in patients with graft-versus-host disease at high risk of invasive mould infections following allogeneic stem cell transplantation. *Bone Marrow Transplantation*, **34**, 447–453.
- Grundmann-Kollmann, M., Behrens, S., Gruss, C., Gottlober, P., Peter, R.U. & Kerscher, M. (2000) Chronic sclerodermic graft-versus host disease refractory to immunosuppressive treatment responds to UVA1 phototherapy. *Journal of American Academy of Dermatology*, **42**, 134–136.
- Hann, I.M., Prentice, H.G., Blacklock, H.A., Ross, M.G., Brigden, D., Rosling, A.E., Burke, C., Crawford, D.H., Brumfit, W. & Hoffbrand, A.V. (1983) Acyclovir prophylaxis against herpes virus infections in severely immunocompromised patients: randomised double blind trial. *British Medical Journal (Clinical Research Edition)*, **287**, 384–388.
- Häusermann, P., Walter, R.B., Halter, J., Biedermann, B.C., Tichelli, A., Itin, P. & Gratwohl, A. (2008) Cutaneous graft-versus-host disease: a guide for the dermatologist. *Dermatology*, **216**, 287–304.
- van der Heiden, P.L., Kalpoe, J.S., Barge, R.M., Willemze, R., Kroes, A.C. & Schippers, E.F. (2006) Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. *Bone Marrow Transplantation*, **37**, 693–698.
- Hildebrandt, G.C., Fazekas, T., Lawitschka, A., Bertz, H., Greinix, H., Halter, J., Pavletic, S.Z., Holler, E. & Wolff, D. (2011) Diagnosis and treatment of pulmonary chronic GvHD: report from the consensus conference on clinical practice in chronic GvHD. *Bone Marrow Transplantation*, **46**, 1283–1295.
- Hilgendorf, I., Freund, M., Jilg, W., Einsele, H., Gea-Banacloche, J., Greinix, H., Halter, J., Lawitschka, A., Wolff, D. & Meisel, R. (2011) Vaccination of allogeneic haematopoietic stem cell transplant recipients: report from the international consensus conference on clinical practice in chronic GvHD. *Vaccine*, **29**, 2825–2833.
- Jampel, R.M., Farmer, E.R., Vogelsang, G.B., Wingard, J., Santos, G.W. & Morison, W.L. (1991) PUVA therapy for chronic cutaneous graft-versus-host disease. *Archives of Dermatology*, **127**, 1673–1678.
- Khalid, M., Al Saghir, A., Saleemi, S., Al Dammas, S., Zeitouni, M., Al Mobeireek, A., Chaudhry, N. & Sahovic, E. (2005) Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *European Respiratory Journal*, **25**, 490–493.
- Kim, S.K. (2006) Update on ocular graft versus host disease. *Current Opinion in Ophthalmology*, **17**, 344–348.
- Kojima, T., Higuchi, A., Goto, E., Matsumoto, Y., Dogru, M. & Tsubota, K. (2008) Autologous serum eye drops for the treatment of dry eye diseases. *Cornea*, **27**(Suppl 1), S25–S30.
- Kopp, M., Schweigkofler, H., Holzner, B., Nachbaur, D., Niederwieser, D., Fleischhacker, W.W., Kemmler, G. & Sperner-Unterwieser, B. (2000) EORTC QLQ-C30 and FACT-BMT for the measurement of quality of life in bone marrow transplant recipients: a comparison. *European Journal of Haematology*, **65**, 97–103.
- Lam, D.C., Lam, B., Wong, M.K., Lu, C., Au, W.Y., Tse, E.W., Leung, A.Y., Kwong, Y.L., Liang, R.H., Lam, W.K., Ip, M.S. & Lie, A.K. (2011) Effects of Azithromycin in bronchiolitis obliterans syndrome after hematopoietic SCT—a randomized double-blinded placebo-controlled study. *Bone Marrow Transplantation*, **46**, 1551–1556.
- Lee, S.J., Klein, J.P., Barrett, A.J., Ringden, O., Antin, J.H., Cahn, J.Y., Carabasi, M.H., Gale, R.P., Giralt, S., Hale, G.A., Ilhan, O., McCarthy, P.L., Socie, G., Verdonck, L.F., Weisdorf, D.J. & Horowitz, M.M. (2002a) Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood*, **100**, 406–414.
- Lee, S., Cook, E.F., Soiffer, R. & Antin, J.H. (2002b) Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation*, **8**, 444–452.
- Leiter, U., Kaskel, P., Krahn, G., Gottlöber, P., Bunjes, D., Peter, R.U. & Kerscher, M. (2002) Psoralen plus ultraviolet-A bath photochemotherapy as an adjunct treatment modality in cutaneous chronic graft versus host disease. *Photodermatology, Photoimmunology, Photomedicine*, **18**, 183–190.
- Lengerke, C., Ljubicic, T., Meisner, C., Loeffler, J., Sinzger, C., Einsele, H. & Hebart, H. (2006) Evaluation of the COBAS Amplicor HCMV Monitor for early detection and monitoring of human cytomegalovirus infection after allogeneic stem cell transplantation. *Bone Marrow Transplantation*, **38**, 53–60.
- Ljungman, P., Wilczek, H., Gahrton, G., Gustavsson, A., Lundgren, G., Lonnqvist, B., Ringdén, O. & Wahren, B. (1986) Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. *Bone Marrow Transplantation*, **1**, 185–192.
- Ljungman, P., Deliliers, G.L., Platzbecker, U., Matthes-Martin, S., Bacigalupo, A., Einsele, H., Ull-

- mann, J., Musso, M., Trenchel, R., Ribaud, P., Bornhäuser, M., Cesaro, S., Crooks, B., Dekker, A., Gratecos, N., Klingebiel, T., Tagliaferri, E., Ullmann, A.J., Wacker, P. & Cordonnier, C. (2001) Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood*, **97**, 388–392.
- Ljungman, P., Camara, De.La.R., Milpied, N., Volin, L., Russell, C.A., Webster, A. & Valacyclovir International Bone Marrow Transplant Study Group. (2002) A randomised study of valacyclovir as prophylaxis against CMV reactivation in allogeneic bone marrow transplant recipients. *Blood*, **73**, 930–936.
- Ljungman, P., Engelhard, D., de la Cámara, R., Einsele, H., Locasciulli, A., Martino, R., Ribaud, P., Ward, K. & Cordonnier, C. & Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. (2005) Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. *Bone Marrow Transplantation*, **35**, 737–746.
- Ljungman, P., Cordonnier, C., Einsele, H., Englund, J., Machado, C.M., Storek, J., Small, T. & Center for International Blood and Marrow Transplant Research; National Marrow Donor Program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Disease Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Diseases Canada; Centers for Disease Control and Prevention (2009) Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplantation*, **44**, 521–526.
- Lucid, C.E., Savani, B.N., Engelhardt, B.G., Shah, P., Clifton, C., Greenhut, S.L., Vaughan, L.A., Kassim, A., Schuening, F. & Jagasia, M. (2011) Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT. *Bone Marrow Transplantation*, **46**, 426–429.
- Marks, C., Stadler, M., Häusermann, P., Wolff, D., Buchholz, S., Stary, G., Lee, S., Lawitschka, A. & Bertz, H. (2011a) German-Austrian-Swiss Consensus Conference on clinical practice in chronic graft-versus-host disease (GvHD): guidance for supportive therapy of chronic cutaneous and musculoskeletal GvHD. *British Journal of Dermatology*, **165**, 18–29.
- Marks, D.I., Pagliuca, A., Kibbler, C.C., Glasmacher, A., Heussel, C.P., Kantecki, M., Miller, P.J., Ribaud, P., Schlamm, H.T., Solano, C., Cook, G. & for the IMPROVIT Study Group. (2011b) Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *British Journal of Haematology*, **155**, 318–327.
- Martino, R., Maertens, J., Bretagne, S., Rovira, M., Deconinck, E., Ullmann, A.J., Held, T. & Cordonnier, C. (2000a) Toxoplasmosis after hematopoietic stem cell transplantation. *Clinical Infectious Diseases*, **31**, 1188–1195.
- Martino, R., Bretagne, S., Rovira, M., Ullmann, A. J., Maertens, J., Held, T., Deconinck, E. & Cordonnier, C. (2000b) Toxoplasmosis after hematopoietic stem transplantation. Report of a 5-year survey from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplantation*, **25**, 1111–1114.
- Mattes, F.M., Hainsworth, E.G., Geretti, A.M., Nebbia, G., Prentice, G., Potter, M., Burroughs, A.K., Sweny, P., Hassan-Walker, A.F., Okwuadi, S., Sabin, C., Amooif, G., Brown, V.S., Grace, S. C., Emery, V.C. & Griffiths, P.D. (2004) A randomized, controlled trial comparing ganciclovir to ganciclovir plus foscarnet (each at half-dose) for preemptive therapy of cytomegalovirus infection in transplant recipients. *Journal of Infectious Diseases*, **189**, 1355–1361.
- Mawardi, H., Stevenson, K., Gokani, B., Soiffer, R. & Treister, N. (2010) Combined topical dexamethasone/tacrolimus therapy for management of oral chronic GvHD. *Bone Marrow Transplantation*, **45**, 1062–1067.
- McQuellon, R.P., Russell, G.B., Cella, D.F., Craven, B.L., Brady, M., Bonomi, A. & Hurd, D. D. (1997) Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplantation*, **19**, 357–368.
- Meier, J.K., Wolff, D., Pavletic, S., Greinix, H., Gosau, M., Bertz, H., Lee, S.J., Lawitschka, A. & Elad, S. (2011) Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGvHD. *Clinical Oral Investigations*, **15**, 127–139.
- Mele, A., Paterson, P.J., Prentice, H.G., Leoni, P. & Kibbler, C.C. (2002) Toxoplasmosis in bone marrow transplantation: a report of two cases and systematic review of the literature. *Bone Marrow Transplantation*, **29**, 691–698.
- Mohty, M., Kuentz, M., Michallet, M., Bourhis, J.H., Milpied, N., Sutton, L., Jouet, J.P., Attal, M., Bordignon, P., Cahn, J.Y., Boiron, J.M., Blaise, D. & Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) (2002) Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: long-term results of a randomized study. *Blood*, **100**, 3128–3134.
- Murray, S.M. & Pindoria, S. (2009) Nutrition support for bone marrow transplant patients. *Cochrane Database of Systematic Reviews*, **21**(1), CD002920.
- Nagler, R.M. & Nagler, A. (1999) Pilocarpine hydrochloride relieves xerostomia in chronic graft-versus-host disease: a sialometrical study. *Bone Marrow Transplantation*, **23**, 1007–1011.
- Norman, B.C., Jacobsohn, D.A., Williams, K.M., Au, B.K., Au, M.A., Lee, S.J., Moravec, C.K. & Chien, J.W. (2011) Fluticasone, azithromycin and montelukast therapy in reducing corticosteroid exposure in bronchiolitis obliterans syndrome after allogeneic hematopoietic SCT: a case series of eight patients. *Bone Marrow Transplantation*, **46**, 1369–1373.
- Olivieri, A., Locatelli, F., Zecca, M., Sanna, A., Cimminiello, M., Raimondi, R., Gini, G., Mordini, N., Balduzzi, A., Leoni, P., Gabrielli, A. & Bacigalupo, A. (2009) Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood*, **114**, 709–718.
- Omar, H., Häggglund, H., Gustafsson-Jernberg, A., LeBlanc, K., Mattsson, J., Remberger, M., Ringdén, O., Sparrelid, E., Sundin, M., Winiarski, J., Yun, Z. & Ljungman, P. (2009) Targeted monitoring of patients at high risk of post-transplant lymphoproliferative disease by quantitative Epstein-Barr virus polymerase chain reaction. *Transplant Infectious Disease*, **11**, 393–399.
- Or, R., Gesundheit, B., Resnick, I., Bitan, M., Avraham, A., Avgil, M., Sacks, Z. & Shapira, M. Y. (2007) Sparing effect by montelukast treatment for chronic graft versus host disease: a pilot study. *Transplantation*, **83**, 577–581.
- Perren, T.J., Powles, R.L., Easton, D., Stolle, K. & Selby, P.J. (1988) Prevention of herpes zoster in patients by long-term oral acyclovir after allogeneic bone marrow transplantation. *American Journal of Medicine*, **85**, 99–101.
- Pidala, J., Kurland, B., Chai, X., Majhail, N., Weisdorf, D.J., Pavletic, S., Cutler, C., Jacobsohn, D., Palmer, J., Arai, S., Jagasia, M. & Lee, S.J. (2011) Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GvHD Consortium. *Blood*, **117**, 4651–4657.
- Platzbecker, U., Bandt, D., Thiede, C., Helwig, A., Freiberg-Richter, J., Schuler, U., Plettig, R., Geissler, G., Rethwilm, A., Ehninger, G. & Bornhäuser, M. (2001) Successful preemptive cidofovir treatment for CMV antigenemia after dose-reduced conditioning and allogeneic blood stem cell transplantation. *Transplantation*, **71**, 880–885.
- Prentice, H.G., Gluckman, E., Powles, R.L., Ljungman, P., Milpied, N., Fernandez Ranada, J.M., Mandelli, F., Kho, P., Kennedy, L. & Bell, A.R. (1994) Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. *Lancet*, **343**, 749–753.
- Ratjen, F., Rjabko, O. & Kremens, B. (2005) High-dose corticosteroid therapy for bronchiolitis obliterans after bone marrow transplantation in children. *Bone Marrow Transplantation*, **36**, 135–138.
- Reusser, P., Einsele, H., Lee, J., Volin, L., Rovira, M., Engelhard, D., Finke, J., Cordonnier, C., Link, H. & Ljungman, P. & Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. (2002) Randomized multicenter trial of foscarnet versus ganciclovir for preemptive

- therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood*, **99**, 1159–1164.
- Rhodes, D.F., Lee, W.M., Wingard, J.R., Pavy, M. D., Santos, G.W., Shaw, B.W., Wood, R.P., Sorrell, M.F. & Markin, R.S. (1990) Orthotopic liver transplantation for graft versus host disease following bone marrow transplantation. *Gastroenterology*, **99**, 536–538.
- Riley, S.A. & Attwood, S.E. (2004) Guidelines on the use of oesophageal dilatation in clinical practice. *Gut*, **53**(Suppl 1), 1–6.
- Ruutu, T., Eriksson, B., Remes, K., Juvonen, E., Volin, L., Remberger, M., Parkkali, T., Hägglund, H., Ringdén, O. & Nordic Bone Marrow Transplantation Group. (2002) Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Blood*, **100**, 1977–1983.
- Sánchez, A.R., Sheridan, P.J. & Rogers, R.S. (2004) Successful treatment of oral lichen planus-like chronic graft-versus-host disease with topical tacrolimus: a case report. *Journal of Periodontology*, **75**, 613–619.
- Saral, R., Burns, W.H., Laskin, O.L., Santos, G.W. & Lietman, P.S. (1981) Acyclovir prophylaxis of herpes-simplex-virus infections. *New England Journal of Medicine*, **305**, 63–67.
- Sari, I., Altuntas, F., Kocyigit, I., Sisman, Y., Eser, B., Unal, A., Fen, T., Ferahbas, A., Ozturk, A., Unal, A. & Cetin, M. (2007) The effect of budesonide mouthwash on oral chronic graft versus host disease. *American Journal of Hematology*, **82**, 349–356.
- Schmook, T., Kraft, J., Benninghoff, B., Nindl, I., Roewert, J., Ulrich, C. & Stockfleth, E. (2005) Treatment of cutaneous chronic graft-versus-host disease with topical pimecrolimus. *Bone Marrow Transplantation*, **36**, 87–88.
- Schwarer, A.P., Hughes, J.M., Trotman-Dickenson, B., Krausz, T. & Goldman, J.M. (1992) A chronic pulmonary syndrome associated with graft-versus-host disease after allogeneic marrow transplantation. *Transplantation*, **54**, 1002–1008.
- Seguy, D., Berthon, C., Micol, J.B., Darré, S., Dalle, J.H., Neuville, S., Bauters, F., Jouet, J.P. & Yakoub-Agha, I. (2006) Enteral feeding and early outcomes of patients undergoing allogeneic stem cell transplantation following myeloablative conditioning. *Transplantation*, **82**, 835–839.
- Shepp, D.H., Dandliker, P.S., Flournoy, N. & Meyers, J.D. (1987) Sequential intravenous and twice-daily oral acyclovir for extended prophylaxis of herpes simplex virus infection in marrow transplant patients. *Transplantation*, **43**, 654–658.
- Shulman, H.M., Kleiner, D., Lee, S.J., Morton, T., Pavletic, S.Z., Farmer, E., Moresi, J.M., Greenson, J., Janin, A., Martin, P.J., McDonald, G., Flowers, M.E., Turner, M., Atkinson, J., Lefkowitz, J., Washington, M.K., Prieto, V.G., Kim, S.K., Argenyi, Z., Diwan, A.H., Rashid, A., Hiatt, K., Couriel, D., Schultz, K., Hymes, S. & Vogelsang, G.B. (2006) Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biology of Blood and Marrow Transplantation*, **12**, 31–47.
- Singhal, S., Powles, R., Treleaven, J., Rattenbury, H. & Mehta, J. (1997) Pilocarpine hydrochloride for symptomatic relief of xerostomia due to chronic graft-versus-host disease or total-body irradiation after bone-marrow transplantation for hematologic malignancies. *Leukaemia Lymphoma*, **24**, 539–543.
- Spinelli, S., Chiodi, S., Costantini, S., Van Lint, M. T., Raiola, A.M., Ravera, G.B. & Bacigalupo, A. (2003) Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica*, **88**, 1163–1168.
- Spiryda, L.B., Laufer, M.R., Soiffer, R.J. & Antin, J. A. (2003) Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biology of Blood and Marrow Transplantation*, **9**, 760–765.
- Stadler, M., Ahlborn, R., Kamal, H., Diedrich, H., Buchholz, S., Eder, M. & Ganser, A. (2009) Limited efficacy of imatinib in severe pulmonary chronic graft-versus-host disease. *Blood*, **114**, 3718–3719.
- Stratton, P., Turner, M.L., Childs, R., Barrett, J., Bishop, M., Wayne, A.S. & Pavletic, S. (2007) Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. *Obstetrics & Gynecology*, **110**, 1041–1049.
- Svahn, B.M., Remberger, M., Heijbel, M., Martell, E., Wikström, M., Eriksson, B., Milovsavljjevic, R., Mattsson, J. & Ringdén, O. (2008) Case-control comparison of at-home and hospital care for allogeneic hematopoietic stem-cell transplantation: the role of oral nutrition. *Transplantation*, **85**, 1000–1007.
- Ullmann, A.J., Lipton, J.H., Vesole, D.H., Chandrasekar, P., Langston, A., Tarantolo, S.R., Greinix, H., Morais de Azevedo, W., Reddy, V., Boparai, N., Pedicone, L., Patino, H. & Durrant, S. (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *New England Journal of Medicine*, **356**, 335–347.
- Vogelsang, G.B., Wolff, D., Altomonte, V., Farmer, E., Morison, W.L., Corio, R. & Horn, T. (1996) Treatment of chronic graft-versus-host disease with ultraviolet irradiation and psoralen (PUVA). *Bone Marrow Transplantation*, **17**, 1061–1067.
- Volin, L., Barkholt, L., Nihtinen, A., Aschan, J., Uotinen, H., Hägglund, H., Juvonen, E., Ringdén, O., Ruutu, T. & Ljungman, P. (2008) An open-label randomised study of oral valganciclovir versus intravenous ganciclovir for pre-emptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Bone Marrow Transplantation*, **42**(Suppl 1), S47.
- Wertheim, M. & Rosenbaum, J.T. (2005) Bilateral uveitis manifesting as a complication of chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Ocular Immunology and Inflammation*, **13**, 403–404.
- Westeneng, A.C., Hettinga, Y., Lokhorst, H., Verdonck, L., van Dorp, S. & Rothova, A. (2010) Ocular graft-versus-host disease after allogeneic stem cell transplantation. *Cornea*, **29**, 758–763.
- Wetzig, T., Sticherling, M., Simon, J.C., Hegenbart, U., Niederwieser, D. & Al Ali, H.K. (2005) Medium dose long-wavelength ultraviolet A (UVA1) phototherapy for the treatment of acute and chronic graft-versus-host disease of the skin. *Bone Marrow Transplantation*, **35**, 515–519.
- White, D.A., Wong, P.W. & Downey, R. (2000) The utility of open lung biopsy in patients with hematologic malignancies. *American Journal of Respiratory and Critical Care Medicine*, **161**, 723–729.
- Winston, D.J., Ho, W.G., Bartoni, K., Du Mond, C., Ebeling, D.F., Buhles, W.C. & Champlin, R. E. (1993) Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. *Annals of Internal Medicine*, **118**, 179–184.
- Winston, D.J., Yeager, A.M., Chandrasekar, P.H., Snyderman, D.R., Petersen, F.B. & Territo, M.C. (2003) Randomized comparison of oral valganciclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. *Clinical Infectious Diseases*, **36**, 749–758.
- Winston, D.J., Baden, L.R., Gabriel, D.A., Emmanouilides, C., Shaw, L.M., Lange, W.R. & Ratanatharathorn, V. (2006) Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. *Biology of Blood and Marrow Transplantation*, **12**, 635–640.
- Wolff, D., Anders, V., Corio, R., Horn, T., Morison, W.L., Farmer, E. & Vogelsang, G.B. (2004) Oral PUVA and topical steroids for treatment of oral manifestations of chronic graft-vs.-host disease. *Photodermatology, Photoimmunology, Photomedicine*, **20**, 184–190.
- Zantomio, D., Grigg, A.P., MacGregor, L., Panek-Hudson, Y., Szer, J. & Ayton, R. (2006) Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. *Bone Marrow Transplantation*, **38**, 567–572.
- Ziemer, M., Gruhn, B., Thiele, J.J. & Elsner, P. (2004a) Treatment of extensive chronic cutaneous graft-versus-host disease in an infant with topical pimecrolimus. *Journal of American Academy of Dermatology*, **50**, 946–948.
- Ziemer, M., Thiele, J.J., Gruhn, B. & Elsner, P. (2004b) Chronic cutaneous graft-versus-host disease in two children responds to UVA1 therapy: improvement of skin lesions, joint mobility, and quality of life. *Journal of American Academy of Dermatology*, **51**, 318–319.