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Mechanisms Implemented in Hematopoietic Transplant Treatments Based on Each Person's Unique Immune System to Improve Overall Success Rates

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Abstract

As Hematopoietic stem cell transplantations (HSCT) are high-risk procedures with a 30-50% likelihood of resulting in Graft Versus Host disease (GVHD), a critical complication that significantly impacts patient outcomes, it is essential to have an effective treatment. However, current efforts to find specific treatments result in low response rates. Understanding the interactions that cause host rejection, GVHD, and a successful transplantation is imperative. This review highlighted innovative therapies such as HLA matching and typing, Antibiotic Prophylaxis, etc. which utilize personalized medicine to increase success rates. Ethical issues such as the risk of adverse reactions due to drugs which were tested in unconventional clinical trials, mishandling of genetic data in commercial genetic testing companies, the wellbeing of an infant produced via preimplantation HSCT typing, and whether the cost of treatment would allow equitable access should all be considered. The challenge of balancing ethical rights with public health interests, especially in the context of genetic testing and research, requires thoughtful consideration. Despite this, the potential of personalized medicine in HSCT is paramount. By implementing some of the following personalized treatment strategies, an increase in success rate along with longer lifespans had been recorded. Nevertheless, fatal side effects such as Cytokine Release Syndrome (CRS) question their integration into mainstream therapies. As precision medicine continues to advance, it is crucial to provide a substantial trial period and find strategies to create a confidential environment. Future research should focus on refining these personalized procedures and exploring their broader applications in the field of HSCT.

Keywords: Hematopoietic stem cells, Transplantation, Graft versus host disease, Personalized medicine, Genetics, Ethics

1. Introduction

Each year, approximately 90,000 people undergo Hematopoietic stem cell transplantations (HSCT); 53% of the procedures are autologous, and 47% are allogenic (Moore, 2023). This makes HSCT an integral therapy for many bone marrow disorders, allowing patients a chance at remission. However, despite advancements in transplantation techniques and post-treatment care, a suboptimal rejection rate persists - 6.64% (Bernasconi, 2019).

Understanding the interactions mediating host rejection and successful transplantation is paramount to overcome this. Globally, there are more than 14 million typed volunteer donors or cord blood units from registries to provide stem cells for patients without family donors, allowing recipients to find an optimal match. However, there is an alternative. A novel approach to promote successful transplantation incorporates using the recipient's cells to maximize optimal outcomes. Therefore, by exploring current research on HLA Typing and matching, Chimeric Antigen Receptor T-cell therapy, Immunogenetic Profiling, and Targeted Therapies. This review aimed to highlight

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current innovative therapies that utilize personalized medicine to increase the success rates of HSCT, with the hope of promoting wider implementation of personalized medicine in transplant treatments.

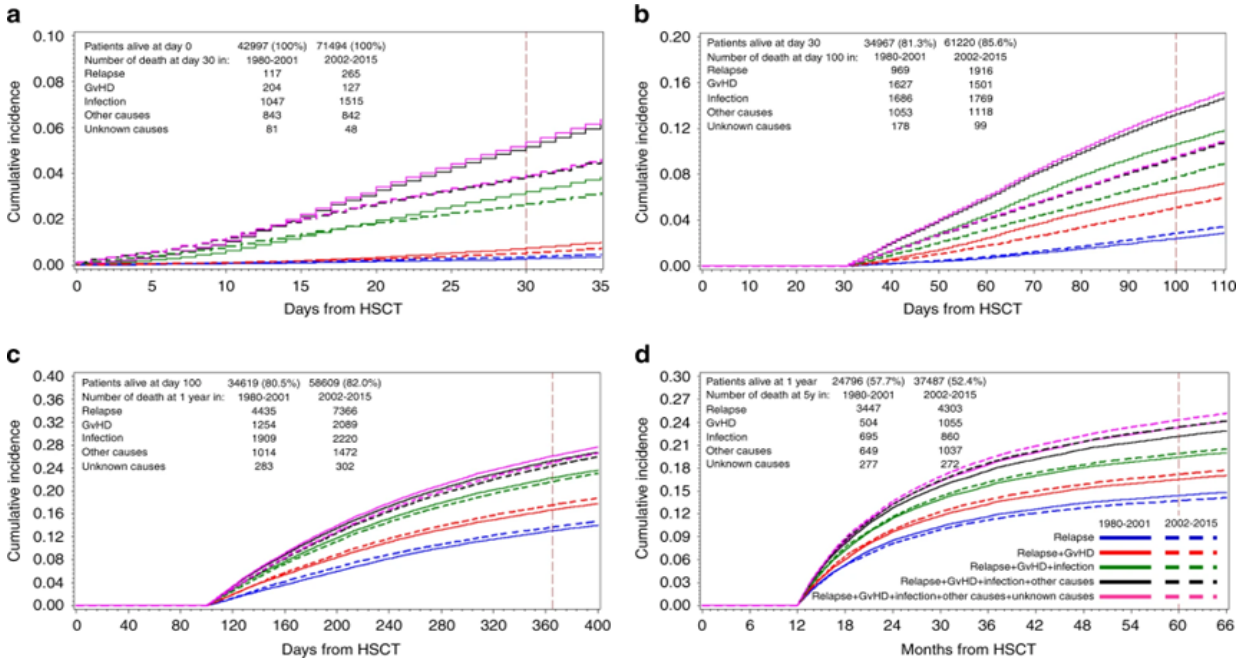

Figure 1 shows the cumulative incidence of morality after a HSCT over 4 post-HSCT phases in two cohorts. (Styczyński et al., 2020)

2. Current Challenges in Transplantation

Transplantation is transferring cells, tissues, or organs from the donor to the recipient to replace or repair dysfunctional body parts and systems. These procedures are crucial in treating a wide spectrum of conditions, including organ failure, autoimmune diseases, and certain types of cancer. One particular transplant is grafting bone marrow, and hematopoietic stem cells (HSCs). Although cases have risen upwards to 90,000 HSC transplants annually (Perkey et al., 2018), limitations such as restricted donor pool, graft rejection, and graft versus host disease (GVHD) persist (Perkey et al., 2018).

Following an allograft, success is determined largely by the individual's immune system. When a newly transplanted tissue is introduced into the recipient's body, the immune system instantly recognizes the foreign tissue, which triggers a cascade of immune responses to protect the body from potential threats the transplant poses. A transplant rejection primarily occurs due to an immune response to the alloantigens on the graft, while GVHD occurs when the donor's immune cells act against allogeneic recipient tissues. (Menendez-Gonzalez et al., 2021) Most frequently, this disease occurs in recipients of a hematopoietic stem cell transplant.

Graft rejection post an allo-HSCT results from an alloreactive immune response, primarily mediated by host T cells. This rejection occurs in both HLA-mismatched and HLA-matched cases due to a response against minor histocompatibility antigens (MiHA), which are a collection of peptide-bound molecules on the surface of tissue cells that determine organ transplant rejection (Brickner, 2006). The effector pathways involved in T-cell-mediated graft rejection are not fully understood (Masouridi-Levrat et al., 2016). However, various mechanisms have been thought to contribute to the response. Natural killer (NK) cells also have adverse involvement in rejection, especially in MHC-mismatched transplantations, through "missing self-recognition" (Masouridi-Levrat et al., 2016) when inhibitory receptors fail to recognize host MHC molecules. Despite their role in rejection, both donor T cells and NK cells can facilitate hematopoietic stem cell (HSC) engraftment. Studies suggest both humoral and cell-mediated immunity can influence allograft rejection in patients (Ingulli, 2008). Regulatory T cells are vital in modulating immune responses

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post-transplant. Indeed, in an allogeneic graft, host and donor regulatory T cells facilitate engraftment.

GVHD, classified as hyperacute, acute, or chronic, can occur from minutes to years post-transplant. Hyperacute rejections occur before engraftments due to mismatched ABO Blood types between the donor and recipient, causing preformed antibodies immediately acting against the donated tissue (Stomp On Step1, 2014). This results in occlusion and thrombosis of the graft and skin rashes.

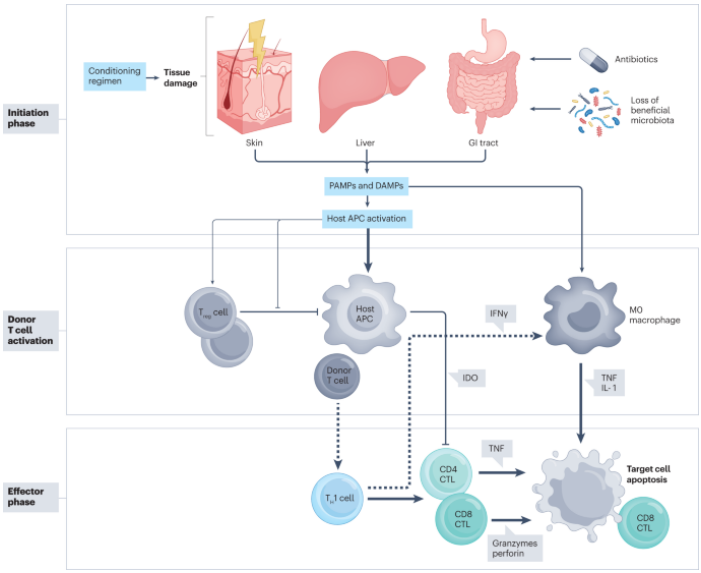

Figure 2 This diagram illustrates the pathophysiology of aGVHD

Conversely, acute GVHD occurs in three phases: Condition-mediated tissue damage, donor T cell activation, and target cell apoptosis (Ghimire et al., 2017). Conditioning, a regimen such as chemotherapy is administered to patients before undergoing HSCT (Nagler et al., 2019.), it is vital for eradicating disease and supporting donor cell acceptance. However, patient's tissues are damaged by disease, treatment, infections, and conditioning. This damage triggers danger signals, like TNF and IL-1, which activate donor T cells. Reduced-intensity conditioning lowers toxicity and GVHD severity. Furthermore, delaying donor cell transfer after conditioning can reduce GVHD risk.

T-cell activation requires the recognition of differences in human leukocyte antigen (HLA) molecules in recipient tissues (Ghimire, et al., 2017). Within activation, T cells recognize differences in HLA (Human Leukocyte Antigens) molecules in recipient tissues. Host antigen-presenting cells (APCs), the immune cells required to present foreign particles to lymphocytes to initiate an immune response, are needed for activating donor T cells and GVHD. Donor T cells can detect alloantigens directly on host APCs or indirectly on donor APCs. T-cell responses depend on HLA differences between donor and recipient. Even in HLA-matched transplants, minor HLA differences can cause GVHD. Over 50 minor HLA antigens have been identified. Therefore, current immunosuppressive strategies target T-cell activation to prevent or lessen GVHD.

During the Target cell Apoptosis phase, innate and adaptive immune cells collaborate to worsen T cell-induced inflammation. Cytotoxic T lymphocytes (CTLs) and NK cells use apoptosis pathways to kill target cells. Inflammatory cytokines and CTLs cause more tissue damage and potential organ dysfunction. Microbial products released during conditioning pass through damaged intestinal mucous membranes and skin, stimulating cells to release more inflammatory cytokines, leading to a cytokine storm and epithelial cell destruction, mainly in the Gastrointestinal tract.

Chronic GVHD may occur alongside acute (aGVHD), as they may overlap near the 100th day post-transplant. Destruction of immune cells and organs by aGVHD, particularly the thymus, bone marrow, and spleen, contributes to cGVHD, leading to allo- and autoimmunity (Ghimire et al., 2017). Deviations in the canonical B cell development pathway predict cGVHD, as it fosters inadequate elimination of auto- and alloantibody-producing B cells. Corticosteroids (an anti-inflammatory medicine) are the primary treatment for acute and chronic GVHD due to their broad activity, including T-cell apoptosis initiation and cytokine release suppression. Despite efforts to find more specific treatments, such as TNF-blocking agents, response rates remain low. These response rates may be low due to the heterogeneity of GVHD; most patients have at least three involved organs (Hamilton et al., 2021), which may vary from patient to patient. Therefore, responses to TNF-blocking agents are variable and ineffective for some. Furthermore, the pathophysiology of the donor and recipient's immune cells, inflammatory cytokines, and tissue damage may not all be targeted by the TNF inhibitors (Choi et al., 2010). While TNF is an important mediator of inflammation in GVHD, blocking TNF alone may not be sufficient to control the disease process fully in all patients.

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The heterogeneity of GVHD among patients means that the underlying pathophysiology can vary, further complicating the effectiveness of TNF-blocking agents. Therefore, given the complexity and heterogeneity of GVHD, TNF blocking agents, as well as similar treatments, may not be the most effective approach. Personalized medicine, which creates a patient-specific treatment, would be necessary to optimize response rates to the pathophysiology of individual patients. (Choi et al., 2010)

Whilst a lot about GVHD is unknown, recent advances have expanded the understanding of GVHD pathophysiology, including the role of danger signals like uric acid, microbiota-derived signals, toll-like receptors (TLRs), NOD-like receptors (NLRs), and regulatory immune cells like Tregs, which help balance immune reactions. (Ghimire et al., 2017)

3. Pioneering precision medicine in transplants

Precision medicine is an ever-evolving medical approach. It utilizes an individual's genetic profile to guide drug treatment decisions (Moore, 2023). It recognizes each person's genetic makeup, environmental influences and lifestyle factors which affect the response to the treatment. This juxtaposes traditional medicine, as precision medicine challenges the "one size fits all" concept by tailoring the treatment to each patient. Personalized medicine can revolutionize transplantation due to the possibility of mitigating the effects of allergies, auto-inflammatory diseases, autoimmunity, or a heightened predisposition for infection (Wiebking et al., 2020).

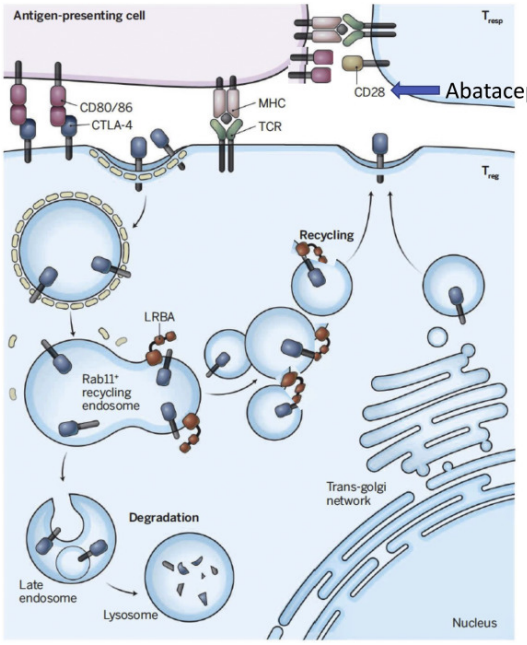

Figure 3 Demonstrates the mechanisms of CTLA-4 in LBRA deficiency

LBRA protein deficiency is an autosomal recessive disorder first identified in individuals with early-onset symptoms such as enteropathy, recurrent infections, autoimmune issues, and hypogammaglobulinemia. Recent findings suggest the disease's clinical phenotype is more variable. Immune dysregulation affects approximately 95% of patients (Leiding et al., 2022). A study found that LRBA regulates CTLA-4 expression by colonizing together in vesicles from the endoplasmic vacuoles. CTLA-4 is one of the two regulatory coreceptors found in T cells: CD28, which provides a signal for T-cell activation, and CTLA-4, which acts as a checkpoint to control T-cell activation and prevent autoimmune responses, mediated by regulatory T (Treg) cells. Maintaining an optimal level of CTLA-4 on the cell surface is crucial for preventing autoimmune responses. LRBA deficiency increases CTLA-4 turnover, reducing CTLA-4 levels in Treg cells and impairing their regulatory function. Some biological drugs used to treat autoimmune diseases mimic CTLA-4's immune modulation by competing for its ligands, CD80/CD86, on antigen-presenting cells. Researchers treated three patients with abatacept (a CTLA-4 immunoglobulin fusion molecule), resulting in significant clinical improvement in inflammatory and autoimmune conditions, as well as improvements in pulmonary function and chest computed tomography scans. This study was one of the first to describe targeted therapies, or precision medicine, for a specific group of patients with primary immunodeficiency (Leiding et al., 2022). Through personalized medicine, physicians can target specific defects and adapt treatments for a chance of long-term remission.

One method of personalized treatment is HLA Typing and Matching. HLA typing involves identifying antigens located on chromosome 6, specifically on the major histocompatibility complex (MHC) (NMDP, 2023). Either polypeptides or glycoproteins, these antigens are commonly found in nucleated cells and platelets. The antigens determine tissue compatibility for transplantation and are linked to certain diseases. Matching of the major

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histocompatibility antigens between transplant donors and recipients is typically done through three serological tests. In the first test, the patient's and donor's human leukocyte antigen (HLA) types are determined to assess the level of mismatch (NMDP, 2023). In the second test, anti-HLA antibodies are identified using a reference cell panel in panel-reactive antibody (PRA) testing. Finally, the crossmatch assay measures the recipient's response to donor-specific antibodies. The purpose of antibody testing (PRA and crossmatch) is to assess the presence and clinical significance of anti-HLA antibodies in the recipient. The ideal match for HLA types would be siblings who share the same HLAs; however, due to the decreasing birth rates, finding genotypically identical siblings is increasingly rare. To address this, alternative sources of hematopoietic stem cells (HSCs) from phenotypically matched unrelated donors have been used with success. These transplants can be phenotypically matched but may not match at all loci, necessitating precise HLA typing to mitigate the risk of graft-versus-host disease (GVHD).

In a study done by Kahraman, 44 sick children and parents had undergone preimplantation HLA matching before having HSCT transplants. Not one of the 44 children had an HLA-matched donor present among their relatives or in national and international registries. HLA analysis was carried out on peripheral blood samples of the parents and child of each family to identify specific characteristics in the makeup. A panel of 50 distinct short tandem repeat (STR) markers on HLA Class I, II, and III genes were used to be tested on genomic DNA to ensure sufficient informative markers for detecting chromosomal abnormalities such as: monosomy, trisomy, recombination, etc in the examined chromosomes and HLA regions. For each family, at least 12 informative STR markers were chosen for the preimplantation genetic diagnosis (PGD) study. In the case that parents showed a low number of fully informative markers, the semi-informative markers present were used to increase the reliability of the HLA analysis to prevent rejection. Only 2 out of the 44 cases were rejected in the HLA area as both showed recombination causing the success in finding a match low (Kahraman et al., 2014). A total of 3973 embryos were biopsied, of which 89.5% were successfully diagnosed. 90 out of the 94 babies born were HLA compatible with their sick siblings, however only 48 of the children had a HSCT preformed. This study found that pre-implantation HLA matching has been shown to be a successful option for children with beta thalassaemia, as well as several other conditions, including sickle cell anaemia which previously wasn't able to be cured by HLA matching. Yet, for some of the sick children who required an urgent transplant, the gestation period was too long and passed away. Therefore, preimplantation provides a realistic option in the treatment of an affected child with no HLA match, however, may not be a solution to all cases.

Table 1 the follow ups of families with children born by IVF-PDG for HLA

	n
Total number	80 family; 94 babies
Allogenic HSCT performed	48
Allogenic HSCT not performed	32
Awaiting	11
Sick sibling passed away	5
Not yet planned	10
Lost to follow up	2
Transplantation from an unrelated donor	1
HLA non-identical	3

Despite the possibility of long-term survival with transplants from unrelated donors, the risks of graft failure and severe acute GVHD are elevated compared to transplants between related donors. This is due to the potential mismatch for antigens, including minor histocompatibility (mH) antigens, in unrelated donor-recipient pairs, which can contribute to alloreactivity. Recent advancements in HLA typing have revealed additional polymorphisms with unknown functional and clinical implications, suggesting that some unrelated donor-recipient pairs perceived as matched may be somewhat mismatched. Furthermore, another controversy which has been raised is the instrumentalization of the child produced from preimplantation HLA matching. The wellbeing of the future child should be brought into question and whether the child is simply present to be a donor. Therefore, the use of HLA typing and matching may be prevented. HLA matching may promote an extended lifespan of a patient, however there are some complications which need to be solved before the treatment can be used in mainstream practice.

As hematopoietic stem cell transplants (HSCTs) are a leading treatment for high-risk leukaemia's, relapse is considered in all HSCTs that derive from treating malignant diseases. A novel approach requires the removal of donor T cells and subsequent genomic editing to engineer the donor cells to express a specific chimeric antigen receptor

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while simultaneously inactivating the T-cell receptor to reduce the risk of alloreactivity and GVHD. Chimeric antigen receptors (CARs) can redirect T-cell cytotoxicity towards cancer-associated antigens, inducing remissions in hematologic malignancies that are otherwise difficult to treat. Studies have demonstrated that these engineered CAR T cells efficiently eliminate leukaemia cells without causing GVHD in a xenograft model. By using donor-derived T cells for CAR T cell therapy, the treatment becomes genetically similar to the graft, reducing the likelihood of rejection. The use of genome editing to engineer donor T cells into CAR T cells offers a chance to improve the anti-leukemic effect of HSCT while minimizing the risk of GVHD (Wiebking et al., 2020).

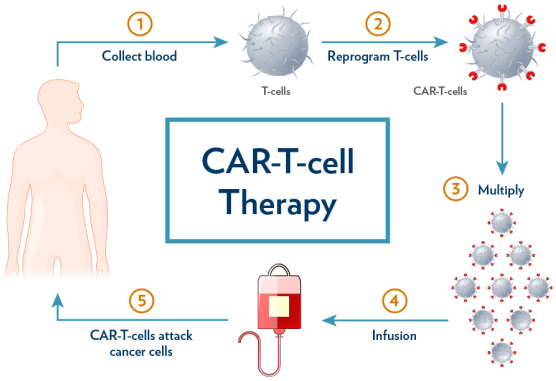

Figure 4 explains the different stages of CAR T cell therapy (Birch, 2021).

Alternatively, research has found other personalized methods of using CAR T-cells to treat B-cell malignancies. This CAR T cell therapy involves isolating T cells from the recipient's blood, genetically modifying them to express a CAR that targets a specific antigen present in cancer cells, and then infusing these modified T cells back into the patient. Once infused, CAR T cells recognize and kill cancer cells expressing the target antigen (Bernasconi, 2019). Clinical trials using this method of therapy have displayed high response rates, with many patients achieving complete remission. In 2021, two clinical trials showed that patients who received CAR T-cell therapy after a single round of chemotherapy had a longer lifespan without their disease progressing than those who underwent the standard chemotherapy approach (Reynolds, 2023). Nevertheless, CAR T cell therapy is linked to several challenges, including CRS and neurotoxicity, which pose life-threatening outcomes. In a case study done, a 34 year old woman who underwent CAR-T cell therapy got CRS, the patient only received complete remission after 12 months (Neelapu et al., 2017). To alleviate these risks, researchers are exploring strategies such as using lower doses of CAR T cells, incorporating safety switches to allow for the elimination of CAR T cells if needed, as well as developing predictive biomarkers to identify patients at higher risk of adverse events (Bernasconi, 2019).

Antibiotic resistance presents a specific challenge to patients undergoing HSCT; the rate of antibacterial resistance can be seen between 20-30% in allogeneic patients (Akova, 2020). The conditioning regimen and subsequent lack of white blood cells in HSCT patients can lead to alterations in gut microbiota, increasing the risk of infections. Bacterial pathogens, especially gram-negative bacteria, are common during neutropenia, the deficit of neutrophils, and can cause the presence of bacteria in the bloodstream. Colonization with antibiotic-resistant bacteria significantly impacts transplant outcomes, with high mortality rates observed in patients with multiple-resistant strains (Akova, 2020).

Personalized antibiotic prophylaxis based on microbial profiling is a formative method to counteract the chance of resistance. It ensures that patients receive the most appropriate antibiotics using biomarkers to predict a patient's risk of infection. Currently, there is ongoing research on a range of biomarkers, such as those of inflammation, immune function, and microbial colonization. Recipients would be separated into risk categories by analyzing these biomarkers before transplantation, enabling tailored prophylactic strategies. As biomarker profiles indicate, patients at higher risk may receive more intensive antibiotic prophylaxis, while those at lower risk may benefit from reduced antibiotic exposure. This is done through antibiotic rotation strategies, which involve periodically changing the antibiotics used for prophylaxis to prevent the overexposure of bacterial populations to specific drugs. By rotating antibiotics, the selection pressure for resistance is reduced, making it harder for bacteria to develop resistance mechanisms and, therefore, reduce the likelihood of infection on the graft.

In 2016-2018, 76 HSCT patients were included in a study on Gut Microbiota profiling to create a personalised antibiotic prophylaxis regime. The patient's stool was collected at the time of pre-engraftment, the culture samples were processed and screened for different antibiotic resistance phenotypes. Bacteria Isolated were classified as Multidrug-resistant, extensively drug-resistant, and Pandrug-resistant. Among 60 culture-positive samples, 41 grew

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one bacterial species, 18 grew two, and 1 grew three different species. HSCT patients had a gut colonization rate of 73.75% with resistant bacteria. After screening, patients were given antibiotic prophylaxis to prevent neutropenia. The regimens ranged from directed antibiotic regimens to total gut decontamination. Overall, the studies data reiterated the importance of individual specific antibiotic prophylaxis to improve the outcomes of immunocompromised HSCT patients (Gill et al., 2019). On the other hand, a study done in 2020 found that in a cohort of 248 patients there was no clinically significant difference in major patient characteristics when administering a personalized antibiotic prophylaxis regimen. Additionally, patients who had allogenic HSCTs showed no significant difference either (Horowitz et al., 2020).

Precision medicine, the process of utilizing genetic profiles to guide treatment decisions, is on the cusp of revolutionizing healthcare by tailoring treatments to individual patients. In transplantation, personalized approaches, such as HLA typing and matching, drastically improve outcomes by reducing the risk of graft rejection and GVHD. Genomic editing of T cells in HSCT enhances anti-leukemic effects while minimizing GVHD risk. CAR T cell therapy shows promise in treating B-cell malignancies, albeit with challenges. Personalized antibiotic prophylaxis based on microbial profiling has shown some cases of mitigating antibiotic resistance risks. Side effects of these novel therapies such as CRS, and lack of clinical significance in some trials could bring into question whether the treatments are worth the risk and money. These personalized treatments have potential to improve transplant outcomes extensively, however additional research and advancements are required before putting them into practice.

4. What are the ethical considerations?

Personalized medicine represents a shift in healthcare, where genetic information could optimize the pre- and post-treatment care of those with HSCT. The benefits of personalized medicine are manifold, including the identification of genetic predispositions, early and improved diagnostic assessments, more effective therapeutic interventions, and reduced adverse effects of medications. Yet, the transition from traditional medicine to personalized medicine is not without its challenges, particularly from an ethical standpoint. The rapid advancement of personalized medicine and its implementation into a high-risk treatment such as HSCT has raised several ethical questions and concerns.

The development of personalized medicine is closely linked with pharmacogenetics. Genes act as the foundation of personalized medicine and our transition to the future of treatment. Pharmacogenetics holds promise in enhancing drug safety by tailoring treatments to individual needs, potentially reducing mortality rates. However, this personalized approach may introduce new challenges, such as the emergence of previously unseen diseases and reactions, which are challenging to assess through conventional trials as treatment is catered to each individual. Furthermore, using pharmacogenetics in HSCT, which already acts as a high-risk treatment, may decrease the success rate of procedure as unforeseen reactions have a greater propensity of occurring due to the lack of testing of the drugs used. The Nuffield Council on Bioethics Report acknowledges pharmacogenetics as a promising avenue for reducing adverse drug effects but questions its potential for substantial impact, given the multifactorial nature of adverse drug reactions. Additionally, the global implication of personalized medicine must be considered. Most phase three clinical trials are conducted in developing countries, where the benefits are limited due to the high costs of new drugs. Supporters of personalized medicine argue that some modalities may not require traditional clinical trials, as they operate based on known mechanisms of action. (Erdmann, et al., 2021) However, critics argue that these disparities in basic research contribute to uneven distribution and participation in studies, exacerbating existing health inequalities.

The rise of personalized medicine has led to the establishment of biobanks worldwide, storing an increasing number and variety of specimens. However, this has raised ethical concerns regarding sample collection, storage, use, informed consent, identifiability, sharing, re-identification, and privacy. Biobanks must adhere to strict ethical guidelines to ensure that these concerns are addressed, and that genetic data are used responsibly and ethically. (Erdmann, et al., 2021)

Informed consent from patients should always be received, especially when attempting novel methods of treatment to their procedures, such as personalized medicine. All Patients must be informed about the potential risks

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and benefits of the procedure with or without the use of precision medicine as well as the procedure of HSCT itself, and the implications for their personal and family information.

A study done demonstrated that many patients who had undergone treatment therapies which included using their genetic profile shared concerns over data confidentiality. (Ahmed et al., 2023) Precision medicine would require in depth data from the patient which may go beyond their genetics, which may give rise to issues such as commercial exploitation highlighting risks associated with individuals mishandling data, such as storing it on personal devices. Patients cite instances of data breaches and advocate for stricter penalties to enforce data security. Those with a history of drug addiction fear that medical professionals may be compelled to disclose information to courts. However, with a careful consideration on the privacy policies when disclosing information on genetics and personal history, a strict quota would reduce the mishandling.

In addition, there are concerns about the confidentiality of genetic information, particularly the familial approach to confidentiality where genetic predispositions are shared with all family members at risk. In a study, healthcare providers (HCPs) debated the pros and cons of this approach, noting potential impacts on family relationships and patient trust in the healthcare system, as well as concerns about resource allocation and liability (Dheensa, et al., 2017).

Precision medicine improves care in HSCT but raises ethical concerns regarding consent, data privacy, and global health disparities. Addressing these issues is crucial for its responsible integration.

5. Conclusions

In considering the integration of personalized medicine into hematopoietic stem cell transplantation (HSCT), we are faced with a complex interplay of potential benefits, possible altercations and ethical considerations. On one hand, the promise of personalized treatments tailored to each individual's unique immune system offers hope for improved outcomes and reduced risks. Techniques like HLA typing and matching, chimeric antigen receptor T-cell therapy, and targeted therapies represent significant advancements in the field.

Whilst the possibilities of these treatments are immense, the risks should not be underscored. Severe adverse effects from CAR T therapy such as CRS, may cause a much longer duration of treatment than initially intended. Preimplantation HLA matching may prove to be both useless for an urgent transplant, or unethical to the future child. Furthermore, the optimization of antibiotic prophylaxis hasn't shown clear significant differences from the mainstream treatment. These factors raise concern whether money should be spent to further research such therapies or if it could be better spent improving pre-existing therapies.

As we venture into this new phase of medicine, we must consider the ethical factors carefully. Issues such as an increased risk of adverse reactions, less clinical trial backing, data confidentiality, and access to treatments regardless of socioeconomic status are major factors. The challenge of balancing individual rights with public health interests, especially in the context of genetic testing and research, requires thoughtful consideration.

Despite these ethical factors and medical concerns, the potential of personalized medicine in HSCT cannot be understated. Upon a clinical trial done on CAR-T cell therapy, improvement on outcomes have been recorded. By leveraging genetic information to personalize the treatment plan of individual patients, we have the opportunity to maximise the success of HSCT outcomes and pave the way for more effective treatments for a range of diseases.

In conclusion, while the road ahead may be fraught with challenges, the benefits of personalized medicine in HSCT are too significant to ignore. As advancements continue in the field of precision medicine, it is imperative that we prioritise minimizing adverse reactions and have a strong ethical foundation, ensuring that personalized treatments are implemented responsibly and equitably. The future of HSCT and the treatment of complex diseases depends on our ability to embrace personalized medicine as a cornerstone of modern healthcare.

References

Alp, S., and Akova, M. (2017). Antibacterial Resistance in PatientswWith Hematopoietic Stem Cell Transplantation. *Mediterranean Journal of Hematology and Infectious Diseases*, *9*(1), e2017002.

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ISSN 2688-3651 [online]

Ahmed, L., Constantinidou, A., & Chatzittofis, A. (2023). Patients' perspectives related to ethical issues and risks in precision medicine: a systematic review. Frontiers in Medicine, 10.

Bardhan, M., & Kaushik, R. (2022). *Physiology, Complement Cascade*. PubMed; StatPearls Publishing.

Bernasconi, P., & Borsani, O. (2019). Immune Escape after Hematopoietic Stem Cell Transplantation (HSCT): From Mechanisms to Novel Therapies. *Cancers*, *12*(1), 69

BeTheMatch.org.(2023) "HLA Basics." *Bethematch.org*

Birch, J. (2021). *Cancer patients get second chance at life, thanks to new CAR-T-cell therapy*. https://hollingscancercenter.musc.edu/news/archive/2021/06/18/cancer-patients-get-second-chance-at-life-thanks-to-new-car-t-cell-therapy#:~:text=William%20said%20family%20is%20what,T%2Dcell%20therapy%20at%20Hollings.

Brickner, A. G. (2006). Mechanisms of minor histocompatibility antigen immunogenicity: the role of infinitesimal versus structurally profound polymorphisms. *Immunologic Research*, *36*(1-3), 33–41.

Choi, S. W., Levine, J. E., & Ferrara, J. L. M. (2010). Pathogenesis and Management of Graft-versus-Host-Disease. *Immunology and Allergy Clinics of North America*, *30*(1), 75–101.

Dheensa, S., Fenwick, A., & Lucassen, A. (2017). Approaching confidentiality at a familial level in genomic medicine: a focus group study with healthcare professionals. *BMJ Open*, *7*(2), e012443.

Erdmann, A., Rehmann-Sutter, C., & Bozzaro, C. (2021). Patients' and professionals' views related to ethical issues in precision medicine: a mixed research synthesis. *BMC Medical Ethics*, *22*(1).

Ghimire, S, et al. (2017). Pathophysiology of GVHD and Other HSCT-Related Major Complications. *Frontiers in Immunology*, *8*(79).

Gill, J. B. et al. (2021). Gut microbiota profiling in hematopoietic stem cell transplant recipients: Towards personalized medicine. *Medical Journal, Armed Forces India*. 77(1), 22 – 27.

Hamilton, B. K. (2021). Updates in chronic graft-versus-host disease. *Hematology*, *2021*(1), 648–654.

Horowitz, J. et al. (2020). Optimization of Antimicrobial Prophylaxis in Patients Undergoing Hematopoietic Stem Cell Transplantation Utilizing an Absolute Neutrophil Count Driven Approach. *Transplantation and Cellular Therapy*, *26*(3), S317.

Ingulli, E. (2008). Mechanism of cellular rejection in transplantation. *Pediatric Nephrology*, *25*(1), 61–74.

Janeway, C. A., et al. (2001). Responses to alloantigens and transplant rejection. *Immunobiology: The Immune System in Health and Disease. 5th Edition*.

Kahraman, S., et al. (2014). Successful haematopoietic stem cell transplantation in 44 children from healthy siblings conceived after preimplantation HLA matching. *RBMO*, *29*(3), 340 - 351.

Leiding, J. W., & Ballow, M. (2019). Redefining Precision Medicine in Disorders of Immune Dysregulation. *The Journal of Allergy and Clinical Immunology: In Practice*, *7*(8), 2801–2803.

Malard, F. (2023). Acute graft-versus-host disease. *Nature Reviews. Disease Primers*, *9*(1), 27.

Masouridi-Levrat, S., Simonetta, F., & Chalandon, Y. (2016). Immunological Basis of Bone Marrow Failure after Allogeneic Hematopoietic Stem Cell Transplantation. *Frontiers in Immunology*, *7*.

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ISSN 2688-3651 [online]

Menendez-Gonzalez, J. B., & Hoggatt, J. (2021). Hematopoietic Stem Cell Mobilization: Current Collection Approaches, Stem Cell Heterogeneity, and a Proposed New Method for Stem Cell Transplant Conditioning. *Stem Cell Reviews and Reports*, *17*(6), 1939–1953.

Moore, T. (2023). Hematopoietic Stem Cell Transplantation (HSCT): Practice Essentials, Historical Background, Indications for HSCT. *EMedicine*.

Nagler, Arnon, and Shimoni, 2019 “Conditioning.” *PubMed*, Springer,

Neelapu. S. S. Et al., (2017). *SCHEDULE 2 -THE SERVICES*.

Nuffield Council On Bioethics. (2003). *Pharmacogenetics : ethical issues*. Nuffield Council on Bioethics.

Perkey, E., & Maillard, I. (2018). New Insights into Graft-Versus-Host Disease and Graft Rejection. *Annual Review of Pathology: Mechanisms of Disease*, *13*(1), 219–245.

Styczyński, J., et al. (2020). Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplantation*, *55*(1), 126–136.

Stomp on Step1., (2014, December) *Transplant Rejection: Hyperacute, Acute, Chronic & Graft versus Host*.

Wiebking,V., et al. (2020). Genome editing of donor-derived T-cells to generate allogenic chimeric antigen receptor-modified T cells: Optimizing αβ T cell-depleted haploidentical hematopoietic stem cell transplantation. *Haematologica*, *106*(3), 847–858.