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

31 October - 1 November 2013
Barcelona, Spain

Organizers: S. Cesaro, R. Duarte, H. Greinix
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)

Biology Blood Marrow Transplantation 2009, 15 (10): 1143-1238
European Conference on Infections in Leukemia (ECIL)

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

Catherine Cordonnier  (Créteil, France)
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Johann Maertens  (Leuven, Belgium)
Oscar Marchetti  (Lausanne, Switzerland)
Georg Maschmeyer  (Potsdam, Germany)
Claudio Viscoli  (Genova, Italy)
### 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### 5º conference (2013), unpublished guidelines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>Strong evidence for efficacy</strong></td>
<td><strong>Moderate evidence for efficacy</strong></td>
<td><strong>Insufficient evidence</strong></td>
<td><strong>Moderate evidence against</strong></td>
<td><strong>Strong evidence against</strong></td>
</tr>
<tr>
<td><strong>Strongly recommended</strong></td>
<td><strong>Generally recommended</strong></td>
<td><strong>Optional</strong></td>
<td><strong>Generally Not recommended</strong></td>
<td><strong>Never recommended</strong></td>
</tr>
</tbody>
</table>

#### Quality of evidence supporting recommendation

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized study</strong></td>
<td><strong>Well-designed trial without randomization</strong></td>
<td><strong>Expert opinions, descriptive studies</strong></td>
</tr>
</tbody>
</table>

*MMWR 2000; 49 (RR-10): 1-125*
### Rating system: ECIL 4 & 5

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

**To support a recommendation**

**FOR or AGAINST USE**

**Generally Not recommended**

**Never recommended**

#### Quality of evidence supporting recommendation

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
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<tr>
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<td><strong>Well-designed trial without randomization</strong></td>
<td><strong>Expert opinions, descriptive studies</strong></td>
</tr>
</tbody>
</table>
Reconstitution kinetics after SCT

Severe combined immunodeficiency

- Neutrophils, Monocytes, NK cells
- B cells, CD8 T cells
- CD4 T cells
- Plasma cells, Dendritic cellss

GVHD

- **CMV**

- **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**
  - MV

- **GVHD**
  - Treatment

- **CMV**

- **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)
Recommendations on

- Diagnosis (techniques; CMV disease)
- Prevention of primary CMV infection
- Prevention of CMV disease
- Treatment of CMV disease
- Antiviral Resistance
- Adoptive Immunoprophylaxis
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, 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 third-party donors, with minimal HLA matching

- Attractive 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
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
Respiratory viruses in SCT

- Four deadly viruses
  - Influenza, RVS, Parainfluenza, Metapneumovirus
- Others (many !!), the era of multiplex NAT
  - Rhinovirus, Coronavirus, Enteroviruses
  - Bocavirus, Polyomaviruses 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 Ganttt, Kieren 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 Gulsan 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><strong>Hospitalized</strong></td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Diagnosis by PCR</strong></td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Pandemic H1N1</strong></td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Nosocomial</strong></td>
<td>0% (exclude)</td>
<td>11.5%</td>
</tr>
<tr>
<td><strong>Without Fever</strong></td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>31.7%</td>
<td>32.5%</td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong></td>
<td>8.8%</td>
<td>11.5%</td>
</tr>
<tr>
<td><strong>Died from A/H1N1</strong></td>
<td>4%</td>
<td>6.3%</td>
</tr>
<tr>
<td><strong>Early treatment (&lt;48h)</strong></td>
<td>Not reported</td>
<td>100 -300 times higher compared with general population</td>
</tr>
</tbody>
</table>
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)
• **Multiplex PCR platforms (microarrays):** can diagnose infections of unknown clinical meaning

• **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)
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 × 10⁹/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 × 10⁹/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

  But ...

- **Other viruses:** treatment CANNOT BE recommended (CIII)

**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)
Mortality Rates of Human Metapneumovirus and Respiratory Syncytial Virus Lower Respiratory Tract Infections in Hematopoietic Cell Transplantation Recipients

Christian Renaud ¹,², Hu Xie ¹, Sachiko Seo ¹, Jane Kuypers ¹,³, Anne Cent ³, Lawrence Corey ¹,³, Wendy Leisenring ¹,³, Michael Boeckh ¹,³,*
Janet A. Englund ¹,²,³

Biol Blood Marrow Transplant 19 (2013) 1220–1226

- **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
Infections after SCT follow a phase-associated pattern (pathocronia)

Day 0
- Neutropenia
- Mucositis

Day 30
- Acute-GVHD

Day 100
- Chronic GVHD

Phase I
- Pre-engraftment

Phase II
- Post-engraftment

Phase III
- Latent

Respiratory viruses
- Gram+/-
- Gram+ (catheter)

Aspergillus
- CMV
- Adeno

P. jiroveci
- HS
- HHV6

Candida
- Nmc, H. influenza

Gram+ (catheter)
- VZ

CMV
Indirect effects: facts

Mortality in HSCT related to CMV: 2 different causes

Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdeM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process

Luca Pierelli, Paolo Perseghin, Monia Marchetti, Chiara Messina, Cesare Perotti, Alessandro Mazzoni, Andrea Bacigalupo, Franco Locatelli, Paolo Carlier, and Alberto Bosi for Società Italiana di Emaferesi and Manipolazione Cellulare (SIdeM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Question 2: Is ECP a therapeutic option for sparing immunosuppressive therapy in patients with viral reactivation?

Recommendations. ECP represents a promising approach for treatment of aGVHD in patients for whom further immunosuppression is contraindicated due to viral reactivation or other infectious complications.
Treatment of influenza

• Efforts should be made to confirm all suspected and probable cases of influenza. (A-III)

• All allogeneic/autologous HSCT recipients should be treated. (A-II)

• Preferred first line treatment is oseltamivir, adult dose of 75 mg BID for a mild case and 150 mg BID for severe disease given for at least 10 days. (B-II)

• In patients with continuing symptoms, it is advised to repeat PCR tests on respiratory specimens every 5-7 days and to continue treatment until they become negative. (C-III)
<table>
<thead>
<tr>
<th>Conference</th>
<th>Location</th>
<th>Dates</th>
<th>Participants</th>
</tr>
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<tbody>
<tr>
<td>ECIL 1</td>
<td>Juan-les-Pins, France</td>
<td>Sept 30-Oct 1st, 2005</td>
<td>59 experts from 24 European countries, one from Australia</td>
</tr>
<tr>
<td>ECIL 2</td>
<td>Juan-les-Pins, France</td>
<td>Sept 28-29th, 2007</td>
<td>53 experts from 24 European countries, one from Australia</td>
</tr>
<tr>
<td>ECIL 3</td>
<td>Juan-les-Pins, France</td>
<td>Sept 25-26th, 2009</td>
<td>57 experts from 18 European countries, 2 from Russia</td>
</tr>
<tr>
<td>ECIL 4</td>
<td>Juan-les-Pins, France</td>
<td>Sept 9-10th, 2011</td>
<td>53 experts from 18 European countries, one from Russia</td>
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<tr>
<td>ECIL 5</td>
<td>Sophia Antipolis, France</td>
<td>Sept 19-21th, 2013</td>
<td>57 experts from 18 European countries, Israel, Saudi Arabia, Russia and Australia</td>
</tr>
</tbody>
</table>

[WWW.kobe.fr/ecil]
Viruses produce “damage” in 2 ways

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

Indirect effects

What happens if the patient survives CMV disease?
- Independent risk factor for invasive Aspergillosis (IA)
  - HR 7 (Acute-GVHD II-IV: HR 2) (2930 Allo-SCTs) (1,2)
  - IA the most common cause of death (4)
- Independent risk factor for candidemia, HR 16.4 (3)

# Impact of CMV serology in SCT-Mortality

*Gratwohl A. Cancer 2009; 115 (20): 475-26*

## Retrospective analysis, EBMT database (1980-2005): 56,605 allogeneic patients (72% identical siblings)

<table>
<thead>
<tr>
<th>CMV serology</th>
<th>HR (TRM)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>R (-) / D (-)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>R (+) / D (+)</td>
<td>1.15</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>R (+) / D (-)</td>
<td>1.18</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>R (-) / D (+)</td>
<td>1.01</td>
<td>.77</td>
</tr>
</tbody>
</table>

**CMV indirect effects:** important impact on SCT mortality  
Risk of TRM was constantly about 5% higher in CMV sero+ recipients, compared with CMV sero (-) recipients
Trends in Transplants by Transplant Type and Recipient Age* 1990-2010

Transplants, %

<table>
<thead>
<tr>
<th>Year</th>
<th>Allogeneic Transplants</th>
<th>Autologous Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997-2003</td>
<td>&lt; 50 years: 18%</td>
<td>&gt; 60 years: 36%</td>
</tr>
<tr>
<td>2004-2010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
# Age as a risk factor for IFI in HSCT

## Older age (≥ 40 years): a risk factor for IFI

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th>Nº Patients</th>
<th>HR (2-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Gratwohl A.</td>
<td>EBMT</td>
<td>6871</td>
<td>3.1 (for fungal death)</td>
</tr>
<tr>
<td>(2) Wald A.</td>
<td>FHCRC</td>
<td>2496</td>
<td>5 (for late IA)</td>
</tr>
<tr>
<td>(3) Marr K.</td>
<td>FHCRC</td>
<td>1642</td>
<td>2.4 (for IA)</td>
</tr>
<tr>
<td>(4) Marr K.</td>
<td>FHCRC</td>
<td>5589</td>
<td>1.8 (for IA)</td>
</tr>
<tr>
<td>(5) Garcia-Vidal C</td>
<td>FHCRC</td>
<td>1248</td>
<td>1.3 Age, by 10-year increase (for IMI)</td>
</tr>
</tbody>
</table>

(1) BMT 2005; 36: 757  
(2) JID 1997; 175: 1459  
(3) Blood 2002; 100: 4358  
(4) CID 2002; 34: 909  
(5) CID 2008; 47: 1041

Clinical Infectious Diseases 2006;43:1143–51

Stephanie A. S. Staras,1,2 Sheila C. Dollard,2 Kay W. Radford,2 W. Dana Flanders,1 Robert F. Pass,3 and Michael J. Cannon1,2

Table 1. Age-adjusted cytomegalovirus (CMV) seroprevalence in the non-institutionalized, civilian population of the United States, aged ≥6 years.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>CMV seroprevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>36.3</td>
</tr>
<tr>
<td>12-19</td>
<td>41.7</td>
</tr>
<tr>
<td>20-29</td>
<td>49.3</td>
</tr>
<tr>
<td>30-39</td>
<td>54.2</td>
</tr>
<tr>
<td>40-49</td>
<td>64.5</td>
</tr>
<tr>
<td>50-59</td>
<td>74.2</td>
</tr>
<tr>
<td>60-69</td>
<td>83</td>
</tr>
<tr>
<td>70-79</td>
<td>88.8</td>
</tr>
<tr>
<td>≥ 80</td>
<td>90.8</td>
</tr>
</tbody>
</table>

More age ➔ More sero + ➔ More CMV complications
CMV pneumonia (allo-SCT)
- Ganciclovir is recommended (AII)
- Foscarnet might be used in place of ganciclovir (AIII)
- The addition of immune globulin to antiviral therapy should be considered (CII)

Other types of CMV disease and in other patients groups ➔ Monotherapy
- Ganciclovir or foscarnet without Ig is recommended (BII)

Has the treatment improved over time?
Mortality at 6 months: 72.4% (CMV attributed 47.6%) – Without changes over time

Combined therapy (Gcv or Fos) + Ig (standard or CMV-specific) vs antiviral MONOTHERAPY – No impact on mortality (global or CMV-related)

Even today, it is better to prevent CMV disease
Combined therapy is not better than monotherapy
Influenza case definitions

- Clinical Criteria
- Epidemiological Criteria
- Laboratory Criteria

Definitions of the ECDC (European Centre for disease Prevention and Control):

Influenza - Clinical Criteria

Any person with at least one of the following clinical forms:

- Influenza-like illness (ILI)
- Acute respiratory infection (ARI)

Definitions of the ECDC (European Centre for disease Prevention and Control):
Influenza-like illness (ILI)

Sudden onset of symptoms **AND**
At least one of the following four systemic symptoms:

- Fever or feverishness
- Malaise
- Headache
- Myalgia

**AND** At least one of the following three respiratory symptoms:

- Cough
- Sore throat
- Shortness of breath

**Definitions of the ECDC** (European Centre for disease Prevention and Control):

Acute respiratory infection (ARI)

Sudden onset of symptoms AND

At least one of the following four respiratory symptoms:
• Cough
• Sore throat
• Shortness of breath
• Coryza

AND

A clinician’s judgment that the illness is due to an infection

Definitions of the ECDC (European Centre for disease Prevention and Control):
Influenza - Epidemiological Criteria

- An epidemiological link by human to human transmission

Definitions of the ECDC (European Centre for disease Prevention and Control):
Influenza - **Laboratory Criteria**

- **Pooled bilateral nasopharyngeal and throat swabs** rather than nasal wash is the preferred technique in order to obtain respiratory specimen.

- Qualitative reverse transcriptase multiplex real time polymerase chain reaction (PCR) of respiratory specimens is the **gold standard laboratory method** to confirm the diagnosis of influenza and other respiratory viruses. **RT-PCR, being multiplex RT-PCR preferably: first level** Flu-A/B, RSV, PIV; **second level** others: MPV, RhV, CoV, EnV if first level negative or progression to LRTI disease.

- **Subtyping of the influenza isolate** should be performed, if possible.

- **Detection of known mutations causing resistance**, such as H275Y mutation can be done using real time PCR.
Influenza - Laboratory Criteria

• Direct immunofluorescence antibody (DFA), indirect immunofluorescence antibody (IFA) and commercially available rapid diagnostic tests (kits) may be alternatives, when PCR is not available, although these methods have lower sensitivity.
Influenza - **Case Classification**

**A. Possible case**
- Any person meeting the clinical criteria (ILI or ARI)

**B. Probable case**
- Any person meeting the clinical criteria (ILI or ARI) and with an epidemiological link

**C. Confirmed case**
- Any person meeting the clinical (ILI or ARI) and the laboratory criteria

**Definitions of the ECDC** (European Centre for disease Prevention and Control):
Vacuna INTRADÉRMICA de Gripe

- 90% más pequeña que las agujas convencionales i.m.
- 40% menos de antígeno
### Síndrome de Guillain-Barre (SGB) e Influenza

<table>
<thead>
<tr>
<th>SGB, asociado con</th>
<th>Incidencia por 1000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>10-20</td>
</tr>
<tr>
<td>Vacunación Gripe 1976</td>
<td>10</td>
</tr>
<tr>
<td>Vacunación Gripe 92-93</td>
<td>1</td>
</tr>
<tr>
<td>Infección por Influenza *</td>
<td>40-70</td>
</tr>
<tr>
<td>Infección por <em>Campylobacter jejuni</em></td>
<td>1000</td>
</tr>
</tbody>
</table>

**GBS asociado a infección natural por Influenza es:**

- 4 -7 veces más frecuente que tras vacunación Gripe 1976
- 40 -70 veces más frecuente que tras vacunación Gripe 92-93

*Sivadon-Tardy V. CID 2009; 48: 48*