Diagnosis and Management of Acute Graft Versus Host Disease

Definition
Acute graft versus host disease (aGvHD) is caused by the immunological reaction of donor T lymphoid cells against host tissue causing skin rash, diarrhoea and jaundice. Onset is typically from engraftment up to 3-4 months post-transplant. Risk factors include:
- donor type and degree of HLA matching
- increasing age of patient and donor
- sex mismatch and parity of female donors
- conditioning intensity

Grade and Stage

It is essential to accurately record the grade AND organ-specific stage of acute GVHD in the EPR and to review this regularly. Where acute GVHD severity increases, the new grade and organ stage should be reported. Where a patient responds to treatment, it is also important to indicate how they have responded using the same system.

The eGVHD app can be used to generate grade and stage of acute GVHD (see https://www.uzleuven.be/egvhd).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Lower GI§</th>
<th>Upper GI*</th>
<th>Liver (bilirubin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rash&lt;25%</td>
<td>500-1000ml diarrhoea/day</td>
<td>Persistent nausea/vomiting/anorexia</td>
<td>34-51umol/l</td>
</tr>
<tr>
<td>2</td>
<td>Rash 25%-50%</td>
<td>1000-1500ml diarrhoea/day</td>
<td></td>
<td>52-102umol/l</td>
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<tr>
<td>3</td>
<td>Rash &gt; 50%</td>
<td>&gt;1500ml diarrhoea/day</td>
<td></td>
<td>103-256umol/l</td>
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<tr>
<td>4</td>
<td>Desquamation and/or bullous</td>
<td>abdominal pain and/or ileus</td>
<td></td>
<td>&gt;256umol/l</td>
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</table>

§ where volume cannot be easily measured, assume 200ml per motion; *anorexia, dyspepsia, food intolerance, nausea and vomiting may be caused by upper GI aGvHD and endoscopic biopsy of stomach and duodenum is required

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin Stage</th>
<th>Liver Stage</th>
<th>Lower GI Stage</th>
<th>Upper GI Stage</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>1 or 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>1 or 1</td>
<td>1 or 1</td>
<td>1 or 1</td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>2-3</td>
<td>2,3 or 4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
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Investigations

If acute GVHD is suspected clinically, a histological diagnosis could be obtained
before initiating treatment. However, treatment should not be delayed if suspected GVHD is grade 2 or greater (see tables above for grading criteria).

**Skin Rash**
- biopsy using a punch biopsy kit.

**Diarrhoea**
- biopsy of the large bowel by flexible sigmoidoscopy or rectal biopsy- standard histological sectioning and staining, for CMV inclusion bodies.
- sample to microbiology for cryptosporidium, clostridium difficile and other bacterial organisms.

**Cholestatic jaundice**
If a skin rash or diarrhoea co-exist with jaundice, skin or gut biopsies should be taken where possible because of ease and safety. Consultation with a hepatologist may be necessary who may advise a trans-jugular liver biopsy where the diagnosis is in doubt.

**Other investigations**
- Doppler ultrasound of liver to exclude hepatic veno-occlusive disease
- CMV PCR
- Hepatitis A (serology) B, C, E PCR – if indicated
- Blood glucose at baseline and intermittently according to risk

**Treatment**

**Consider clinical trials if these are available**

**Grade I aGvHD** – no additional systemic treatment required, although topical steroids (such as betamethasone [Betnovate] for body and 1% hydrocortisone for face) may be beneficial for skin management. Please refer to B.2.7c Guidelines for Diagnosis and Management of Cutaneous Graft-Versus-Host Disease protocol.

**Grade II**
1. Continue prophylaxis with CNI (CSA or TAC)
2. Consider Treatment with 1 mg/kg prednisolone daily.
3. In some cases of isolated stage III skin aGvHD, topical steroids may be used without the use of systemic steroids. See guidance in B.2.7c Guidelines for Diagnosis and Management of Cutaneous Graft-Versus-Host Disease protocol.
4. For gastrointestinal symptoms of GVHD (such as nausea and anorexia), consider starting budesonide 3mg tds po.

**Grade III-IV aGVHD**
1. Continue prophylaxis with CSA
2. Start Methylprednisolone 2 mg/kg od IV

Corticosteroid resistance is defined as no response after 5-7 days (2 mg/kg/day methylprednisolone) or progressive GvHD after 3-5 days

**Response**
1. Reduce methylprednisolone dose and convert to oral prednisolone as tolerated
No response
1. If not responding discuss secondary therapy options with consultant (see Secondary Treatments below)
2. Ruxolitinib is the standard-of-care for second line therapy but is not currently commissioned by NHSE (see Ruxolitinib protocol).

If aGvHD flares up during steroid dose reduction, reintroduce previous dose and assess in 5 days. Lack of response or repeated flare is an indication for second line therapy. Lack of tolerance of glucocorticoids is also an indication for second line therapy.

Secondary Treatments

There is no clear choice of other salvage treatments and response is generally poor. Consider entry into a clinical trial. The following are options that have been considered:

- Mycophenolate mofetil (MMF)
- ECP
- Mesenchymal stem cells
- Methotrexate
- Antithymocyte globulin (ATG)
- Pentostatin
- Alemtuzumab
- Anti TNF antibody (Infliximab, Etanercept – See B.23 Etanercept for the Second Line Treatment of Acute Graft-Versus-Host Disease protocol)
- Sirolimus
- Microbiome restoration

Supportive care

Fluid and electrolyte balance
Close fluid balance and electrolyte monitoring and appropriate management are essential. Diarrhoea volume measurement is essential.

Monitor glucose levels in patients on high dose steroids
Seek advice of diabetic team where correction of hyperglycaemia is indicated.

Diarrhoea
1. Initiate Loperamide 4-8 mg stat with reassessment of the diarrhoea, after 24 hours, if there is no improvement increase dose to 2 mg every 2 hours.
2. Octreotide, 100 to 150 mcg subcutaneously every 8 hours, should be considered for patients who continue to experience low grade diarrhoea after 24 hours of high-dose Loperamide as well as those with severe diarrhoea. Increasing the dose to 500 mcg subcutaneously or by intravenous bolus every 8 hours may be necessary. Octreotide should be discontinued within 24 hours of resolution of diarrhoea to prevent ileus. If diarrhoea has not resolved, Octreotide should be continued for a maximum of 7 days.
3. Discuss with dietician. Patients may require parenteral feeding. See B.2.25 Nutrition BMT protocol. NSSG/BMT/Clinical management.

Infection prophylaxis
Aciclovir and Septrin prophylaxis should be continued. Refer to NSSG for fungal management policy (H.94 Antifungal therapy guidelines). Weekly CMV PCR screening should continue.

**Treatment of infection**
Treat infection as per standard policy, beware of steroids masking fever.

**Monitoring and assessment**
In order to ensure consistency of monitoring and assessment, (and for data accurate capture to support BSBMT data submission), please use the acute (B.2.14a) GvHD assessment tool, found on the NSSG BMT/GvHD. Assessment should begin from admission for transplant, continue through readmission if possible GvHD and continue in OPD.

**Link Documents:**
- B.2.14a: Acute GvHD Assessment
- B.2.7c Guidelines for Diagnosis and Management of Cutaneous Graft-Versus-Host Disease
- B.23 Etanercept for the Second Line Treatment of Acute Graft-Versus-Host Disease

**References**
2. Bacigalupo. A Third EBMT/Amgen workshop on reduced intensity conditioning allogeneic haemopoietic stem cell transplants (RIC-HSCT), and panel consensus. Bone Marrow Transplant. 2004; 33:691-696.

**Authors**
Andy Peniket, Consultant Haematologist – Original, 2003
Ram Malladi, Haematology Registrar – Version 2, 2004
Claire Humphries, Specialist Pharmacist – Version 2, 2004
Andy Peniket, Consultant Haematologist – Version 3, 2009
Denise Wareham, BMT Co-ordinator – Amendments, 2009
Audit
These processes are subject to the OxBMT audit programme

Circulation
NSSG Haematology Website

Review

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<tr>
<td>Dr Andy Peniket</td>
<td>Clarification of grading insertion of Jacie standards into document</td>
<td>Jan 2013</td>
<td>3.2</td>
<td>Jan 2015</td>
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<td>Dr Yisu Gu, SpR</td>
<td>Addition of Upper GI staging and grading, revision of supportive care, link documents.</td>
<td>Mar 2016</td>
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<td>Mar 2018</td>
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<td>Correction of measurement error</td>
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<td>Dr Ronjon Chakraverty</td>
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