1548. Risk of Severe Herpes Zoster (HZ) in Allogeneic Hematopoietic-Cell Transplantation (HCT) Recipients

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Background. Allogeneic-HCT recipients are at increased risk for varicella zoster virus (VZV) reactivation and associated complications. Prevalence, timing, and risk factors for severe HZ are uncertain in the era of acyclovir (ACV) prophylaxis. Identification of patients at risk for severe HZ can help target need for prolonged prophylaxis or vaccine administration. In this study, we characterized HZ infection requiring hospitalization in a cohort of allogeneic HCT recipients.

Methods. We performed a retrospective, single-center, cohort study of all patients who underwent allogeneic HCT transplantation from October 2006–December 2015. We defined severe HZ as infection requiring hospitalization or administration of IV antiviral medication. We defined HZ diagnosis by either microbiology confirmatory testing or classic dermatomal examination as agreed upon by two or more clinicians. We followed patients until December 2017 for the development of HZ complications.

Results. In a cohort of 2,163 allogeneic HCT recipients, 23 patients (1.1%) developed severe HZ infection, 14 had microbiological confirmation and nine diagnosed clinically. The median age was 37 years (range 18–63); 13/23 (56.5%) were male. Six patients had dermatomal HZ, five with disseminated cutaneous HZ, five with HZ ophthalmicus (one with retinal necrosis), three with VZV meningitis/encephalitis, two with VZV pneumonia, one with VZV viremia, and one with erythema multiforme with mucosal involvement. Ninety-day mortality from onset of diagnosis was 5/23 (21.7%). HZ reactivation occured a median of 14 months after transplant (range 4-day pre-HCT to 80 months). Twelve patients (52.2%) were compliant on ACV prophylaxis at the time of reactivation, of which 10 (83.3%) were on concurrent immunosuppression, including five (41.6%) on a steroid dose >20 mg prednisone per day. In contrast, only 4/11 (36.4%) patients off ACV prophylaxis were on immunosuppression.

Conclusion. In the era of ACV prophylaxis, severe HZ reactivation was identified in 1.1% of HCT recipients. The majority of cases occurred <24 months after transplant despite ACV use in many. HZ virus vaccination might be an additional means of prophylaxis in this vulnerable group.

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1549. Development and Validation of a Cycle-Specific Risk Score for Febrile Neutropenia After Chemotherapy in Patients with Cancer: The ^{CSR}FENCE Score

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Background. Prediction of febrile neutropenia (FN) with initiation of preventive measures in high-risk populations may lead to better outcomes in cancer treatment. We have previously developed a score to predict FN in the first cycle of chemotherapy.[1] We aimed to develop and validate a cycle-specific score to predict FN in cycles two to six as guidelines recommend assessing the risk of FN at each cycle start.

Methods. We included consecutive patients with solid cancers at Rigshospitalet, University of Copenhagen, 2010–2016. FN was defined as neutrophils $<0.5 \times 10^9$/L or leukocytes $\leq 2.0 \times 10^9$/L at the time of either a blood culture sample or death. Predictors of FN were analysed using Poisson regression adjusted for repeated measurements using 2:1 random split sampling. Risk factors assessed were: FENCE risk groups,[1] sex, body surface area, Charlson Comorbidity Index score, haemoglobin, leukocyte and platelet levels, chemotherapy drugs, radiotherapy, prophylactic granulocyte colony-stimulating factors (G-CSF), previous FN or neutropenia, dose delays, dose reductions, and cycle number. Parameter estimates were scaled and summed to create the risk score.

Results. There were 324 FN events among the 4,590 patients in the derivation cohort with a median 3 (IQR 2–5) chemotherapy cycles. The FENCE risk groups[1] (0/+25/+25/+30 points for low/intermediate/high/very high risk), anaemia (+15 points), chemotherapy drugs (+9/+11 for platinums/taxanes), concurrent radiotherapy (+19 points), prophylactic G-CSF (−14 points), previous FN or neutropenia (0/+19/+43/+59 points for no neutropenia/neutropenia/1 FN event/>1 FN event in previous cycles), and cycle number (0/−9/−11/−12/−19 points for cycle 2/3/4/5/6) predicted FN. Discrimination of the ^{CSR}FENCE score was good with a Harrell's C-statistic of 0.79 (95% CI 0.77–0.82) and similar in the validation cohort (Table 1). Numbers needed to treat with G-CSF to avoid one FN event over 21 days were 748, 121, and 34 in the low-, intermediate-, and high-risk groups, respectively.

Conclusion. We developed and validated a risk score to predict FN in cycles two to six of chemotherapy. The ^{CSR}FENCE score provides good differentiation of risk groups but needs validation.

Reference

1. Aagaard et al. Poster 2352. **ID**Week; 2017; San Diego, CA.

Table 1. Performance of the ^{CSR}FENCE score in the derivation (patient *n*=4590, cycle *n*=15 419) and validation (patient *n*=2295, cycle *n*=7670) cohorts

	Derivation cohort	Validation cohort
Cycle *n* by risk group, low/intermediate/high	6277/6195/2947	3142/3063/1465
FN by risk group, low/intermediate/high	21/108/195	13/61/88
Incidence rate per 1000 person-days of follow-up (95% CI)		
Low risk (score ≤ 32)	0.15 (0.09-0.21)	0.19 (0.10-0.32)
Intermediate risk (score 33-63)	0.78 (0.63-0.93)	0.89 (0.66-1.11)
High risk (score ≥64)	2.93 (2.52-3.34)	2.61 (2.07-3.16)
Incidence rate ratio (95% CI)		
Low risk (score ≤ 32)	1	1
Intermediate risk (score 33-63)	5.20 (3.25-8.30)	4.77(2.62-8.68)
High risk (score ≥64)	19.56 (12.47-30.67)	14.06 (7.85-25.17)
Kaplan-Meier percent with FN at 14 days (95% CI)		
Low risk (score ≤ 32)	0.27 (0.17-0.44)	0.26 (0.13-0.52)
Intermediate risk (score 33-63)	1.49 (1.22-1.83)	1.57 (1.19-2.08)
High risk (score ≥64)	5.66 (4.88-6.56)	4.93 (3.94-6.17)
Adjusted incidence rate ratio per 10 point increase in score (95% CI)	1.48 (1.41-1.54)	1.43 (1.34-1.52)
Harrell's C-statistic (95% CI)	0.79 (0.77-0.82)	0.78(0.75-0.81)

FN, febrile neutropenia; CI, confidence interval

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1550. Pediatric Febrile Neutropenia: Does Depth and Duration of Neutropenia at Presentation Predict Outcomes?

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Background. The 2010 Infectious Diseases Society of America (IDSA) guidelines define febrile neutropenia (FN) patients as high risk if they have profound neutropenia [ANC (absolute neutrophil count) ≤100 cells/μL] anticipated to last >7 days. Formal studies to clearly evaluate the significance of the depth of neutropenia are lacking.

Methods. A retrospective cohort study of all pediatric oncology patients presenting with FN between July 2009–December 2016 was performed to evaluate if the depth and duration of neutropenia prior to presentation was correlated with blood stream infection (BSI), invasive fungal disease (IFD), pediatric intensive care unit (PICU) admission or length of stay (LOS). Patients were categorized into three groups based on ANC at time of presentation: <100, 100–500, and >500 cells/mL with decreasing ANC over the subsequent 48 hours. Durations of neutropenia prior to presentation were also assessed.

Results. A total of 585 FN episodes (FNEs) were identified in 265 patients presenting with 411(70%) ANC <100, 119(20%) ANC 100–500 and 55 (10%) ANC >500 with subsequent decline over 48 hours. Underlying diagnoses included ALL (32%), AML (29%), lymphoma (16%), neuroblastoma (16%) and other solid tumors (9%). In group ANC >500; 70% (39/55) of received chemotherapy within 2 weeks of presentation and 35% were s/p SCT. Rates of IFD and BSI were higher in the group with ANC > 500 with decline in 48 hours compared with ANC < 100 (OR = 5.9, $P = 0.03$) and ANC 100–500 (OR = 5.6, $P = 0.034$). Patients with ANC>500 cells/mL were significantly more likely to be admitted to the PICU (OR = 5.00, $P = 0.017$) and had an increased LOS (hazard ratio = 0.55, $P = 0.002$) when compared with the other two groups. No difference in PICU admission or mortality was found when patients presenting with fevers and ANC < 100 were compared with ANC 100–500. Neutropenia ≥7 days prior to FN was an independent risk factor for BSI (OR = 2.8, $P = 0.001$).

Conclusion. Pediatric patients presenting with febrile neutropenia and initial ANC >500 cells/mL with decine over 48 hours had a higher incidence of BSI, IFD, PICU admissions Clinicians should not be reassured when patients present with fever and initial ANC >500 cells/mL after undergoing recent chemotherapy if continued decline is expected. More work needs to be done to evaluate for risk factors at the time of presentation with FN to guide clinical care.

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1551. The Impact of Recurrent CMV Disease on Long-Term Survival in Solid Organ Transplant Recipients

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Background. Cytomegalovirus (CMV) remains a significant contributor to morbidity and mortality following solid-organ transplantation (SOT). While relapse after treatment completion can occur in up to 30% of patients, the effect of this on mortality is not clear. The aim of this study was to explore the impact of recurrent CMV disease on long-term survival in SOT recipients.

Methods. We performed a retrospective cohort study of heart, liver and kidney transplant recipients who completed treatment for an episode of CMV disease. Data on potential confounders were collected from the time of CMV treatment completion.

Censoring occurred at the time of death, loss to follow-up or 10 years. Univariable and multivariable hazard ratios (HR) were calculated using a Cox model, treating relapse and rejection following CMV as time-varying covariates.

Results. Seventy-nine kidney, 52 heart, 34 liver and five liver-kidney transplant recipients were included. Sixty-two of 170 died, at a median of 3.8 years (interquartile range [IQR] 0.8–6.6 years). Median follow-up amongst the 108 survivors was 7.4 years (IQR 3.7–10 years) although 22 (13%) were censored before 3 years. CMV relapse occurred in 49/170 (29%), 67% within 6 months of treatment completion. Overall mortality amongst those who relapsed was 39% (19/49) vs. 36% (43/121) in those who remained relapse free. On univariable analysis, CMV relapse was not associated with a significantly increased risk of death (unadjusted HR 1.59, 95% CI 0.92–2.75, $P = 0.10$). After controlling for age and transplanted organ type, findings were similar (adjusted HR 1.68, 95% CI 0.93–3.04, $P = 0.09$).

Conclusion. Mortality rates following CMV remain high even in the valganciclovir era. In our study, we did not identify a significant relationship between the development of recurrent CMV disease and death. However, the complex nature of these patients, multiple layers of potential confounding and limited statistical power of our cohort make detection of small effects difficult. Future prospective studies evaluating the clinical efficacy of strategies to reduce recurrence are needed to further assess this relationship.

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1552. Absolute Lymphocyte Threshold: A Simple Readily Available Tool to Predict Risk of Cytomegalovirus Infection After Transplantation

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Background. Cytomegalovirus (CMV) is a common infection after solid-organ (SOT) and hematologic stem cell transplantation (HSCT). We correlated peripheral blood absolute lymphocyte count (PBALC) with risk of CMV infection in transplant patients.

Methods. Thirty-six SOT and 28 HSCT consecutive patients with plasma CMV viral load (VL) testing for surveillance were enrolled. Clinical variables, including PBALC, were abstracted for correlation with CMV infection.

Results. The median age was 54.5 years (IQR 40–63). Forty-three (67.2%) patients developed CMV infection (asymptomatic, 67.4%; CMV syndrome, 14%; gastrointestinal disease, 14%) at median of 4.4 months (IQR 1.4–7.7). Median VL was higher for symptomatic than asymptomatic infection (10,110 vs. 262 IU/mL, $P = 0.006$). PBALC <830 cells/mm^3 correlated with CMV infection (sensitivity 95%; specificity 71%). Median PBALC among CMV infection patients was lower than those without infection (450 vs. 1,060 cells/mm^3, $P < 0.0001$). Among SOT patients, PBALC <610 cells/mm^3 correlated with CMV infection (sensitivity 80%; specificity 73%); median PBALC was significantly lower among those who developed CMV infection (270 and 450 vs. 1,120 cells/ mm^3). Among HSCT recipients, PBALC <830 cells/mm^3 correlated with CMV infection (sensitivity 100%; specificity 80%); median PBALC was lower among those who developed CMV infection (520 and 510 vs. 1,020 cells/ mm^3) (Table 1).

Conclusion. In the current era when sophisticated immunologic measures are being proposed as CMV prognosticator, we highlight the clinical importance of a simple readily available PBALC.

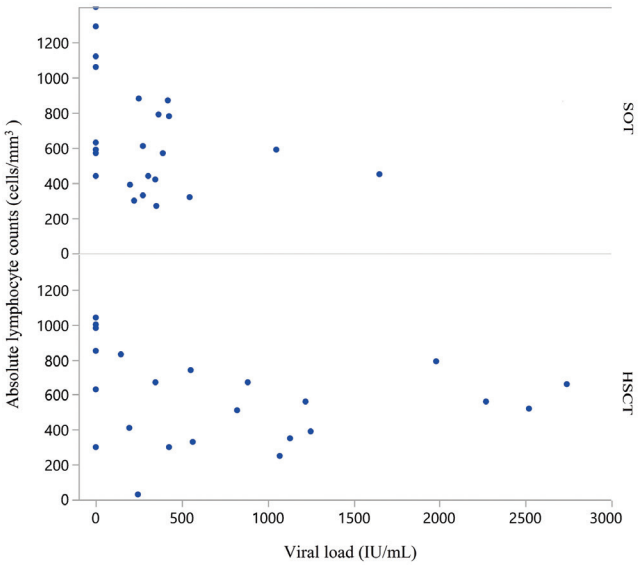
Table 1. CMV VL and PBALC in Patients with or Without CMV Infection

	CMV Disease	Asymptomatic CMV Viremia	No CMV infection	*P* Value
SOT, *N* = 36	*N* = 7	*N* = 18	*N* = 11	
Median CMV VL (IQR) (IU/mL)	32,500 (352–118,000)	423 (297–6,315)	0	0.05*
Median PBALC (IQR) (cells/mm^3)	270 (140–460)	450 (388–675)	1,120 (590–1,400)	0.001
HSCT, *N* = 28	*N* = 3	*N* = 15	*N* = 10	
Median CMV VL (IQR) (IU/mL)	1,220 (426–2,520)	884 (347–1,980)	0	0.62*
Median PBALC (IQR) (cells/mm^3)	520 (300–560)	510 (330–670)	1,020 (795–3,308)	0.03

PBALC, peripheral blood absolute lymphocyte count; CMV, cytomegalovirus; HSCT, hematologic stem cell transplantation; IQR, interquartile range; SOT, solid-organ transplantation; VL, viral load.

*Comparison between CMV disease and CMV viremia recipients.

Figure 1. CMV viral load and absolute lymphocyte count by solid organ transplantations (SOT) and hematologic stem cell transplantations (HSCT)



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1553. Infectious Complications Following Hematopoietic Cell Transplantation in Patients With Primary Immunodeficiency Diseases

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Background. Hematopoietic cell transplantation (HCT) has significantly improved long-term survival for children with primary immunodeficiency diseases (PID). Little is known about specific risk factors for infections after transplant in PID patients and differences from others undergoing HCT. Factors impacting success of HCT in PID include age at HCT, underlying genetic defect, type of donor and conditioning regimen, and importantly, the presence of pre-existing infection. We describe the epidemiology and risk factors for bacterial, viral and fungal infections in patients undergoing HCT for PID.

Methods. After IRB approval, medical records of patients undergoing HCT at Seattle Children's Hospital for PID between 1998 and 2017 were reviewed. Donor and stem cell source, conditioning regimen, development of graft vs. host disease (GVHD), chimerism and mortality were considered, in addition to details of pre-HCT infections. Timing, character and treatment details of each incident infection during 12 months post-HCT were collected. Standardized antimicrobial prophylactic regimens were administered. Primary outcomes included mortality and infection-free survival. Kaplan–Meier curves were used to examine infection-free survival, by diagnosis and by HCT era.

Results. Sixty-nine patients with PID underwent HCT during the study period. Mean age at HCT was 6.2 years and varied by underlying PID. Altogether, 24 children (34.8%) had severe combined immune deficiency (SCID), 14 (20.3%) had chronic granulomatous disease (CGD), nine (13%) had combined immune deficiency (CID), and six (8.7%) had hyper IgM syndrome. Fifty-six patients received HLA-matched grafts. Umbilical cord blood was utilized in 10% of patients. Acute GVHD grades II–IV developed in 46 (67%) patients. Bacterial infections were the most common infection post-HCT, followed by respiratory and herpes group viral infections. Overall mortality at 1 year was 19%, of which at least 50% was infection related.

Conclusion. Infection occurs frequently and contributes to morbidity and mortality in patients undergoing HCT for PID. Understanding the timing of infections and contributing risk factors could help develop preemptive and monitoring strategies to improve outcomes in this patient population.