How do anti-infective guidelines apply to patients with GvHD? Viral infections
How do anti-infective guidelines apply to patients with GvHD? Viral infections

What viruses?

- Herpes (CMV, HS, VZ, EBV)
- Respiratory viruses (Influenza, others)
- Norovirus

What guidelines?

- International Consensus (2009)
- European Conference on Infections in Leukemia (ECIL)
Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective.

Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and the Centers for Disease Control and Prevention (CDC)
The ECIL is a common initiative of:
- the Infectious Diseases Working Party of the EBMT
- the Infectious Diseases Group of the EORTC
- the Supportive Care group of the European LeukemiaNet
- the International ImmunoCompromised Host Society (ICHS)

ORGANIZATION COMMITTEE

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Oscar Marchetti (Lausanne, Switzerland)
Georg Maschmeyer (Potsdam, Germany)
Claudio Viscoli (Genova, Italy)
European Conference on Infections in Leukemia (ECIL)

2º conference (2007), published guidelines
- CMV, HHV6, 7 & 8 (Ljungman P. BMT 2008, 142: 227-40)
- HS, VZ, EBV (Styczynski J. BMT 2009; 43: 757-70)

4º conference (2011), published guidelines
- Influenza (Engelhard D. TID 2013, 15: 219-232)
- Other resp.viruses (Hirsh H. CID 2013; 56: 258-266)
- Adenovirus (Matthes-Martin S. TID 2012; 14: 555-63)

5º conference (2013), unpublished guidelines
- Hepatitis viruses (A, B, C, E) (comming soon!!)

WWW.kobe.fr/ecil
Rating system for Recommendations

- **ECIL (1, 2, 3), International consensus:**
  - A, B, C, D, E / I, II, III (“Traditional” system)

- **ECIL (4 & 5)**
  - A, B, C / I, II, III

- **NCCN system:**
  - 1, 2A, 2B, 3
## Rating system: ECIL 1-3, International C

### Strength of recommendations

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong evidence for efficacy</td>
<td>Moderate evidence for efficacy</td>
<td>Insufficient evidence</td>
<td>Moderate evidence against</td>
<td>Strong evidence against</td>
</tr>
<tr>
<td>Strongly recommended</td>
<td>Generally recommended</td>
<td>Optional</td>
<td>Generally Not recommended</td>
<td>Never recommended</td>
</tr>
</tbody>
</table>

### Quality of evidence supporting recommendation

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
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<td>Well-designed trial without randomization</td>
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**MMWR 2000; 49 (RR-10): 1-125**
## Rating system: ECIL 4 & 5

### Strength of recommendations

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<tbody>
<tr>
<td>Good evidence</td>
<td>Moderate evidence</td>
<td>Poor evidence</td>
<td>Moderate evidence against</td>
<td>Strong evidence against</td>
</tr>
</tbody>
</table>

*To support a recommendation FOR or AGAINST USE*

**Generally Not recommended**

**Never recommended**

### Quality of evidence supporting recommendation

<table>
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Reconstitution kinetics after SCT

Severe combined immunodeficiency

Immunosuppression

- Cords
- Haploidentical with massive TCD

Viral control depends on T (and B cell) reconstitution
- Neutropenia is less important (could affect severity/course)
Viruses produce “damage” in 2 ways

Direct effects

- Recognized viral disease (e.g. CMV pneumonitis)

Indirect effects

- Clinical events associated with virus seropositivity or the development of viral infection but not with the viral disease itself

Patients

- HSCT
- SOT
- HIV

Viruses

- CMV
- HHV6
- Respir. viruses

Events, for CMV in SCT

- ↑ GVHD
- ↑ Bacterial & fungal infect.
- ↑ TRM and ↓ Survival
CMV seropositivity or / and CMV infection: is an independent risk factor for:

- ↑ acute-GVHD (RR 3)
- ↑ extensive chronic GVHD (RR 3.1)
- ↑ mortality due to bacterial and fungal infections (RR 2)
- ↑ Invasive Aspergillosis (HR 2)
- ↑ TRM (HR 2-5)
- ↓ Survival (HR 1.5-2.7)

• These negative effects occurred mainly in:
  • Transplants from unrelated donors
  • T-cell depleted transplants

  But also in HLA identical sibling SCTs
Immunosuppression

CMV

GVHD

GVHD Treatment

Vicious circle

Immunosuppression

- Cords
- Haploidentical with massive TCD

- Viral control depends on T (and B cell) reconstitution
- Neutropenia is less important (could affect severity/course)
In this setting (GVHD)

- It is better to prevent than to treat viral diseases (= like IFIs)
- Improve GVHD and decrease immunosuppressive treatment
- Improve immunity (adoptive immunotherapy)
Infection is a necessary condition although not sufficient for the development of CMV disease.

Development of CMV disease after SCT

Allogeneic vs autologous

CMV infection: +/- similar

• CMV disease: Allo >> auto

Other factors (GVHD)
ECIL Guidelines: CMV (BMT 2008; 42(4) 227-40)

- Based on a review of the English-language literature following a predefined methodology
- Studies reviewed: 76 (29 randomized)
- Discussed in a consensus conference

- **Recommendations on**
  - Diagnosis (techniques; CMV disease)
  - Prevention of primary CMV infection
  - Prevention of CMV disease
  - Treatment of CMV disease
  - Antiviral Resistance
  - Adoptive Immunoprophylaxis
Diagnosis of CMV disease

- **Gastrointestinal disease**, when co-exist with gut GVHD
  - Difficult to diagnose
  - Difficult to evaluate the response to Treatment

CMV monitoring in allo-SCT

- All allo-SCT patients should be monitored for CMV (A I)
  - in peripheral blood
  - at least weekly
  - using either CMV antigenemia assay or a technique for the detection of either CMV DNA or RNA
  - The duration of monitoring should be at least 100 days (B III)
- **Longer monitoring** is recommended in patients with acute or chronic GVHD (B II)
Prevention of CMV disease in allo-SCT

The strategy of choice: pre-emptive therapy

- **Pre-emptive antiviral therapy** based on detection of CMV antigen or nucleic acid (A I)
- Either intravenous ganciclovir or foscarnet can be used for first line pre-emptive therapy (A I)

- **Iv ganciclovir prophylaxis** could be used in sub-groups of patients at high risk for CMV disease (B I) (not specified)
  - Nonetheless, GVHD is a risk factor for CMV disease

Adoptive immunoprophylaxis

- Infusion of CMV specific lymphocytes or DC vaccination are interesting options and should undergo controlled prospective clinical trials (C II)

But ..., patients with GVHD are excluded from these trials!!
Cellular therapy in viral infections

Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation

Ann M. Leen,1 Catherine M. Bollard,1 Adam M. Mendizabal,2 Elizabeth J. Shpall,3 Paul Szabolcs,4 Joseph H. Antin,5 Neena Kapoor,6 Sung-Yun Pai,5,7 Scott D. Rowley,8 Partow Kebriaei,2 Bimalangshu R. Dey,9 Bambi J. Grilley,1 Adrian P. Gee,1,10 Malcolm K. Brenner,1 Cliona M. Rooney,1,10 and Helen E. Heslop1

1Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children’s Hospital, The Methodist Hospital, Houston, TX; 2The EMMES Corporation

Blood 2013; 121 (26): 5113-5123

• Infusion of virus-specific T cells for viral infections: 20 years of studies
• What is new in this study?

Comment on Leen et al, page 5113

Antiviral cell therapy: is this the future?

Juan C. Gea-Banacloche1 1NATIONAL CANCER INSTITUTE
3rd party VST therapy

Blood donor

Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
Adv activity – A1, A24, DR15

MDACC
EBV – A1, 11; B8, 35; DR8

Boston
CMV – A2, 24; B7, 27; DR1, 15

CHLA
Adv – A1, 11; B7, 8; DR3, 11

Leen AM. ICAAC 2013
Cellular therapy (Leen’s study 2013): summary

Safe & effective in the treatment of CMV, Adv, EBV:
Response: 74%  GVHD ≥ II: 5%

- Multicentric setting
- With Trivirus-specific T cells
- Prebanked cryopreserved, ready to use (off-the-self)
- From thrid-party donors, with minimal HLA matching

- Atractive therapy for patients with TCD without GVHD
  - Haplos TCD, cords
- Not for patients with
  - GVHD > I
  - Prednisone > 0.5 mg/kg
  - anti-thymocyte globulin or alemtuzumab

Leen AM. Blood 2013; 121 (26): 5113-5123
ECIL (2009) & International guidelines: HS, VZ

The strategy of choice: Chemoprophylaxis Should be longer if GVHD !!

Prevention HS (in sero + patients):
- Allo-SCT should receive antiviral drug prophylaxis (AI) until engraftment occurs or mucositis resolves, whichever is longer (Int.)
- Patients who develop GVHD or receive immunosuppressive treatment, usually require prolonged prophylaxis (BII) (ECIL)

Prevention VZ (in sero + patients):
- Chronic GVHD: The most significant risk for VZV infections
- Allogeneic SCT recipients: Oral ACV (800mg x 2) or ValaACV (500 mg 1-2 daily) for 1 year (AII) (BI Int)
  - or longer if GVHD and immunosuppressive therapy (BII)
- Prophylaxis in autologous SCT is controversial (CIII).
Prevention VZ, in sero negative patients after exposure to varicella or zoster: 2 options

a) Passive immunization (A II) with i.v. or i.m. ZIG or IVIG should be given as soon as possible after exposure (<96 h) to patients who have
   - chronic GVHD or /and
   - are on immunosuppressive treatment or /and
   - whose SCT was within 2 years

b) Postexposure prophylaxis (A III) is recommended where passive immunization is not available, starting during 3–21 days after exposure

**THERAPEUTIC DOSES**

- Acyclovir: 800 mg four times daily
- Valaciclovir: 1000 mg three times daily
- Famciclovir: 500 mg three times a day
The important complication of EBV replication is PTLD
- Prevention is based on a pre-emptive strategy

**EBV monitoring in allo-SCT (≈ as CMV)**
- Prospective monitoring of EBV-viremia by quantitative PCR is recommended after high-risk allo-SCT (B II)
- Start at the day of SCT, last for 3 months, at least once a week
  - longer monitoring is recommended in patients undergoing treatment for GVHD, after haplo-SCT, in those with an early EBV reactivation (C II)

**Prevention of EBV-LPTD: pre-emptive therapy**
- anti-CD20 therapy (rituximab) (A II)
- reduction of immunosuppressive therapy (B II)
- donor EBV-specific CTL infusion (C II) if available
• Four deadly viruses
  Influenza,  RVS,  Parainfluenza,  Metapneumovirus

• Others (many !!), the era of multiplex NAT
  Rhinovirus,  Coronavirus,  Enteroviruses
  Bocavirus,  Polyomavirus KI & WU
Influenza definitions: ECDC criteria (confirmed, probable, possible)

Diagnostic techniques:
- Sample: pooled bilateral nasopharyngeal + throat swabs (URTI)
- Technique: Qualitative PCR

Prevention:
- General precautions \((A\ II)\) / Vaccination \((A\ II)\)
- Post-exposure prophylaxis \((C\ III)\) for high-risk patients

Treatment ALL SCT patients with influenza should be Treated! \((A\ II)\)
Pandemic H1N1 (2009): transplant patients

Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study

Deepali Kumar, Marian G Michaels, Michele I Morris, Michael Green, Robin K Avery, Catherine Liu, Lara Danziger-Isakov, Valentina Stosor, Michele Estabrook, Soren Gantt, Kieran A Marr, Stanley Martin, Fernanda P Silveira, Raymund R Razonable, Upton D Allen, Marilyn E Levi, G Marshall Lyon, Lorraine E Bell, Shirish Huprikar, Gopi Patel, Kevin S Gregg, Kenneth Pursell, Doug Helmersen, Kathleen G Julian, Kevin Shiley, Bartholomew Bono, Vikas R Dharnidharka, Gelareh Alavi, Jayant S Kalpoe, Shmuel Shoham, Gail E Reid, and Atul Humar, on behalf of the American Society of Transplantation H1N1 Collaborative Study Group

Lancet Infect Dis 2010; 10: 521–26

Outcome of pandemic H1N1 infections in hematopoietic stem cell transplant recipients

Per Ljungman,1 Rafael de la Camara,2 Lena Perez-Bercoff,1 Manuel Abecasis,3 Jose Bartolo Nieto Campuzano,4 M. Jimena Cannata-Ortiz,2 Catherine Cordonnier,5 Hermann Einsele,6 Marta Gonzalez-Vicent,7 Ildefonso Espigado,8 Jörg Halter,9 Rodrigo Martino,10 Bilal Mohty,11 Gülşan Sucak,12 Andrew J Ullmann,13 Lourdes Vázquez,14 Katherine N. Ward,15 and Dan Engelhard16 for the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) and the Infectious Complications Subcommittee of the Spanish Group of Haematopoietic Stem-cell Transplantation (GETH)

Haematologica 2011; 96: 1231-5
### Pandemic H1N1 (2009): transplant patients

<table>
<thead>
<tr>
<th></th>
<th>SOT (EEUU) n° = 237</th>
<th>SCT (Europe) n° = 286</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td>Diagnosis by PCR</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>Pandemic H1N1</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>0% (exclude)</td>
<td>11.5%</td>
</tr>
<tr>
<td>Without Fever</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Peumonia</td>
<td>31.7%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>8.8%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Died from A/H1N1</td>
<td>4%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

**Early treatment (<48h)**
- Lower hospital & ICU admission and ventilation reported

**100 -300 times higher compared with general population**
Risk factors for severe influenza (LRTI)

- Older age*
- Early infections (First 12 months post HSCT)
- Lymphopenia** (several cutoffs <100, <200, <300)
- Immunosuppression (not in multivariate analysis)
- Having an unrelated or mis-matched family donor

*continuous variable (Ljungman et al, Haematologica 2011)

** Interaction between lymphopenia and GVHD
Influenza vaccination to allogeneic/autologous HSCT recipients

• **Yearly vaccination** with seasonal inactivated influenza vaccine is recommended. *(A-II)*

• The vaccine is preferably given prior to the influenza season, usually at least 3 months after HSCT. *(B-III)*

• **A second dose of vaccine** after 3–4 weeks is advised, although it may only have marginal benefit. *(B-II)*

• No data exist about **live attenuated influenza vaccine** safety and efficacy in HSCT patients, and it should not be used. *(A-III)*

Hospital staff

• Annual seasonal influenza vaccination is **strongly recommended for all health-care workers** of HSCT recipients and non-transplant leukemic patients. *(A-II)*
• Frequent asymptomatic excretion in SCT:
  • Metapneumovirus, Coronavirus, Rhinovirus

• Not clear role in SCT
  • Bocavirus, Enterovirus
  • Not related to disease in SCT
  • Polyomavirus Ki y Wu

• Prioritizing tests: First line: Influenza A & B, RSV and HPIV (A II) By case / negative first line: others viruses (B II)

• Multiplex PCR platforms (microarrays): can diagnose infections of unknown clinical meaning
Table 2. Risk Factors of Respiratory Syncytial Virus–Associated Complications in Hematopoietic Stem Cell Transplantation Patients

<table>
<thead>
<tr>
<th>Progression to LRTID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia &lt;0.2 × 10^9/L</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Mismatched/unrelated donor</td>
</tr>
<tr>
<td>Allogeneic HSCT &lt;1 mo</td>
</tr>
<tr>
<td>Neutropenia &lt;500/μL</td>
</tr>
<tr>
<td>No therapy with aerosolized ribavirin + IVIG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preengraftment</td>
</tr>
<tr>
<td>Lymphopenia &lt;0.2 × 10^9/L</td>
</tr>
<tr>
<td>Allogeneic HSCT &lt;1 mo</td>
</tr>
<tr>
<td>Severe immunodeficiency</td>
</tr>
<tr>
<td>Older age (&gt;65 y)</td>
</tr>
</tbody>
</table>
Respiratory viruses: treatment (CID 2013)

- **Allogeneic SCT:**
  - **RSV** SHOULD BE treated (B II) in cases with
    - **URTD** with risk factor for LRTID/death
    - **LRTID**
  - **HPIV** Treatment MAY BE CONSIDERED (B III) in cases with
    - **LRTID**
    - **Other viruses:** treatment CANNOT BE recommended (CIII)

**But ...**

**Recommended Treatment:** Ribavirin + Ig

- **Ribavirin:** Aerosolized (B II) or **ORAL** (B III) or intravenous (C III)
- **Ig (B III):** conventional IvIg in children < 2 years old: specific monoclonal (palivizumab) (C III)

- **Autologous SCT**
  - Treatment of **CARV RTID** other than influenza is not generally recommended (C III)
Study: retrospective, PCR+ for RSV or HMPV on BAL (2006-2011)
Patients with LRTD: HMPV (23) vs RSV (23)
  - Type of SCT: Allo (29), Auto (7), Pre-SCT (10)
  - RSV treatment: 22/23 aerosolized ribavirina + palivizumab
  - HMPV treatment: 15/23 10 aerosolized ribavirina +/-Ig, 5 Ig

Similar clinical & virologic characteristics
Mortality at 100 days: 43% (HMP=RSV), virus-related 39 vs 35%
Conclusion:
  - HMPV LRTD: high mortality, similar to RSV

In vitro studies and animal models have shown the efficacy of ribavirin against HMPV
Norovirus: a cause of diarrhoea in SCT

- RNA virus, family *Caliciviridae*. Discovered in 1972
- The most common cause of outbreaks of nonbacterial gastroenteritis

- Diarrhoea: a frequent complication in allo-SCT (80%)
  - GVHD is also a cause of diarrhoea

- Norovirus diarrhoea in SCT: can be life-threatening
  - sudden onset: vomiting + prolonged secretory nonbloody diarrhea

- Diagnosis: PCR (better than electron microscopy)
  - Histology can be misleading: crypt apoptosis is sometimes seen in norovirus infection

- Treatment: crucial to distinguish norovirus from clinical GVHD, since these conditions require diametrically treatment
  - Norovirus: decreasing immunosuppression!!
Viral Infections in patients with GVHD

- BETTER to Prevent than Treat viral disease
- More FREQUENT Virological Monitoring
- LONGER Chemoprophylaxis
- HIGHER Index of suspicion

- In general, guidelines do not specify in detail the management of viral infections in patients with GVHD
Thank you