**Title**

Excellent Outcomes in Children after Hematopoietic Stem Cell Transplantation for Hepatitis-associated Aplastic Anaemia Following Liver Transplantation

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**Abbreviations**

AA: aplastic anaemia

ATG: anti-thymocyte globulin

BM: bone marrow

CMV: Cytomegalovirus

CSA: Cyclosporin

CVVHD: continuous veno-venous hemofiltration

EBER: EBV-encoded small RNAs

EBV: Epstein-Barr virus

GvHD: graft versus host disease

HAAA: hepatitis associated aplastic anaemia

HHV-6: Human Herpes Virus 6

HSCT: haematopoietic stem cell transplantation

HSV: Herpes Simplex Virus

ICP: Intracranial pressure

IST: immunosuppressive therapy

LF: liver failure

LT: liver transplantation

MMF: Mycophenolate Mofetil

MMUD: mismatched unrelated donor

MSD: matched sibling donor

MUD: matched unrelated donor

NA: not available

PBSC: peripheral blood stem cells

PICU: paediatric intensive care unit

PRES: posterior reversible encephalopathy syndrome

PTLD: post-transplantation lymphoproliferative disorder;

RSV: Respiratory Syncytial Virus

SAA: severe aplastic anaemia

TBI: total body irradiation

**Keywords**

Severe aplastic anaemia, liver transplant, HSCT, hepatitis associated aplastic anaemia.

## Introduction

First described in 1955, hepatitis associated aplastic anemia (HAAA), defined as presence of cytopenia and marrow hypoplasia at the time of hepatitis or within 6 months of it, is a rare blood disorder, predominantly of children and young adults, with a incidence of 2-10% and predominantly affective males.[1–4] The pathogenesis of HAAA is unclear but is thought to be an unknown trigger causing immunological destruction of haematopoietic stem cells; probably the same immunological trigger that caused the non-viral hepatitis. Although the outcomes of HAAA are similar to that of other causes of acquired Aplastic Anaemia (AA), some patients present with or progress rapidly to acute liver failure necessitating urgent liver transplant (LT).[5,6] The higher

reported incidence of AA following LT for non-viral hepatitis (as high as 28%)[7], compared to the small incidence of less than 1% after LT for other indications, further corroborates the immune destruction theory in its pathogenesis.[7–11] Depending on the severity of the AA, the clinical condition of the patient post LT and the availability of a suitable stem cell donor, immunosuppressive therapy (IST) or a haematopoietic stem cell transplant (HSCT) may be therapeutic options[5,6] for the treatment of AA. Here, we describe excellent outcomes in a very high-risk cohort of 10 children, across 4 transplant centres in The United Kingdom (UK), who underwent HSCT for HAAA after having received an LT.

**Patient Characteristics**

Ten children (7 male, 3 female) who had had an LT for acute liver failure (LF) due to non-A-E hepatitis, subsequently presented with severe aplastic anaemia (SAA) and received an HSCT at UK transplant centres between 2010 and 2024. All patients consented to anonymous data sharing through their individual transplant centres.

Median age at presentation with LF was 4.5 years (range 1 to 12 years). All the children were described as ‘well’ before the presentation with LF. Most of the children were extremely unwell at presentation, with seven of them needing admission to paediatric intensive care unit (PICU) for LF related complications. Urgent liver transplantation was carried out at a median of 17 days (range 4-27 days) since the development of fulminant hepatitis. Liver donors were deceased donors (n=7), live related (n=2) or live unrelated donors (n=1). Split liver transplantation was performed in seven children, while two underwent auxiliary liver transplantation and one had

whole liver transplantation. Standard immunosuppression of tacrolimus and steroids was used in most of the children post-LT. Patient characteristics are detailed in **table 1**.

## Results

### Post-LT course

The post-operative course was complicated by hepatic encephalopathy (n=5), pleural effusion needing chest drain (n=3), malignant hypertension (n=2), bleeding (n=1), renal failure (n=1), seizures (n=1). Infectious complications included CMV viraemia (n=6), EBV viraemia (n=3), Covid-19 infection (n=2) and HSV infection (n=1). Three children had a proven fungal infection with disseminated Candida (n=1), disseminated Mucormycosis (n=1) and widespread lung Aspergillosis (n=1). Four children had bacterial sepsis. Post-LT complications are summarised in **table 2.**

Two children showed features of graft rejection post-LT. One of them responded to increasing immunosuppression, the other progressed to atrophy of the donor liver with regeneration of the patient's native liver, allowing cessation of IST.

### Progression to SAA

Seven of the 10 children had normal blood counts when they presented with LF. Three children had varying degrees of neutropenia and thrombocytopenia. Seven children with normal blood counts progressed to SAA, based on Camitta's criteria,[12,13] at a median of 81 days (range 35 to 1634 days) after LF.

Immunosuppressive therapy with anti-thymocyte globulin (ATG) with cyclosporin and thrombopoietin receptor agonist (Eltrombopag) was tried unsuccessfully before HSCT in 1 and 2 children respectively.

HSCT for SAA

HSCT was performed at the median of 163 days (range 41 to 1802 days) following LT.

Donors for HSCT were MUD (n=6), MSD (n=2), MMUD (n=1), haploidentical (n=1). Bone marrow (BM) was the source of stem cells in 8 children and peripheral blood (PBSC) was used in 2 children. The median CD34 cell dose was 6.8 x 10^6/kg. All children received reduced intensity conditioning regimen with fludarabine (30mg/m^2/day x 5 days) and cyclophosphamide (60mg/kg/dose x 2 days) being the most common conditioning protocol. Serotherapy was with either Alemtuzumab or ATG. GvHD prophylaxis was tacrolimus (n = 9) and cyclosporine (n=1) with steroids (n=5) or without steroids (n=5). Where steroids were used, this had been started post LT. Mycophenolate mofetil (MMF) was used as GVHD prophylaxis in 3 children.

Haematopoietic stem cell transplantation characteristics are described in **table 3.**

Nine of 10 children engrafted, one child died before engraftment on day 10 post-HSCT of invasive aspergillosis of lungs. Neutrophil and platelet engraftment occurred at a median of 17 days and 24 days post-HSCT, respectively.

Viral infections were most common occurring post-HSCT in 7/9 children. CMV (n=6) and EBV (n=6) reactivations were most common, and this resulted in organ-based disease in 2 children.

Two children developed Aspergillus lung infection (present pre-HSCT in one patient) with one requiring various interventions including surgical excision and intralesional injection of voriconazole. Non-infectious complications included acute kidney injury (AKI) (n=3) and hypertension (n=2).

Acute GvHD post-HSCT was observed in two children (maximum grade 2) and there was no chronic GvHD.

Post-HSCT complications are detailed in **table 4.**

Donor chimerism data with cell lineage chimerism was collected at engraftment and after 3 months, 6 months, 12 months and on last follow up post-HSCT. Complete chimerism (>95% donor) was present in 7 of 9 children at last follow up and the other 2 had high level donor chimerism sufficient for cure. At a median follow-up of 38 months (range 23 to 122 months) post-LT and of 30 months (range 12 to 120 months) post-HSCT, 9 of the 10 children are alive, engrafted and have normal blood counts. On the last follow up, 8 of 9 children continue to be on immunosuppressive medication post-LT (stopped in one child who had regeneration of native liver). Surviving children have normal liver function and have a good quality of life with a Lansky performance score of 100% in 8 children and 90% in one child.

**Table 1**

**Patient characteristics**

| Patient No. | Age at LF (years) | Sex | Time from LF to LT (days) | LT donor | Onset time of AA after LT (days) | Time from AA to HSCT (days) | Survival outcome | Follow-up duration (months) | Chimerism at the last follow-up | Liver status | Lansky performance score at the last follow up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4 | M | 8 | Deceased | 50 | 263 | Alive | 193 | 100% | Normal | 100 |
| 2 | 9 | M | 27 | Deceased | Pre-LT | 71 | Alive | 57 | 100% | Normal | 90 |
| 3 | 4 | F | 25 | Living related | 17 | 56 | Alive | 161 | 89% | Normal | 100 |
| 4 | 10 | M | 16 | Deceased | 123 | 100 | Alive | 59 | 96% | Normal (regeneration of the native liver | 100 |
| 5 | 7 | F | 23 | Deceased | Pre-LT | 99 | Alive | 114 | 100% | Normal | 100 |
| 6 | 5 | M | 20 | Living related | 15 | 498 | Alive | 32 | 100% | Normal | 100 |
| 7 | 2 | M | 18 | Living unrelated | 87 | 320 | Alive | 92 | 90% | Normal | 100 |
| 8 | 12 | F | 4 | Deceased | 77 | 26 | Dead | | | | |
| 9 | 1 | M | 9 | Deceased | Pre-LT | 40 | Alive | 47 | 95% | Normal | 100 |
| 10 | 4 | M | 12 | Deceased | 1622 | 180 | Alive | 78 | 98% | Normal | 100 |

Abbreviations: AA, aplastic anaemia; F, female; HSCT, haematopoietic stem cell transplantation; LF, liver failure; LT, liver transplantation; M, male.

**Table 2**

**Post liver transplantation complications**

| Patient No. | Non-infectious complications during/post liver transplant | Infectious complications post liver transplant | | | PICU admission |
|---|---|---|---|---|---|
| | | Viral | Fungal | Bacterial | |
| 1 | Nil | CMV, EBV | Nil | Pseudomonas, Escherichia *coli,* Staphylococcus (blood) | Nil |
| 2 | Encephalopathy, Intestinal obstruction due to internal hernia – resolved by laparotomy | CMV, EBV | Candida *guilliermondi* (blood and endotracheal secretions), Candida *fermentati* (pleural fluid) | Enterococcus *faecium,* Staphyloccus *pattenkoperi* (blood) | First for encephalopathy, second for fungal lung infection |
| 3 | Hypertension, right pleural effusion, Pilomatrixoma of upper lip | CMV, HSV | Nil | Nil | Post-operative |
| 4 | Nil | COVID-19 | Nil | Nil | Nil |
| 5 | Encephalopathy | Nil | Nil | Nil | Encephalopathy |
| 6 | Encephalopathy | CMV, COVID-19, Rhinovirus | Mucorales moulds (mucormycosis of right arm causing necrotising fasciitis) | Bacillus *cereus* (blood) | Encephalopathy |
| 7 | Acute kidney injury, upper gastro-intestinal bleeding, hypertension, right | Nil | Nil | Escherichia *coli* (blood), Liver abscess | Post-operative |

| | | | | | |
|---|---|---|---|---|---|
| | pleural effusion, shock | | | | |
| 8 | Acute kidney injury, bilateral pleural effusion, encephalopathy, hypertension, QT prolongation, steroid induced hyperglycaemia, ventricular tachycardia causing cardiac arrest | Nil | Aspergillus (blood and bronchoalveolar lavage) | Nil | Encephalopathy |
| 9 | Acute kidney injury, encephalopathy, hospital acquired pneumonia, raised ICP, seizures, pleural effusion, lower gastro-intestinal bleeding | EBV, Rhinovirus | Nil | Neutropenic colitis | Pre-operative for encephalopathy and raised ICP requiring continuous CVVHD, post-operative for seizures, pneumonia and pleural effusion |
| 10 | Pleural effusion | Nil | Nil | Nil | Nil |

Abbreviations: CMV, Cytomegalovirus; CVVHD, continuous veno-venous hemofiltration; EBV, Epstein-Barr virus; HSV, Herpes Simplex Virus; ICP, Intracranial pressure; LT, liver transplantation; PICU, paediatric intensive care unit.

**Table 3**

**HSCT characteristics**

| **Patient No.** | **Donor** | **Stem cell source** | **Conditioning regimen** | **Number of CD34 cells (x 10^6/kg)** | **Number of CD3 cells (x 10^8/kg)** | **GvHD prophylaxis** | **Days till neutrophil engraftment** | **Days till platelet engraftment** |
|---|---|---|---|---|---|---|---|---|
| 1 | MUD | PBSC | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 17.5 | 6.6 | CSA + MMF | 11 | 22 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2 | MUD | PBSC | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 20.4 | 4.7 | Tacrolimus + MMF | 8 | 22 |
| 3 | MSD | BM | Cyclophosphamide (50mg/kg x 4 days) | 7 | 0.11 | Methotrexate + tacrolimus + steroids | 20 | 26 |
| 4 | MUD | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 4.2 | 0.38 | Tacrolimus + steroids | 22 | 24 |
| 5 | MSD | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 4.3 | 0.11 | Tacrolimus + steroids | 14 | 35 |
| 6 | Haploidentical father | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (14.5mg/kg x 2 days) + TBI 4 Gy + ATG (4.5mg/kg) | 12 | 0.93 | Tacrolimus + MMF | 17 | 29 |
| 7 | MMUD | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (14.5mg/kg x 2 days) + TBI 2 Gy + alemtuzumab (0.3mg/kg x 3 days) | 9.1 | 0.47 | Tacrolimus + steroids | 33 | 16 |
| 8 | MUD | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 4.2 | 0.39 | Tacrolimus | NA | NA |
| 9 | MUD | BM | Fludarabine (30mg/m^2 x 5 days) + cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | 6.6 | 0.57 | Tacrolimus | 14 | 24 |
| 10 | MUD | BM | Fludarabine (30mg/m^2 x 5 days) + | 3.6 | NA | Tacrolimus + steroids | 25 | 26 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | cyclophosphamide (60mg/kg x 2 days) + alemtuzumab (0.2mg/kg x 5 days) | | | | | |

Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; CSA, Cyclosporin; GvHD, graft versus host disease; MMF, Mycophenolate Mofetil; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; NA, not available; PBSC, peripheral blood stem cells; TBI, total body irradiation.

**Table 4**

**Post HSCT complications**

| **Patient No.** | **Non-infectious complications during/post HSCT** | **Infectious complications post HSCT** | | | **PICU admission** |
|---|---|---|---|---|---|
| | | **Viral** | **Fungal** | **Bacterial** | |
| 1 | Acute kidney injury | CMV | Nil | Enterococcus *faecium,* Stenotrophomonas *maltophilia* (blood), Clostridium *difficile* (stool) | Nil |
| 2 | PRES | Adenovirus, BK virus (haemorrhagic cystitis), EBV | Lung Aspergillus *flavus* infection – needed segmentectomies and intralesional injections of voriconazole | Stenotrophomonas (sputum) | PRES |
| 3 | Nil | CMV, EBV | Nil | Clostridium *difficile* (stool) | Nil |
| 4 | Nil | Adenovirus, EBV, HHV-6 | Nil | Nil | Nil |
| 5 | Nil | BK virus (haemorrhagic cystitis), CMV (left eye CMV retinitis), HHV-6, EBV induced PTLD, EBER positive | Nil | Nil | Nil |

| | | | | | |
|---|---|---|---|---|---|
| | | diffuse large B cell lymphoma – abdominal mass and right forearm lesion | | | |
| 6 | Nil | CMV, EBV | Nil | Nil | Nil |
| 7 | Nil | Adenovirus, CMV, EBV, Rhinovirus, RSV | Nil | Nil | Nil |
| 8 | Acute kidney injury, transaminitis | CMV | Aspergillus infection (blood and lung) | Staphylococcus *epidermidis* (blood) | Pulmonary aspergillosis |
| 9 | Acute kidney injury | Rhinovirus | Nil | Enterobacter *cloacae* (blood) | Nil |
| 10 | Hypertension | Nil | Nil | Nil | Nil |

Abbreviations: CMV, Cytomegalovirus; HSCT, haematopoietic stem cell transplantation; EBER, EBV-encoded small RNAs; EBV, Ebstein-Barr virus; HHV-6, Human Herpes Virus 6; PICU, paediatric intensive care unit; PRES, posterior reversible encephalopathy syndrome; PTLD, post-transplantation lymphoproliferative disorder; RSV, Respiratory Syncytial Virus.

**Discussion**

Since the first description in 1987 by Stocks of AA following LT for non-viral hepatitis[14], several case reports have been published.[9,15,16] Many studies have tried to delineate the etiopathogenesis of this serious condition with the majority proposing an immune-mediated pathophysiology based on the high incidence of AA following LT for non-viral hepatitis, the recovery of the AA in some patients following IST used after LT[5,9] and the finding of T-cell clonal expansion with increased CD8 T cells in the explanted liver and BM of patients.[17–19]

The treatment of this vulnerable group of patients is challenging due to their post-operative status, concerns about rejection of the transplanted liver, the ability of the newly transplanted liver to tolerate chemotherapy conditioning and existing infectious complications. Delehaye *et al* described the outcomes of 9 children who were treated for AA following LT[5]. 8/9 received immunosuppressive therapy (IST) and results were very good with 6/8 achieving a complete remission (CR) and 2/8 in partial remission (PR) at a median follow-up of 4 years. They concluded that in the absence of a matched sibling donor (MSD), IST can yield good results if started early in the course of the disease. The long-term outcome following IST will, of course, need further follow-up.

In recent years, the results of unrelated donor HSCTs in paediatric AA are excellent, equivalent to that of MSD HSCTs and superior to IST.[20] Upfront HSCT with a matched donor has become the standard of care at many centres. The post-LT group is, however, a much higher risk group of children.

Mohseny *et al* described the European outcome of 6 patients (5 children) who received an HSCT from matched donors for AA following LT.[6] 4/6 are alive and disease free and with normal liver function. Matched sibling donor HSCTs had a better outcome (3/3 alive) compared to matched unrelated donors (1/3 alive).

As in previous reports, all our patients were previously healthy and predominantly male (7/10). The median duration from presentation with fulminant hepatitis to LT was 17 days reflecting the

the severity of acute liver failure. Extensive investigations showed no cause for the fulminant hepatitis and the explanted liver showed…….on histology in all the children (Adarsh to check). Our

patients were a very high-risk group of children with 7/10 children requiring PICU admission post liver transplant due to post-operative complications and for management of multiple life-threatening infections.

The onset of AA was contemporaneous to the liver failure in 3/10 children. These children were critically unwell with disseminated fungal infection prior to HSCT (Candida n=1, Mucormycosis n=1, lung Aspergillosis n=1). Six children developed aplastic anaemia at a median duration of 69 days after liver failure (range 35 to 139 days) which is comparable to other studies.[3,5,6] The median time to develop AA after LT was 63 days (range 15 to 123 days) in these 6 children. One child presented with AA 4.4 years after LT which is extremely uncommon.

IST can take up to 6 months for a response to be seen and with most of our patients being seriously unwell with infections at presentation or post LT (7/10) this was not a viable option. Only one patient had an unsuccessful trial of IST prior to HSCT in our cohort, the others had upfront HSCT. Further, all patients were on steroids and tacrolimus (one patient on cyclosporine) post-LT and it was questionable whether adding further IST would have been successful.

Despite their critical condition, the median time to proceeding with HSCT following diagnosis of HAAA was 99 days and median time following LT was 163 days. With this approach, our overall outcome was excellent with 9/10 patients surviving, cured of AA and with good liver function. All patients tolerated their conditioning regimen well, with no liver toxicity, including 2 patients who received low dose TBI (total body irradiation). The outcome following matched sibling donor HSCT 2/10 (100% survival) and alternate donor 8/10 (7/8 surviving) was comparable. One patient died before engraftment due to progression of invasive Aspergillosis.

The post HSCT course was stormy with 9/10 patients developing viral reactivations/disease and disseminated fungal infections needing surgical resection of lung lesions in one patient. Excellent supportive care by multidisciplinary teams is crucial to the management of these patients.

In solid organ transplantation, the concept of inducing tolerance to the transplanted organ by using the same donor for the organ and bone marrow (BM) transplant is an attractive one and this would mean that the burden of life-long immunosuppression is not needed. There is a precedence for this in renal+BM transplants[21,22] and in liver+BM transplants.[23] In our cohort, only 2 patients had a living related liver donor and in one of them the liver donor and BM donor was the same. This patient is a year post HSCT and there is a prospect of him stopping immunosuppression in the future (Adarsh, please check this is right).

In summary, we describe the largest cohort of children who received an HSCT for SAA following LT. Despite the patients being extremely unwell and the donors being predominantly unrelated, results were excellent with 90% long term cure of SAA and with preserved liver function. Long term chimerism results were very good and there was a very low incidence of GVHD. Multidisciplinary support by infectious diseases, surgical, intensive care and nursing teams is crucial to the care of these patients. With the right supportive care, upfront HSCT in this rare condition, even using unrelated donors, can be successful.

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