COVID-19 infection in paediatric recipients of allogeneic stem cell transplantation: the UK experience

In January 2020, a novel coronavirus was sequenced in China (SARS-CoV-2) and it was linked to cases of severe acute respiratory syndrome as part of a new disease which was named COVID-19. Its worldwide spread has led to the declaration of a global health emergency by the World Health Organization on 30 January 2020. The first COVID case in the United Kingdom was reported on February, 6 2020. Since then more than 4 375 800 cases have been confirmed countrywide as of 14/04/2021.

In the general population, it has been shown that children are affected with a milder disease than adults. The role and pathogenicity of this virus in the setting of paediatric allogeneic haematopoietic stem cell transplantation (HSCT) is still being evaluated. A single centre in Spain reported 3% of the HSCT paediatric population was diagnosed with COVID-19 infections, with two of eight identified patients requiring admission to intensive care and one of eight patients dying from COVID-related morbidity. In the Spanish cohort, risk factors for severe COVID-19 in paediatric SCT recipients were male sex and low CD4/CD8 ratio. Paediatric cases were included in a French retrospective analysis for risk factors of severe COVID-19 infection post SCT in which older age represented a risk factor for death from COVID-19.

The UK/Ireland paediatric BMT (bone marrow transplantation) group comprises 12 HSCT centres with an average of 300 HSCTs/year. The UK paediatric BMT group aimed to record all centre cases of COVID and to hold biweekly teleconferences to discuss cases and share practice during the first UK COVID-19 surge. The results of this data collection are described in this report.

Nine paediatric patients (six female and three male) were diagnosed with COVID-19 via positive polymerase chain reaction (PCR) between February and July 2020. Cases were reported from Birmingham, Glasgow, Manchester, Leeds, London and Newcastle with no geographic prevalence. Transplant characteristics are summarized in Table I.

Five patients were of Caucasian ethnicity, two Asian, two African. Median age at HSCT was 12 years (range 6–16). Median time from HSCT to COVID-19 diagnosis was 62 days (range 16–261). All patients had achieved neutrophil engraftment at COVID-19 diagnosis. Comorbidities at COVID-19 infection were severe graft-versus-host disease (GVHD) in one patient and severe GVHD with transplant-associated thrombotic microangiopathy (TA-TMA) requiring multiple lines of immunosuppression in another case. Three patients were off immunosuppression at COVID-19 diagnosis, four were on ciclosporin and two were on multiple agents, including steroid. Median CD3 count at COVID diagnosis was 212 × 10^3/l (90–887, available for six patients). There was no uniform presentation with symptoms including fever in four cases, and one case each of cough, shortness of breath, vomiting and abdominal pain. Patient #4 showed significant hypotension accompanying fevers and required aggressive fluid resuscitation with good response at the onset of COVID-19 infection. Two patients were asymptomatic and tested as part of routine admission screening. Median time between appearance of symptoms and PCR testing was 24 h (range 0–5 days). In eight patients, the diagnosis was made via PCR on nasopharyngeal swab and in one case on nasopharyngeal aspirate. In two patients the initial swab proved negative but repeated swabs 12 and 14 days later were positive. In those patients, the persistence of symptoms led to repeat testing.

Eight patients had a mild disease course with no requirement for respiratory or inotropic support. Of those, two developed maximum Common Terminology Criteria for Adverse Events (CTCAE) grade 2 acute kidney injury and four patients developed grade 2 to 3 neutropenia. No patient developed liver failure or myocarditis. Mild to moderate chest X-ray/computed tomography changes were documented in two patients. Three patients suffered from a concomitant infection (one adenoviraemia, one Pseudomonas bacteremia and one Clostridium difficile infection). None of the eight patients with a mild course of disease received COVID-19-directed treatment.

One patient (#6) had been transplanted for sickle cell disease and was fully engrafted from her unaffected donor at the time of COVID-19 infection. She had a severe course developing cytokine-release syndrome treated with tocilizumab and remdesivir, requiring positive pressure for respiratory support and evolving into secondary haemophagocytic lymphohistiocytosis (HLH) treated with dexamethasone leading to full recovery.

While her indication to transplant included cerebrovascular disease and haepatic bridging fibrosis, she had had no endothelial-related problems in the time between transplantation and COVID-19 infection.

Two out of the eight patients with a mild course of disease developed haematological sequelae in the recovery
Correspondence

phase. Patient #3 became pancytopenic with no clear identifiable cause other than the COVID-19 viral insult. The bone marrow aspirate/trephine at a median time of 40 days from COVID-19 diagnosis was severely hypocellular (5%) with no signs of recurring malignancy, no other concomitant viral infections and full donor engraftment. COVID-19 PCR became negative on day +63 post HSCT. The patient was treated with granulocyte-colony stimulating factor (G-CSF) and transfusions as required and the cytopenia eventually resolved at day +129 post HSCT.

A second patient (#8) who had been transplanted for A20 haploinsufficiency4 was admitted 28 days following her PCR-positive swab and 14 days after testing negative for the same for TA-TMA, which was proven on renal biopsy on two occasions and required treatment with multiple agents including defibrotide and eculizumab. The patient had no GVHD, no other viral infections and was not on calcineurin inhibitors at the time of TA-TMA diagnosis, thus having none of the usually recognized risk factors for TA-TMA. Her COVID-19 infection presented with cough and shortness of breath but no oxygen requirement; her X-ray showed left upper zone consolidation. She spontaneously recovered and was discharged 10 days after the first COVID-19 positivity. Twenty-eight days post COVID-19 infection she presented with TA-TMA-like symptoms with cytopenia, increased schistocyte count, pleural and pericardial effusion and renal impairment. She required a pericardial window and bilateral chest drains to treat the serositis together with haemodialysis and multiple lines of immunosuppressive treatment.

The COVID-19 PCR test became negative a median time of 27 days from the first positive result (range 2–76). All patients had recovered from COVID-19 infection at the time of writing. All but patient #2 are alive. Patient #2 died from TA-TMA-derived complications unrelated to COVID-19 infection. No patient in this cohort has been assessed for the emergence of COVID-19 antibodies. Median length of inpatient stay for COVID-19 infection in this cohort was 10 days.

This paper describes the UK experience of COVID-19 infection in paediatric HSCT recipients. The paper has the limitation of including only cases that were brought to medical attention; as such we cannot rule out that other HSCT recipients contracted COVID-19 and remained asymptomatic. Considering the annual recording of HSCT, the nine described cases correspond to 4% of the transplanted patients in the same time frame, thus making it a comparable number to other reported series.4 It is important to underline that up to August 2020 a strict shielding policy applied to extremely vulnerable patients in the UK. This may have considerably reduced the number of HSCT recipients who were exposed to the virus. Moreover, HSCT activity in the UK was limited to non-deferrable cases during the time frame considered in this paper; as such, a significant number of transplants for non-malignant conditions were deferred, making the impact of COVID in selected subgroups of patients non-evaluable. Consequently, further observation is required to assess the broader impact of the virus on this specific population of patients.

Our case series demonstrated that most children had mild COVID-19-related disease only and eight of nine patients fully recovered. This is in line with previously reported data form single centres.4 As only a single patient developed severe COVID-19-related infection, our data do not allow for the identification of risk factors for COVID-19 severity disease in this population. Of note, and in contrast to the Spanish data, the most severely affected patient was nine months post SCT, off immunosuppression and with good immune reconstitution (CD3 > 800 × 10⁹/l). While a single case is represented here, it is worth mentioning that reported observations from an adult Italian transplant centre (Rambaldi, unpublished) also suggested that post-HSCT patients were at higher risk once their immunity had fully recovered, thus underpinning the importance of a significant but dysregulated immune-mediated reaction as trigger to severe viral pathology. The same has been described in the general population.7

Despite a mild course of the disease, two of eight of our patients developed medium-term life-threatening complications, which required medical attention and had no attributable causes other than COVID-19. TA-TMA can be seen in up to 10% of the patients post HSCT, but conventional risk factors for TA-TMA (typically GVHD and calcineurin inhibitor administration)8 were absent in pt #8 who had a delayed but severe TA-TMA. Viral-related TA-TMA has been described in post-HSCT settings and COVID has been recognized as a potent trigger of both endothelial derangement and microangiopathy in the general population.9,10

Cytopenias post transplantation/immunotherapy can occur in a variety of situations ranging from immune phenomena to viral insult or cytokine-driven damage. No alternative cause for the severe cytopenia to COVID-19 was identified in patient #3. Severe aplasia of non-immune origin has been reported in a patient affected with COVID-19 disease,11 as such allowing for the potential relationship between COVID-19 and post-HSCT cytopenia as well. Of note, patient #3 developed COVID-19 infection early post HSCT (day +16), following multiple cycles of pre-HSCT chemotherapy for leukaemia as well as irradiation-based conditioning. These factors might have resulted in increased marrow fragility at the time of COVID infection.

Overall, our finding is of a limited toxicity profile of COVID-19 viral disease in paediatric HSCT recipients with the important caveat that COVID-19 could trigger potentially life-threatening complications beyond the resolution of the acute infection. Of note, three of the reported cases suffered from a concomitant viral or bacterial illness, underlying the importance of screening for COVID-19 despite the identification of other pathogens, more common in the post-transplant setting. These data will require confirmation with longitudinal monitoring of further cases. Taken as a whole,
| #  | Diagnosis | Conditioning regimen | Donor/stem cell source | Ongoing immuno suppression at COVID-19 infection | Day post-SCT at COVID-19 diagnosis | COVID-related symptom | Comorbidities | T-cell count/CD4/CD8 ratio at COVID-19 diagnosis (<10⁷/l) | Course of COVID-19 disease | Day post-SCT negative COVID-19 test | Specific COVID-19 treatment received/Outcome |
|----|-----------|----------------------|-----------------------|-----------------------------------------------|----------------------------------|----------------------|---------------|-----------------------------------------------|--------------------------|-----------------------------|---------------------------------------------|
| 1  | ALL       | TBI 1200 cgy, VP16, alemtuzumab | MUD/BM | CSA | +54 | Cough | None | NA | Mild | None | None/alive |
| 2  | AML       | Busulphan, cyclophosphamide | MSD/BM | MMF, steroid, ruxolitinib, tocilizumab | +62 | Asymptomatic | Severe acute GVHD, hypertension and TA-TMA | NA | Mild | +64 | None/recovered from COVID-19 but died from TA-TMA day +166 from HSCT |
| 3  | ALL       | TBI 1200 cgy, VP16, alemtuzumab | MUD/BM | Steroid, MMF, CSA | +16 | Fevers | Acute GVHD | NA | Mild | +63 | None/alive experienced profound cytopenia post-COVID-19 |
| 4  | HD        | Fludarabine, melphalan, alemtuzumab | MUD/BM | None | +96 | Fevers | None | 110 (20-8) | Mild | +172 | None/alive |
| 5  | SCD       | Treosulphan, fludarabine, thiota, alemtuzumab | MFD/BM | CSA | +48 | Fevers | None | 250 (NA) | Mild | +78 | None/alive |
| 6  | SCD       | Treosulphan, fludarabine, thiota, ATG | MSD/BM | None | +261 | Fevers, vomiting and abdominal pain | None | 887 (0-4) | Severe | +271 | Remdesivi, dexamethasone and tocilizumab/alive |
| 7  | β-thal    | Treosulphan, fludarabine, thiota, ATG | MSD/BM | CSA | +157 | Fevers | None | 370 (0-9) | Mild | +184 | None/alive |
| 8  | A20       | Treosulphan, fludarabine, thiota, ATG | MMFD/PB* | None | +139 | Cough and shortness of breath | None | 175 (1-7) | Mild | +168 | None/alive, developed TA-TMA ongoing on renal dialysis |
| 9  | Secondary AML | Treosulphan, fludarabine, thiota, alemtuzumab | MUD/PB | CSA | +40 | Asymptomatic | None | 90 (NA) | Mild | NA | None/alive |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HD, Hodgkin disease; SCD, sickle-cell disease; β-thal, beta thalassaemia major; A20, A20 haploinsufficiency; TBI, total body irradiation; ATG, antithymocyte globulin; MUD, matched unrelated donor; BM, bone marrow; MSD, matched sibling donor; MFD, matched family donor; MMFD, mismatched family donor; PB, peripheral blood; *alfa beta T- and B-cell-depleted product; CSA, ciclosporin; MMF, mycophenolate mofetil the; GVHD, graft-versus-host disease; TA-TMA, transplant-associated thrombotic microangiopathy; NA, not applicable; HSCT, haematopoietic stem cell transplantation.
the data were considered sufficiently reassuring for transplant activity in non-urgent cases to be restarted within the UK paediatric HSCT transplant network.

Author contributions

GL and CF wrote the paper; JDF and PA designed the data collection and coordinated the national network to report the cases; SL, BJ, MS, RW, BC, BS and RH reported the cases and the follow-up data, and contributed to critical revision of the paper. All the authors reviewed and approved the content of the paper.

Giovanna Lucchini1
Caroline Furness2
Sarah Lawson3
Brenda Gibson4
Robert Wynn5
Mary Slatter6
Ben Shillitoe6
Beki James7
Ben Carpenter8
Rachael Hough8
Persis Amrolia1
Josu de la Fuente9

the UK and Ireland Paediatric BMT Group

1Bone Marrow Transplant Unit, Great Ormond Street Hospital NHS Foundation Trust, London, 2Haematology/BMT Unit, Royal Marsden NHS Foundation Trust, London, 3Bone Marrow Transplant Unit, Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham, 4Haematology Unit, Royal Hospital for Children, Glasgow, 5Bone Marrow Transplant Unit, Royal Manchester Children’s Hospital, Manchester, 6Bone Marrow Transplant Unit, The Great North Children’s Hospital, Newcastle upon Tyne, 7Bone Marrow Transplant Unit, Leeds Children’s Hospital NHS Trust, Leeds, 8Bone Marrow Transplant Unit, University College Hospital NHS Foundation Trust, London and 9Haematology Unit, St Mary’s Hospital, London, UK.

E-mail: giovanna.lucchini@gosh.nhs.uk

Keywords: COVID-19 infection, COVID-19 outcomes, Immunosuppression, paediatric allogeneic stem cell transplantation

References

1. Wu F, Zhao SU, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265–9.
2. https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov)
3. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. 2020;39:355–68.
4. Vicent MG, Martinez AP, Trabazo Del Castillo M, Molina B, Sisini L, Moron G, et al. COVID-19 in pediatric hematopoietic stem cell transplantation: the experience of Spanish group of transplant (GETMON/GETH). Pediatr Blood Cancer. 2020;67:e28514.
5. Xhaard A, Xhaard C, D’Aveni M, Salvator H, Chabi ML, Berceanu A, et al. Risk factors for a severe form of COVID-19 after allogeneic stem cell transplantation: a Societe Francophone de Greffe de Moelle et de therapie Cellulaire multicentre cohort study. Br J Haematol. 2021;192:e121–e124.
6. Duncan CJA, Dinnigan E, Theobald R, Grainger A, Skelton AJ, Hussain R, et al. Early-onset autoimmune disease due to a heterozygous loss-of-function mutation in TNFAIP3 (A20). Ann Rheum Dis. 2018;77:783–6.
7. McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
8. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–4.
10. Jhaveri KD, Meir LR, Flores Chang BS, Parikh R, Wanchoo R, Barilla-LaBarca ML, et al. Thrombotic microangiopathy in a patient with COVID-19. Kidney Int. 2020;98:509–12.
11. Figlerowicz M, Mania A, Lubarski K, Lewandowska Z, Szymczewski W, Derbyshire K, et al. First case of convalescent plasma transfusion in a child with COVID-19-associated severe aplastic anemia. Transfus Apher Sci. 2020;59:102866.