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

<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>
</tr>
<tr>
<td>3</td>
<td>Rash &gt; 50%</td>
<td>&gt;1500ml diarrhoea/day</td>
<td></td>
<td>103-256umol/l</td>
</tr>
<tr>
<td>4</td>
<td>Desquamation and/or bullous</td>
<td>abdominal pain and/or ileus</td>
<td></td>
<td>&gt;256umol/l</td>
</tr>
</tbody>
</table>

*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</th>
<th>Liver</th>
<th>Lower GI</th>
<th>Upper GI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage</td>
<td>Stage</td>
<td>Stage</td>
<td>Stage</td>
</tr>
<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 or 1</td>
<td>1 or 1</td>
<td>1 or 1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>2-3</td>
<td>or 2,3 or 4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4 or 4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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 bodics.
- 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

**Treatment**

**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 1 mg/kg bd 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. Increase methylprednisolone to 5 mg/kg/bd and reassess after 3-5 days
2. If not responding discuss secondary therapy options with consultant.

If aGvHD flares up during steroid dose reduction, reintroduce previous dose and assess in 5 days.

**Secondary Treatments**
There is no clear choice of secondary 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)
- Ruxolitinib
- 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.

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
NSSSG Haematology Website

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Andy Peniket BMT Programme Director</td>
<td>Clarification of grading insertion of Jiacie standards into document</td>
<td>Jan 2013</td>
<td>3.2</td>
<td>Jan 2015</td>
</tr>
<tr>
<td>Dr Yisu Gu, SpR, Dr Andy Peniket Sandy Hayes, Quality manager</td>
<td>Addition of Upper GI staging and grading, revision of supportive care, link documents.</td>
<td>Mar 2016</td>
<td>4.0</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>Sandy Hayes</td>
<td>Correction of measurement error</td>
<td>Mar 2016</td>
<td>4.1</td>
<td>Mar 2016</td>
</tr>
<tr>
<td>Dr Katalin Balassa BMT Fellow</td>
<td>Minor amendments including drugs Update link documents</td>
<td>Apr 2018</td>
<td>4.2</td>
<td>Apr 2020</td>
</tr>
</tbody>
</table>