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 from engraftment and up to 3-4 months post-transplant. Risk factors include:
- degree of HLA matching
- CMV seropositivity of recipient
- increasing age of patient and donor
- sex mismatch

Grade and Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Upper GI</th>
<th>Lower 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>
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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>
</tr>
</tbody>
</table>

*anorexia, dyspepsia, food intolerance, nausea and vomiting may be caused by lower GI aGvHD and endoscopic biopsy of stomach and duodenum is required

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 below 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 PCR – if indicated

Treatment
Grade I aGvHD – no additional systemic treatment required, although topical steroids (Betnovate for body, 1% hydrocortisone for face) may be beneficial for skin management

Grade II
1. Continue prophylaxis with CSA
2. Consider Treatment with 1mg/kg/daily prednisolone.
3. In some cases of isolated stage III skin aGvHD, topical steroids may be used without the use of systemic steroids.
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/IV bd

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

Response
1. Reduce methylprednisolone dose and convert to oral prednisolone as tolerated

No response
1. Increase methylprednisolone to 5mg/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:
- Mycophenelate mofetil (MMF)
- ECP
- Mesenchymal stem cells
- Methotrexate
- Antithymocyte globulin (ATG)
- Pentostatin 1.5mg/m²/day iv for 3 days
- Daclizumab (Anti IL2 receptor) 1mg/m² iv on days 1, 4, 8, 15, 22)
- Alemtuzumab
- Anti TNF antibody (infliximab)
- Entanercept

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 4-8mg stat with reassessment of the diarrhoea, after 24 hours, if there is no improvement increase dose to 2mg 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 to 1500mcg 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 Nutrition protocol. NSSG/BMT/Clinical management.

Infection prophylaxis
Aciclovir and Septrin prophylaxis should be continued. Refer to NSSG policy for fungal management policy. 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) and chronic(B.2.14b) GvHD assessment tools, 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.2.14b: Chronic GvHD Assessment

References


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

Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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</table>
| Dr A Peniket  
BMT Programme  
Director | Clarification of grading insertion of Jacie standards into document | Jan 2013 | 3.2 | Jan 2015 |
| Dr Yisu Gu, SpR  
Dr Andy Peniket  
Sandy Hayes, Quality manager | Addition of Upper GI staging and grading, revision of supportive care, link documents. | March 2016 | 4.0 | March 2018 |
| Sandy Hayes | Correction of measurement error | March 2016 | 4.1 | March 2016 |