Infective gastrointestinal complications in patients with GvHD

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Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
Timeline summary of hepatic and gastrointestinal complications of stem cell transplantation

Tuncer et al., WJG, 2012
NAUSEA AND VOMITING

Patients usually experience the chemotherapy related side effects during the early post-transplant period before engraftment.

Nausea and vomiting in later phases may be due to other potential etiologies including: upper GI acute GVHD and infections such as HSV, VZV, CMV, adenovirus, fungus and *Helicobacter pylori*.

MUCOSITIS AND DYSPHAGIA

Infectious causes of mucositis include HSV, VZV, CMV, Candida species and bacterial pathogens.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Diarrhea Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning regimen-related</td>
<td>Antibiotic-related</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>Opioid withdrawal</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>MMF toxicity</td>
</tr>
<tr>
<td>Tacrolimus (TMA)</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Promotility agents</td>
<td>Magnesium salts</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Others</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Malabsorption</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
</tr>
<tr>
<td></td>
<td>Rotavirus</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td>EBV</td>
</tr>
<tr>
<td></td>
<td>HSV</td>
</tr>
<tr>
<td></td>
<td>Astrovirus</td>
</tr>
<tr>
<td></td>
<td>Norovirus</td>
</tr>
<tr>
<td></td>
<td>Bacterial infections including ESBL</td>
</tr>
<tr>
<td></td>
<td>Fungal infections</td>
</tr>
<tr>
<td></td>
<td>Parasitic infections</td>
</tr>
<tr>
<td></td>
<td>(Cryptosporidium, Microsporidia, Giardia)</td>
</tr>
<tr>
<td></td>
<td>Mycobacterial infections</td>
</tr>
</tbody>
</table>

Tuncer et al., WJG, 2012
GASTROINTESTINAL BLEEDING

The incidence of bleeding: 1%-2%
It remains one of the major causes of transplant related mortality.

Non-infectious causes of bleeding:
(mucosal necrosis)
- conditioning therapy
- acute and chronic GVHD
- peptic ulcer disease
- MMF-related ulcerations
- gastric antral vascular ectasia (GAVE)

Common infectious etiologies:
- CMV
- VZV
- adenovirus
- fungal infections
- clostridial infections

Tuncer et al., WJG, 2012
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   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
HSCT PREDISPOSES TO INFECTIONS OF GI TRACT

1. Conditioning

Intense chemotherapy and irradiation result in damage to the gastrointestinal tract

2. Longer periods of impaired host immunity

Neutropenia, longer hospitalizations, allo-HSCT, HLA mismatch, antibiotic exposure

3. The source of most blood-stream infections (BSI) is likely the skin, the oral mucosa and the gastrointestinal tract.
Multivariable analysis of predictors of BSI after HSCT

BSI = Bloodstream infections

Poutsiaka et al., BMT, 2007
Mortality associated with BSI after HSCT

Poutsiake et al., BMT, 2007
Multivariable analysis of predictors of death after HSCT

- Conventional allogeneic HSCT\(^1\), death w/in 3m
- Conventional allogeneic HSCT\(^1\), death after 3m
- Reduced intensity allogeneic HSCT\(^1\)
- Acute GVHD Grades 3-4\(^2\), death w/in 3 m
- Acute GVHD Grades 3-4\(^2\), death after 3 m
- Blood stream infection

HAZARD RATIO AND 95%CI

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>16.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Type of HSCT, compared to autologous HSCT
\(^2\)Compared to Grades 0-2

Poutsiaika et al., BMT, 2007
Mortality due to Aspergillus infection

Lin et al. CID 2001
Impact of acute GVHD (aGVHD) grade II–IV on the incidence of infection-related mortality (IRM)

Impact of an invasive fungal infection (IFI) (a) and CMV disease (b) on the incidence of non-relapse mortality (NRM)

The development of IFIs and CMV disease continue to have an impact on NRM.

Martino et al., BMT, 2011
GVHD PREDISPOSES TO INFECTIONS OF GI TRACT

1. Conditioning

Intense chemotherapy and irradiation result in damage to the gastrointestinal tract, allowing bacterial constituents to enter the systemic circulation.

2. Impaired host immunity (neutropenia, longer hospitalizations)

- prolonged and profound immune deficiency,
- immunosuppressive medication and GVHD
- the disruption of protective barriers such as mucosal surfaces of GI tract and the skin (both in acute and chronic GVHD)

3. Polymorphism of NOD – increased risk of GI infection and GVHD

IMMUNE DEFICIENCY AFTER HSCT

Graph showing immune cell counts (% normal) over time (weeks, months, years posttransplant). Key categories include:
- Neutrophils, Monocytes, NK cells
- B cells, CD8 T cells
- CD4 T cells
- Plasma cells, Dendritic cells

Key landmarks:
- Graft infusion
- Upper normal limit
- Lower normal limit

Source: Storek et al. Expert Opin Biol Ther; 2008
Local infection in the gut may further propagate this cycle by destroying epithelial integrity in the beginning and/or by augmenting responses during a cycle of inflammation.

Ferrara et al., Lancet, 2009
A. HSCT predisposes to infections

B. Infections can escalate GVHD

C. GVHD predisposes to infections of GI tract
Infective gastrointestinal complications in patients with GvHD

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   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
Biology of the crypts of Lieberkühn: possible mechanism of sepsis and GVHD

• Paneth cells secrete a large number of antibiotic peptides and proteins in addition to proinflammatory mediators.

• GVHD involving the small bowel in recipient mice was associated with a substantial loss of Paneth cells.

• Presence of *E. coli* in the intestine of recipients suffering from acute GVHD – associated with translocation of the organisms into the systemic circulation, and development of GVHD.
The prophylactic administration of polymixin B orally, a cell membrane active antibiotic with a particular efficacy against gram negative bacteria, suppressed the growth of *E coli*.

Reintroduction of a specific strain of *Lactobacillus* before transplantation led to an improvement in the survival of mice undergoing allo-HSCT (Jenq et al., 2012).

Alterations in the gastrointestinal microbiome may influence the risk for transplant complications such as: (A) bacteremic episodes, (B) development of GVHD.
Development of BSI after HSCT
Multivariable analysis of cause-specific hazard ratios for the acquisition of blood stream infection (n=199)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA matching</td>
<td>0.40</td>
<td>0.20, 0.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Engraftment</td>
<td>0.74</td>
<td>0.31, 1.81</td>
<td>0.51</td>
</tr>
<tr>
<td>Acute GVHD grade ≥2</td>
<td>2.21</td>
<td>1.15, 4.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous HSCT</td>
<td>1.38</td>
<td>0.83, 2.29</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL (CDI)
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
**Clostridium difficile** infection (CDI)

CDI = diarrheal unformed stool + positive test result for toxin-producing C. difficile.

Recurrent CDI = occurring after the completion of a course of metronidazole or vancomycin for an initial episode.

Kelly CP. JAMA 2009

HSCT recipients appear to be one of the most vulnerable populations for the development of CDI.

Epidemiologic changes have been linked to an epidemic strain of the pathogen known as NAP1/BI/027, which has been associated with increased frequency and severity of disease.

Loo VG, et al. NEJM, 2005;

A bidirectional relationship between CDI and GI-GVHD: CDI contribute to development of GI-GVHD.

Alonso&Marr, COID 2013
**Clostridium difficile** infections: risk factors

1. Nosocomial exposures:
   - prolonged hospital stays increased age, and antimicrobial exposure

2. Host factors:
   - degree of immune impairment
   - chemotherapy-related disruption of enteric mucosal barriers

Gerding et al. 1986
Alonso & Marr, 2013
# Rate of CDI in HSCT recipients

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study period</th>
<th>Patients</th>
<th>Rate of CDI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chopra (2011) [26]</td>
<td>2005–2006</td>
<td>361</td>
<td>14.1 (Both); 18.1 (Allo); 8.3 (Auto)</td>
</tr>
<tr>
<td>Alonso (2012) [28]</td>
<td>2003–2008</td>
<td>999</td>
<td>9.2 (Both); 6.5 (Auto); 12.5 (Allo)</td>
</tr>
<tr>
<td>Kamboj* (2012) [5*]</td>
<td>2008–2009</td>
<td>597</td>
<td>18.4 (Both); 9.0 (Auto); 27.0 (Allo)</td>
</tr>
<tr>
<td>Trifilio (2012) [29*]</td>
<td>2004–2008</td>
<td>822</td>
<td>10.3 (Both); 8.5 (Auto); 14.5 (Allo)</td>
</tr>
</tbody>
</table>

Comparison:
0.36% (Rhode Island Hospital, a tertiary care hospital, 1 yr)  
6.6% (ICU, 3 hospitals in St Louis, 2 yrs)  

Mermel et al., 2013  
Micek et al., 2013
One-year incidence of Clostridium difficile infection

Alonso et al, CID 2012
Among autologous HSCT recipients, 26 cases (86.7%) occurred within the first month after HSCT (median time, 6.5 days; interquartile range [IQR], day 21 to day 21).

Among allogeneic HSCT recipients, the median time to infection was 33 days (IQR, 5–70 days).
RISK FACTORS FOR CDI AFTER HSCT

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>2</td>
<td>1–3.8</td>
<td>0.04</td>
</tr>
<tr>
<td>TBI≥12 Gy</td>
<td>2.3</td>
<td>1.2–4.5</td>
<td>0.01</td>
</tr>
<tr>
<td>aGVHD≥2</td>
<td>27</td>
<td>3.5–210</td>
<td>0.002</td>
</tr>
</tbody>
</table>

A total of 50% of cases occurred within the first month of HSCT

Willems et al, 2012

RISK FACTORS:
- Age >60 years, P<0.001
- Second allo-HSCT, P<0.001
- VRE colonization, P<0.001

Trifilio et al., 2011
## RISK FACTORS FOR CDI AFTER HSCT

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior chemotherapy regimens</td>
<td>6.63</td>
<td>1.04–42.22</td>
<td>0.045</td>
</tr>
<tr>
<td>High-risk C. difficile antibiotic use*</td>
<td>4.76</td>
<td>(1.20–18.88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Acute GHVD</td>
<td>4.45</td>
<td>1.54–12.84</td>
<td>0.006</td>
</tr>
<tr>
<td>VRE colonization</td>
<td>5.87</td>
<td>1.97–17.47</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Antipseudomonal penicillins, fourth-generation cephalosporins, carbapenems, absorbable fluoroquinolones, and clindamycin were considered high-risk antibiotics.

Recurrent CDI was observed in 21.7% of cases. Acute GI-GVHD is the strongest risk for recurrent CDI (OR 4.23, 95% CI 1.20–14.86, P=0.02).
• The strongest association was observed between CDI and aGVHD involving the GI tract (OR, 3.38; P=0.004).

• Receipt of a proton pump inhibitor (PPI) demonstrated a protective effect on CDI in the univariate analysis and remained significant in the multivariate analysis (OR, 0.29; 95%CI, 0.11-0.78; P=0.01).
CONCLUSIONS 2

A. aGVHD predisposes to BSI/sepsis

B. aGVHD predisposes to CDI

C. aGVHD of GI predisposes to recurrent CDI
Infective gastrointestinal complications in patients with GvHD

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   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
### Viral infections after HSCT

<table>
<thead>
<tr>
<th>Latent infections</th>
<th>Sporadic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>% seropositive patients</td>
</tr>
<tr>
<td>HSV 1/2</td>
<td>50-90%</td>
</tr>
<tr>
<td>VZV</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>CMV</td>
<td>45-90%</td>
</tr>
<tr>
<td>HHV-6</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>EBV</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>BKV</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

Marr KA. Hematology, ASH 2012
Infectious phases following HSCT

**PRE-TRANSPLANT**
- Common bacteria (endogenous)
  - staphylococci (skin)
  - Gram-negative bacilli (gut)
- Viruses: HSV (reactivation)

**ENGRAFTMENT**
- Common bacteria (endogenous)
  - streptococci (oral)
  - staphylococci (skin)
  - Gram-negative bacilli (gut)
- Fungi: Candida spp. (mucosa), Aspergillus spp. (airways)
- Viruses: HSV (reactivation), RSV

**EARLY POST-ENGRAFTMENT**
- Viruses: CMV (reactivation), VZV (reactivation), HHV-6, Adenovirus, RSV
- Fungi: Aspergillus spp. (airways), P. carinii (airways)
- Protozoa: T. gondii

**LATE POST-ENGRAFTMENT**
- Bacteria (encapsulated): S. pneumoniae, S. aureus
- Viruses: VZV (reactivation), CMV (reactivation), RSV
- Fungi: P. carinii (airways)
- Protozoa: T. gondii

Adapted from LaRocco & Burgert, *Clin Microbio Rev* 1997, 10:277-97
GVHD and CMV replication are pathogenetically associated: multiple studies show that a/cGVHD and its treatment increase risk for CMV replication.

Miller et al. Blood. 1986
Martino et al. Haematologica. 2001
Ljungman et al. Haematologica. 2006

Martino et al. Haematologica. 2001
Impact of allogeneic graft type and acute graft-versus-host disease (aGVHD) on the incidence of late cytomegalovirus rate

Ozdemir et al., BMT, 2007
Multivariate Analysis for CMV Reactivation at Day +100

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No acute GVHD</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Acute GVHD grade I</td>
<td>1.35 (0.82-2.21)</td>
<td>.01*</td>
</tr>
<tr>
<td>Acute GVHD grade II-IV</td>
<td>1.61 (1.11-2.36)</td>
<td></td>
</tr>
<tr>
<td><strong>Graft</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Peripheral stem cells</td>
<td>0.70 (0.49-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Conditioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide + TBI ± Etoposide</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide + Busulfan</td>
<td>0.88 (0.56-1.41)</td>
<td>.60</td>
</tr>
<tr>
<td>Fludarabin + TBI</td>
<td>0.30 (0.12-0.78)</td>
<td>.01</td>
</tr>
<tr>
<td>Other</td>
<td>1.13 (0.61-2.10)</td>
<td>.69</td>
</tr>
</tbody>
</table>

Cantoni et al., BBMT, 2010
CONCLUSIONS 3

A. aGVHD grade III/IV predisposes to CMV infection

B. Chronic GVHD predisposes to CMV infection
Infective gastrointestinal complications in patients with GvHD

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   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
INVASIVE FUNGAL DISEASE

- Increasing incidence and evolving epidemiology
  - Invasive aspergillosis
  - Recipients of allogeneic stem cell transplantation
- High mortality rate
- High health-care costs

Risk factors
- classical
- metabolic
- center-related/geographic
- genetic
### Classical risk factors for IFI
- HSCT
  - Alternative donor allo-HSCT
  - GVHD (steroids, anty-TNF)
  - CMV
- Neutropenia
- Steroid therapy
- Immunosuppressive therapy
- Acute leukemia
- Age
- History of IFI
- Colonization
- Central catheters

### Genetic risk factors for IFI
- Polymorphism for TLR4
- Polymorphism for plasminogen
- Polymorphism for IL-1
- Polymorphism for CXC10
- Dectin-1 deficiency

### Metabolic risk factors for IFI
- Diabetes
- Iron overload
GVHD IS A RISK FACTOR FOR DEATH DUE TO IA

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female vs. male</td>
<td>1.34 (0.62–2.87)</td>
<td>.458</td>
</tr>
<tr>
<td>Age in 2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 years</td>
<td>0.62 (0.15–2.60)</td>
<td>.511</td>
</tr>
<tr>
<td>12–35 years</td>
<td>2.49 (1.14–5.47)</td>
<td>.023</td>
</tr>
<tr>
<td>36–47 years</td>
<td>1.27 (0.59–2.75)</td>
<td>.546</td>
</tr>
<tr>
<td>&gt;47 years</td>
<td>0.41 (0.16–1.01)</td>
<td>.051</td>
</tr>
<tr>
<td>Disseminated IA: several localizations vs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 initial localization</td>
<td>2.71 (1.13–6.49)</td>
<td>.026</td>
</tr>
<tr>
<td>Pleural effusion: presence vs. absence</td>
<td>3.44 (1.36–8.75)</td>
<td>.009</td>
</tr>
<tr>
<td>Monocyte count: &lt;120 vs. ≥120 cells/mm³</td>
<td>2.81 (1.19–6.62)</td>
<td>.018</td>
</tr>
</tbody>
</table>

| GvHDa                                    |                       |      |
| None                                     | 0.57 (0.23–1.39)      | .214 |
| Controlled                               | 0.76 (0.33–1.77)      | .529 |
| Uncontrolled                             | 4.02 (1.54–10.49)     | .005 |

Steroid treatment for >2 weeks in the 2 months before IA diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.36 (0.16–0.81)</td>
<td>.014</td>
</tr>
<tr>
<td>&lt;2 mg/kg at time of IA diagnosis</td>
<td>0.97 (0.39–2.41)</td>
<td>.954</td>
</tr>
<tr>
<td>≥2 mg/kg at time of IA diagnosis</td>
<td>3.05 (1.43–6.49)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Variable                                    | HR (95% CI) | P   |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient-related factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of IA diagnosis (2002–2004 vs. previous)</td>
<td>0.6 (0.5–0.9)</td>
<td>.008</td>
</tr>
<tr>
<td>Good-risk underlying disease(^a)</td>
<td>0.7 (0.5–0.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Severe impairment on PFT(^b)</td>
<td>1.6 (1.0–2.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Transplant-related factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA mismatch</td>
<td>1.3 (1.0–1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>1.3 (1.1–1.6)</td>
<td>.008</td>
</tr>
<tr>
<td>Receipt of PBSCs</td>
<td>0.7 (0.6–0.9)</td>
<td>.009</td>
</tr>
<tr>
<td>Nonmyeloablative conditioning</td>
<td>0.6 (0.4–0.9)</td>
<td>.006</td>
</tr>
<tr>
<td>Transplant complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia(^c)</td>
<td>2.3 (1.7–3.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lymphopenia(^d)</td>
<td>1.9 (1.5–2.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Monocytopenia(^e)</td>
<td>1.3 (1.0–1.6)</td>
<td>.05</td>
</tr>
<tr>
<td>Acute GVHD(^f)</td>
<td>1.8 (1.5–2.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperbilirubinemia(^g)</td>
<td>43.8 (33.5–57.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Elevated creatinine level(^h)</td>
<td>10.4 (7.5–14.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cytomegalovirus disease(^i)</td>
<td>2.1 (1.6–2.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Corticosteroid dosage of ≥2 mg/kg per day</td>
<td>3.1 (2.2–4.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IA-related factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated IA</td>
<td>4.1 (3.3–5.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Late IA</td>
<td>3.7 (2.6–5.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Proven IA</td>
<td>2.7 (2.0–3.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Voriconazole monotherapy</td>
<td>0.6 (0.4–1.0)</td>
<td>.06</td>
</tr>
</tbody>
</table>

\(^a\) Severe acute GVHD
\(^b\) PFT: post-transplant fever
\(^c\) Neutropenia <0.5 × 10⁹/L
\(^d\) Lymphopenia <0.5 × 10⁹/L
\(^e\) Monocytopenia <0.2 × 10⁹/L
\(^f\) Acute GVHD: defined by the National Marrow Transplant Research Group criteria
\(^g\) Hyperbilirubinemia >34.4 µmol/L
\(^h\) Elevated creatinine level >200 µmol/L
\(^i\) Cytomegalovirus disease: documented or highly suggestive at transplantation

Cordonnier et al. CID 2006, Upton et al. CID 2007
GVHD increases the risk of IFI

Figure 1  Cumulative incidence of invasive fungal infections after allogeneic BMT.

Figure 2  Incidence of invasive fungal infections according to the grade of acute GVHD.

Figure 3  Incidence of late invasive fungal infections (diagnosed >100 days post-transplant) according to the severity of chronic GVHD.
CONCLUSIONS 4

A. Acute and chronic GVHD increases the risk of IA

B. GVHD is a risk factor for IA therapy failure
Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL (BSI)
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
Time to aGVHD≥2 with and without early blood stream infection (BSI)

Early BSI - before D+10

Acute GVHD appeared at a median of 16 days after stem cell infusion

Critical events that promote aGVHD occur within days to weeks after HSCT, consistent with the timing of early BSI.

<table>
<thead>
<tr>
<th>Early BSI</th>
<th>N</th>
<th>Developed acute GVHD grades 2-4</th>
<th>Censored (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>183</td>
<td>40</td>
<td>143 (78)</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>9</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Total</td>
<td>211</td>
<td>49</td>
<td>162 (77)</td>
</tr>
</tbody>
</table>

Poutsiaka et al., BMT, 2011
### Multivariable analysis of cause-specific hazard ratios for the development of aGVHD≥2 (n=199)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV seropositivity (recipient)</td>
<td>0.45</td>
<td>0.25, 0.81</td>
<td>0.008</td>
</tr>
<tr>
<td>Early BSI (up to D+10)</td>
<td>2.17</td>
<td>1.05, 4.49</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous HSCT</td>
<td>0.50</td>
<td>0.20, 1.27</td>
<td>0.15</td>
</tr>
<tr>
<td>Etoposide</td>
<td>0.39</td>
<td>0.12, 1.26</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Bacterial components, specifically lipopolysaccharide from GI microorganisms (G-negative), leak from the GI tract after tissue damage induced by the conditioning regimen and enter the systemic circulation, where the bacterial components contribute to the activation of donor T-cells via APCs, favoring the development of aGVHD.

Duran-Struuck et al. Transplantation 2008
Rationale for development of acute GI-GVHD after BSI

Early BSI was associated with an increased risk of aGVHD.

Pousiaka et al, BMT, 2011

Patients with higher degrees of GI injury and mucosal permeability during the HSCT process had an increased likelihood of developing aGVHD.


In the course of BSI: similar (like during HSCT) consequences for GI-aGVHD.

Pousiaka et al, BMT, 2011
Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL (CDI)
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
ASSOCIATION BETWEEN C. DIFFICILE INFECTION AND SUBSEQUENT DEVELOPMENT OF GVHD (4 studies)

- CDI was associated with severe GVHD (grade 3-4) (OR 9.8) in a retrospective analysis of 75 allo-HSCT recipients. Isolation of C. difficile in the stool appeared to be temporally associated with the development or worsening of GVHD in 60% of case patients.  
  Chakarbarti et al., BMT, 2000

- Patients with CDI were more likely to develop new-onset: GVHD (P<0.001), severe GVHD (P<0.001), GI-GVHD (P=0.007).  
  Dubberke et al., Clin Transplant, 2010

- CDI diagnosis preceded GVHD diagnosis in 85.7% of patients who developed biopsy-proven GI-GVHD.  
  Alonso et al., CID, 2012

- CDI patients were more likely to develop severe GVHD at day 60 and day 100 after HSCT.  
  Trifilio et al., BBMT, 2012

With these observations, there appears to be mounting evidence for an association between CDI and GVHD.
Acute GVHD following allo-HSCT:
patients who developed CDI were more likely to develop GI-GVHD compared with patients who never developed CDI

Alonso et al, CID 2012
The diagnosis of CDI preceded the diagnosis of GI-GVHD in the majority of subjects (12/14 patients, 85.7%).

Among the 12 patients who developed GI-GVHD following CDI, GI-GVHD diagnosis occurred at a median of 21.5 days after CDI (IQR, 12-49 days).

CDI increases the risk for GI-GVHD due to:
- microbial antigenicity
- response to mucosal damage
Fever at the time of CDI: 29.3% of patients - mean duration of 2 days.

Cytopenia was common,

Traditional markers of severe CDI were infrequent;
   white blood cell counts of >20 000 cells/mm3 (2.2%),
   hypoalbuminemia (5.4%),
   acute renal failure (10.9%).
Most pts had normal serum albumin levels and leukopenia

Colonoscopies / sigmoidoscopies: pseudomembranes - 3.3%
Radiographic imaging: ascites - the most common finding - 36.4%
PATHOGENESIS OF INFECTION

Colonic ulceration and subsequent accumulation of proteins, mucus, and inflammatory cells result in the development of pseudomembranous colitis, a finding that has been considered virtually pathognomonic for CDI.

CLINICAL PRESENTATION AND DISEASE SEVERITY

This infection may be different in immunosuppressed patients, with an absence of pseudomembranes.

Few markers of severe disease: white blood cell (WBC) and creatinine elevation – NOT in immunosuppressed pts

It is possible that immunosuppression may attenuate the disease.

PROTECTION: Colonization with nonpathogenic strains of the bacterium may provide some protection from CDI in some individuals, possibly by inhabiting the microbial space that toxigenic strains need to infect the patient.

Alonso et al., 2012
TREATMENT/PROPHYLAXIS FOR CDI AFTER HSCT

METRONIDAZOLE p.o. - for mild and moderate cases of CDI.
VANCOMYCIN p.o. - for the treatment of severe cases.

Cohen et al. Infect Control Hosp Epidemiol 2010; (IDSA)

CURRENT PRACTICE: up-front therapy with vancomycin p.o. in immunosuppressed patients.

Alonso et al., CID, 2012

NEW: FIDAXOMICIN
• 183 patients with cancer (67.8% solid tumor, 20.2% hematologic malignancy, and 12.0% solid tumor and hematologic malignancy)
• Patients with cancer had lower overall cure rates, but similar rates of recurrent CDI when compared to patients without cancer.
• Overall cure rates were: 97.3% in fidaxomicin group vs 87.5% in vancomycin group (OR 5.07, 95% CI 1.07-23.98, P=0.04).

Cornely et al, ECCMID, 2012
CONCLUSIONS 5

A. BSI increases GI injury. Early BSI is a risk factor for aGVHD.

B. There is an important bidirectional association between CDI and GI-GVHD.
Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
Hypothesis: CMV replication might induce GVHD

The increased risk of GVHD development in patients with pretransplant CMV seropositivity.

Broers et al., Blood, 2000
Ljungman et al., Blood, 2003
Ringden et al., BBMT, 2004

Reduced rates of chronic GVHD after preemptive CMV treatment.

Larsson et al., Transplantation, 2004

CMV-infected endothelial cells produce inflammatory cytokines such as IL-6, which plays a crucial role in the initial phase of the acute GVHD.

Grefte et al., JID, 1993
CMV gastrointestinal disease

- **CMV gastrointestinal disease** and pneumonia are by far the most common manifestations of CMV disease in the current era.

- CMV and GVHD are frequently known to be seen concomitantly in the GI tract, but GI manifestations, CMV-antigenemia or DNA-emia (negative in 25%), and endoscopic findings cannot distinguish CMV-GI disease from GI-GVHD.

- The diagnosis of GI disease relies on detection of CMV in biopsy specimens by culture (rapid or conventional), immunohistochemistry, or detection of inclusion bodies.

- Although each of these methods is sufficient to diagnose CMV GI disease, the diagnostic yield is significantly increased if more than one method is used.

- At least 2 different methods should be used on biopsy specimens to diagnose CMV disease, especially if PCR is used.

Boeckh&Ljungman, Blood, 2009
Cho et al., Ann Hematol, 2013
Impact of CMV replication on aGVHD incidence: during phases of CMV replication, patients were at increased risk of developing aGVHD.

In multivariate analysis, patients were at increased risk of developing aGVHD during episodes of CMV replication (HR for development of any grade aGVHD: 2.18, P<0.01).

Hazard ratios were adjusted for patient age, disease, disease stage, donor type, stem cell source, conditioning regimen, degree of HLA match, and type of pharmacological GVHD prophylaxis.
Impact of aGVHD on duration and severity of CMV reactivation

Presence of GVHD increased the risk of CMV replication

Cantoni et al., BBMT, 2010
CMV serologic constellation was not a significant predictor of GVHD after correction for individual CMV replication

\[
\begin{align*}
D-/R- & \quad HR=1.00: \\
D+/R- & \quad HR= 0.90 [0.62-1.28], \\
D-/R+ & \quad HR= 0.94 [0.71-1.26], \\
D+/R+ & \quad HR= 1.18 [0.87-1.59]).
\end{align*}
\]

These data suggest that CMV replication rather than CMV serostatus is the true risk factor for GVHD development.
CONCLUSIONS 6

A. There is an increased risk of developing aGVHD during episodes of CMV replication

B. Presence of GVHD increased CMV replication
Infective gastrointestinal complications in patients with GvHD

1. SPECIFICITY OF GI TRACT AFTER HSCT
2. GVHD INCREASES THE RISK OF GI-INFECTION
   2A. BACTERIAL
   2B. VIRAL
   2C. FUNGAL
3. INFECTION INCREASES THE RISK OF GI-GVHD
   3A. BACTERIAL
   3B. VIRAL
   3C. FUNGAL
4. CONCLUSIONS
Preventing infection improves survival

1418 patients who received 1st allo HSCT 1993-1997 vs. 2003-2007

Goal: evaluate significance of improvement in supportive care strategies

Components of pre-transplant assessment of mortality score to adjust for severity of illness

Hazard of death not preceded by relapse decreased over time period

Gooley et al. NEJM 2010
Anti-Candida prophylaxis with fluconazole up to +75 post allo-HSCT

The development of invasive candidiasis and candidiasis-related death

Decrease in death
Decrease in symptomatic GI tract GVHD

Marr et al, Blood 96 (6) 2000
Patients who received fluconazole had significantly less severe gut GVHD, compared with placebo patients.

Marr et al., Blood, 2000
## Outcome variables before and after day 110 in patients who received fluconazole compared with placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>On or before day 110 (%)</th>
<th>$P$ †</th>
<th>After day 110 (%)</th>
<th>$P$ †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>52 (35)</td>
<td>.004</td>
<td>55 (57)</td>
<td>.043</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>31 (20)</td>
<td>53 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8 (5)</td>
<td>.37</td>
<td>31 (32)</td>
<td>.09</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>5 (3)</td>
<td>27 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute GVHD grade ≥ 2</strong></td>
<td></td>
<td></td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>Placebo</td>
<td>82 (55)</td>
<td>.17</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>96 (63)</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic GVHD§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>21 (14)</td>
<td>.49</td>
<td>27 (28)</td>
<td>.75</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>26 (17)</td>
<td>32 (21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Decreased mortality was due to overall acute GVHD and gut GVHD in the fluconazole arm.

Gut mucosal breakdown is a risk factor for candidiasis.

Goodrich et al., JIC, 1991

Antimicrobial administration might impact the development of gut GVHD by decreasing microbial colonization (RTC study).

Beelen et al., Blood, 1999

Fluconazole-associated decrease of gut GVHD can be explained by decreased local antigenic stimulation as a result of intestinal microbial “decontamination.”

Van Bekkum et al., JNCI, 1974
Secondary to a low amount of gastrointestinal colonization after 75 days of fluconazole in patients, who have cGVHD involving GI mucosal barriers.

Marr et al., Blood, 2000
Dectin-1 and Candida

Dectin-1: C-type ligand that recognizes β-glucan

142 HCT recipients screened Polymorphism (Y238X) associated with increased GI Candida colonization

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Homozygous wild-type for DECTIN-1</th>
<th>Heterozygous for DECTIN-1 Y238X</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida species colonization at hospital admission</td>
<td>31.5 (35/111)</td>
<td>84.6 (11/13)</td>
<td>&lt;.001</td>
<td>11.9</td>
</tr>
<tr>
<td>Candida species colonization on day of HSCT (day 0)</td>
<td>45.1 (50/111)</td>
<td>92.3 (12/13)</td>
<td>.001</td>
<td>14.6</td>
</tr>
<tr>
<td>Surveillance-culture guided fluconazole therapy</td>
<td>37.8 (42/111)</td>
<td>69.2 (9/13)</td>
<td>.03</td>
<td>3.7</td>
</tr>
<tr>
<td>Early candidemia (day 21 or earlier)</td>
<td>8.0 (9/112)</td>
<td>18.2 (2/11)</td>
<td>.26</td>
<td>2.5</td>
</tr>
<tr>
<td>Invasive mold disease (day 100 or earlier)</td>
<td>3.0 (3/100)</td>
<td>5.0 (1/20)</td>
<td>.52</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Plantiga et al. CID 2009
Dectin-1 and Candida and GI-aGVHD

Dectin-1: C-type ligand that recognizes β-glucan

Patients who were colonized with Candida had more GI tract aGVHD

Patients from patient-donor pairs bearing the wild-type allele who were colonized with Candida had a significant increased incidence of acute GvHD compared to non-colonized patients (OR=2.6, P=0.04).

Van der Velden et al., Clinical Immunology, 2010
Dectin-1, fungi, and the gut

Dectin-1 knock-out mice had:
- more colitis after chemical exposure,
- increased exposure to indigenous fungi (C. tropicalis)

Prophylaxis with fluconazole decreased incidence of colitis.

This polymorphism can possibly be associated with the Candida colonization, fungal gut infection and risk of GVHD.

It can possibly explain secondary observations with fluconazole preventing GVHD.

Iliev et al., Science 2012
CONCLUSIONS 7

A. Fluconazole *possibly* prevents severe gut GVHD in allogeneic BMT recipients

B. Genetic predispositions *might* contribute to fungal infections and GI-aGVHD
Infective gastrointestinal complications in patients with GvHD

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