Clinical and immunological outcome after paediatric stem cell transplantation in inborn errors of immunity

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Part 4

Late effects after haematopoietic stem cell transplantation for inborn errors of immunity

Chapter 7

Outcome of autoimmune cytopenia after haematopoietic cell transplantation in primary immunodeficiency

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Abstract

Background: Post haematopoietic cell transplantation (HCT) autoimmune cytopenia is a potential life-threatening complication but studies focusing on in large cohorts of patients transplanted for primary immunodeficiency (PID) are lacking.

Objective: We aimed to study the incidence, risk factors and outcomes of post-HCT AIC and B-lymphocyte function following rituximab.

Methods: Retrospective study of 502 PID children who transplanted at our centre from 1987 to 2018.

Results: Thirty-six (9%) developed post-HCT AIC, with median onset at 6.5 months post-HCT. On univariate analysis, pre-HCT AIC, mismatched donor, alemtuzumab, ATG, acute and chronic GvHD were significantly associated with post-HCT AIC. After multivariate analysis, alemtuzumab (SHR 9.0, 95% CI, 1.50-54.0, p=0.02) was independently associated with post-HCT AIC. Corticosteroid and high-dose IVIg achieved remission in 50% (n=18), additional rituximab led to remission in 25% (n=9), and the remaining 25% were treated with combination of various modalities including sirolimus (n=5), bortezomib (n=3), mycophenolate mofetil (n=2), splenectomy (n=2), and second HCT (n=3). The mortality of post-HCT AIC reduced from 25% (4/16) prior to 2011 to 5% (1/20) after 2011. The median follow-up of 5.8 years (range, 0.4 to 29.1 years) showed that 26 of 30 survivors (87%) were in complete remission, 4 were in remission with ongoing sirolimus and low dose steroid. Of 17 who received rituximab, 7 had B-lymphocyte recovery, 5 had persistent low B-lymphocyte count and remained on IVIg replacement, 2 had second HCT and 3 died.

Conclusion: The frequency of post HCT AIC in out cohort was 9%, and the most significant risk factors for its occurrence were the presence of GvHD and the use of alemtuzumab and ATG.

Introduction

Autoimmune cytopenia (AIC) is increasingly reported following haematopoietic cell transplantation (HCT) for malignant and non-malignant diseases. The incidence of post-HCT AIC has been reported between 2%-6% in adults and children.(1-7) A higher incidence of 15%-44% has been reported following T-depleted HCT in children with severe combined immunodeficiency (SCID) and infants who received cord blood transplantation. (8, 9) Other risk factors identified in paediatric HCT are younger age at HCT, non-malignant or metabolic indication for HCT, unrelated donor, alemtuzumab and cytomegalovirus (CMV) reactivation. (1-4) Treatment of post-HCT AIC is challenging and to date, there is no consensus or guideline on the best approach to deal with this potentially life-threatening transplant complication. Reported immunomodulating strategies include corticosteroids, high-dose intravenous immunoglobulin (IVIG), rituximab, splenectomy, plasmapheresis, and emerging therapies including sirolimus, bortezomib and daratumumab. Corticosteroids are the mainstay of therapy to control autoimmunity, but toxicities limit their long-term use. Mortality up to 53% has been reported in children who developed post-HCT AIC. (4, 6)

Studies focusing on post-HCT AIC in large cohorts of patients who are transplanted for primary immunodeficiency (PID) are lacking. Children with PID represent a unique transplant cohort as these patients have a wide spectrum of clinical phenotypes including infection, malignancy, allergy, auto-immunity and autoinflammation. Some have features of autoimmunity which are treated with multiple immunomodulators prior to HCT. HCT is a well-established therapy for SCID, non-SCID PID and an increasing number of new emerging PID in the era of next generation sequencing. It is therefore important that the incidence of post-HCT AIC and the risk factors that associated with the post-HCT AIC in the PID cohort are recognized. With this aim, we conducted a retrospective analysis of incidence, risk factors and outcome of post-HCT AIC in children with PID.

Methods

Patients and Methods

Between January 1987 to December 2018, 502 PID patients who underwent first allogeneic HCT for PID at the Great North Children's Hospital were included in the study. Clinical and laboratory data were retrieved from the transplantation database, patients' medical files and laboratory records. Written informed consent was obtained from the parents or legal guardians of the patients as per institutional practice for HCT.

Definition and endpoints

The primary endpoint was cumulative incidence of post-HCT AIC. Other end points assessed were outcomes after post-HCT AIC, mortality after post-HCT AIC, and B-lymphocyte function after rituximab treatment for post-HCT AIC. Autoimmune hemolytic anaemia (AIHA) was defined by positive direct anti-globulin test (DAT) with laboratory evidence of hemolysis (anaemia, raised bilirubin and reticulocytosis). Immune red cell aplasia (RCA) was defined as positive DAT with reticulocytopenia. Immune thrombocytopenia (ITP) was defined as platelet <100 $x10^9$/L in the absence of an identifiable cause according to international guidelines, following platelet engraftment >100 $x10^9$/L and transfusion independent. (10) Autoimmune neutropenia (AIN) was defined as the presence of autoantibodies against granulocytes, or other causes of neutropenia excluded at the discretion of attending clinicians. Complete remission was defined as resolution of AIC independent of on-going treatment. The intensity of the conditioning regimens for the purpose of this manuscript has been classified as myeloablative conditioning (MAC), reduced toxicity conditioning (RTC), and reduced intensity conditioning (RIC). MAC referred to Busulfan (16mg/kg)-Cyclophosphamide (200mg/kg) (Bu16-Cy). RTC included pharmacokinetic targeted Busulfan (area under the curve 45-65mg/Lxh)-Fludarabine (Bu-Flu), Treosulfan-Cyclophosphamide (Treo-Cy), and Treosulfan-Fludarabine (Treo-Flu) with or without thiotepa (Treo-Flu-Thio). RIC regimens were Fludarabine-Melphalan (Flu-Melp), Busulfan (8mg/kg)-Cyclophosphamide (200mg/kg) (Bu8-Cy), and Fludarabine-Cyclosphosphamide (30mg/kg) (Flu-Cy). Serotherapy used in the cohort was decided based on the institutional guideline at the time of HCT.

Statistical analysis

Quantitative variables were described with median and range while categorical variables were reported with counts and percentages. The association between variables was assessed with the use of Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. If the minimal expected requirement for Chi-square test was not met, the Fisher's exact test was used. Cumulative incidence was calculated using a competing risk analysis, considering death as a competing event. Gray's test was used for univariate comparison. The selected variables were: gender, age at transplant, indication for HCT (SCID versus non-SCID PID), pre-HCT AIC, donor type (matched family donor (MFD) versus matched unrelated donor (MUD) versus mismatched family/unrelated donor (MMFD/MMUD) (HLA-matching < 9/10 at HLA-A, B, C, DQ and DR) versus haploidentical donor), donor-recipient ABO matching (ABO compatible versus major versus minor versus bidirectional ABO mismatched), stem cell source (marrow versus peripheral blood versus cord blood), ex-vivo T-lymphocyte depletion, stem cell doses, conditioning regimen (none versus MAC versus RTC

versus RIC), serotherapy (none versus alemtuzumab versus anti-thymocyte globulin, ATG), graft-versus-host disease (GvHD) prophylaxis, acute GvHD, chronic GvHD and viraemia. All factors associated with a *p*-value <0.10 by univariate analysis were included in a multivariate analysis using subdistribution hazard model of Fine-and-Gray. Univariate logistic regression was used to identify predictors of needing more than two agents to treat post-transplant AIC. All variables in univariate analysis with a p-value <0.10 were included in a multivariate logistic regression to assess their independent contribution to needing more than two agents to treat post-transplant AIC. B-lymphocyte immune reconstitution kinetics for first 12 months were compared between surviving patients with post-HCT AIC without rituximab (n=18), post-HCT treated with rituximab (n=12, pre- and post-rituximab B-lymphocyte reconstitution) and disease controls (n=24). The patients who received rituximab were matched with 2 patients with primary immunodeficiency who underwent HCT for the following variables: age (difference < 2 years at transplant), donor type, stem cell source, conditioning regimen, serotherapy and GvHD prophylaxis. Controls (n=24) included were patients who were transplanted for severe combined immunodeficiency (SCID) (n=5), chronic granulomatous disease (n=4), Wiskott-Aldrich syndrome (n=3), CD40 ligand deficiency (n=2), juvenile idiopathic arthritis (n=2), IPEX (n=1), STAT3 gain-of-function (n=1), STAT1 gain of function (n=1), PNP deficiency (n=1), IFKBA (n=1), DOCK8 deficiency (n=1), congenital neutropenia (n=1) and T-cell defect (n=1). Multilevel mixed effects modelling was performed for the longitudinal analysis of $CD19^{+}$ lymphocyte and controls were used as a reference group. All *p*-values quoted are two-sided, with a level of significance of 0.05. Statistical analyses were performed using STATA 14.2.

Results

Patient characteristics

Patient and transplantation characteristics are summarized in Table 1 and Table 1S. Of 502 patients included for this analysis, the median age at HCT for SCID and non-SCID PID was 0.4 years (range, 0.02 to 4.6 years) and 4.0 years (0.1-19.3 years), respectively. The 5-year overall survival for the entire cohort was 76% (95% CI, 71-79%). The median follow-up of surviving patients was 6.6 years (range, 0.6 to 30.5 years). The cumulative incidence of post-HCT AIC was 6% (95% CI, 4-9%) at one-year post-HCT and 9.4% (95% CI, 7-13%) at 5-year post-HCT (Figure 1).

Detailed information of patients with post-HCT AIC is shown in supplemental Table 2S. The median onset of post-HCT AIC was 6.5 months (range, 2.5 months to 18.2 years). AIC occurred within 12 months post-HCT in 72% (n=26) of patients and 92% (n=33) developed the first episode of AIC within two years post-HCT. Two patients (6%; Patient) developed post-

HCT AIC at 3 years post-transplant and one patient (3%; Patient 17 with common gamma chain SCID and Patient 31 with activated PI3K-delta syndrome) developed AIC at 18.2 years post-HCT (Patient 3 with Artemis defect). AIHA (n=19, 53%) was the most-common post-transplant AIC, followed AIHA+ITP (n=8, 12%), ITP (n=4, 11%), AIHA+ITP+AIN (n=4, 11%) and RCA (n=1, 3%). None had isolated AIN. Of the affected patients 10 were transplanted for SCID (10/36, 28%) and 26 for non-SCID PID (26/36, 72%). Of 7 patients who were transplanted for cartilage hair hypoplasia, 3 (42%) developed post-HCT AIC.

Thirty-five (7%) patients had pre-HCT AIC; the underlying diagnoses were: CTLA4 haploinsufficiency (n=7), SCID (n=5, 3 had *RAG1* mutation), STAT3 gain-of-function (n=3), zinc transport defect (n=2), RAS-associated autoimmune lymphoproliferative disease, RALD (n=2), IPEX/IPEX-like disease (n=3), autoimmune enteropathy (n=2), Wiskott-Aldrich syndrome (n=1), systemic lupus erythematosus (n=1), autoimmune lymphoproliferative diseases (n=1), cartilage hair hypoplasia (n=1), DOCK 8 deficiency (n=1), interferon gamma-receptor 2 deficiency (n=1), *IRF8* mutation (n=1), *PSTPIP1* mutation (n=1), Nijmegen Breakage syndrome (n=1), and complex immune dysregulation with undefined genetics (n=2). The types of pre-HCT AIC were: AIHA (n=6, 17%), ITP (n=8, 23%), immune RCA (n=1, 3%), AIN (n=2, 6%), AIHA + ITP (n=11, 31%), AIHA + ITP + AIN (n=4, 11%), ITP + AIN (n=2, 6%) and AIHA + AIN (n=1, 3%). Four patients underwent splenectomy for AIC prior to transplant. All the patients with pre-HCT AIC were in remission prior to HCT procedure. Six of 35 patients (17%) who had pre-HCT AIC developed post-HCT AIC. There was a trend that the onset of post-transplant AIC was earlier in patients with pre-HCT AIC (median: 5.3 months; range, 2.4 to 7.5 months) compared to patients without pre-HCT AIC (median: 9.1 months; range, 3.6 to 218.5 months) (p=0.05).

Risk factors of post-transplant AIC

On univariate analysis, pre-HCT AIC, mismatched donor, alemtuzumab, ATG, acute and chronic GvHD were significantly associated with post-HCT AIC (Table 1, Figure 1). The 5-year cumulative incidence of post-HCT AIC was significant higher in patients with pre-HCT AIC (18%, 95% CI, 7-43%) compared to patients without pre-HCT AIC (9%, 95%CI, 4-12%) (p=0.015). Mismatched donor (17%, 95% CI, 9-35%, p=0.04) was associated with higher incidence of post-HCT AIC compared to matched family donor (5%, 95%CI, 2-12%), matched unrelated donor (11%, 95%CI, 7-18%) and haploidentical donor (6%, 95%CI, 2-16%). Post-HCT AIC was highest in alemtuzumab recipients (13%, 95%CI, 9-19%, p=0.004), followed by ATG (10%, 95%CI, 4-25%, p=0.025) and no serotherapy (2%, 95% CI, 5-7%). Ex-vivo T-depletion (10%, 95% CI, 5-21% versus unmanipulated graft, 9%, 95%CI, 6-14%) was not associated with higher incidence of AIC (p=0.91). Grade II-IV acute GVHD (20%, 95% CI, 12-36% versus none/grade

I acute GvHD, 7%, 95% CI 5-11%, *p*=0.04) and chronic GvHD (44%, 95% CI 13-55% versus no chronic GvHD, 9%, 95% CI, 6 to 13%, *p*=0.04) had significant associations with post-HCT AIC. Gender, age at transplant, diagnosis, conditioning, GvHD prophylaxis, stem cell source, stem cell dose, neutrophil engraftment and viraemia had no association with post-HCT AIC. After multivariate analysis, alemtuzumab (SHR 9.0, 95% CI, 1.50-54.0, *p*=0.02) was independently associated with post-HCT AIC (Table 2).

Subgroup analysis was performed to determine the risk factors of post-HCT AIC in patients with and without pre-HCT AIC (Table 3). In 35 patients with pre-HCT AIC, all 6 (17%) who developed post-HCT AIC received alemtuzumab and dual GvHD prophylaxis with CSA and MMF, and did not have acute and chronic GvHD. On univariate analysis, none of the patient (gender, *p*=0.63; age at HCT, *p*=0.52; indication of HCT, *p*=0.56), transplant (donor, *p*=0.70; stem cell source, *p*=1.0, conditioning, 0.83; serotherapy, *p*=0.63; GvHD prophylaxis, *p*=0.76) and post-transplant (Grade II-IV aGvHD, *p*=0.30; cGvHD, *p*=0.14; viraemia, *p*=0.67) factors was associated with post-HCT AIC in patients who had pre-HCT AIC. In 467 patients without pre-HCT AIC, 30 (6%) developed post-HCT AIC. On univariate analysis, mismatched donor (*p*=0.04), ATG (*p*=0.02), alemtuzumab (*p*=0.008), grade II-IV aGvHD (*p*=0.005) and cGvHD (*p*=0.008) were associated with higher incidence of post-HCT AIC in patients without pre-HCT AIC. After multivariate analysis, ATG (*p*=0.01), alemtuzumab (*p*=0.02), Grade II-IV aGvHD (*p*=0.01) remained significantly associated with post-HCT AIC in patients without pre-HCT AIC (Table 2).

Treatment and outcome

Treatment for the entire cohort is summarized in Table 4. Patients were treated with a median of 3 agents (range, 1-6). Eighteen patients (50%) achieved complete remission with steroid and/or high dose immunoglobulin. Seventeen patients (47%) received rituximab and 3 (8%) had bortezomib. Sirolimus was used in five (14%) patients. Two patients underwent splenectomy (patient 2 and 10). None had plasmapheresis. Three patients (8%) underwent second HCT: one for refractory cytopenia (patient 2), one for secondary aplasia (patient 10), and one for refractory cytopenia and GvHD (patient 17). Four patients with ITP alone resolved with steroid and high-dose IVIg (n=3) or high dose IVIg alone (n=1). There was no significant difference between number of treatment modalities between patients with single cell line cytopenia (n=24) and patients with multiple cell line cytopenia (n=12) (*p*=0.64) (Table S3). The proportion of patients who required < 2 therapies was significantly highest in patients who received *ex vivo* T cell depletion (Odd ratio (OR) 0.08, 0.01-0.74, *p*=0.03) while reduced intensity conditioning (OR 16, 1.09-234, *p*=0.04) was significantly associated with needing more than 2 therapies to treat post-transplant AIC and these factors remained significant after multivariate analysis. (Table 4S).

Cumulative incidence of TRM was 6% (95% CI, 2-21%) at 1-year post-HCT and increased to 12.4% (95% CI, 5-29%) at 5-year post-HCT in patients with post-HCT AIC, compared to cumulative incidence of TRM of 21% (95% CI, 17-25%) and 24% (95% CI, 20-29%) in patients without post-HCT AIC. There was no significant difference in TRM between patients with and without post-HCT AIC (p=0.13). Five patients with post-HCT AIC (14%) died of transplant-related complications (3 infections; 1 HHV6 pneumonitis; 1 cerebral post-transplant lymphoproliferative disease) and one patient died of a disease-related complication.

After a median follow-up of 5.8 years (range, 0.4 to 29.1 years) after the onset of post-HCT AIC, all 30 survivors were in remission but 4 patients (13%) were still on treatment with no active AIC. All 4 patients were on sirolimus with low dose steroid (median follow-up after onset of AIC: 5.2 years, range, 3.8 to 9.7 years).

B-lymphocyte function in 12 of 17 patients who received rituximab is summarized in Table 5. Data for 5 patients were not available: 2 underwent second HCT and 3 died (2 TRM; 1 DRM). Five (42%) patients (median duration after rituximab: 10.5 years, range, 2.6 to 15.2 years) still required immunoglobulin replacement. Of these five patients, two patients (Patients 3 and 11) were still on treatment for post-HCT AIC, one (Patient 9) had persistent AIN requiring a second course of rituximab and two (Patients 11 and 33) were on immunomodulators for juvenile idiopathic arthritis. Of 7 patients (58%) who discontinued immunoglobulin replacement, two had low IgG level but normal IgM and good vaccine response to tetanus and *haemophilus influenza*. The median interval between HCT and rituximab was 1.95 years (range, 0.96-19.9) in patients who were IVIg dependent and 0.73 (range0.30 to 2.3 years) in patients who were IVIg-free on last follow-up (p=0.17). Comparison of B-lymphocyte immune reconstitution kinetics between surviving patients with post-HCT AIC without rituximab (n=18), post-HCT AIC treated with rituximab (n=12, pre- and post-rituximab B-lymphocyte reconstitution) and controls (n=24) is shown in Figure 2. Compared to controls, B-lymphocyte recovery was significant slower in patients with post-HCT AIC without the need for rituximab treatment. Of 12 patients who received rituximab for AIC, 5 patients who did not have poor B-lymphocyte recovery after rituximab had no B-lymphocyte reconstitution within the first 12 months post-rituximab, compared to 7 patients who had B-lymphocyte recovery after rituximab.

Discussion

The present study is the largest analysis to document post-HCT AIC from a cohort of 502 children with PID over the past three decades. The 5-year cumulative incidence of post-HCT AIC in our cohort is 9%, which is higher than the majority reported results in paediatric cohorts. (1, 2, 4, 6). Post-HCT AIC occurred in 3 of 7 patients (42%) who were transplanted for cartilage hair hypoplasia. Our analysis indicates patients who received in vivo T-cell depletion

with alemtuzumab have a significantly higher risk of post-HCT AIC. Use of a reduced toxicity conditioning regimen and *ex vivo* T-cell depletion were not associated with post-HCT AIC. The majority of patients achieved complete remission with first line therapy. Impaired B-lymphocyte function after rituximab in our cohort is multifactorial, including mixed chimerism, on-going immune dysregulation, and use of immunomodulators for either active primary or development of secondary autoimmunity such juvenile idiopathic arthritis.

There are limited studies which examine post-HCT AIC in paediatric patients. Faraci *et al*. (2014) reported a 10-year cumulative incidence of 2.5% in 1574 paediatric patients from 9 transplant centers in Italy and identified alternative donor and non-malignant transplant indication were positively associated with post-HCT AIC.(6) A previous report (2004) by the University of Minnesota paediatric transplant unit which specializes in patients with metabolic disorders showed a 3-year cumulative incidence of 5% in 439 paediatric patients, rising to 11% in HCT for metabolic disorders.(4) Kruizinga *et al.* (2017) reported a 3-year cumulative incidence of 5% in 479 children; the risk factors in this cohort were non-malignant disease, use of alemtuzumab and CMV reactivation.(2) Our PID cohort shows a 5-year cumulative incidence of 9%, which is higher than in these reports. Similar to Kruizinga's report, use of alemtuzumab is an independent risk factor for post-HCT AIC in our cohort.

The mechanism of post-HCT autoimmunity is uncertain and may reflect a complex interplay between recipient and donor immunity during immune reconstitution and thymopoiesis post-HCT leading to abnormal central and/or peripheral tolerance. Factors that interfere with this process may result in the development of new autoimmunity post-transplant. Potential negative factors on immune reconstitution and thymopoiesis are in vivo T-cell depletion using Alemtuzumab or ATG, steroid therapy and graft-versus-host disease.(6, 11-14) Prolonged lymphodepletion by alemtuzumab might delay immune reconstitution and allow expansion of autoreactive memory cells (11, 12, 15) Although viral infection is not associated with post-HCT AIC in our cohort, it has been postulated to initiate an immune dysregulatory process. (16) CMV has been associated with polyclonal B-lymphocyte stimulation, autoantibody production and CD8 expansion which interrupts the normal development of the T lymphocyte compartment in patients after stem cell and solid organ transplants. (17-19) In our cohort, post-HCT AIC is more common in our patients with pre-HCT AIC which might represent residual host autoimmunity. However, all six of 35 patients with pre-HCT AIC who developed post-HCT, were treated with pre-HCT immunomodulators, received potent T-lymphodepleting agent with alemtuzumab and dual GvHD prophylaxis with CSA and MMF. None had acute or chronic GvHD. Therefore, it is difficult to explain the pathogenesis of post-HCT AIC in these patients using the concept of residual host autoimmunity or dysregulated donor immunity from GvHD.

There is no standardized treatment guideline for post-HC AIC. Our first line therapy is with corticosteroids and high-dose intravenous immunoglobulin (2gm/kg, repeat every 2 weeks if needed). This has led to remission in 50% of patients and the remaining 50% required second line therapy. Management of refractory or frequent relapse of AIC is challenging as prolonged steroid use in post-HCT patients is associated with delayed immune reconstitution, impaired thymopoiesis and increased susceptibility to infection, alongside unwanted side effects of steroids in children such as growth failure, osteopenia and cataracts. For second line therapy we use rituximab, an anti-CD20 monoclonal antibody, and this achieved remission in 9 of 18 (50%) patients who did not respond to first line therapy. Bortezomib, which is a dipeptide boronate proteasome inhibitor that inhibits the 26S proteasome function, leads to accumulation of polyubiquitinated proteins and induces cell death in short- and long-lived plasma cells, has been reported to successfully control post-HCT AIC in case series. (20, 21) It was only used in 3 patients in our cohort and its efficacy on long-term remission is difficult to assess as one achieved complete remission, one died of infection and one did not respond and had a second transplant for refractory cytopenia and GvHD. Recently, we have increasingly used sirolimus as a steroid-sparing agent in our patients with recurrent post-HCT AIC. Sirolimus targets the mammalian target of rapamycin (mTOR) and induces cell death and apoptosis in abnormal lymphocytes. It increases peripheral regulatory T lymphocytes (Tregs) and may improve post-transplant autoimmunity. (22) Its efficacy has been demonstrated in patients with autoimmune lymphoproliferative disease (ALPS). (23) Daratumumab, an anti-CD38 antibody that targets specifically CD38 on plasma cells and induces cellular apoptosis, has been reported to be effective in post-HCT AIC which is refractory to conventional immunosuppressive therapy or B-cell depletion strategy.(24) Persistent autoantibody production in spite of B-cell depletion therapy may indicate that a residual population of host plasma cells is producing antibodies against donor's cells. As immunotherapy with daratumumab eliminates long-lived immunological memory plasma cells, it is rational to use daratumumab to target autoantibody-producing plasma cells in post-HCT AIC after failure of B-cell depletion therapy. Splenectomy should be avoided if at all possible in view of the risk of overwhelming sepsis, and as poor antibody response to pneumococcal vaccine has been reported in post-splenectomised patients.(25, 26) Both of our patients who underwent splenectomy for post-HCT AIC died of infection-related complications.

Transplant-related mortality after post-HCT AIC in our cohort is 14%, which is similar to Faraci *et al.* (15%) but lower than reported by Kruizinga *et al.* (21%) and O'Brien (53%). (2, 4, 6) Four deaths (4/16, 25%) occured in post-HCT AIC prior to 2011 and only one (1/20, 5%) after 2011. This reflects the shift in pattern of our management for patients post-

HCT AIC with early institution of steroid-sparing agents including B-lymphocyte directed immunotherapy, rituximab and sirolimus. Impaired B-lymphocyte immunity has been reported in up to 56% of patients who received rituximab and some of the patients have long-lasting B-cell dysfunction. (27-29) The spectrum of secondary hypogammaglobinaemia in non-transplanted patients ranges from mild with no significant increase in infection rate to severe with life-threatening infection. (30, 31) Factors affecting B-cell reconstitution post-rituximab which have been reported in non-transplanted patients include low pre-rituximab immunoglobulin level, low pre-rituximab CD19 count, a higher number of rituximab doses, use of other immunosuppressive therapy, older age, underlying disease, co-existing medical illness or a combination of these factors.(29, 32, 33) In our cohort, it is difficult to delineate the exact cause of impaired B-lymphocyte function in 5 patients who had B-lymphocyte aplasia/dysfunction and required immunoglobulin replacement after rituximab. Three of these had demonstrated B-lymphocyte repopulation by number but no production of IgM, and the remaining two had no B-lymphocyte repopulation. This might be due to impaired interaction between T-lymphocytes and B-lymphocytes secondary to on-going treatment with immunomodulators, immune dysregulation, development of secondary autoimmunity and mixed chimerism. Interestingly, two patients who had B-lymphocytopenia and low IgG were able to discontinue immunoglobulin replacement as they had good normal IgM level, good vaccine responses and were infection-free. Overall, rituximab might contribute to, but it is not the only culprit of impaired B-lymphocyte function in our cohort and its use should be still considered early in patients with refractory and severe post-HCT AIC.

Whilst transplant-related complications such as veno-occlusive disease and graft-versus-host disease have reduced with the development of newer transplant strategies, post-HCT AIC remains an important and potentially fatal complication in children with PID. The change of treatment strategy has reduced the mortality in affected patients in our cohort. As alemtuzumab has been consistently associated with post-HCT AIC in two large paediatric cohorts, an alemtuzumab pharmacokinetic study might play a role in reducing the incidence of post-HCT AIC. (2) There is a need for a specific study to focus on the impact of immune reconstitution, thymopoiesis and donor chimerism on post-HCT AIC in current transplant practice using reduced toxicity and intensity conditioning regimens. We propose forming a working group of transplant experts with the aim to develop a consensus for diagnosis and step-wise management for post-HCT AIC in children.

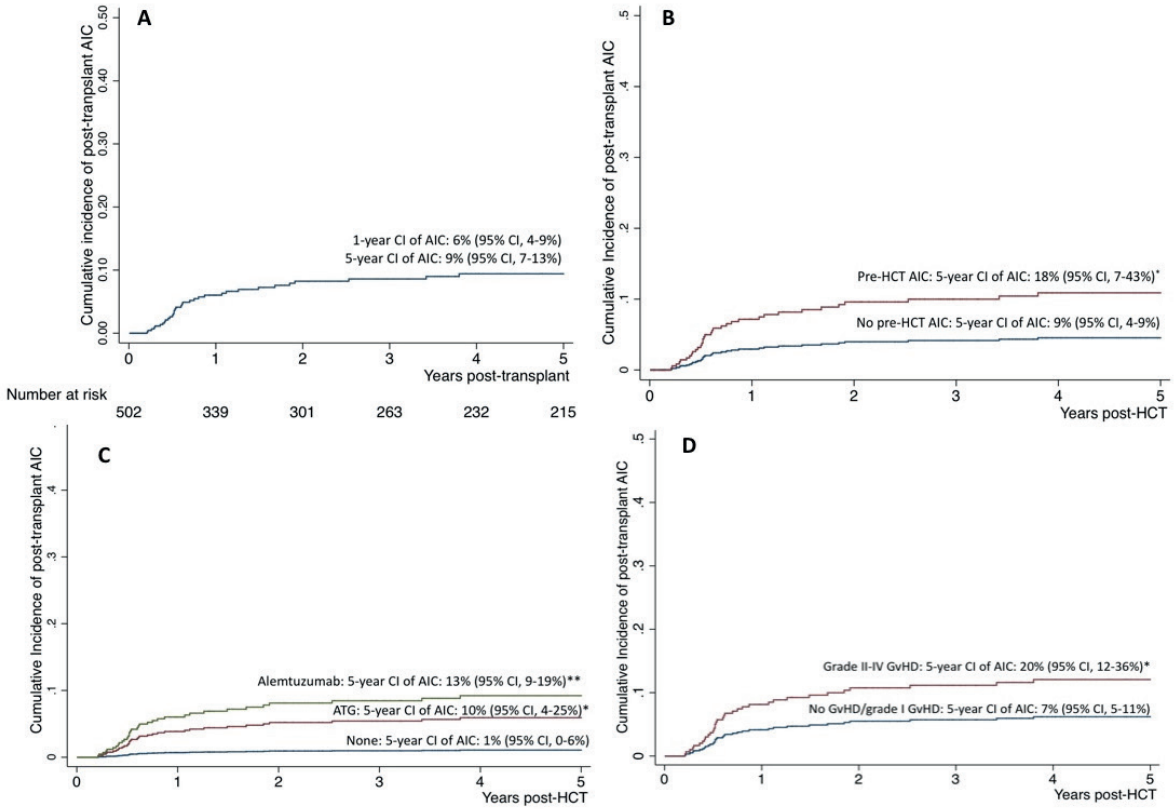
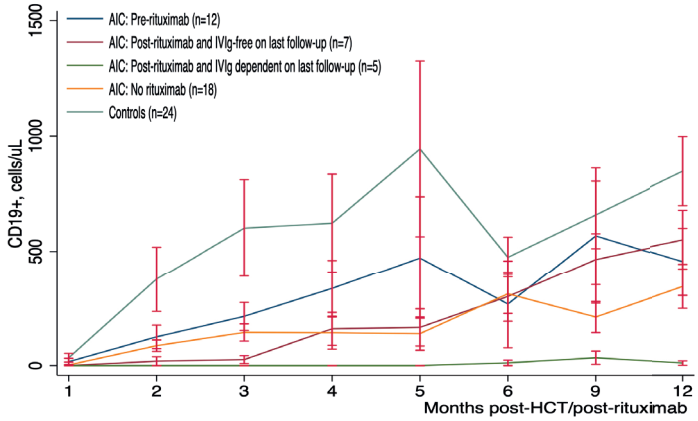


Figure 1: Cumulative incidence of post-transplant autoimmune cytopenia. (A) Entire cohort (B) Patients with pre-transplant AIC versus patients with no pre-transplant AIC. (C) Alemtuzumab versus ATG versus no serotherapy. (D) Grade II-IV GvHD vs no/grade I GvHD. * indicates $p<0.05$ on Gray's test and ** indicates $p<0.05$ on Fine-and-Gray's test



		M1	M2	M3	M4	M5	M6	M9	M12
Control (n=24)	n	21	21	22	20	11	12	12	16
	CD19+, mean±SE	34±19	377±141	602±211	623±213	944±381	475±87	659±147	846±150
AIC: pre-rituximab (n=12)	n	9	9	11	8	6	9	5	3
	CD19+, mean±SE	19±14	125±51	214±61	336±124	472±266	268±190	568±296	450±145
AIC: post-rituximab and off IVIg (n=7)	n	7	6	7	7	6	6	6	7
	CD19+, mean±SE	0	19±19*	26±17*	160±72	164±81	301±107	465±111	546±128
AIC: post-rituximab and IVIg dependence (n=5)	n	5	5	5	5	5	5	5	4
	CD19+, mean±SE	0	0*	0*	0*	0*	12±12*	34±28*	11±10*
AIC: no rituximab (n=18)	n	10	13	16	10	10	16	13	12
	CD19+, mean±SE	2.5±2	86±25*	144±37*	143±72*	139±72*	312±85	211±68*	345±150*

Figure 2: B-lymphocyte immune reconstitution kinetics in controls, patients who received rituximab (before rituximab, post-rituximab with B-lymphocyte recovery and off IVIg and post-rituximab with poor B-lymphocyte recovery and IVIg dependence). Compared to controls, B-lymphocyte recovery was significant slowly in patients with post-HCT AIC without the need of rituximab treatment. Patients who had poor B-lymphocyte recovery after rituximab had no B-lymphocyte reconstitution within 12 months post-rituximab, compared to patients who had B-lymphocyte recovery after rituximab. Of note, patients who were IVIg dependence * indicates $p<0.05$

Table 1: Transplantation characteristics and post-HCT AIC risk factors – univariate analysis, death as competing event

	All patients	Post-HCT AIC	No post-HCT AIC	SHR (95% CI)	*p-value*
No. patients	502	36	466		
Patient characteristics					
Male, n (%)	327 (65)	20 (57)	307 (66)	0.66 (0.35-1.29)	0.23
Age at HCT, years					
Median	1.3	2.4	1.3	1.01 (0.96-1.07)	0.54
Range	0.02-19.3	0.2-17.2	0.02-19.3		
Indication of HCT, n (%)					
SCID	176 (35)	10 (28)	166 (36)	1	
Non-SCID	326 (65)	26 (72)	300 (64)	1.54 (0.75-3.15)	0.24
Pre-HCT immune cytopenia, n (%)	35 (7)	6 (17)	29 (6)	**3.00 (1.24-7.25)**	**0.015**
Donor characteristics, n (%)					
Matched family donor	142 (29)	6 (17)	136 (29)	1	
Matched unrelated donor	201 (40)	17 (47)	184 (40)	2.11 (0.83-5.39)	0.12
Mismatched family/unrelated donor	64 (13)	8 (22)	56 (12)	3.09 (1.07-8.89)	**0.04**
Haploidentical donor	95 (18)	5 (14)	90 (19)	1.43 (0.44-4.59)	0.55
Donor-recipient ABO matching, n (%)					
ABO compatible	277 (55)	19 (53)	258 (55)	1	
Major ABO mismatched	96 (19)	8 (22)	88 (19)	1.34 (0.59-3.06)	0.49
Minor ABO mismatched	96 (19)	4 (11)	92 (20)	0.63 (0.22-1.83)	0.40
Bidirectional mismatched	33 (7)	5 (14)	28 (6)	2.44 (0.90-6.61)	0.08
Stem cell source, (%)					
Marrow	278 (55)	17 (47)	261 (56)	1	
PB	174 (35)	15 (42)	159 (34)	1.75 (0.85-3.60)	0.13
CB	50 (10)	4 (11)	46 (10)	1.34 (0.46-3.97)	0.59
Ex-vivo T-cell depletion, n (%)	112 (22)	8 (22)	104 (22)	0.95 (0.44-2.06)	0.91
Cell dose					
Median Total nucleated cell dose (range), $x10^8$/kg	5.7 (0.05-96)	5.2 (0.07-40.7)	5.8 (0.05-96)	1.00 (0.96-1.05)	0.86
Median CD 34 cell dose (range), $x10^6$/kg	6.3 (0.07-70.0)	5.8 (0.46-32.7)	6.4 (0.07-70.0)	0.99 (0.85-1.03)	0.62
Transplant characteristics					
Conditioning regimen					
MAC	152 (30)	10 (28)	142 (31)	1	
RTC	218 (43)	19 (53)	199 (43)	1.57 (0.71-3.45)	0.27
RIC	83 (17)	5 (13)	78 (17)	0.85 (0.29-2.46)	0.76
None	49 (10)	2 (6)	47 (10)	0.60 (0/14-2.69)	0.51
Serotherapy					
None*	138 (28)	3 (8)	135 (29)	1	
Alemtuzumab	287 (57)	27 (75)	260 (56)	**8.40 (1.96-36.10)**	**0.004**
ATG	77 (15)	6 (17)	71 (15)	**6.21 (1.25-30.83)**	**0.025**

	All patients	Post-HCT AIC	No post-HCT AIC	SHR (95% CI)	*p-value*
GVHD prophylaxis, n (%)					
CSA	91 (18)	8 (22)	83 (18)	1	
CSA/MMF[+]	277 (55)	23 (64)	254 (55)	1.12 (0.49-2.54)	0.79
Others	66 (13)	2 (6)	64 (14)	0.32 (0.07-1.50)	0.15
None	68 (14)	3 (8)	65 (14)	0.49 (0.14-1.74)	0.27
Haematopoietic recovery					
Median days of neutrophil engraftment**,** (range)	17 (5-61)	19 (5-35)	17 (6 – 61)	1.00 (0.96-1.02)	0.87
Graft-versus-host disease (GvHD)					
Grade I-IV aGvHD	187 (37)	16 (44)	171 (37)	1.25 (0.70-2.61)	0.37
Grade II-IV aGvHD	107 (21)	13 (36)	94 (20)	**2.01 (1.02-3.97)**	**0.04**
Chronic GvHD	13 (3)	13 (8)	10 (2)	**3.33 (1.08-10.28)**	**0.04**
Viraemia (for HCT after 2000)	423	30	393		
Any viraemia	183 (43)	17 (55)	166 (42)	1.66 (0.82-3.38)	0.16
≥ 2 viraemia	61 (14)	5 (17)	56 (14)	1.43 (0.52-3.97)	0.14
CMV viraemia	78 (18)	9 (29)	69 (17)	1.79 (0.92-3.91)	0.14
Adenoviraemia	72 (17)	6 (19)	65 (17)	1.16 (0.47-2.83)	0.75
HHV 6 viraemia	71 (17)	66 (17)	5 (17)	1.27 (0.53-3.07)	0.59
EBV viraemia	36 (8)	34 (9)	2 (6)	0.69 (0.17-2.88)	0.61

*6 had anti-CD2 and LFA2
[+]10 tacrolimus/MMF; 1 sirolimus/MMF
Others (54 CSA/MTX; 12 CSA/steroid)

Table 2: Transplantation characteristics and AIC risk factors according to presence of pre-HCT AIC – univariate analysis, death as competing event

	Pre-HCT AIC (n=35)				No pre-HCTAIC (n=467)			
	Post-HCT AIC	**No post-HCT AIC**	**SHR (95% CI)**	***p-value***	**Post-HCT AIC**	**No post-HCT AIC**	**SHR (95% CI)**	***p-value***
No. patients	**6**	**29**			**30**	**437**		
Patient characteristics								
Male, n (%)	3 (50)	18 (62)	0.68 (0.14-3.33)	0.63	18 (60)	288 (66)	0.71 (0.24-1/47)	0.36
Age at HCT, years								
Median	8.1	4.3	0.96 (0.86-1.07)	0.52	1.91	1.16	1.01 (0.94-1.08)	0.76
Range	0.44-19.3	2.3-16.0			0.2-17.2	0.02-18.3		
Indication of HCT, n (%)				0.56*				
SCID	0	3 (10)[+]	NA		10 (33)	163 (37)	1	
Non-SCID	6 (100)	26 (90)	NA		20 (67)	274 (63)	1.27 (0.60-2.68)	0.52
Donor characteristics, n (%)				1.0*				
Matched family donor	1 (17)	7 (23)	1		5 (17)	129 (30)	1	
Matched unrelated donor	4 (66)	17 (59)	1.90 (0.16-22.0)	0.61	13 (43)	167 (38)	2.01 (0.71-5.66)	0.17
Mismatched family/unrelated donor	1 (17)	3 (10)	1.82 (0.09-37.1)	0.70	**7 (23)**	**53 (12)**	**3.25 (1.04-10.2)**	**0.04**
Haploidentical donor	0	2 (7)	NA		5 (17)	88 (20)	1.67 (0.49-5.64)	0.41
Donor-recipient ABO matching, n (%)								
ABO compatible	3 (50)	18 (62)	1				1	
Major ABO mismatched	2 (33)	3 (10)	4.07 (0.70-23.6)	0.12	16 (54)	240 (55)	1.15 (0.45-2.95)	0.76
Minor ABO mismatched	0	7 (24)	NA		6 (20)	85 (20)	0.75 (0.25-2.21)	0.60
Bidirectional mismatched	1 (17)	1 (4)	6.00 (0.68-52.4)	0.11	4 (13)	85 (20)	2.22 (0.73-6.74)	0.16
Stem cell source, (%)				1.0*	4 (13)	27 (5)		
Marrow	2 (33)	12 (41)	1				1	
PB	4 (67)	15 (52)	1.62 (0.26-10.3)	0.61	5 (50)	249 (57)	1.63 (0.75-3.55)	0.22
CB	0	2 (7)	NA		11 (37)	144 (33)	1.55 (0.52-4.66)	0.43
Ex-vivo T-cell depletion, n (%)	0	3 (10)	NA	0.55*	4 (13)	44 (10)	1.15 (0.52-2.55)	0.72
Cell dose								
Median Total nucleated cell dose (range), x10^8/kg	6.2 (1.9-16.2)	7.9 (1.5-36.5)	0.94 (0.80-1.10)	0.44	5.1 (0.07-41.0)	5.6 (0.05-96.0)	1.15 (0.52-2.55)	0.72
Median CD 34 cell dose (range), x10^6/kg	8.0 (4.3-13.1)	7.6 (0.3-23)	0.99 (0.90-1.11)	0.97	4.7 (0.5-32.7)	6.1 (0.07-70.0)	0.99 (0.95-1.03)	0.74

	Pre-HCT AIC (n=35)				No pre-HCTAIC (n=467)			
	Post-HCT AIC	**No post-HCT AIC**	**SHR (95% CI)**	***p-value***	**Post-HCT AIC**	**No post-HCT AIC**	**SHR (95% CI)**	***p-value***
Transplant characteristics								
Conditioning regimen				0.83*				
MAC	1 (17)	6 (21)	1		9 (30)	136 (30)	1	
RTC	4 (66)	13 (45)	1.80 (0.22-14.4)	0.58	15 (50)	186 (43)	1.41 (0.60-3.27)	0.43
RIC	1 (17)	10 (35)	0.57 (0.03-9.40)	0.70	4 (13)	68 (16)	0.82 (0.26-2.60)	0.73
None	0	0	NA		2 (7)	47 (11)	0.64 (0.14-2.89)	0.56
Serotherapy				0.63*				
None	0	1	NA		2 (7)	134 (31)	1	
Alemtuzumab	6	23	NA		**22 (73)**	**237 (54)**	**7.2 (1.66-31.5)**	**0.008**
ATG	0	5	NA		**6 (20)**	**66 (15)**	**6.6 (1.33-32.8)**	**0.02**
GVHD prophylaxis, n (%)				0.76*				
CSA	0	4	NA					
CSA/MMF	6	22	NA		8 (27)	79 (18)	1	
Others	0	0	NA		17 (56)	232 (53)	0.85 (0.36-2.00)	0.72
None	0	3	NA		2 (7)	64 (15)	0.30 (0.06-1.43)	0.13
Haematopoietic recovery					3 (10)	62 (14)	0.49 (0.14-1.73)	0.27
Median days of neutrophil engraftment, (range)	16 (5-23)	15 (9-23)	0.98 (0.78-1.23)	0.89	19.5 (9-55)	17 (6-61)	1.00 (0.99-1.02)	0.50
Graft-versus-host disease (GvHD)								
Grade II-IV aGvHD	0	9 (31)	NA	0.30*	**13 (43)**	**85 (19)**	**2.79 (1.35-5.77)**	**0.005**
Chronic GvHD	0	2 (7)	NA	0.14*	**3 (10)**	**8 (2)**	**4.50 (1.47-13.7)**	**0.008**
Viraemia (for HCT after 2000)								
Any viraemia	3 (50)	16 (60)	0.71 (0/15-3.43)	0.67	14 (56)	154 (42)	1.81 (0.82-3.99)	0.14
CMV viraemia	2 (33)	5 (19)	1.79 (0.38-8.39)	0.46	7 (28)	69 (18)	1.72 (0.71-4.15)	0.23
Adenoviraemia	2 (33)	8 (30)	1.11 (0.2-5.62)	0.89	4 (16)	60 (16)	0.97 (0.33-2.85)	0.97
HHV 6 viraemia	0	7 (26)	NA	0.30*	6 (24)	59 (16)	0.91 (0.22-3.84)	0.90
EBV viraemia	0	4 (15)	NA	0.42*	2 (8)	30 (8)	1.74 (0.70-4.32)	0.24

[+]2 RAG 1/2; 1 undefined SCID; *Chi-square test/Fisher's exact test if < 5 in cells; NA: not applicable as 0 in cells for Gray's test

Table 3: Multivariate analysis for post-transplant autoimmune cytopenia

	All patients (N=502)			Patients without pre-HCT AIC (N-467)		
	SHR	**95% CI**	***p*-value**			
Pre-transplant immune cytopenia, n (%)	2.48	0.94-6.57	0.07			
Donor-recipient ABO matching						
ABO compatible	1					
Major ABO mismatched	1.39	0.57-3.37	0.47			
Minor ABO mismatched	0.49	0.15-1.58	0.24			
Bidirectional mismatched	2.52	0.38-8.97	0.10			
Serotherapy						
None	1			1		
Alemtuzumab	9.00	1.50 – 53.95	**0.02**	7.91	1.35-46.3	**0.02**
ATG	5.68	0.92-35.2	0.06	7.43	1.50-36.7	**0.01**
Donor						
Matched family donor	1			1		
Matched unrelated donor	1.29	0.48-3.44	0.61	1.18	0.43-3.21	0.75
Mismatched family/unrelated donor	1.51	0.48-4.88	0.47	1.40	0.42 – 4.70	0.59
Haploidentical donor	2.27	0.58-0.11	0.25	1.65	0.37-7.29	0.51
Grade II-IV aGvHD	2.24	0.95-5.26	0.06	2.86	1.25-6.58	**0.01**
Chronic GvHD	1.84	0.38-8.97	0.49	2.17	0.53-8.97	0.28

Table 4: Treatment of post-HCT AIC according to type of type of post-HCT AIC

	AIHA/RCA (n=20)	**ITP (n=4)**	**≥2 cell lines affected*** **(n=12)**	**All patients (N=36)**
Steroid or HD-IVIg only, n (%)	1 (5)	1 (25)	0	2 (6)
Steroid + HD-IVIg, n (%)	7(35)	3 (75)	6[1] (50)	16 (44)
Steroid + HD-IVIg + rituximab, n (%)	7[3] (35)	0	3[2] (25)	10 (28)
Steroid + HD-IVIg + sirolimus, n (%)	1 (5)	0	0	1 (3)
Steroid + HD-IVIg + rituximab + sirolimus, n (%)	2[4] (10)	0	2 (17)	4 (11)
Steroid + HD-IVIg + rituximab + bortezomib, n (%)	2[5] (10)	0	1 (8)	3 (8)

*8 had AIHA+ITP; 3 had AIHA+ITP+AIN; 1 had AIHA+AIN
[1] One patient proceeded to two additional transplant and splenectomy (patient 2, 1995)
[2] One patient required additional MMF and splenectomy (patient 10, 2005)
[3]One patient had HD-IVIg, rituximab and tacrolimus (patient 18, 2011)
[4]One patient required additional MMF (patient 11, 2006)
[5]One patient had second transplant for refractory cytopenia and GvHD (patient 17, 2010

Table 5 B lymphocyte function after rituximab treatment (n=12)

Pt no	Diagnosis	Type of AIC/ status	Interval between rituximab and last follow up, years	Latest donor chimerism, %	IVIg replace-ment	CD19 (cells/μL)	IgM level	Vaccine response
3	Artemis SCID	AIHA: in remission with low dose steroid and sirolimus	2.6	CD15: 0 CD3: 98	Yes[1]	0	0	Not done
9	PNP deficiency	AIHA+ITP+AIN AIHA and ITP - in complete remission Persistent AIN required intermittent GCSF and second course of rituximab in 2019	15.2	CD15: 100 CD19: 98 CD3: 99	Yes	272 (before second course of rituximab)	0 (before second course of rituximab)	Not done
11	ZAP70 deficiency	AIHA + ITP In remission with low dose steroid and sirolimus	10.5	CD15: 100 CD19: 100 CD3: 100	Yes	522	0.08 (¯)	Not done
12	RAG1 SCID	AIHA; complete remission Developed JIA and on methotrexate on last review	10.4	NA	Yes	462	0	Not done
13	IPEX	AIHA; complete remission	9.3	CD15: 27 CD19: 33 CD3: 45	No	252	0.71	Protective level to Tet and Hib
20	Cartilage hair hypoplasia	AIHA; complete remission	6.1	CD15: 43 CD19: 82 CD3: 99	No	1509	2.36 (IgG 2.43)	Protective level to Tet and Hib
23	Severe T-cell lymphopenia	AIHA; in remission with low dose steroid and sirolimus	5.2	CD15: 39 CD19: 54 CD3: 93	No	406	0.91 (IgG 3.7)	Protective level to Tet and Hib

Pt no	Diagnosis	Type of AIC/ status	Interval between rituximab and last follow up, years	Latest donor chimerism, %	IVIg replace-ment	CD19 (cells/μL)	IgM level	Vaccine response
24	Combined immuno-deficiency	AIHA; complete remission	5.4	CD15: 57 CD19: 88 CD3: 86	No	435	0.52 (IgG 6.5)	Protective level to Tet and Hib
27	Congenital neutropenia	AIHA; complete remission	4.4	CD15: 100 CD19: 100 CD3: 97	No	340	1.44 (IgG 7.2)	Protective level to Tet and Hib
29	Nigmegen breakage syndrome	AIHA + ITP; complete remission	5.1	CD15: 33 CD19: 92 CD3: 89	No	426	1.48 (IgG 23.5)	Awaiting completion of immuni-zation
31	Activated PI3-delta syndrome	AIHA; complete remission	1.9	CD15: 100 CD19: 100 CD3: 93	No	185	2.27 (13.7)	Awaiting completion of immuni-zation
33	Juvenile idiopathic arthritis	AIHA + ITP+ AIN; complete remission Active JIA on tocilizumab, ruxolitinib and steroid	2.1	CD15: 70 CD3: 95	Yes	26	0.17	Not done

[1]IVIg was stopped after HCT and had good IgM production and vaccine response prior to onset of post-transplant AIC (18.2 years post-HCT)
JIA: Juvenile idiopathic arthritis; NA not available
Reference range: IgG: 4.9-16.1 g/L; IgM: 0.5 to 1.9 g/L

Table 1S: Patient characteristics

Patient characteristics	
Diagnosis	
SCID, n (%)	176 (35.1)
IL2RG	39 (7.8)
RAG 1/2	29 (5.8)
ADA	24 (4.8)
IL7Rα	17 (3.4)
JAK3	16 (3.2)
DCLRE1C (Artemis)	14 (2.8)
Reticular dysgenesis	3 (0.6)
CD3δ	1 (0.2)
CD3ε	1 (0.2)
Cernunnos	1 (0.2)
Undefined genetics	31 (6.2)
Non-SCID PID, n (%)	326 (64.9)
CGD	62 (12.4)
WAS	25 (5.0)
MHC class II deficiency	24 (5.0)
CD40 ligand	18 (3.6)
HLH	16 (3.2)
DOCK 8 deficiency	10 (2.0)
IPEX/IPEX-like	8 (1.6)
CTLA4 haploinsufficiency	7 (1.4)
Cartilage hair hypoplasia	7 (1.4)
Leukocyte adhesion defect	7 (1.4)
Autoimmune enteropathy	7 (1.4)
XLP/XLP-like	7 (1.4)
STAT3 gain-of-function	6 (1.2)
STAT3 loss-of-function	4 (0.8)
STAT1 gain-of-function	3 (0.6)
ZAP70 deficiency	6 (1.2)
Congenital neutropenia	5 (1.0)
ICF syndrome	5 (1.0)
JIA	5 (1.0)
PI3 kinase deficiency	4 (0.8)
CHARGE syndrome	4 (0.8)
DNA ligase IV	3 (0.6)
ALPS	3 (0.6)
IRF8 deficiency	3 (0.6)
NK deficiency	3 (0.6)
Nigmegen Breakage syndrome	3 (0.6)
SLE	3 (0.4)
CTPS1	2 (0.4)
NEMO	2 (0.4)
FADD defect	2 (0.4)

Patient characteristics	
PNP deficiency	2 (0.4)
RALD	2 (0.4)
Zinc transport defect	2 (0.4)
ITK deficiency	2 (0.4)
ICOS	2 (0.4)
STK4	2 (0.4)
HyperIgD syndrome	2 (0.4)
CID with no genetic diagnosis	20 (4.0)
Other PIDs	28 (5.6)
Median age at diagnosis (range), years	
SCID	0.22 (at birth – 2.9)
Non-SCID PID	15 (at birth – 18.3)
Median age at transplant (range), years	
SCID	0.4 (0.02-4.6)
Non-SCID PID	4.0 (0.1-19.3)
Year of transplant, n (%)	
1987-1998	63 (12)
1999-2008	170 (34)
2009-2018	269 (54)

Table 2S: Detailed characteristics of patients with post-HCT AIC (N=36)

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
1/1989	ADA SCID	No	0.3	Bu (16mg)/Cy Alemtuzumab No GvHDp	HID Campath-1M depleted marrow	No	No	No	AIHA	9.1	No	CD15: NA CD3: 98%	Steroid HD-IVIg	Resolved
2/1995	RAG1 SCID	No	0.6	Unconditioned Alemtuzumab CSA	7/18 C-MMFD Marrow	Grade 3, skin, gut	Yes	EBV	AIHA ® RCA progress to AIHA + ITP	21.2	CSA	CD15: NA CD3: 100%	Steroid HD-IVIg, Second HCT	Persistent AIC post second HCT. Had splenectomy and 3rd HCT Died of cerebral PTLD
3/1996	Artemis SCID	No	0.6	Bu (8mg)/Cy ATG No GvHDp	HID Campath-1M depleted marrow	No	No	No	AIHA	218.5	No	CD 15: 0 CD3: 100%	Steroid HD-IVIg Rituximab Sirolimus	In remission with steroid, sirolimus and IVIg on last review (23 years post-HCT and 5 years after the onset of AIC)
4/1997	Artemis SCID	No	0.2	Bu (8mg/Cy) No serotherapy No GvHDp	6/8 A, DQ-MMUD Campath-1M depleted marrow	Grade 2, skin	Yes	No	AIHA + ITP	2.6	No	CD15:100% CD3: 100% CD19: 100%	Steroid HD-IVIg	Resolved
5/1998	WAS	No	1.6	Bu (16mg)/Cy No serotherapy CSA/MTX	MFD Marrow	No	No	No	ITP	9.2	CSA	CD15: 100% CD3: 100%	Steroid HD-IVIg	Resolved

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
6/2000	Cartilage hair hypoplasia	No	4.1	Bu (16)/Cy ATG CSA	9/10 A-MMUD CD34+ selected marrow	No	No	HHV6	RCA	20.4	No	CD15: 100% CD3: 100%	Steroid HD-IVIG	Resolved
7/2000	RAG1 SCID	No	1.5	Bu (8mg)/Cy ATG CSA	HID CD34+ selected marrow	No	no	No	AIHA	3.6	CSA	NA	Steroid HD-IVIg	Died of HHV6 pneumonitis during treatment for AIHA
8/2000	WAS	No	2.4	Bu (16mg)/Cy ATG CSA	7/10 C, DQ, DR-MMUD CD34+ selected marrow	No	No	No	ITP	6.3	No	CD15: 34% CD15: 95%	Steroid HD-IVIg	Resolved
9/2002	PNP deficiency	No	0.2	Bu (16mg)/Cy Alemtuzumab CSA/MTX	MUD Marrow	No	No	No	AIHA + ITP + AIN	5.4	CSA	CD15: 100% CD3: 99%	Steroid HD-IVIg Rituximab	Intermittent neutropenia despite regular GCSF at 17 years post-HCT. Given additional course of Rituximab.
10/2005	*SKT4* CD4 lymphope-nia	No	2.0	Bu (16mg)/Cy Alemtuzumab CSA	MFD Marrow	Grade 2, skin	No	CMV	AIHA + ITP + AIN	15.4	CSA	WB: 100%	Steroid HD-IVIg Rituximab MMF Splenec-tomy	Died of infection with multi-organ failure and pancreatitis

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
11/2006	ZAP70 deficiency	No	1.1	Flu/Melph Alemtuzumab CSA	MUD Marrow	Grade 2, skin	No	No	AIHA + ITP	9.7	CSA	CD 15: 100% CD3: 100%	Steroid, HD-IVIg Rituximab MMF Sirolimus	4 relapses; in remission with low dose steroid and sirolimus at 13 years post-HCT Still on Ig replacement
12/2007	RAG1 SCID	No	1.6	Flu/Melph Alemtuzumab CSA	MRD Marrow	No	No	No	AIHA	6.1	No	WB: 100%	Steroid HD-IVIg Rituximab	Two relapses; resolved with steroid and second course of Rituximab
13/2009	IPEX	No	0.5	Flu/Treo Alemtuzumab Tacrolimus/MMF	MUD Cord	No	No	No	AIHA	5.0	Tacroli-mus	CD15: 52% CD3: 91%	Steroid HD-IVIg Rituximab	Resolved
14/2010	Cartilage hair hypoplasia	Immune red cell aplasia; treated with steroid and rituximab); in remission prior to HCT	1.1	Flu/Treo Alemtuzumab CSA/MMF	9/10 A-MMUD Marrow	No	No	No	AIHA	2.5	CSA	CD15: 72% CD3: 96%	Steroid HD-IVIg Rituximab	Developed aplasia and underwent second HCT Resolved
15/2010	CTLA4 haploinsuf-ficiency	AIHA + ANI + ITP (Evan syndrome); treated with steroid, HD-IVIg and rituximab; in remission prior to HCT	15.9	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	No	No	No	AIHA	5.4	CSA, steroid	CD15: 100% CD3: 42%	Steroid	Resolved

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
16/2010	CID	AIHA+ITP; treated with steroid, HD-IVIg and rituximab; in remission prior to HCT	11.1	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	No	No	No	AIHA + ITP	3.7	CSA, steroid	WB: 100%	Steroid HD-IVIg	Died of adenoviral encephalitis at 4 months post-HCT
17/2010	CGC SCID	No	0.7	Unconditioned No serotherapy	MUD CB	Grade 3, skin	No	Adeno, HHV6	AIHA	46.1	Tacroli-mus Steroid	WB: 100%	Steroid HD-IVIg Rituximab Bortezomib	Had second transplant with TCR αβ/CD19 depleted parental PBSC for refractory GvHD and refractory cytopenia. Resolved AIC and GvHD.
18/2011	FADD defect	No	2.7	Flu/Treo Alemtuzumab CSA/MMF	MFD PBSC	No	No	No	AIHA+ITP	7.5	No	CD15: 9% CD3: 65%	IVIg Rituximab Tacrolimus	Resolved Still on IVIg replacement at 9 years post-transplant Died of non-TRM at 9 years post-HCT
19/2011	IL2RG SCID	No	0.7	Flu/Treo Alemtuzumab CSA/MMF	HID CD3/CD19 depleted PBSC	No	No	CMV	AIHA+ITP	6.5	No	WB: 100%	Steroid HD-IVIg	Resolved

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
20/2012	Cartilage hair hypoplasia	No	0.6	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	Grade 2, skin	No	No	AIHA	8.4	No	CD15: 96% CD3: 100%	Steroid HD-IVIg Rituximab	Resolved Off Ig replacement
21/2012	Artemis SCID	No	0.6	Flu/Treo Alemtuzumab CSA/MMF	MUD Cord	Grade 2, skin	No	No	AIHA + ITP	22.5	No	WB: 100%	Steroid HD-IVIg	Resolved Off Ig replacement
22/2012	RAG1 SCID	No	0.2	Flu/Treo Alemtuzumab CSA/MMF	9/10 C-MMUD Cord	Grade 1, skin	No	No	AIHA	4.7	CSA	CD15: 100% CD3: 100%	Steroid HD-IVIg Rituximab Bortezomib	Died of infection
23/2013	Severe T-cell lymphope-nia	No	12.7	Flu/Treo Alemtuzumab CSA/MMF	9/10 A-MMUD Marrow	No	No	CMV	AIHA	13.7	No	CD15:32% CD3: 94%	Steroid HD-IVIg Rituximab Sirolimus	In remission with sirolimus at 6-years post-HCT
24/2013	CID	No	11.8	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	Grade 2, skin	No	No	AIHA	2.7	CSA	CD15: 100% CD3: 42%	Steroid HD-IVIg Rituximab	Resolved Off Ig replacement
25 /20013	APDS	No	6.1	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	Grade 2, skin	No	No	AIHA	6.5	No	CD15: 100% CD3: 68%	Steroid HD-IVIg	Resolved
26/2013	Chediak-Higashi syndrome with EBV driven HLH	No	7.8	Flu/Treo Alemtuzumab CSA/MMF	MSD Marrow	Grade 1, skin	Yes	No	ITP	5.1	No	CD15: 100% CD3: 100%	HD-IVIg	Resolved
27/2013	Congenital neutrope-nia	No	1.9	Flu/Treo Alemtuzumab CSA/MMF	9/10 DQ-MMUD PBSC	Grade 1, skin	No	Adeno, HHV6	AIHA	4.3	CSA	CD15:100% CD3: 97%	Steroid HD-IVIg Rituximab	Resolved

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
28/2014	Chronic granulo-matous disease	No	7.2	Flu/Treo Alemtuzumab CSA/MMF	9/10 A-MMUD Marrow	Grade 2, skin and gut	No	No	AIHA	13.1	CSA/MMF	WB: 100%	Steroid HD-IVIg	Resolved
29/2014	Nijmegen Breakage syndrome	AIHA + AIN; treated with steroid, HD-IVIg and rituximab; in remission prior to HCT	3.7	Flu/Cy ATG CSA	MSD Marrow	No	No	Adeno	AIHA+ITP	5.2	No	CD15: 20% CD3: 93%	Steroid HD-IVIg Rituximab Bortezomib	Resolved
30/2015	CD40 ligand deficiency	No	1.9	Flu/Treo/Thio Alemtuzumab CSA/MMF	HID TCR αβ/CD19 depleted PBSC	Grade 2, skin	No	Adeno, CMV	AIHA	6.3	No	WB: 100%	Steroid HD-IVIg Sirolimus	In remission with low dose steroid and sirolimus 4 years post-HCT
31/2015	APDS	No	16.2	Flu/TreoThio Alemtuzumab CSA/MMF	MUD PBSC	Grade 2, skin	No	HHV6	AIHA	41.7	CSA/ steroid	WB: 100%	Steroid HD-IVIg Rituximab	Resolved
32/2015	SIFD	No	17.2	Flu/Treo/thio Alemtuzumab CSA/MMF	MUD PBSC	Grade 2, skin	No	CMV	AIHA + AIN	3.6	No	CD15: 100% CD3: 100%	Steroid HD-IVIg	Resolved
33/2016	JIA	No	5.0	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	No	No	Adeno, HHV6	AIHA + ITP + AIN	7.3	No	CD15: 86% CD3: 94%	Steroid HD-IVIg Rituximab Sirolimus	Resolved

No/year	Diagnosis	Pre-HCT AIC	Age at HCT (years)	Conditioning (dose/kg)/ Serotherapy/ GvHD prophylaxis	Donor/stem cell source	aGvHD	cGvHD	Post-HCT viraemia	Type of post-HCT AIC	Onset (mos post-HCT)	IST at onset of HCT	Donor chimerism at onset of IMC	Treatment	Outcome
34/2016	RALD	AIHA + AIN + ITP; treated with steroid, HD-IVIg and sirolimus; in remission prior to HCT	4.8	Flu/Treo/Thio Alemtuzumab CSA/MMF	MUD PBSC	No	No	No	AIHA	7.5	No	CD15: 90% CD3: 90%	Steroid HD-IVIg	Resolved
35/2017	CGD	No	4.6	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	No	No	EBV	AIHA	6.2	CSA	CD 15: 93% Cd3: 77%	Steroid HD-IVIg	Resolved
36/2018	RAG1 SCID	AIHA + ITP; treated with steroid and HD-IVIg; in remission prior to HCT	2.5	Flu/Treo Alemtuzumab CSA/MMF	MUD PBSC	No	No	No	ITP	5.7	CSA	CD15: 27% CD3: 100%	Steroid HD-IVIg	Resolved

ADA-SCID: adenosine deaminase deficiency SCID; AIHA: autoimmune haemolytic anaemia; AIN: autoimmune neutropenia; APDS: activated protein kinase delta syndrome; Bu: Busulfan; CGC: common gamma chain; CID: combined immunodeficiency; CMV: cytomegalovirus; CSA: ciclosporin; Cy: cyclophosphamide; EBV: Epstein Barr virus; Flu: fludarabine; GvHD: graft-versus-host disease; GvHDp: graft-versus-host prophylaxis; HHV-6: human herpesvirus 6; HD-IVIg: high dose intravenous immunoglobulin; HID; haploidentical donor; IL2RG: interleukin receptor common gamma chain; HLH: haemophagocytic lymphohistiocytosis; IPEX: immunodysregulation polyendocrinopathy enteropathy X-linked; IST: immunosuppressive therapy; ITP: immune thrombocytopenia; MAC: myeloablative conditioning; Melph: melphalan; MMFD: mismatched family donor; MUD: mismatched unrelated donor; MTX: methotrexate; NA: not available; PBSC: peripheral blood stem cell; PNP: purine nucleoside phosphorylase (PNP); RALD: RAS associated autoimmune lymphoproliferative disorder; RCA: red cell aplasia; SCID: severe combined immunodeficiency; SIFD: sideroblastic anaemia with B-cell immunodeficiency, periodic fevers and developmental delay; PTLD: post-transplant lymphoproliferative disease; Thio: Thiotepa; Treo: treosulfan; WAS: Wiskott Aldrich syndrome; WB: whole blood

Supplemental table 3S: Number of therapy according to number of cell line affected in AIC

Number of therapy	Single cell line cytopenia (n=24)	≥2 cell lines cytopenia (n=12)	*p*-value
≥ **3 therapies, n (%)**	12 (50)	7 (58)	0.64
Splenectomy, n (%)	0	2 (17)	0.10
Second procedures, n (%)	2 (8)	1 (8)	1.00

Supplemental table 4S: Comparison of patient, transplantation and post-transplant factors for number of agents required for treatment of post-HCT AIC

	All patients	< 2 agents	≥ 3 agents	Odd ratio (95% CI)	*p-value*
No. patients	36	17	19		
Patient characteristics					
Male, n (%)	21 (58)	12 (70)	9 (47)	0.38 (0.09-1.49)	0.16
Age at HCT, years					
Median	2.4	2.46	2.02	0.93 (0.81-1.07)	0.33
Range	0.2-17.2	0.2-17.2	0.2-16.2		
Age at onset of AIC, years					
Median	3.3	2.9	3.3	0.97 (0.87-1.09)	0.64
Range	0.59-19.63	1.09-19.4	0.6-19.6		
Interval between HCT and post-transplant AIC, years, median (range)	0.6 (0.2-18.0)	0.52 (0.2-8.3)	0.7 (0.2-18.0)	1.09 (0.84-1.41)	0.50
Indication of HCT, n (%)					
SCID	10	5 (29)	5 (26)	1	
Non-SCID	26	12 (91)	14 (74)	1.16 (0.28-5.02)	0.84
Pre-HCT immune cytopenia, n (%)					
Donor characteristics, n (%)					
Matched family donor	6 (17)	2 (12)	4 (21)	1	
Matched unrelated donor	17 (47)	8 (47)	9 (47)	0.56 (0.8-2.94)	0.56
Mismatched family/unrelated donor	8 (22)	3 (18)	5 (26)	0.83 (0.09-7.68)	0.87
Haploidentical donor	5 (14)	4 (23)	1 (5)	0.13 (0.01-2.00)	0.14
Donor-recipient ABO matching, n (%)					
ABO compatible	19 (53)	7 (41)	12 (63)	1	
Major ABO mismatched	8 (22)	2 (12)	6 (32)	1.75 (0.27-11.2)	0.55
Minor ABO mismatched	4 (11)	3 (18)	1 (5)	0.19 (0.02-2.25)	0.19
Bidirectional mismatched	5 (14)	5 (29)	0	NA	NA
Stem cell source, (%)					
Marrow	17 (47)	7 (41)	10 (53)	1	
PB	15 (42)	9 (53)	6 (32)	0.47 (.11-1.92)	0.29
CB	4 (11)	1 (6)	3 (16)	2.10 (0.18-24.6)	0.56

	All patients	< 2 agents	≥ 3 agents	Odd ratio (95% CI)	*p-value*
Ex-vivo T-cell depletion, n (%)	8 (22)	7 (41)	1 (5)	0.08 (0.01-0.74)	**0.03**
Cell dose					
Median Total nucleated cell dose (range), $x10^8$/kg	5.2 (0.07-40.7)	4.1 (0.07-16.2)	5.6 (1.9-40.7)	1.08 (0.97-1.20)	0.15
Median CD 34 cell dose (range), $x10^6$/kg	5.8 (0.5-32.7)	6.6 (0.5-18.7)	5.6 (0.87-32.7)	1.03 (0.93-1.12)	0.56
Transplant characteristics					
Conditioning regimen					
MAC	10	8 (47)	2 (11)	1	
RTC	19	8 (47)	11 (58)	5.5 (0.91-33.2)	0.06
RIC	5	1 (6)	4 (21)	16 (1.09-234)	**0.04**
None	2	0	2 (11)	NA	
Serotherapy					
None*	2 (6)	2	0	NA	
ATG	6 (17)	5	1	1	
Alemtuzumab	28 (78)	10	18	9.0 (0.92-88.2)	0.06
GVHD prophylaxis, n (%)					
CSA	8 (22)	4 (24)	4 (22)	1	
CSA/MMF+	23 (64)	10 (59)	13 (68)	1.3 (0.26-6.52)	0.75
Others	2 (6)	1 (6)	1 (5)	1 (0.04-22.2)	1.00
None	3 (8)	2 (12)	1 (5)	0.5 (0.03-8.00)	0.62
Haematopoietic recovery					
Median days of neutrophil engraftment, (range)	19 (5-35)	21 (5-35)	17.5 (9-32)	0.94 (0.85-1.05)	0.29
Graft-versus-host disease (GvHD)					
Grade II-IV aGvHD	13 (36)	5 (29)	8 (42)	1.75 (0.44-6.97)	0.43
Chronic GvHD	3 (8)	2 (12)	1 (5)	0.4 (0.03-5.05)	0.49
Viraemia (for HCT after 2000)					
Any viraemia	17 (55)	8 (57)	9 (53)	0.84 (0.20-3.50)	
CMV viraemia	9 (29)	6 (43)	3 (18)	0.29 (0.05-1.47)	0.13
Adenoviraemia	6 (19)	2 (14)	4 (24)	1.85 (0.28-12.0)	0.53
HHV 6 viraemia	6 (19)	1 (7)	5 (29)	5.42 (0.55-53.3)	0.15
EBV viraemia	2 (6)	1 (7)	1 (6)	0.81 (0.05-14.3)	0.89

NA: not applicable as 0 in cells

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