How I Treat: Allogeneic HSCT for adults with Inborn Errors of Immunity

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Abstract:
Inborn Errors of Immunity (IEI) are rare inherited disorders arising from monogenic germline mutations in genes that regulate the immune system. The majority of IEI are Primary Immunodeficiencies characterised by severe infection often associated with autoimmunity, autoinflammation and/or malignancy. Allogeneic hematopoietic stem cell transplant (HSCT) has been the corrective treatment of choice for many IEI presenting with severe disease in early childhood and experience has made this a successful and comparatively safe treatment in affected children. Early HSCT outcomes in adults were poor, resulting in extremely limited use worldwide. This is changing due to a combination of improved IEI diagnosis to inform patient selection, better understanding of the natural history of specific IEI and improvements in transplant practice. Recently published HSCT outcomes for adults with IEI have been comparable with pediatric data, making HSCT an important option for correction of clinically severe IEI in adulthood. Here we discuss our practice for patient selection, timing of HSCT, donor selection and conditioning, peri- and post HSCT management and our approach to long term follow up. We stress the importance of multidisciplinary involvement in the complex decision-making process that we believe is required for successful outcomes in this rapidly emerging area.

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How I Treat:

Allogeneic HSCT for adults with Primary Immunodeficiency

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Abstract

Inborn Errors of Immunity (IEI) are rare inherited disorders arising from monogenic germline mutations in genes that regulate the immune system. The majority of IEI are Primary Immunodeficiencies characterised by severe infection often associated with autoimmunity, autoinflammation and/or malignancy. Allogeneic hematopoietic stem cell transplant (HSCT) has been the corrective treatment of choice for many IEI presenting with severe disease in early childhood and experience has made this a successful and comparatively safe treatment in affected children. Early HSCT outcomes in adults were poor, resulting in extremely limited use worldwide. This is changing due to a combination of improved IEI diagnosis to inform patient selection, better understanding of the natural history of specific IEI and improvements in transplant practice. Recently published HSCT outcomes for adults with IEI have been comparable with pediatric data, making HSCT an important option for correction of clinically severe IEI in adulthood. Here we discuss our practice for patient selection, timing of HSCT, donor selection and conditioning, peri- and post HSCT management and our approach to long term follow up. We stress the importance of multidisciplinary involvement in the complex decision-making process that we believe is required for successful outcomes in this rapidly emerging area.

Introduction

Inborn errors of immunity (IEI) encompass a large and heterogenous group of rare diseases caused by monogenic germline mutations in over 400 separate genes that regulate the immune system[1]. The majority of IEI are primary immunodeficiency disorders characterised by severe and recurrent infection, which is associated with differing degrees of autoimmunity, autoinflammation and malignancy secondary to dysregulated immunity. Enormous phenotypic variation is seen in IEI, in part determined by the specific gene mutated and in part due to other factors, even within a single family, such as environment and epigenetic landscape[2-4]. While a monogenic diagnosis is frequently achieved when IEI presents in childhood, the majority of IEI patients first presenting in adulthood do not yet have a known genetic diagnosis, even in sequenced cohorts[5].

HSCT for severe pediatric onset IEI is well established and often the 'gold standard' treatment. Indications for pediatric HSCT are agreed upon by international groups such as the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Transplantation and Cellular Therapy (ASTCT) and are regularly revised to incorporate emerging data[6,7]. In contrast, the indications for HSCT in adult IEI patients are less well described and have only recently been included in the updated EBMT and ASTCT indications for HSCT[6,7], as a clinical option for some diseases. Regularly updated guidelines are produced by European Society for Immunodeficiency (ESID)/EBMT Inborn Errors Working Party (IEWP) and the most recent version includes a section on adults with IEI[8].

A rapidly growing body of publications detail HSCT outcomes for IEI in adults[9-25] and additional data on >200 adults have been published in abstract form. In most published series, the overall survival (OS) was similar to that achieved in children and infants (80% or greater at a median follow-up of between 14 months and 5 years). Age at transplantation (whether adolescent, young adult or older adult) remains an important consideration, as several studies report less favourable outcomes (both OS and graft versus host disease, GVHD rates) in older patients[9,10,14,19,44]. The most frequent IEI diagnoses in published series including older adolescents and adult patients are CGD, primary hemophagocytic lymphohistiocytosis HLH (including genetically undefined) and GATA2 deficiency (including patients with associated bone marrow failure and/or hematological malignancies in addition to immunodeficiency), however, in specialist centers a much wider range of IEI are proceeding to HSCT.

This review will discuss how HSCT can be applied to adults with IEI and give our own insights into how this can be done safely and for whom.

Patient selection: How we identify adult IEI patients who may benefit from HSCT

The potential benefit of HSCT should always outweigh the risks of the procedure. The challenge with many IEI patients that survive to, or present in, adulthood is that neither HSCT outcomes nor outcomes with conservative management are well described. Specific considerations in determining which adults should be transplanted are highlighted in Box 1.

To date we have mainly reserved HSCT for adults with a monogenic IEI and severe clinical disease. Although the many different genetic causes and broad phenotypic variation present challenges for optimal patient selection, criteria have been agreed in the United Kingdom by an expert group[26] (Supplementary Table 1). To provide oversight for clinical practice and enable complex decision making around HSCT, all adult IEI patients in England being considered for HSCT are discussed at a national multidisciplinary meeting involving transplant physicians, immunologists and other specialist physicians from multiple centers (Figure 2).

Case 1

42 year-old man with Wiskott- Adrich Syndrome (WAS). Known pathogenic mutation in the WAS gene resulting in preserved partial WAS protein (WASp) expression. Diagnosed in infancy (positive family history), his two older affected brothers both died from their disease: one in childhood from bleeding and the other in adulthood from WAS-associated large vessel vasculitis. Recurrent bacterial respiratory tract infections (RTIs) throughout life, requiring hospitalisation resulting in moderately severe bronchiectasis. Recurrent mucosal bleeding related to severe thrombocytopenia (platelets <10) and moderate eczema, but no autoimmune or malignant complications. Married with two young children and a full-time job. He was keen to explore HSCT given the relatively sudden deterioration and death of his brother in adulthood.

WAS is an X-linked IEI, characterised by microthrombocytopenia, recurrent infections and eczema[27] commonly complicated by autoimmunity and hematological malignancy that indicate severe disease [27,28]. A milder form of WAS, known as X-linked thrombocytopenia (XLT)[29], is typically associated mutations that preserve partial protein expression and lacks significant immunodeficiency or immune dysregulation [30] although complications can develop later in life[31]. The use of HSCT for severe WAS is considered gold standard therapy

in childhood with excellent outcomes[32] while patients with mild disease managed conservatively do well and the use of HSCT for XLT is not routinely recommended[33].

Case 2

24 year-old man with X-linked CGD. Diagnosed following aspergillus pneumonia aged 17 years requiring intensive care admission. Subsequent severe pseudomonal pneumonia and colitis. Progressive colitis after initial response to steroids, despite azathiaprine and regular vedoluzimab infusions.

Cases 1 and 2 illustrate adult patients with monogenic IEI diagnosed in childhood or adolescence but not transplanted, who have developed further disease complications in adulthood. HSCT may not have been offered earlier for various reasons including: (i) satisfactory initial responses to conservative management and/or less severe phenotype; (ii) perceived or actual unacceptable risk of HSCT; (iii) HSCT not considered; or (iv) the formal IEI diagnosis was made later.

For case 1 (42 years, WAS), the presence of severe infections, bronchiectasis and the need for immunoglobulin replacement therapy (IRT) place him in a moderately severe category. With optimal conservative management the potential to develop additional autoimmune and malignant complications is high, suggesting his WAS may be life-limiting with an accumulation of complications over an uncertain time frame.

For case 2 (24 years, X-CGD) his poorly controlled, steroid refractory colitis and a previous history of severe fungal infection requiring ICU admission predict a poor outcome with conservative therapy alone[34], which together with good outcomes following HSCT for adults with CGD[10,12] supported proceeding to HSCT in early adulthood.

Case 3

26 year-old lady. Well until aged 19 years when she developed vaccine-associated yellow fever requiring prolonged hospitalisation. Subsequently human papillomavirus (HPV) warts affected hands, feet and perineum leading to severe dysplasia and extensive anal intraepithelial neoplasia. Subsequent inflammatory bowel disease and RTIs leading to bronchiectasis. Treated with prophylactic antibiotics and IRT. Bone marrow examination confirmed trilineage myelodysplasia (MDS) with no increase in blasts. A subsequent genetic diagnosis of GATA2 deficiency was made[35,36].

Case 3 typifies onset of IEI in adulthood with subsequent genetic diagnosis (newly described IEI). Achieving a genetic diagnosis assists HSCT decision-making, particularly if the disease phenotype is only moderately severe or the disease is newly described with little or no HSCT experience. At the time, it was unclear whether the HPV-driven neoplasia would be amenable to HSCT. In this case the presence of trilineage MDS (albeit with a low IPSS score) and future risk of leukemic transformation supported the rationale for HSCT. Recent natural history data for GATA2 deficiency has confirmed poor outcomes with conservative management alone with early death from infections and malignancy (35% death rate by 40 years of age)[37]. In contrast, good disease-free survival approaching 90% suggests HSCT may be the treatment of choice, although issues remain around optimal timing and risks of GVHD reported in some studies[21,38]. For patients with bone marrow failure and/or leukemic transformation of MDS the indication for HSCT is clear[37]. The very recently reported lack of genotype-phenotype correlation[39] adds further complexity to patient selection.

Case 4

35 year-old man with CVID. Presented with progressive vitiligo and recurrent respiratory tract bacterial infections at 17 years of age. Pan-hypogammaglobulinaemia identified aged 30 years and diagnosed with common variable immunodeficiency (CVID). Initial management was with prophylactic antibiotics and IRT. Rapid development of multiple CVID-associated complications over 3 years: bronchiectasis, chronic norovirus gastrointestinal infection, splenomegaly, hypersplenism, granulomatous hepatitis with nodular regenerative hyperplasia (NRH) on liver biopsy and portal hypertension. Synthetic liver function preserved. Grade 2 oesophageal varices, spironolactone-controlled ascites, refractory norovirus infection and progressively worsening quality of life at last review.

CVID is a clinical diagnosis and the most common form of immunodeficiency requiring treatment in adults[40]. Most patients remain well on IRT with a normal life expectancy, but a subset with additional features of immune dysregulation develop progressive, severe organ complications[41]. Although this complex group are more likely to have a monogenic diagnosis the majority remain genetically undefined even in thoroughly sequenced cohorts[5,42,43]. The transition from being well on IRT to severely unwell with complex complications can occur rapidly and unpredictably. Patients may therefore present to transplant physicians 'too late' with complications precluding HSCT. Published retrospective data for HSCT in adult patients with complex CVID have indicated worse outcomes than for other IEI[14] underlining the need for better information to select patients and timing of HSCT in CVID. We do not currently recommend HSCT for these patients in the absence of a clinical study.

Optimal timing of HSCT in adult IEI patients.

Many published studies have demonstrated worse outcomes with increasing age at HSCT, with a greater risk of GVHD and poorer overall survival[10,25,44,45]. In pediatric series typically age >5yrs at HSCT is associated with poorer outcomes and in series including adolescents and adults, age at HSCT remains significant[10]. However, recent detailed analysis of 284 patients ≥15 years at HSCT for IEI conducted by the EBMT IEWP has shown that number of IEI-related complications, comorbidity score pre-HSCT and prior splenectomy influenced outcome rather than age (*Albert MA, et al EBMT 2021 oral presentation),* suggesting that older age *per se* is not a barrier to HSCT in the absence of IEI-related comorbidities. The challenge remains to identify patients for HSCT as soon as possible after diagnosis or the development of an IEI related complication which predict for poor outcome with conservative therapy alone. The immune deficiency and dysregulation activity (IDDA) score prior to HSCT is currently being evaluated as a tool to predict outcome following HSCT in IEI patients[17] (*and Fox T et al, EBMT 2021 oral presentation).*

How we perform HSCT in adult IEI patients

As for all HSCT, donor selection, stem cell source, conditioning regimen and GVHD prophylaxis all influence outcome and transplant specific complications. Additional factors may influence donor and graft choice, regimen and GVHD prophylaxis such as the presence of inherited disease within the family, inflammatory manifestations which may increase GVHD risk and active infection pre-HSCT.

Donor Selection

Preferred stem cell donors are 10/10 Human Leukocyte Antigen (HLA)-matched, CMV sero-matched, unaffected donors to minimise transplant related mortality (TRM) and GVHD risk, while optimising prompt engraftment and immune reconstitution[46-48]. HLA-matched family members should be genetically screened if a known pathogenic variant has been identified in the recipient and the use of female carriers of X-linked disease as stem cell donors should be avoided where possible. It is notable that MUD searches for IEI patients are more likely to identify either no or very poor donor options, in part related to patient ethnicity. As related donor options are reduced due to the presence of inherited disease, the use of haploidentical donors and/or mutation carriers may sometimes be the best family option available[49].

In general, the use of unrelated donors is common for IEI HSCT with acceptably good results[10,12,50,51]. The use of haploidentical donors is widespread in pediatrics[50,51,52] with

excellent outcomes. Despite growing use of haploidentical donors for adults with IEI, there are currently insufficient published data in older IEI patients to definitively support the use of haploidentical donors in preference to 1Ag MMUDs in adults.

Conditioning regimen selection

IEI patients surviving to adulthood typically have residual functional cellular immunity necessitating conditioning to permit engraftment of allogeneic stem cells and prevent graft rejection. A wide variety of regimens are used for IEI patients with varying degrees of myeloablation from minimally ablative Fludarabine with low dose Cylcophosphamide (20-40mg/kg) used in patients with DNA repair or radio-sensitivity disorders, to Fludarabine with Melphalan (140mg/m^2), Treosulfan (30-42g/m^2) or Busulfan (AUC 60-70mg*h/L) through to more myeloablative Fludarabine with Busulfan (AUC 85-95mg*h/L) or Fludarabine with Treosulfan (30-42g/m^2) and Thiotepa (8-10mg/kg) indicated for younger patients with no pre-existing organ damage where complete donor chimerism is desired for optional disease correction. We recommend using reduced toxicity or reduced intensity conditioning for the majority of adult IEI patients to limit TRM. Most experience to date has been with Fludarabine -based regimens in combination with the alkylating agents Busulfan, Melphalan or Treosulfan and incorporating serotherapy (Alemtuzumab or ATG/ATLG) for *in vivo* T cell depletion as GVHD prophylaxis. Excellent results have also been achieved recently using a radiation-free, serotherapy-free reduced intensity T cell replete regimen incorporating pentostatin, low dose cyclophosphamide and busulfan with post-transplant cyclophosphamide (PT Cy) as GVHD prophylaxis[51]. At present there is insufficient evidence in adult IEI to definitively recommend one reduced toxicity regimen over another.

Conditioning regimens using reduced doses of cytoreductive agents are better tolerated in older recipients with higher co-morbidities hence the recommendation, but they carry the risk of failing to eradicate host hematopoiesis[53,54]. This can result in mixed chimerism in any lineage, with the T cell compartment frequently affected unless donor T cells have a significant survival advantage. The impact of mixed chimerism post HSCT varies with underlying IEI and may be deleterious as in GATA2 deficiency where the risk of myeloid malignancies persists if full donor myeloid chimerism is not achieved. As such, more myeloablative regimens may be indicated in specific patients with the aim of maximising engraftment and full lineage donor chimerism.

As a general principle, high degrees of donor chimerism are more likely to result in sustained functional correction of the underlying IEI and optimal long-term outcome as has been documented in patients with WAS[32,44,55], however, there may be some IEI for which this is

not true. There is good evidence in X-CGD that the use of carriers as donors may not result in full immunological correction, even in the presence of full donor chimerism (depending on carrier neutrophil function tests). However, in other X-linked and autosomal recessive disorders, carriers may be used as donors if the relevant functional immunological assays are normal. It is not yet known what degree of chimerism is sufficient to correct the clinical phenotype in GOF diseases.

Serotherapy and GVHD prophylaxis

Serotherapy with ATG/Thymoglobuline® (polyclonal rabbit anti-thymocyte globulin), ATLG/ Grafalon® (anti-T lymphocyte globulin) or alemtuzumab (CD52 monoclonal antibody) are commonly used to prevent both GVHD and graft rejection, being of most value in unrelated and mismatched related donor transplants. Serotherapy may also be useful in IEI with inflammatory manifestations. These biologics have different properties and exposure following standard dosing is highly variable, with studies demonstrating both patient weight and lymphocyte count pre-infusion as influential[56-58]. Timing of administration is also important, particularly when unmanipulated grafts are infused and the concentration of ATG/ATLG or alemtuzumab on day 0 influences both engraftment and prevention of GVHD through donor T cell depletion. Over-exposure can lead to prolonged lymphocyte depletion, delayed immune reconstitution and mixed chimerism. Personalised dosing using real-time pharmacokinetic and pharmacodynamic analysis is not widely available.

If no serotherapy is used in unrelated, mismatched related or haploidentical HSCT additional measures are required to prevent GVHD. Strategies such as PTCy and αβTCR depletion to selectively deplete donor-derived alloreactive T cells have facilitated the use of alternative donors in older recipients with hematological malignancies, without prohibitive risks of GVHD and/or graft rejection[59] and in pediatric series, excellent results have been achieved in IEI[50,52,60,61]. However, at the time of writing there remains little cumulative experience transplanting older adults with IEI using haploidentical donors and we use these donors in younger adults where no other options are available. Further studies are warranted and may result in the wider adoption of Haplo-HSCT for older adults with IEI in the future.

Specific HSCT management for adults with IEI to optimise outcome

Identification of IEI-specific co-morbidities

In addition to routine pre-HSCT investigations we recommend documenting the presence or absence of specific pathogens, anti-microbial sensitivities and/or degree of organ damage in adult IEI patients. Specialist infectious disease advice should be sought for patients with a history of refractory or atypical infections preceding transplant. Table 1 lists some common non-infectious co-morbidities seen in adult IEI patients, which increase HSCT risk and if present will alter the risk: benefit ratio and may influence the final transplant decision and/or conditioning regimen selection. For patients proceeding to HSCT with pre-existing end-organ damage the consent process must involve a clear discussion about which disease-associated symptoms/complications can be improved by transplant and which cannot (eg, bronchiectasis/pulmonary fibrosis, gut strictures). The same discussion is required for extra-hematologic complications of IEI.

Optimisation of IEI-related complications pre-HSCT

Where possible control of infection, autoimmunity and/or inflammation should be achieved prior to transplant. Reducing the inflammatory cytokine milieu at the time of transfer of allogeneic cells reduces the risk of acute GVHD and ensures end organ function is optimised pre-transplant. Patients with granulomatous and lymphoproliferative manifestations of IEI, including granulomatous lymphocytic inflammatory lung disease (GLILD) should receive immunosuppressive therapies to reduce inflammation and optimise end-organ function pre-HSCT. Pre-existing IEI-associated malignancies should be treated and in remission as per routine practice in HSCT for lymphoid malignancies. However, in some cases, IEI-associated malignancies are challenging to treat as cytopenias or concurrent infection may preclude optimal anti-neoplastic therapy due to excess toxicity. Such patients are more likely to proceed to HSCT without achieving a CR. When considering lymphoma, as with non IEI-associated lymphomas, the risk of relapse post HSCT is lower for patients who have chemo-responsive disease and reduced disease burden pre-HSCT. Patients with IEI associated HLH should be in remission or have stably controlled disease prior to HSCT as outcome for patients transplanted with frank HLH are poor[62,63]. For patients with EBV handling disorders, the inclusion of rituximab in the conditioning regimen can bridge the gap until functional immune reconstitution is achieved post-transplant.

IEI-specific peri-HSCT management

In addition to routine HSCT management, regular post-transplant monitoring for recurrence of previous, persistent or latent opportunistic pathogens is indicated on a per-patient basis.

We recommend the continued use of prophylactic antimicrobials until cessation of systemic immune suppression as either GVHD prophylaxis or treatment and the continuation of IRT until a minimum of 6 months post HSCT.

Post-HSCT monitoring and long-term follow-up

Standard post-HSCT monitoring: Patients require standard post-HSCT follow-up and monitoring to evaluate for HSCT related complications such as GVHD, reactivation of latent viruses, late graft failure, secondary malignancies and other known late effects.

IEI-specific post-HSCT monitoring: Other important endpoints for IEI patients include the reconstitution of normal pathogen-specific immunity, adequate B cell reconstitution and immunoglobulin production, resolution of autoimmunity and/or inflammation and reduction in future malignancy risk. For patients with EBV handling disorders (such as CD27 or CD70 deficiency, XLP1 and XIAP deficiency) regular monitoring for EBV reactivation is essential as persistent EBV viraemia is associated with HLH and lymphoproliferation[64,65]. Other additional monitoring is disease specific, and influence by the degree of lineage specific chimerism achieved post-HSCT. For example, patients with transplanted for GATA2 deficiency who do not achieve full myeloid chimerism post HSCT will be at risk of relapse of MDS or AML and should be monitored appropriately.

In adult IEI the indication for transplant is often the prevention of progressive decline in quality of life secondary to the accumulation of IEI-related medical complications. Because of this, we recommend including patient reported outcomes (PROs) and quality of life assessments when evaluating success[66].

Chimerism monitoring: During the first year following reduced intensity HSCT chimerism often fluctuates. The use of DLI to promote conversion from mixed chimerism to full donor chimerism carries a risk of GVHD and typically is only used when worsening mixed chimerism raised concerns of incipient graft rejection. However, recently emerging data from the long-term follow up of pediatric HSCT recipients indicates that persistent mixed chimerism post-transplant is associated with reduced event free survival after as long as 20 years (*Cheminant M et al, ESID 2020 oral presentation)* and late complications such as autoimmunity, which has been observed in patients transplanted for WAS, but not for other IEI[44,45,65]. For patients with phagocytic defects achieving high level stable myeloid chimerism is essential. Studies in female carriers of X-linked CGD, have identified inflammatory disease similar to that seen in male patients in carriers with extreme degrees of lyonisation (resulting

in <20-30% normally functioning phagocytes), although the risk of serious infection is rarely present if >10% of circulating neutrophils are functional[67,68]. Carriers of X-linked diseases typically have 50% normal and 50% abnormal cells in the relevant lineage, whereas in autosomal recessive disorders carriers typically have normal function in 100% of cells. Therefore, the impact of post-HSCT mixed chimerism will depend on the specific IEI if a carrier is used as stem cell donor. For rarer IEI such as APDS, CTLA4 Deficiency, LRBA Deficiency, DOCK8 Deficiency and STAT1 GOF there is insufficient data regarding the optimal lineage-specific chimerism required for long term immunological correction and cure, although insight into disease specific pathophysiology may predict which lineages are critical to correct. For example, even small populations of residual recipient cells may be problematic in GOF diseases.

Reconstitution of normal immune function: Lineage specific donor chimerism can be used as a surrogate marker for functional correction, but 'proof' of transplant efficacy relies on immunological assessment (eg. neutrophil function tests, response to vaccination, T cell proliferation, normalisation of lymphocyte subsets and assessment of thymopoiesis) and clinical responses. Post HSCT vaccination schedule is as for other HSCT indications. Vaccination should not be undertaken until patients are off IRT, typically 6-12 months post HSCT. In specific cases additional vaccination may be warranted, for example HPV vaccination in patients with IEI conferring HPV susceptibility such as GATA2 Deficiency. Protective specific antibody responses to vaccination should be documented where tests are available, for example serotype-specific pneumococcal antibodies. Currently, specific vaccination of donors to provide pathogen-specific immunity is not routine.

Malignancy: Patients with previous HPV-associated dysplasia or malignancy should continue to have regular surveillance (e.g. cervical smears, colposcopy +/- biopsy). Patients with previous lymphoma should have regular imaging (CT/PET or PET/MRI) as per standard post-HSCT practice.

Specific HSCT management of our cases

With suitably matched donors, we expect TRM to be in the region of 10-15% based on our own center's HSCT outcome data for carefully selected adult patients in the absence of major end organ dysfunction or active HLH[12].

Case 1 (42 years, WAS) has moderately severe bronchiectasis but preserved pulmonary function with an FEV1 >50% predicted. With a well-matched unrelated donor we would recommend HSCT using a reduced toxicity conditioning regimen with serotherapy or PTCy as GVHD prophylaxis to prevent disease progression and predict a TRM of 15-20% in view of the bronchiectasis.

Case 2 (24 years, CGD) had excellent end organ function and proceeded to an unrelated donor HSCT to restore pathogen immunity and achieve remission of his refractory CGD-colitis. The majority of CGD patients transplanted to date have received Fludarabine and targeted Busulfan (AUC 70) with either ATG (for MRD) or Alemtuzumab (for MUD/MMUD)[10,12]. He is now 19 months post-HSCT with tri-lineage full donor chimerism, no active colitis, off immune suppression and no further infections. He is exercising again and well enough to apply for work.

Case 3 (26 years, GATA2 deficiency) had a number of moderate co-morbidities when referred for HSCT. She underwent 1 antigen MMUD with Flu/Mel-Alemtuzumab conditioning. No additional rituximab was given prior to transplant in the absence of EBV viraemia. She is now 7 years post HSCT, off immune suppression and with no GVHD. Complete resolution of HPV disease occurred at 5 years post HSCT and she has since had 2 normal cervical smears. She is currently deciding whether to proceed to IVF with a limited number of cryopreserved eggs with or without pre-implantation genetic diagnosis.

Finally, Case 4 (35 years, complex CVID) represents a major challenge. Although the published HSCT data for CVID patients included a large number of patients who received myeloablative transplants, the outcomes were significantly poorer than for other IEI[14] and prospective studies are urgently required to assess safety and efficacy of more modern regimens in carefully selected patients. Our patient has very significant comorbidities (bronchiectasis, chronic norovirus infection, portal hypertension, massive splenomegaly, ascites and non-cirrhotic liver fibrosis), which predict an excessive TRM even with reduced intensity conditioning. However, due to preserved synthetic liver function he does not currently meet the criteria for liver transplantation. His best stem cell donor is a 1 Ag MMUD and we would not recommend proceeding to HSCT in this case without prior liver transplant.

When we consider gene therapy as an alternative to HSCT

Some patients referred to us have a clear indication for HSCT, but no well-matched donor. In these cases, the decision between using multiple mismatched cord units, a mismatched

unrelated donor, a haploidentical donor or to consider gene therapy (GT) is complex. Currently, GT approaches where autologous hematopoietic stem cells (HSC) are genetically modified ex vivo using viral vectors encoding a wild type version of the mutated gene are only available for a few monogenic diseases including X-SCID, ADA-SCID, WAS and X-CGD. Only one GT is currently licensed (Strimvelis for ADA-SCID), although at the time of writing unavailable while an occurrence of insertional mutagenesis is being investigated, and for other diseases patients will need to be recruited into clinical trials. The potential advantage of gene therapy is the requirement for less immunosuppressive conditioning and no risk of GVHD as it utilises autologous HSCs. However, engraftment of gene-modified HSCs requires myeloablative pre-conditioning chemotherapy which is associated with significant toxicities in older patients. Further, current GT approaches result in only partial correction of autologous cells generating a setting equivalent to achieving mixed chimerism post HSCT. The degree of correction is influenced by ex vivo HSC transduction efficiency, degree of engraftment of the modified HSCs, potential survival advantage (or not) of the gene corrected immune cells and durability of gene expression. The impact of these factors on clinical outcome following GT is likely to vary between IEI. Gene therapy has been successfully used in adults for WAS[69,70] and X-linked CGD[71] where appropriately matched allogeneic stem cell donors were not available. This is an appealing option for adults with significant co-morbidities and/or poorly matched donors and if long-term correction and immune reconstitution is proven to be effective and durable, GT may become the preferred option for adults with IEI in the future.

Conclusion

The application of HSCT to adults with IEI is a rapidly emerging field. Decision making is complex given the heterogenous nature of IEI, the variety of associated complications and the paucity of outcome data. Despite this, our experience is that HSCT can be delivered as successfully to carefully selected adults as to children with IEI. Identifying adult IEI patients for whom HSCT is appropriate requires both detailed understanding of the disease and the transplant process and should involve the combined input of immunologists and transplant physicians, ideally in a joint clinical setting. Over the coming years we expect that HSCT for adult IEI will expand both in terms of patient numbers and range of conditions treated. We also expect gene therapy and editing approaches to become more widely available as alternative options. While there remains a pressing need to enrich outcome data both for conservative management and corrective therapies to help our patients make the most informed choice for their care, these are promising times for adults with IEI.

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Legends to Figures

Figure 1. Example of adult IEI HSCT MDT impact on patient management.

MDT aims include: (i) standardising practice; (ii) sharing experience in the clinical management of rare HSCT indications; and (iii) providing patient specific advice regarding the risk of transplant, choice of conditioning regimens and selection of most appropriate transplant center. Green, amber and red boxes represent a traffic light system, with green being favourable and red unfavourable.

Text Box 1

Box 1: Specific considerations in determining which adults should have HSCT

- Adult IEI patients being considered for HSCT are more likely to have had a mild phenotype in childhood or late onset presentation of an IEI-associated complication.
- The natural history of most IEI in adulthood are not well described and therefore the outlook for an individual patient with conservative management is often not easy to predict.
- The HSCT outcome data for some conditions are poor or unclear e.g. XIAP, CVID.
- We do not yet fully understand the pathogenesis and/or prognosis of some newly discovered genetic defects.
- Some diseases have extra hematopoietic aspects that may not be corrected by HSCT, e.g. STAT3 LOF.
- Adults with IEI have generally accumulated complications and end organ damage that increases risk or precludes HSCT.
- Fertility preservation for younger adults should include access to pre-natal genetic diagnosis if indicated/requested.

Table 1: Common non-infectious co-morbidities to consider in adults with IEI that confer worse outcome for HSCT

System	Complications commonly seen in adults with IEI	Investigations recommended	Influence on transplant planning
Pulmonary	Structural lung disease including: • Bronchiectasis • Fibrosis • Pneumatocoele	Lung function: spirometry and gas transfer. High resolution chest CT. Bronchoscopy and BAL if suspect active undiagnosed infection.	FVC and FEV1 <60% predicted – acceptable if not oxygen-dependent and possibility for stabilisation post-HSCT. Ensure optimal management of bronchiectasis and/or ILD prior to HSCT. Sputum surveillance to inform peri-transplant antimicrobial prophylaxis and treatment.
	Inflammatory lung disease (ILD) including: • Granulomatous interstitial lung disease (GLILD) • Cryptogenic organising Pneumonia (COP)	Lung function: gas transfer is a good marker of extent of ILD. High resolution CT chest. Bronchoscopy and BAL if suspect active undiagnosed infection.	DLCO <50% predicted – – acceptable if not oxygen-dependent and possibility for stabilisation post-HSCT. ILD anticipated to improve with immunosuppression conferred by conditioning. Associated structural change, such as fibrosis, may be a barrier to HSCT (see above). Occasionally thoracic surgery indicated prior to HSCT (eg. resection of infected cavity/lobe).
Renal	Chronic renal impairment including: • Autoimmune renal disease • Vasculitis • Drug induced injury	Urea, Creatinine, electrolytes and estimated GFR. Renal biopsy (occasionally indicated when renal diagnosis unclear).	GFR <30mls/kg/min poses a significant barrier to HSCT due to reduced drug tolerance and increased risk of sepsis associated acute kidney injury (AKI). For patients with GFR <30mls/kg/min and no other severe end organ damage, peri-transplant hemofiltration can be considered, but requires highly specialist care and complicates drug dosing especially for chemotherapy.
Hepatic	Chronic liver disease including: • Nodular regenerative hyperplasia (NRH) • Fibrosis/Cirrhosis • Portal hypertension +/- ascites	Liver function testing to include transaminases, alkaline phosphatase, bilirubin, albumin, INR, Hepatitis B and C DNA/RNA* Liver ultrasound. Fibroscan measuring liver stiffness. Liver biopsy. Portal venous pressure measurements. If portal hypertension, upper endoscopy for oesophageal varices.	Severe chronic liver disease is an absolute barrier to HSCT including: • Liver synthetic failure • Decompensated portal hypertension with ascites • Severe portal hypertension with large splenomegaly • Cirrhosis Decision making requires involvement of an experienced hepatology team. Prior liver transplant or surgical TIPPS procedure (for portal hypertension) can be considered but there is little data for these procedures in adults with IEI to date, making this high risk.

	Active inflammation • Autoimmune hepatitis	As above Also tissue specific autoantibodies.	Control of active inflammation using immunosuppression advised prior to HSCT. Decision making requires involvement of an experienced hepatology team and prior liver transplant may be required for refractory inflammation leading to liver failure.
GI	Chronic diarrhoea Malabsorption and poor nutrition	Stool samples for microscopy & culture/PCR to exclude bacterial and parasitic pathogens including disease specific considerations: Eg. cryptosporidium in CD40L deficiency. PCR for viruses, including norovirus. Vitamin levels.	Infectious disease or microbiology input indicated for chronic or relapsing infections. Eradication pre-HSCT may not be feasible but peri- and post- HSCT prophylaxis may be required. Nutrition should be optimised if possible, prior to HSCT, including use of parenteral nutrition if required.
	Active inflammation/Colitis • Inflammatory bowel disease • Granulomatous inflammation	Faecal calprotectin Upper and lower endoscopy with biopsies if pathogens excluded and diagnosis unclear.	Conditions with active inflammation typically improve with immunosuppression conferred by conditioning.
Spleen	Splenomegaly for example • As a feature of the specific IEI • With autoimmune cytopoenias • Secondary to liver disease and portal hypertension (see above)	US or CT of abdomen to ascertain size. Liver investigations if liver disease suspected (see above)	Large splenomegaly increases risk of engraftment failure and is associated with poor count recovery. If secondary to liver disease, follow advice for liver complications (see above) If related to immune dysregulation of the underlying IEI, consider whether size can be reduced prior to HSCT eg with immunosuppression such as sirolimus or rituximab or with control of autoimmune cytopoenias. Splenectomy not advised due to risk of post-HSCT infections, in particular pneumococcal sepsis. Embolization also not advised due to risk of abscess formation, unless urgent need to reduce spleen size for control of severe refractory autoimmune cytopenia.
	Prior splenectomy	none	Ensure pneumococcal antibiotic prophylaxis post HSCT, typically life-long. Ensure pneumococcal vaccination post -HSCT with confirmation of protective antibody response.

NB. *serology is unreliable in IEI as antibody production is commonly impaired or patients are on immunoglobulin replacement therapy. Autoantibodies are usually unhelpful for the same reasons.

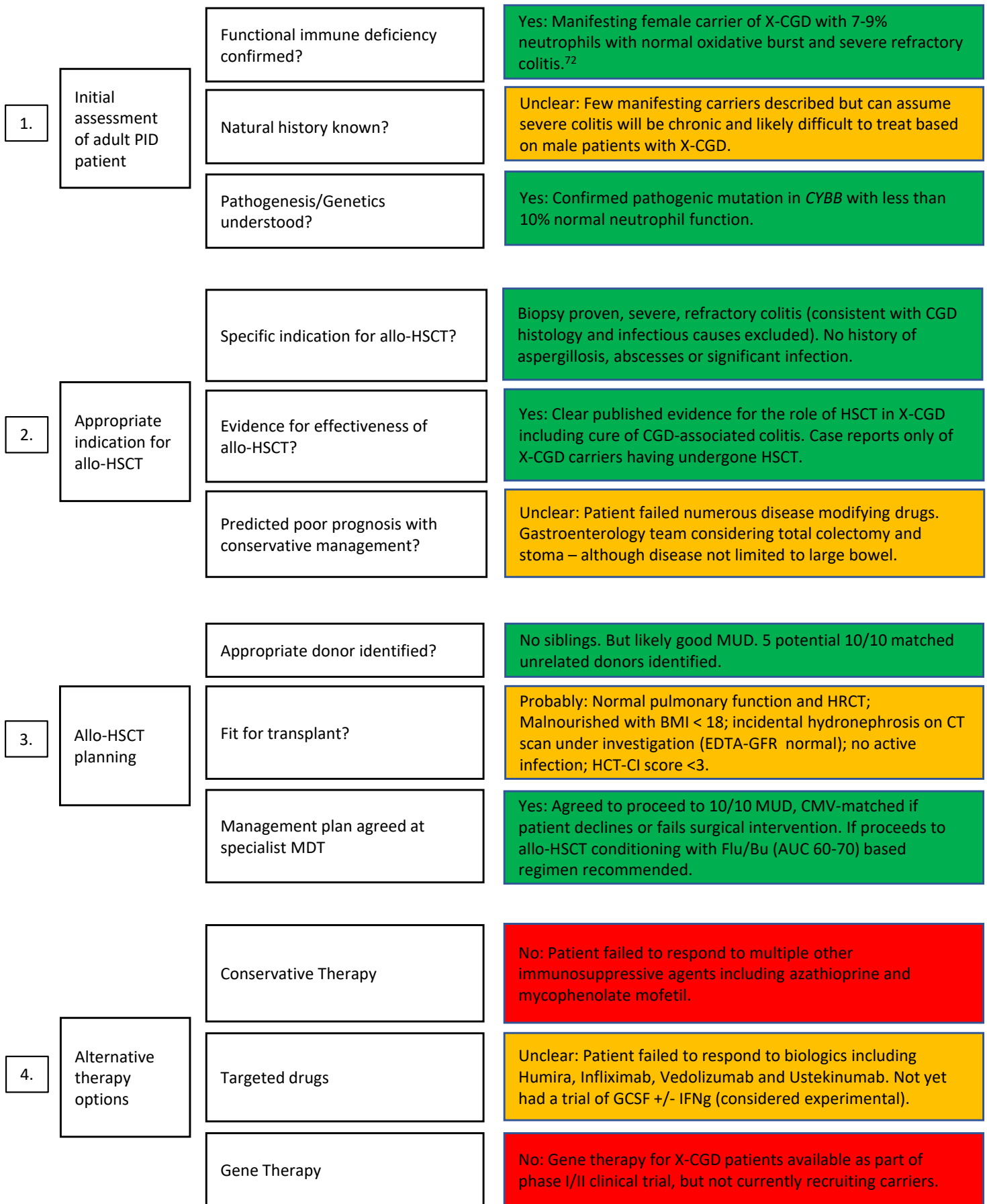| Step	Category	Question	Assessment
1.	Initial assessment of adult PID patient	Functional immune deficiency confirmed?	Yes: Manifesting female carrier of X-CGD with 7-9% neutrophils with normal oxidative burst and severe refractory colitis.[72]
		Natural history known?	Unclear: Few manifesting carriers described but can assume severe colitis will be chronic and likely difficult to treat based on male patients with X-CGD.
		Pathogenesis/Genetics understood?	Yes: Confirmed pathogenic mutation in *CYBB* with less than 10% normal neutrophil function.
2.	Appropriate indication for allo-HSCT	Specific indication for allo-HSCT?	Biopsy proven, severe, refractory colitis (consistent with CGD histology and infectious causes excluded). No history of aspergillosis, abscesses or significant infection.
		Evidence for effectiveness of allo-HSCT?	Yes: Clear published evidence for the role of HSCT in X-CGD including cure of CGD-associated colitis. Case reports only of X-CGD carriers having undergone HSCT.
		Predicted poor prognosis with conservative management?	Unclear: Patient failed numerous disease modifying drugs. Gastroenterology team considering total colectomy and stoma – although disease not limited to large bowel.
3.	Allo-HSCT planning	Appropriate donor identified?	No siblings. But likely good MUD. 5 potential 10/10 matched unrelated donors identified.
		Fit for transplant?	Probably: Normal pulmonary function and HRCT; Malnourished with BMI < 18; incidental hydronephrosis on CT scan under investigation (EDTA-GFR normal); no active infection; HCT-CI score <3.
		Management plan agreed at specialist MDT	Yes: Agreed to proceed to 10/10 MUD, CMV-matched if patient declines or fails surgical intervention. If proceeds to allo-HSCT conditioning with Flu/Bu (AUC 60-70) based regimen recommended.
4.	Alternative therapy options	Conservative Therapy	No: Patient failed to respond to multiple other immunosuppressive agents including azathioprine and mycophenolate mofetil.
		Targeted drugs	Unclear: Patient failed to respond to biologics including Humira, Infliximab, Vedolizumab and Ustekinumab. Not yet had a trial of GCSF +/- IFNg (considered experimental).
		Gene Therapy	No: Gene therapy for X-CGD patients available as part of phase I/II clinical trial, but not currently recruiting carriers.

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