The 46th annual meeting of the European society for blood and marrow transplantation: working parties and statistics (WP01-WP09)

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29 August - 1 September, 2020 ● Virtual Meeting

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Sponsorship Statement: Publication of this supplement is sponsored by the European Society for Blood and Marrow Transplantation. All content was reviewed and approved by the EBMT Committee, which held full responsibility for the abstract selections.

Working parties and statistics

WP01.

Infectious Diseases Working Party EBMT activity 2019-2020: ECIL project and analysis of abstracts submitted for Annual Meeting

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Infectious Diseases Working Party (IDWP) EBMT is a transversal Working Party, with scientific interests involving infectious complications in patients undergoing hematopoietic cell transplantation (HCT), regardless of primary diagnosis. The mission of IDWP is: (1) to organize high level accredited annual educational activities related to infectious diseases of HCT; (2) to design and support prospective studies in the field of infectious diseases; (3) to provide a platform for high quality retrospective studies and surveys addressing prevention, diagnosis and therapy of infectious complications after transplant; (4) to generate guidelines on management of infections in this population also in collaboration with other international societies/groups in the field of infections in immunocompromised host. IDWP is one of the co-founders of ECIL (European Conference on Infections in Leukemia), which in 2019 had eight edition (ECIL-8).

Currently ongoing prospective non-interventional studies run by IDWP: (1) Incidence and outcome of HHV-6 encephalitis in patients who undergo allogeneic haploidentical HSCT; (2) Impact of pre-existing invasive aspergillosis on allogeneic stem cell transplantation (IPAT); (3) Prospective evaluation of central nervous system complications following HCT; (4) Infections following CAR T-cell therapy; (5) Real life management of antibiotic therapy in HSCT recipients.

This report summarizes also general data of abstracts submitted to EBMT-2020 Annual Meeting: infectious diseases every year belongs to the Top-3 areas of interest. Among 1108, a total number of 99 abstracts were submitted for the topic of infectious complications for EBMT-2020, being this year the second most popular topic. Their characteristics: 68 (69%) retrospective studies, 31 (31%) prospective studies: 23 (23%) abstracts reported the results of multicenter studies (including 1 Phase II study; and 10 studies from IDWP-EBMT, heading 8/12 best abstracts in this topic); 4 (4%) were case reports, and in-vitro or pharmacological studies (one each). 90 (91%) abstracts concerned adult (76%) or mixed (12%) populations, and only 9 (9%) to children. 95 abstracts (96%) focused on allogeneic±autologous transplants, and 4 (4%) on autologous transplant. Viral infections were studied in 63 (64%) abstracts (including 9 abstracts on letermovir or brincidofovir), fungal infections in 7 (7%), bacterial infections in 19 (19%) (including fecal microbiota in 2), parasite in 3 (3%),
and various infections in 8 (8%); vaccination was the focus of 1 abstract. The objective of 48 (49%) abstracts was epidemiology/risk factors/outcome, prophylaxis of 15 (15%), diagnosis of 2 (2%), immunity of 9 (9%), therapy of 24 (24%), and economy of 1 abstract. In comparison to EBMT-2019, more abstracts were based on retrospective studies; the number of studies focused on viral infections was similar; and the number of abstracts related to pediatric population was again low.

**Conflict of interest:** All authors declare no conflict of interest.

**WP02.**

**Current scientific proposals of IDWP**

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Infectious Diseases Working Party (IDWP) of EBMT dedicated to infectious complications in patients undergoing hematopoietic stem cell transplantation, regardless of primary diagnosis. The current scientific proposals comprise prospective studies, retrospective studies based on collection of cases and sometimes also controls, and registry-based retrospective analyses. Currently ongoing prospective non-interventional studies run by IDWP are: (1) Incidence and outcome of HHV-6 encephalitis in patients who undergo allogeneic haploidentical HSCT, (2) Impact of pre-existing invasive aspergillosis on allogeneic stem cell transplantation (IPAT), (3) Real life management of antibiotic therapy in HSCT recipients, (4) Central nervous system complications following hematopoietic stem cell transplantation. With additional two prospective studies starting soon: (5) Infections following CAR T-cell therapy, and (6) Viral infections after unmanipulated allo-HSCT in pediatric patients. The currently ongoing retrospective studies include: (1) Hepatitis E infection after HSCT, (2) Progressive Multifocal Leukoencephalopathy (PML) after allogeneic HSCT, (3) Nocardia Invasive Infections post-HSCT, (4) Tuberculosis after HSCT, (5) Listeria infections after HSCT, (6) Atypical mycobacterial infections in allogeneic HSCT recipients, (7) Incidence and outcome of Adenovirus infection in patients who undergo allogeneic haploidentical HSCT. The participation in these studies is most appreciated since we are aware how difficult it is to find time to fit all the initiatives but truly believe that you such a contribution might result in better understanding of infectious complications in this population. In addition, our current educational proposal includes the 23rd IDWP Educational Course titled “Infectious complications following HSCT: Vision 2020” to be held in Jerusalem, Israel, 28–30 October 2020.

**Conflict of interest:** All authors declare no conflict of interest.

**WP03.**

**Infectious complication after CART cell therapy**

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Patients after CD19+ chimeric antigen receptor T-cell therapy (CART) for B-cell malignancies are at risk for infectious complications development, due to immunosuppression related to the primary disease and its treatment, neutropenia, hypogammaglobulinemia or CART-complications treatment (steroids, tocilizumab, ICU stay). Infections occur mainly as early events within the first 30 days and are caused by bacteria (17%) and viruses (9%), mainly respiratory. Fungal infections are seen rarely (4%), however the risk is higher in patients with prolonged neutropenia, prolonged steroid therapy and previous alloSCT. Early infections are generally mild to moderate, however, it is difficult to distinguish from cytokine-release syndrome. Late infections observed in less than 15% of patients are related to hypogammaglobulinemia, prolonged neutropenia or primary disease relapse/progression. Prophylactic strategies are required to prevent infectious complications after CART cell therapy. The treatment of infections should be based on standard guidelines.

**WP04.**

**Infections following chimeric antigen receptor-modified T (CAR-T) cells therapy: a proposal for prospective study (ICART)**

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**Introduction:** Targeted chimeric antigen receptor-modified T (CAR-T) cells are increasingly used in cancer treatment. Infections were reported in ~40% of patients during the treatment course; predisposing factors include previous immune suppression, neutropenia, hypogammaglobulinemia, and others. Infections can mimic other complications, as a cytokine-release syndrome. Data in the literature on infections following CAR-T therapy is scarce. Information about infections is not reported in the Cell therapy MEDA forms of the EBMT registry. The aim of the ICART study is to analyze infections following CAR-T therapy in the EBMT centers.

**Methods and analysis:** We plan to perform a prospective multicenter study on infections following CAR-T therapy. The primary endpoint will be the infection rate within three months following CAR-T therapy. The secondary endpoints will be an analysis of clinical characteristics, risk factors and outcome of infections. All patients who received CAR-T therapy, regardless of transplantation history, age and underlying disease, will be included. Both clinically and microbiologically documented infections will be reported. In each infectious episode, we will obtain data on etiology, timing, clinical manifestations, laboratory data, treatment, and outcome. Background information on CAR-T therapy, like conditioning, cell numbers, disease status and presence of complications will be obtained from the cell therapy MEDA form of Promise database.

The study was approved by the EBMT Infectious Diseases Working Party (IDWP) and by the EBMT Scientific Committee.

**WP05.**

2019 Update of Guidelines for Diagnosis and Treatment of Community-acquired respiratory virus (CARV) in Patients with Haematological Malignancies (HM) or undergoing autologous (auto-) or allogeneic (allo-) Hematopoietic Cell Transplantation (HCT)

**Hans H. Hirsch, Anne Bergeron-Lafaurie, Michael Boeckh, Roy Chemaly, Francesca Compagno, Hermann Einsele, Dan Engelhard, Per Ljungman, David Navarro, Christine Robin, Marie von Lilienfeld-Toal**

8th ECIL, a joint venture of Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN)

**Background:** In 2011, the ECIL-4 conference prepared three sets of guidelines on prevention, diagnosis and treatment of community-acquired respiratory viruses (CARVs) such as Human Influenzavirus (IV-A/B), Human Respiratory Syncytial Virus (HRSV), Metapneumovirus (HMPV), Parainfluenzavirus (HPIV), Rhinovirus/Enterovirus (HRV/ EV), Coronavirus (HCoV) and Adenovirus (HAdV).

**Purpose:** To provide one single comprehensive update on management of CARVs in patients with HM, auto-HCT, and allo-HCT.

**Method:** Experts from Europe and the USA reviewed the CARV literature since 2011 and prepared updates as of September 2019. The group suggested changes to previous recommendations using the ECIL grading and presented these to the delegates of ECIL-8 (http://www.ecil-leukemia.com/program2019.htm), who suggested revisions, and approved the finalized slide set (http://www.ecil-leukemia.com/resources.htm).

**Results:** In general, most data were available for adult allo-HCT patients, but only limited evidence for children, for auto-HCT, and HM patients. The need for harmonized clinical case definitions was approached by working definitions covering upper and lower respiratory tract infectious disease (RTID), and specifically CARV pneumonia. Nucleic acid testing (NAT) detecting CARV genomes in respiratory specimens are recommended for a laboratory-confirmed diagnosis of RTI (AII), and rapid tests preferred for decisions regarding infection control, antiviral and/or antibiotic treatment, and deferral considerations regarding chemotherapy or HCT (BIII). Detailed tables provide infection control and deferral recommendations for specific CARVs and patients at risk. IV-A/B vaccination is recommended, whereby quadrivalent vaccines are preferred if available (BIII). Neuraminidase inhibitors (NAI) for routine seasonal prophylaxis was discouraged (BIII), but post-exposure prophylaxis using treatment dose was recommended (AII). Insufficient evidence limits recommendations regarding NAI double-dose, prolonged administration or use of baloxavir. RSV prophylaxis with palivizumab for seasonal or post-exposure prophylaxis in children >2 yrs or severely immunocompromised patients is limited by insufficient evidence and high costs (CIII). Allo-HCT patients at high risk of progression to, or with diagnosis of RSV-lower-RTID should be treated with systemic or aerosolized ribavirin (BIII). HMPV and HPIV treatment recommendations are limited by evidence, but some centers consider systemic ribavirin in allo-HCT patients at high risk (CIII). Adjunct use of intravenous immunoglobulins (IVIg) for HRSV, HMPV, and HPIV was judged as insufficient even in patients with
hypogammaglobulinemia of <4.5 g/L. Corticosteroid use of >1 mg/kg/day has been associated with poor course, and reduction to <1 mg/kg bw/day could be considered (II). Insufficient data exist for treatment recommendations of HCoV and HRRv/EV RTID. If HAdV is detected in blood >1000 c/mL in lymphopenic patients (<100 cells/μL) with upper RTID or with HAdV LRTID/pneumonia, intravenous cidofovir may be considered (5 mg/kg bw once weekly; together with probenecid, hyper-hydration, and monitoring of renal function) (II). No recommendations regarding brincidofovir for HAdV could be given.

Conclusions: Despite significant progress in adult allo-HCT, the working group identified significant gaps in knowledge and treatment of CARVs. Most data are available for IV-A/B and HRSV, less for HMPV, HPIV, HCoV, HRRv/EV, and HAdV. Prospective multicenter cohort studies determining the risk factors of progression to LRTID and attributable mortality, validation of risk scores for progression to LRTID, morbidity, mortality, and more efficacious prevention and treatment options are urgently needed including novel antivirals, monoclonal antibodies, and vaccines.

WP06.

Highlights of ECIL: Recommendations in Invasive Fungal Disease in Children

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Pediatric patients with leukemia and those undergoing allo-genic hemato-poietic stem cell transplantation (HSCT) are at high risk to develop invasive fungal diseases (IFDs). Apart from differences in the biology of underlying conditions and comorbidities relative to adults, IFDs in infants, children and adolescents are unique in terms of their epidemiology, the validity of current diagnostics, the pharmacology of antifungal compounds, and regarding the absence of sufficiently powered phase III clinical trials as guidance of evidence-based interventions. In 2011, the 4th European Conference on Infection in Leukemia (ECIL-4) convened a Pediatric Group that elaborated evidence-based guidelines for diagnosis, prevention and treatment of IFDs that were published in 20141. As considerable time has elapsed since the completion of this first pediatric specific guideline, the group was reconvened in the Spring of 2019 for an update of the guideline, which was finalized in September 2019 during the ECIL-8 consensus conference. The key recommendations of the updated ECIL-8 guideline will be presented at this session.

Relevant issues, questions and outcomes addressed in the ECIL-4 guideline were evaluated prior to the consensus conference through a systematic literature review. Medical subject heading (MESH) terms were used as keywords to search articles published in English between 2010 and June 2019 in Medline, PubMed or Cochrane databases, and abstracts presented during the period 2017–2019 at annual international meetings (ASH, ASCO, ECCMID, ID-Week) were screened. In addition, ECIL guidelines for adult patients and important randomized or observational studies in adult patients were considered. The ESCMID/ECMM grading system was used for the recommendations, which incorporates two independent evaluations, strength of recommendation, graded A-D; and quality of evidence, graded I-III with annotation of sources of level II evidence. As in ECIL-4, consistent with pediatric drug development regulations and guidelines from the European Medicines Agency (EMA), the recommendations for interventions were based on: (1) evidence for efficacy from adult phase II and III trials corresponding to adult ECIL recommendations; (2) existence and quality of pediatric pharmacokinetic data and dosing recommendations; (3) specific pediatric safety data and supportive efficacy data; and (4) regulatory approval for use in pediatric age group(s) by the EMA. For diagnostic interventions, the group assumed potential differences in children, and therefore, adult data were used as supportive and not as major evidence for useful performance in children.
Issues addressed in the ECIL-8 Pediatric Fungal Disease guideline include a review of potentially new data on risk factors and the epidemiology of IFDs in pediatric cancer/HSCT patients and their impact on risk stratification; diagnostic considerations with focus on biomarkers for early detection of IFDs and indication and timing of imaging; recommendations on antifungal prophylaxis in high risk patients; empiric and pre-emptive (diagnostic-driven) antifungal therapy; and targeted first- and second line therapies for the most relevant fungal entities.

The update of the first pediatric-specific recommendations for invasive fungal diseases finalized at ECIL-8 provides important evidence-based guidance for clinical decision making and will hopefully contribute to further improvements in in the control of life-threatening IFDs in high risk patient populations.

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WP07.

Highlights of ECIL: Recommendations in Pediatric Febrile Neutropenia

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on behalf of the 8th European Conference on Infections in Leukemia, a joint venture of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS), and the European Leukemia Net (ELN)

Children with leukemia/lymphoma or undergoing hematopoietic stem cell transplantation are at high risk for gram-negative and gram-positive bacterial infections. Whereas ECIL-recommendations for antibacterial prophylaxis and treatment in adults have been published before (ECIL-1), pediatric-specific recommendations for children suffering from leukemia and lymphoma, or undergoing autologous or allogeneic hematopoietic stem cell transplantation have been addressed for the first time in ECIL-8, which took place in September 2019. For generating the recommendations, randomized and larger observational pediatric (≥90% ≤ 18 y) or mixed pediatric/adult studies with separately retrievable pediatric data from high- and middle income countries published after 2000 were included. In addition, ECIL guidelines for adult patients and important randomized or observational studies in adult patients published until 6/2019 were considered. The ESCMID/ECMM grading system was used for the recommendations, which incorporates two independent evaluations (strength of recommendation and quality of Evidence), allowing strong recommendations in the absence of highest quality of evidence. For the evaluation of antibacterial prophylaxis, the following endpoints were included in the analysis of the five randomized controlled trials, of the six meta-analyses, the 16 trials with historical controls and of one prospective observational study: mortality, bacterial blood stream infections, febrile neutropenia, resistance emergence, collateral damage (e.g., Clostridium difficile-associated disease and invasive fungal infections) and adverse effects. Initial antibiotic therapy focused 1) on children with stable clinical condition and without previous infection and/or colonization with resistant bacteria and 2) on clinically unstable children, or children with previous infection and/or colonization with resistant bacteria, or on children treated in centers with a high rate of resistant pathogens. The choice of antibiotic stepdown to outpatient and/or oral therapy, of antibiotic de-escalation, or of antibiotic discontinuation included the following considerations: initial presentation (clinically stable or unstable), the identification of a pathogen, local infrastructure and whether the patient has been defined as low or high risk for adverse events.

These pediatric-specific recommendations by ECIL-8 will hopefully optimize antibacterial prophylaxis and treatment in children suffering from leukemia/lymphoma or undergoing hematopoietic stem cell transplantation.

WP08.

Methods for Missing Data in Competing Risks

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Background: Missing data are a common problem in observational studies. It can be addressed by simple (complete-case analysis, CCA) or more complex methods, such as multiple imputation. However, the behavior of these methods for competing risks models has not been well studied.
Methods: The standard claim with the use of multiple imputation by chained equations (MICE) is that it uses more of the available information in the data (greater efficiency) than complete-case analysis, and that estimates of interest are minimally biased. For this, the missing-at-random assumption must hold, which means that the missing values do not depend on variables outside the dataset. For survival outcomes and in the additional presence of competing risks, the validity of this claim has not yet been thoroughly evaluated. To address this issue, an extensive simulation study was performed. Scenarios were based on observational data describing outcomes after HSCT, with competing events relapse and non-relapse mortality.

Particular attention was paid to when performing a CCA was sufficient. In other words, evaluating under what conditions a CCA may be biased and/or inefficient, and whether using MICE offered a substantial improvement. Furthermore, we also compared the performance of both CCA and MICE to more modern imputation methods. These are ‘substantive model compatible fully conditional specification’ (smcfcs, Bartlett and Taylor 2016), and the fully Bayesian approach as implemented by Erler et al. (2016).

Results: Generally, the performance of all methods varied depending on (a) how much data are missing, (b) the nature of the missingness mechanism (i.e., missing-at-random, or other), and (c) the magnitude of covariate effects.

For CCA, results were unbiased as long as missingness depended on other covariates. In the face of more complex missingness mechanisms, CCA was severely biased, and the lack of efficiency was apparent when the proportion of missing cases was higher.

The use of MICE meant a more efficient analysis. However, in the presence of large covariate effects, substantial bias was present - estimates were on average smaller than the true effects. Under complex missingness mechanisms, performance suffered further. By comparison, the use of smcfcs and fully Bayesian imputation yielded estimates with reduced bias.

Conclusions: The results of the simulation study represent a call for caution regarding the use of MICE to impute missing covariate values in competing risks analyses. Careful thought must be given not only to the amount of missing, but importantly how they are missing. Even under reasonable assumptions, MICE will likely still yield estimates that are biased downwards. In light of this, both the smcfcs and fully Bayesian approaches may offer improved alternatives.

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Conflict of interest: Nothing to declare.

WP09.

SENSITIVITY ANALYSIS: E-VALUE BASED ON DIRECT ADJUSTED SURVIVAL PROBABILITIES

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The estimated treatment effect from an observational study may be biased and potential unmeasured confounding bias could be a central limitation of observational studies. Sensitivity analysis is useful in evaluating such bias due to unmeasured or uncontrolled confounding. Recently, a new “E-value” measure has been proposed, which is the minimum strength of an unmeasured confounder would need to fully explain away a treatment-outcome association. In observational hematopoietic stem cell transplant (HSCT) studies, comparing Cox model-based direct adjusted survival probabilities has been commonly used to examine the treatment effect. In this talk we consider a new sensitivity analysis method using the E-value based on the ratio of two average of direct adjusted survival probabilities under a stratified Cox model. We derived a consistent variance estimator for the observed ratio and a consistent lower confidence bond for the proposed E-value. The method is illustrated by an application in an HSCT study from the Center for International Blood & Marrow Transplant Research (CIBMTR).