# Pediatric Hematopoietic Stem Cell Transplantation: Indications and Conditioning Protocols Guide from RIOHCT

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**First Edition**

**ISBN: 978-600-156-119-1**

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First published in October 2024 as the first edition



Pediatric Hematopoietic Stem Cell Transplantation: Indications and Conditioning Protocols Guide from RIOHCT will be reviewed approximately every four years. Check the publication date above to ensure this copy is up to date.

**Editor: Tahereh Rostami.**

Printer: TUMS Print

Layout & Designed By: Nashreonline.com



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## Acknowledgments

We would like to express our sincere gratitude to the dedicated team of physicians, fellows, and staff at the RIOHCT for their tremendous efforts in making this project possible. Their expertise, hard work, and commitment to excellence have been instrumental in developing this comprehensive handbook.

We also extend our heartfelt thanks to the healthcare professionals, consumers, and editorial teams who contributed to this inaugural edition of Pediatric Hematopoietic Stem Cell Transplantation: Indications and Conditioning Protocols Guide from RIOHCT. Their valuable insights, feedback, and support have been crucial in shaping this resource into a practical and informative guide for clinicians and families dealing with this challenging disease.

Without this remarkable team's collective efforts and dedication, this handbook would not have been possible. We are truly grateful for their contributions and look forward to continuing our collaboration in the future.

## Research Institute for Hematology, Oncology & Cell Therapy (RIOHCT)

The Research Institute for Oncology, Hematology & Cell Therapy (RIOHCT) is the leading cell therapy research center at Tehran University of Medical Sciences (TUMS). It plays a crucial role in advancing pediatric cell therapy, particularly hematopoietic stem cell transplantation, through its dedication to high-quality research, provision of essential information and services to patients in need of cell therapy, and fundraising efforts to support these vital programs.

This book has been made possible through the generous research budget allocated by TUMS. The institute is committed to providing the best possible care and support to pediatric patients requiring cell therapy.

To contribute to this important cause and help make a difference in the lives of children in need, please consider donating by visiting the RIOHCT website at riohct.tums.ac.ir or calling +98-21 88203797. Your support can help expand access to cutting-edge cell therapy treatments and improve outcomes for young patients battling complex medical conditions.

Together, we can advance the field of pediatric cell therapy and bring hope to those who need it most. Join us in our mission to provide every child with the opportunity for a healthier future.

## شناسنامه کتاب

**عنوان و نام پدیدآورنده:** Pediatric hematopoietic stem cell transplantation: indications and conditioning / [Tahereh Rostami...[et al.].p rotocols guide from RIO HCT[Book

**مشخصات نشر:** تهران: دانشگاه علوم پزشکی و خدمات بهداشتی درمانی تهران، ۱۴۰۴ = ۲۰۲۵م.

**مشخصات ظاهری:** ۲۰۴ص : مصور(رنگی)، جدول(رنگی).

**شابک:** ۹۷۸-۶۰۰-۱۵۶-۱۱۹-۱

**وضعیت فهرست نویسی:** فیپا

**یادداشت:** عنوان به فارسی: راهنمای پیوند سلولهای بنیادی خونساز کودکان: اندیکاسیون‌ها و پروتکل‌های آماده‌سازی (پژوهشکده انکولوژی، هماتولوژی و سل تراپی)

**یادداشت:** نویسندگان طاهره رستمی، قاسم جان‌بابایی، آزاده کیومرثی، بیتا شهرامی، رومینا کاوه آهنگران، سعید محمدی، ندا علیجانی، مجتبی آذری، مرتضی آذری، اشرف السادات حسینی.

**آوانویسی عنوان:** پدیاتریک...

**موضوع:** یاخته‌های بنیادی خون‌ساز پیوند؛ Hematopoietic stem cells -- Transplantation؛ یاخته‌های بنیادی خون‌ساز پیوند پرستاری و مراقبت؛ Hematopoietic stem cells -- Transplantation -- Nursing

**شناسه افزوده:** رستمی، طاهره، ۱۳۵۳؛ Rostami, Tahereh 1975,

**شناسه افزوده:** دانشگاه علوم پزشکی و خدمات بهداشتی درمانی تهران؛ Tehran University of Medical Sciences and Health Services

**رده بندی کنگره:** ۵/۱۲۳RD

**رده بندی دیویی:** ۹۵۴/۶۱۷

**شماره کتابشناسی ملی:** ۱۰۱۴۲۴۶۵

**صفحه آرایی و طراحی جلد:** نشرآنلاین


## Note to readers

This book serves as a comprehensive and reliable guide to the preparative protocols for hematopoietic stem cell transplantation (HSCT) in pediatric patients, based on the latest scientific evidence available at the time of publication. However, it is essential to acknowledge that information regarding HSCT conditioning protocols is continually evolving, as medical professionals and the research community make ongoing advancements in this field.

Therefore, readers and treating physicians are strongly encouraged to consult the most recent local and international practice guidelines. It is also advisable to verify the information presented in this booklet with additional sources to ensure the best possible decision-making for patient care. By staying informed and up-to-date, healthcare providers can optimize treatment strategies and improve outcomes for pediatric patients undergoing HSCT.

*To all our colleagues, contributors, trainees, and patients who have taught us so much*

**The Author**

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# Preface

Hematopoietic stem cell transplantation (HSCT) has become a well-established, life-saving treatment for many pediatric patients suffering from hematological malignancies, inborn errors of metabolism and immunity, bone marrow failure syndromes, hemoglobinopathies, and other conditions. The rapid advancements in preparative protocols, graft-versus-host disease (GVHD) prophylaxis, donor selection, human leukocyte antigen (HLA) typing, graft manipulation, and supportive care have significantly improved survival rates for patients undergoing HSCT.

Pediatric Hematopoietic Stem Cell Transplantation: Indications and Conditioning Protocols Guide from RIOHCT offers a comprehensive overview of the conditioning protocols currently utilized in the Pediatric Cell Therapy Unit at RIOHCT. This book serves as an essential resource for healthcare professionals seeking insights into HSCT practices.

We trust that this information will provide you with a comprehensive understanding of the conditioning protocols used for HSCT in pediatric patients or reinforce your existing knowledge. We hope you will keep this booklet readily accessible and consider it a valuable guide when treating your patients.

As medicine is an ever-evolving field, new information or treatments may have emerged since this book was published. We acknowledge that this text may not be entirely free of errors, and we welcome any feedback you may have. Your input will help us ensure that we fulfill our commitment to providing accurate and up-to-date information to the best of our abilities.

***Tahereh Rostami***

## Foreword by the Director of the Research Institute for Oncology, Hematology, and Cell Therapy

As the field of pediatric hematopoietic stem cell transplantation (HSCT) progresses, a critical factor influencing outcomes is the conditioning regimen employed before transplantation. This book is dedicated to exploring the various conditioning regimens used in pediatric HSCT, highlighting their roles, rationale, and implications on patient care.
In pediatric patients, conditioning regimens are not merely preparatory steps; they profoundly affect the success of the transplant and the overall well being of the child. Understanding the intricacies of these regimens—ranging from myeloablative to non-myeloablative options—is essential for clinicians, caregivers, and researchers. The choice of conditioning not only impacts engraftment and relapse rates but also influences the risk of complications and long-term outcomes.
This book aims to provide healthcare professionals with evidence-based insights into the development and application of conditioning regimens tailored for pediatric patients. We delve into the pharmacology, dosing, and timing of various agents, as well as the considerations for specific patient populations. Moreover, the guidelines outlined herein address how to navigate the complexities associated with the unique physiology and developmental needs of children undergoing HSCT.
By consolidating current knowledge and expert perspectives, this book aspires to be a valuable resource in optimizing conditioning regimens, ultimately enhancing the overall success of HSCT in pediatric patients. We encourage active engagement with this material to ensure that all children receive the best possible care during this critical phase of their treatment journey.

***Ghasem Janbabaei***
***Director of Research Institute for Oncology, Hematology and Cell Therapy***

# INTRODUCTION 1

Hematopoietic stem cell transplantation (HSCT) has emerged as a critical treatment option for pediatric patients with a variety of malignant and non-malignant disorders. An essential component of both allogeneic and autologous HSCT is the conditioning regimen administered prior to the hematopoietic cell infusion.

The aim of conditioning regimens in HSCT is multifaceted, primarily focusing on eradicating hematological malignancies in cases where the transplant is indicated, providing sufficient immunosuppression to ensure engraftment, preventing both rejection and graft-versus-host disease (GVHD), and creating stem cell niches within the host bone marrow (BM) for the incoming stem cells. When evaluating a patient for allogeneic HSCT, several critical factors influence the choice of conditioning regimen, including the diagnosis, disease status, donor availability (such as human leukocyte antigen (HLA) disparity and the associated risk of rejection), graft source, and patient-related factors like comorbid conditions (1, 2).

Conditioning regimens used in HSCT have traditionally been classified into three main categories: myeloablative, reduced-intensity, and non-myeloablative (NMA) (3).

## Myeloablative Regimens

Myeloablative, or "high-dose" regimens, typically consist of alkylating agents with or without total body irradiation (TBI). These regimens are expected to completely ablate marrow hematopoiesis, preventing autologous hematologic recovery. Myeloablative conditioning (MAC) regimens are associated with significant toxicity and require stem cell support to restore normal blood cell production.

### Toxicity-Reduced Myeloablative Conditioning

Toxicity-reduced MAC aims to maintain the myeloablative intensity of the conditioning regimen while reducing toxicity. This approach involves replacing certain components of

the conditioning regimen with less toxic alternatives, without compromising the overall myeloablative effect. Two examples of this strategy include:

- Replacing cyclophosphamide (CY) with a less toxic immunosuppressive agent, such as fludarabine (FLU)
- Substituting busulfan (BU) with the alkylating agent treosulfan (TREO)

These modifications allow for a reduction in toxicity while preserving the myeloablative intensity necessary for successful HSCT. By carefully selecting alternative agents with comparable myeloablative properties but improved safety profiles, toxicity-reduced MAC regimens aim to minimize treatment-related complications and improve outcomes for patients undergoing HSCT (4-7).

## Non-Myeloablative Regimens

NMA regimens, although causing minimal cytopenia, do not require stem cell support. These regimens rely more on the graft-versus-tumor (GVT) effect to eradicate malignant cells rather than on high-dose cytotoxic therapy. NMA regimens are associated with lower toxicity compared to MAC regimens.

## Reduced-Intensity Regimens

Reduced-intensity conditioning (RIC) regimens are those that do not fit the definition of MAC or NMA conditioning regimens. These regimens result in potentially prolonged cytopenia and require hematopoietic stem cell (HSC) support for engraftment. RIC regimens aim to strike a balance between reducing toxicity while maintaining sufficient immunosuppression to allow for donor cell engraftment and the desired GVT effect.

RIC regimens are differentiated from myeloablative regimens by a reduction in the dose of alkylating agents or TBI, typically by at least 30%. It is essential to understand that “intensity” in this context refers to the level of reversible and irreversible myelotoxicity, rather than non-hematologic toxicity (8, 9).

### Augmented (intensified) Reduced-Intensity Regimen

RIC regimens have been associated with higher rates of engraftment failure compared to MAC. To address this issue, augmented (intensified) RIC regimens have been developed and evaluated. By intensifying certain components of the RIC regimen, such as increasing the dose of specific agents or adding additional drugs, the augmented approach aims to enhance the myeloablative effect while maintaining the reduced toxicity profile associated with RIC. Studies have shown that the use of augmented RIC regimens can lead to improved overall survival (OS) rates, decreased relapse rates, and without significant increase in treatment-related mortality (TRM) (10).

## Transplant Conditioning Intensity

The traditional classification into MAC, RIC, and NMA regimens has several shortcomings. The incorporation of novel agents like thiotepa (TT) and TREO, which have reduced non-hematological toxicity compared to traditional alkylating agents, is not adequately captured by the current MAC/RIC/NMA framework. Moreover, this classification system fails to account for the added intensity contributed by purine analogs used for immunosuppression (e.g., FLU) or disease-specific drugs employed to reduce relapse risk (e.g., cytarabine, etoposide (ETO)). This leads to a loss of important prognostic information. On the other hand, the lack of clear definitions has led to the arbitrary use of terms like "sequential conditioning" by many authors.

Given these limitations, a more comprehensive approach, such as the transplant conditioning intensity (TCI) score, has been proposed to address them. This tool assigns weighted scores to individual conditioning regimen components based on their myeloablative potential and non-hematological toxicity (Table 1). The sum of these scores categorizes patients into three groups: low TCI (1-2), intermediate TCI (2.5-3.5), and high TCI (4-6). This classification provides a finer categorization of conditioning regimens, allowing for a nuanced assessment of conditioning intensity and a better evaluation of non-relapse mortality (NRM) and relapse risk. However, its performance in the pediatric population has yet to be established (11).

**Table 1.** Intensity-Weighted Scores for Common Components of Transplantation Conditioning Regimens

| Component | Dose Level | | | Added Points for Each Dose Level |
|---|---|---|---|---|
| | Low | Intermediate | High | |
| TBI Fractionated (Gy) | ≤5 | 6-8 | ≥9 | 1 |
| Busulfan (mg/kg) | ≤6.4 IV & ≤8 PO | 9.6 IV & 12 PO | 12.8 IV & 16 PO | 1 |
| Treosulfan (g/m2) | 30 | 36 | 42 | 1 |
| Melphalan (mg/m2) | <140 | ≥140 | ≥200 | 1 |
| Thiotepa (mg/kg) | <10 | ≥10 | ≥20 | 0.5 |
| Fludarabine (mg/m2) | ≤160 | >160 | | 0.5 |
| Clofarabine (mg/m2) | ≤150 | >150 | | 0.5 |
| Cyclophosphamide (mg/kg) | <90 | ≥90 | | 0.5 |
| Carmustine (mg/m2) | ≤250 | 280–310 | ≥350 | 0.5 |
| Cytarabine (g/m2) | <6 | | ≥6 | 0.5 |
| Etoposide (mg/kg) | <50 | ≥50 | | 0.5 |

*IV: intravenously, PO: per os, TBI: total body irradiation*

# Pharmacology of Drugs Used in High-Dose Chemotherapy

## Alkylating Agents

Alkylating agents exert their cytotoxic effects through a shared mechanism of interfering with DNA transcription into RNA, thereby inhibiting protein synthesis. These agents work by substituting alkyl groups for hydrogen atoms on the DNA molecules of cancer cells. Alkylating agents are classified into two categories:

- **Monofunctional Alkylating Agents:** Contain a single active chemical moiety.
- **Bifunctional Alkylating Agents:** Contain two reactive groups that bind to separate DNA sites (12, 13).

## Busulfan

Busulfan (BU) is an antineoplastic alkylating agent used since the 1950s. It directly attacks cancer cells by cross-linking guanine bases on DNA strands and binding to cysteine molecules in histone proteins, leading to DNA-protein cross-links. BU also increases oxidative stress in cancer cells by interacting with sulfhydryl groups of glutathione (13). While its primary effect is on myeloid cells, it is extremely toxic to hematopoietic cells, leading to broad myelosuppressive effects. High doses result in myeloablation, while repeated doses deplete BM precursors (14). ***[Supplement 1]***

## Bendamustine

Bendamustine (BEN) is an alkylating agent classified as a nitrogen mustard analog with concomitant alkylating and antimetabolite properties. This dual activity creates a unique pattern of cytotoxicity compared to conventional alkylating agents. BEN induces cell death via apoptotic and non-apoptotic pathways, affecting cancer cells even when they lack a functional apoptotic pathway. As a bifunctional alkylating agent, it forms interstrand and intrastrand DNA cross-links, leading to cell apoptosis. BEN also induces a more complex repair process, making cells more susceptible to damage. In vitro, BEN demonstrates partial cross-resistance with other alkylating agents (15). ***[Supplement 2]***

## Cyclophosphamide

Cyclophosphamide (CY) is a non-cell-cycle phase-specific nitrogen mustard agent that works through the alkylation of DNA. It is metabolized by liver enzymes (mainly cytochrome P450) to produce the active alkylating agent phosphoramide mustard and acrolein. The phosphoramide metabolite inhibits protein synthesis by forming DNA-RNA cross-links, while acrolein is responsible for the common adverse effect of hemorrhagic cystitis. CY also has selective immunosuppressive effects on T cells. High doses are used for eradicating malignant hematopoietic cells, while lower doses are preferred for immunomodulation (16). ***[Supplement 3]***

### Melphalan

Melphalan (MEL) is an antineoplastic alkylating agent derived from nitrogen mustard. It interferes with DNA and RNA synthesis by cross-linking interstrand guanine bases in DNA. Cytotoxicity is related to the extent of cross-link formation. As a bifunctional alkylating agent, MEL is effective against resting and rapidly dividing tumor cells (17). ***[Supplement 4]***

### Thiotepa

Thiotepa (TT) is a chemotherapeutic alkylating agent related to nitrogen mustard. It interferes with DNA and RNA synthesis by alkylating the guanine base and forming cross-links within DNA strands (18). ***[Supplement 5]***

## Topoisomerase Inhibitors

### Etoposide

Etoposide (ETO) is a semi-synthetic topoisomerase II inhibitor that primarily affects the late S and G2 phases of the cell cycle. Topoisomerase II normally cuts and reseals double-stranded DNA during replication. ETO inhibits this process by poisoning the topoisomerase II cleavage complexes, preventing DNA re-ligation. This mutagenic pathway is most effective in tumor cells with high levels of topoisomerase II (19). ***[Supplement 6]***

## Nucleoside Analogs

### Cytarabine

Cytarabine (also known as arabinosylcytosine or ARA-C) is a pyrimidine analog that is converted into its triphosphate form, which competes with cytidine for incorporation into DNA. This interrupts DNA replication during the S phase of the cell cycle, making cytarabine effective against rapidly dividing cells like cancer cells. Cytarabine also inhibits DNA polymerase, further preventing replication and repair. To maintain efficient intracellular levels, bolus doses are administered at 8 to 12-hour intervals (20). ***[Supplement 7]***

### Fludarabine

Fludarabine (FLU) is an antimetabolite that inhibits ribonucleotide reductase. As a prodrug, it is rapidly converted to F-ara-A, which is further phosphorylated to generate 2-fluoro-ara-ATP. This metabolite blocks DNA synthesis by inhibiting ribonucleotide reductase, DNA primase, and DNA polymerase alpha. FLU also decreases p27kip1 expression, leading to apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells. It induces immunosuppression by inhibiting the phosphorylation of STAT1 (21). ***[Supplement 8]***

# Platinum Compounds

## Carboplatin

Carboplatin (CBDCA) is a second-generation platinum compound and a cisplatin analog. It works similarly to cisplatin by inducing DNA adduct formation and interstrand cross-linking. However, CBDCA has a different toxicity profile, which is generally considered to be an improvement over cisplatin. Despite this, CBDCA is more myelotoxic than cisplatin (22). ***[Supplement 9]***

# GRAFT VERSUS HOST DISEASE PROPHYLAXIS 2

Graft-versus-host disease (GVHD) is the leading cause of non-relapse mortality (NRM) beyond day 100 in patients who have undergone hematopoietic stem cell transplantation (HSCT) from human leukocyte antigen (HLA)-matched sibling donors (MSDs). It is also the second most common cause of NRM in matched unrelated donor (MUD) recipients. The incidence of GVHD is significantly higher following myeloablative conditioning (MAC) regimens than reduced-intensity conditioning (RIC) regimens. Specifically, grade II-IV acute GVHD incidence ranges from 25% to 50%, while grade III-IV acute GVHD occurs in 5% to 20% of cases. Furthermore, chronic GVHD following MAC can affect 15% to 65% of patients (22).

The development of GVHD is more common in pediatric patients, with approximately 50% of pediatric transplants performed for non-malignant disorders. In these cases, tissue repair defects can influence the development of GVHD, as seen with the increased incidence of acute GVHD in patients with Fanconi anemia. Additionally, the high frequency of typically transient viral erythema in children can be mistaken for manifestations of acute GVHD, complicating diagnosis. Therefore, there is a clear need for the development of GVHD symptom scales and assessment tools specifically tailored to the pediatric population (23, 24). The grading criteria for acute GVHD are well-established for the skin, liver, and gastrointestinal (GI) tract, with higher grades associated with poorer transplant outcomes. The Mount Sinai Acute GVHD International Consortium (MAGIC) has developed consensus guidelines that offer more precise definitions for acute GVHD organ staging **(Table 2&3)**. Notably, the MAGIC group has introduced the concept of diagnostic confidence levels for acute GVHD, categorizing cases as “confirmed,” “probable,” “possible,” and “negative.” These levels correspond to histological confirmation, initiation of treatment, resolution without therapeutic intervention, and definitive alternative histological diagnosis, respectively (25, 26).

**Table 2.** MAGIC Criteria for Acute GVHD Organ Staging in Children

| Organ | Severity Stage | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Skin | No rash | Rash <25% of BSA | Rash 25% to 50% of BSA | Rash >50% of BSA | Generalized erythroderma (>50% of BSA) plus bullous formation and desquamation >5% of BSA |
| Liver | Total serum bilirubin <34 µmol/L (<2 mg/dL) | Total serum bilirubin 34–50 µmol/L (2 to 3 mg/dL) | Total serum bilirubin 51–102 µmol/L (3.1 to 6 mg/dL) | Total serum bilirubin 103–255 µmol/L (6.1 to 15 mg/dL) | Total serum bilirubin >255 µmol/L (>15 mg/dL) |
| Upper GI | *No or intermittent a anorexia or nausea or vomiting | *Persistent anorexia or nausea or vomiting | | | |
| Lower GI | Diarrhea <10 mL/kg/day or <4 episodes/day** | Diarrhea 10-19.9 mL/kg/day or 4-6 episodes/day | Diarrhea 20-30 mL/kg/day or 7-10 episodes/day | Diarrhea >30 mL/kg/day or >10 episodes/day | Severe abdominal pain with or without ileus or grossly bloody stools (regardless of stool volume) |

*BSA: body surface area, GI: gastrointestinal*
**To be suggestive for GVHD: Anorexia should be accompanied by weight loss, nausea should last at least 3 days, or be accompanied by at least 2 vomiting episodes per day for at least 2 days.*
***One episode of diarrhea is considered to be about 3 ml/kg for a child (<50 kg).*

**Table 3.** MAGIC Criteria for Overall Severity Grading

| Overall Grade | MAGIC Criteria |
|---|---|
| 0 | No organ involvement (skin= 0; and liver= 0; and GI= 0) corresponds to the absence of acute GVHD |
| I | Stage 1-2 skin without liver, upper GI or lower GI involvement |
| II | Stage 3 skin and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI |
| III | Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI |
| IV | Stage 4 skin, liver or lower GI, with stage 0-1 upper GI |

*GI: gastrointestinal, GVHD: graft-versus-host disease*
*The overall acute GVHD grade typically corresponds to the highest grade conferred by the individual staging of each organ.*

## Current Standard Approaches

The most common backbone for GVHD prophylaxis is the combination of a calcineurin inhibitor (CNI) and an antimetabolite. The CNIs used in this context include tacrolimus (TAC) and cyclosporine A (CSA), while the antimetabolites consist of methotrexate (MTX) and mycophenolate mofetil (MMF) (27). The combination of CSA and MTX remains the gold standard prophylaxis regimen and is the most widely used approach in Europe today, particularly following MAC regimens (21). Various MTX schedules are employed, ranging from the standard initial regimen of 15 mg/m² on day +1 and 10 mg/m² on days +3, +6, and +11 to reduced dosing strategies, such as omitting the day +11 dose in cases of grade III/IV mucositis (28).

## Cyclosporine

**Mechanism of Action:** CSA acts as a CNI to suppress cell-mediated immune responses through several mechanisms, including the inhibition of interleukin (IL) synthesis (e.g., IL-2, which is crucial for T lymphocyte activation and differentiation). It also inhibits CD4+ CD25+ regulatory T cells (Tregs) and disrupts host immune tolerance. Additional-

ly, CSA is a major substrate of cytochrome P450 3A4 and P-glycoprotein/ABCB1, with at least 25 known metabolites (25).

**Dosage Forms:** CSA is available in both intravenous (IV) and oral formulations. Oral products are offered as oral solutions and capsules, which are available in both modified and non-modified forms. These forms are not bioequivalent and should not be used interchangeably. Some IV formulations of CSA, as well as certain oral products, contain polyoxyethylated castor oil, which is commonly associated with anaphylactoid hypersensitivity reactions (26). Additionally, some dosage forms may contain propylene glycol, which, in larger amounts (e.g., >3000 mg/day), is associated with potentially fatal toxicities in neonates (23). Other products may also contain corn oil and/or ethanol (24).

**Dosing:** For infants, children, and adolescents, the initial dose of CSA IV formulation is typically 3-5 mg/kg/day [based on total body weight (TBW)], administered in 2 divided doses every 12 hours. The starting time differs upon protocol variations. Once tolerated, the IV formulation can be substituted with the oral formulation using an intravenous-to-oral ratio of approximately 1:2. CSA may also be cautiously initiated at a lower dose of 1.5 mg/kg/day [TBW] in the presence of population-specific pharmacokinetic (PK) variations. The dose may be adjusted to achieve the target trough concentrations ($C_0$) through therapeutic drug monitoring (TDM) using whole blood sampling.

**Therapeutic Drug Monitoring:** Blood samples should be collected 12 hours after the administered dose and immediately before the next dose at steady-state, as this is the accepted method for monitoring. For optimal GVHD prophylaxis, the target $C_0$ should be maintained within the range of 200 to 300 ng/mL during the first three to four weeks. In the absence of GVHD, the target concentration is adjusted to 100 to 200 ng/mL until three months post-HSCT. After this period, dose reduction or tapering is considered if GVHD has not occurred (27).

**Pharmacokinetics:** The oral absorption of CSA is influenced by various gastric factors, including the presence of food, bile acids, and GI motility. Modified oral formulations are typically absorbed up to 30% more efficiently than non-modified products, as they are less affected by these gastric factors. Pediatric patients may require larger oral doses due to shorter bowel length, which limits absorption. The bioavailability of oral CSA, particularly with non-modified formulations, is dependent on both population factors and transplant type. Non-modified formulations tend to have lower bioavailability in HSCT recipients, who often experience GI dysfunction. For instance, the bioavailability of non-modified oral products is approximately 28% (range: 17-42%) compared to 43% (range: 30-68%) for modified formulations in pediatric patients. The bioavailability of oral solutions and capsules under the same trade name is equivalent. After oral administration, non-modified formulations typically reach peak plasma concentrations in 2-6 hours, although some patients may experience a second peak between 5-18 hours. Modified formulations peak earlier, usually within two hours (based on renal transplant data). CSA is extensively metabolized in the liver by cytochrome P450 3A4, with a significant first-pass effect following oral intake. The drug's elimination is biphasic and varies bet-

ween modified and non-modified formulations. In general, children eliminate CSA more rapidly due to higher metabolic and clearance rates. In contrast, hepatic impairment can delay elimination, and severe liver dysfunction may lead to significantly increased CSA exposure. The drug is primarily excreted in the feces, with approximately 6% excreted in the urine (24).

**Toxicity:** CSA can be nephrotoxic, neurotoxic, and cardiotoxic, and may also cause metabolic adverse events and an increased risk of infection (25). Among its various toxicities, acute nephrotoxicity, hepatotoxicity, neurotoxicity, gingival overgrowth, hypertension, and hyperkalemia are major dose-related or dose-dependent adverse effects. Thrombotic microangiopathy (TMA), malignancies, and chronic nephrotoxicity are both dose- and time-related.

Drug-induced gingival overgrowth is more common with CSA than TAC and may be reversible upon discontinuation of the medication. It typically occurs within the first 3 months of therapy.

CSA-associated TMA can have a variable onset and may lead to multi-organ impairment. Early detection and appropriate supportive care, along with dose reduction or discontinuation, may allow for recovery.

Hepatotoxicity with CSA results from impaired bile acid flow and is primarily characterized by hyperbilirubinemia. It has a variable onset and usually resolves with dose reduction.

Hyperkalemia, related to the pharmacological mechanism of CNIs, is class-dependent but tends to be less severe and shorter in duration with CSA compared to TAC. Concomitant drugs should be considered to address hyperkalemia and its complications.

Hypertension is more prevalent with CSA than TAC. The onset is variable, and this complication can occur even with therapeutic doses.

Regarding malignancies, CSA has been shown to have a lower risk of malignant lymphoma compared to TAC in several studies.

Nephrotoxicity can occur even at therapeutic doses of CSA, but the risk increases with higher doses and longer therapy duration. Both acute and chronic nephrotoxicity are associated with CNIs and are more common with CSA than TAC. Acute nephrotoxicity, characterized by a moderate increase in serum creatinine and elevated CSA trough levels in the absence of other significant causes of acute kidney injury, is generally reversible with dose reduction or discontinuation. In contrast, chronic nephrotoxicity tends to be progressive and irreversible. The median onset for acute nephrotoxicity is about 6 months, while chronic nephrotoxicity typically manifests after 3 years.

Neurotoxicity is less common with CSA than with TAC, but it can range from mild to severe. A rare but important reversible neurological side effect of CNIs is posterior reversible encephalopathy syndrome (PRES), which is often due to higher peak concentrations resulting from IV administration, drug interactions, or altered PKs (e.g., altered drug metabolism/clearance, fluid overload, or GVHD). PRES may improve with dose reduction or discontinuation of therapy (24).

In cases of overdose, there is no known antidote for CSA, and hemodialysis removes only about 1% of the dose. Monitoring serum CSA levels is essential, and dose adjustments based on $C_0$, followed by TDM, should be considered. In some cases, activated charcoal may be useful (28).

### Dose Modification

- **Renal Impairment**
  Renal impairment does not significantly alter the PKs of CSA; therefore, no dose adjustment is necessary for pre-existing kidney impairments. However, in patients with a creatinine clearance (CrCl) <60 mL/min, it is advisable to target the lower end of the therapeutic range and avoid concurrent nephrotoxic drugs whenever possible. In cases of nephrotoxicity during treatment, although a specific dose-reduction strategy based on serum creatinine increase may be recommended for non-transplant indications, no general guidelines exist for dose adjustment in the post-HSCT population.

  CSA is not dialyzable, and no specific dose adjustments or supplemental doses are required during hemodialysis, peritoneal dialysis, continuous renal replacement therapy (CRRT), or prolonged intermittent renal replacement therapy (PIRRT).
- **Hepatic Impairment**
  No dose modification is required in cases of hepatic impairment (24).
- **Obesity**
  There is insufficient data on CSA dose adjustments for obese patients. For lipophilic agents like CSA, it is believed that maintenance levels can be achieved similarly to those in normal-weight patients when initial dosing is based on adjusted ideal body weight (ABW) in conjunction with TDM (29).

## Tacrolimus

**Mechanism of Action:** As a CNI, TAC works by inhibiting T-cell proliferation through binding to FK506 binding protein. TAC is metabolized via the cytochrome P450 3A4, cytochrome P450 3A5, and P-glycoprotein/ABCB1 pathways, breaking down into fifteen possible metabolites, with 13-O-dimethyl-tacrolimus being the primary metabolite (30).

**Dosage Forms:** TAC is available in various IV and oral formulations. Extended-release (ER), once-daily oral products are not interchangeable with each other due to differences in bioavailability and cannot be substituted for immediate-release TAC (which is intended for twice-daily administration). IV formulations may be administered via continuous or intermittent infusion. ER oral products should be taken on an empty stomach. Oral products contain lactose, while IV formulations contain dehydrated alcohol USP 80% and polyoxyl 60 hydrogenated castor oil (HCO-60), similar to polyoxyethylated castor oil, which has been associated with hypersensitivity reactions, including anaphylaxis (31).

**Dosing:** For GVHD prevention, IV TAC may be initiated with either 0.03 mg/kg/day

[based on lean body weight (LBW)] as a continuous infusion or 0.015 mg/kg/dose every 12 hours as a 2-hour infusion, with different starting times upon protocol variations. It should be converted to immediate-release oral formulations as soon as possible, using a 1:4 ratio, and administered in two divided doses, 12 hours apart. Dose adjustments should be made based on TDM using whole blood samples to achieve the appropriate $C_0$ (data from the adult population). For treating GVHD, TAC can be administered orally with 0.06 mg/kg twice daily using immediate-release tablets, or IV with 0.03 mg/kg/day [based on LBW] as a continuous infusion (data from the adult population).

**Therapeutic Drug Monitoring:** Samples should be taken immediately before the next dose at steady-state, which is the accepted measure for monitoring. For optimal GVHD prophylaxis, the target $C_0$ should be maintained within the range of 3 to 12 ng/mL during the first three to four weeks. In the absence of GVHD, the target concentration is adjusted to 8 to 12 ng/mL until three months post-HSCT. After this period, dose reduction or tapering is considered if GVHD has not occurred. Younger children typically require higher maintenance doses based on LBW (32).

**Pharmacokinetics:** The oral absorption of TAC varies between 5% and 67%. Food, particularly high-fat meals, reduces the rate and extent of absorption by approximately 27%. This effect may be more pronounced in HSCT recipients with oral mucositis. Bioavailability is incomplete and varies between patients. Oral formulations typically peak within 0.5 to 6 hours after intake. TAC is extensively metabolized in the liver via cytochrome P450 3A4. Elimination differs between immediate-release and ER formulations and is also dependent on the type of transplant. TAC is primarily excreted in the feces, with about 7% excreted in the urine. Children eliminate TAC more rapidly due to higher metabolic clearance. Severe hepatic impairment may prolong the drug's elimination, and vice versa.

**Toxicity:** TAC may cause cardiotoxicity, nephrotoxicity, neurotoxicity, metabolic adverse effects, and increase the risk of infections. Among its varied toxicities, acute nephrotoxicity, hepatotoxicity, neurotoxicity, gingival overgrowth, hypertension, and hyperkalemia are dose-related or dose-dependent. TMA, malignancies, and chronic nephrotoxicity are both dose- and time-related.

Similar to other CNIs, TAC can lead to both acute and chronic nephrotoxicity, but with a lower incidence compared to CSA. TAC-related nephrotoxicity typically presents as acute renal failure, which may be associated with serum concentration levels >20 ng/mL. Close monitoring of serum creatinine, glomerular filtration rate (GFR), and urine output is necessary, and this form of nephrotoxicity is generally reversible. In contrast, chronic nephrotoxicity is structural and irreversible.

TAC may also cause cardiotoxicity, particularly in the case of myocardial hypertrophy, necessitating dose reduction or discontinuation. Neurotoxicity, more common with IV administration or immediate-release oral formulations of TAC, should also lead to dose reduction or discontinuation. The drug should be discontinued if pure red cell aplasia (PRCA) is diagnosed.

There is no known antidote for TAC in the event of overdose, and hemodialysis does

not significantly remove the drug. Serum TAC levels should be monitored closely, and dose adjustments based on $C_0$, followed by TDM, should be considered (30).

### Dose Modification

- **Renal Impairment**

  Renal impairment does not affect the PKs of TAC, but the drug itself can cause nephrotoxicity, which may require dose reduction. In patients with pre-existing kidney impairment, TAC should be initiated at the lower end of the dosing range.

  TAC is not significantly dialyzable, and no specific dose adjustments or supplemental doses are needed in patients undergoing hemodialysis, peritoneal dialysis, or CRRT.

- **Hepatic Impairment**

  No dose adjustment is necessary in cases of mild hepatic impairment. However, close monitoring of serum levels is recommended for patients with moderate to severe hepatic impairment. Due to reduced clearance, dose reduction may be considered for severe impairment (31).

- **Obesity**

  Reduced TAC clearance has been observed in obese patients, and dosing should be adjusted based on ideal body weight (IBW) or LBW at the initiation of therapy (data from renal transplantation) (33).

## Methotrexate

**Mechanism of Action:** MTX is widely used for various malignancy and non-malignancy indications, with distinct mechanisms of action. As a folate antimetabolite used to prevent acute GVHD, both MTX and its metabolite, methotrexate-polyglutamate, inhibit the enzyme dihydrofolate reductase and interfere with the production of purine and thymidylate synthase, thereby inhibiting DNA synthesis and suppressing T-cell responses (28).

**Dosage Forms:** MTX is included in GVHD prophylaxis protocols as an injectable solution, which is administered intravenously either as a slow push over approximately 1 minute (10 mg/min) or as a bolus infusion over 30 minutes to 1 hour. The solution shoul be diluted with 0.9% sodium chloride or 5% dextrose water to a concentration of ≤25 mg/mL before administration.

**Dosing:** For GVHD prevention, MTX is administered as either a standard or mini-dose, depending on patient-specific factors and protocol variations. For standard dosing, 15 mg/m²/dose [body surface area (BSA) based on total body weight (TBW)] is administered on day 1 after HSCT, followed by 10 mg/m²/dose on days 3, 6, and 11, depending on protocol variations. Mini-doses are administered as 10 mg/m²/dose on day 1 after HSCT, followed by 6 mg/m²/dose on days 3, 6, and 11. Therapeutic MTX is administered following GVHD in weekly doses of 3–10 mg/m²/dose until GVHD resolves. Although not considered high-dose, leucovorin is recommended to prevent toxicities (34, 35).

**Therapeutic Drug Monitoring:** TDM is not needed for standard and mini-dose ad-

ministration.

**Pharmacokinetics:** PK data are limited, particularly in pediatric populations. MTX slowly penetrates third-space fluids and remains there longer than in plasma. With approximately 50% protein binding, MTX is metabolized by hepatic aldehyde oxidase and excreted primarily unchanged in the urine. Therefore, renal impairment may increase serum MTX levels (35).

**Toxicity:** Most known side effects of MTX are associated with high doses or chronic use. However, nausea, vomiting, and mucositis are the most common adverse events observed at doses used for GVHD prevention (36). Doses exceeding 10 mg/m² are typically classified as moderate to high risk for these side effects (35).

**Drug Interactions:** MTX is highly bound to plasma proteins, so interactions with drugs that displace MTX from these proteins can increase blood levels. Additionally, any drug that affects the renal clearance of MTX can lead to an increase in its concentration.

Nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, proton pump inhibitors (PPIs), CSA, trimethoprim (TMP), penicillin, warfarin, valproate, and cisplatin are known to increase the risk of MTX toxicity by elevating its blood concentration. Conversely, aminoglycosides, neomycin, and probenecid can reduce the absorption of MTX. The most significant and serious interactions are with NSAIDs and PPIs, as these are commonly used therapeutic agents.

Leucovorin, thymidine, and glucarpidase are three known antidotes for MTX toxicity, along with hydration and urine alkalinization. For low-dose MTX, leucovorin therapy is recommended. In cases of very high MTX levels, hemodialysis and hemoperfusion may also be beneficial (37).

## Dose Modification

- **Renal Impairment**

  In cases of renal impairment, no dose adjustment is necessary when the creatinine clearance (CrCl) is >50 mL/min/1.73m². For CrCl between 10 and 50 mL/min/1.73m², a 50% dose reduction is required, and for CrCl <10 mL/min/1.73m², administration of 30% of the dose is recommended. For patients undergoing hemodialysis or peritoneal dialysis, administration of 30% of the dose is required, and for CRRT, MTX should be administered at half the standard dose.

- **Hepatic Impairment**

  No specific dose modifications are recommended for hepatic impairment in pediatric patients. However, in adults with a bilirubin level of 3.1–5 mg/dL or transaminases >3 times the upper limit of normal, administration of 75% of the dose is recommended. MTX should be avoided in patients with bilirubin levels >5 mg/dL.

- **Obesity**

  In obese patients with a body mass index (BMI) ≥30 kg/m², the initial dosing or any dose modifications should be calculated using TBW (35).

## Mycophenolate Mofetil

**Mechanism of Action:** MMF is a prodrug that reversibly inhibits inosine-5'-monophosphate dehydrogenase (IMPDH) through its active metabolite, mycophenolic acid (MPA). By blocking DNA synthesis and cell division in T and B lymphocytes, MMF suppresses both cellular and humoral immune responses without significant additive side effects (38). MMF is generally reserved for non-myeloablative (NMA) and reduced-intensity conditioning regimens, as well as a replacement for antimetabolites in MAC (39).

**Dosage Forms:** MMF is available in various oral and parenteral forms. These products are not equivalent to each other or to mycophenolate sodium formulations. Some products may contain polysorbate 80 (also known as Tween), which can cause delayed allergic reactions. Additionally, some formulations contain phenylalanine and should be avoided in patients with specific metabolic disorders.

**Dosing:** Dosing data are primarily based on adult protocols and are used in children with limited evidence, although they are generally well-tolerated. MMF may be initiated either intravenously or orally, depending on the patient's tolerability. The dosing regimen can vary by protocol, with options including 15 mg/kg/dose every 12 hours starting on day 0 of HSCT or 10–15 mg/kg/dose every 8 to 12 hours beginning on day 0 or day +1. Doses may be adjusted in cases of toxicities or co-administration of CNIs. Additionally, the protocol may be individualized based on factors such as the risk of relapse or GVHD. Generally, MMF is administered for approximately 1 month in matched related donor transplants and 2–3 months in matched unrelated donor transplants. In haploidentical HSCT, it is typically administered as thrice-daily dosing (39, 40).

**Therapeutic Drug Monitoring:** Although TDM is recommended for optimizing MMF in GVHD prevention, no universally accepted sampling approach is available. TDM targets the area under the concentration-time curve (AUC) of MPA, the active metabolite, with a therapeutic target range of 30–60 mg×h/L for $AUC_{0–12}$ (>40 mg×h/L according to some studies). Whole blood sampling is required just before the dose and at least 3 days after initiating the drug or making dose modifications to reflect steady-state concentrations (41).

**Pharmacokinetics:** MMF is rapidly and well-absorbed, with approximately 50% lower AUC values of MPA during the first-month post-HSCT compared to later periods (>3 months). MMF demonstrates a bioavailability of 94% with oral administration relative to the IV form. It is metabolized via both the GI tract and the liver, where it is hydrolyzed to MPA, which has a protein-binding rate of 97%. MPA may further concentrate through enterohepatic recirculation and is glucuronidated to an inactive metabolite with 82% protein binding. The time-to-peak concentration of MPA varies depending on dosing and indications and has been reported in a range of 0.8 to 1.8 hours following oral intake. Finally, MPA is primarily excreted as the glucuronidated form in urine (>60%) and to a lesser extent as MPA in urine and feces (<1% and 6%, respectively). Severely impaired renal function (GFR <25 mL/min/1.73m²) may increase the AUC of MPA by 75% and its glucuronidated form by 3- to 6-fold.

**Toxicity:** Administration of MMF may lead to various infections, GI effects, bone marrow (BM) suppression, lymphoproliferative disorders, PRCA, and acute inflammatory syndrome (AIS) as the most significant adverse reactions.

The risk of infections correlates with the immunosuppressive effects of MMF and may manifest as a variety of severe bacterial, viral, fungal, and protozoal infections. In cases of reported viral infections associated with MMF, nephropathy and kidney deterioration may result from the activation of polyomavirus, which can further activate the BK virus. The GI tract may also be affected by cytomegalovirus (CMV) activation, leading to symptoms such as diarrhea. Progressive multifocal leukoencephalopathy (PML) may occur as a result of JC virus infection. Reactivation of hepatitis B virus (HBV) and hepatitis C virus (HCV) may also occur, as well as coronavirus disease 2019 (COVID-19) infection. The majority of these infections occur within the first 180 days, and the risk is associated with any form of immunosuppression, including the concomitant administration of other drugs or preexisting impairments, as well as increased exposure to the drug itself.

GI effects are among the most common adverse effects associated with MMF and include diarrhea, abdominal pain, nausea, and vomiting. Dyspepsia, constipation, flatulence, and loss of appetite may also occur but are less prevalent. GI ulcers, hemorrhage, and perforation are rare but possible. Some of these GI symptoms may also result from infections, which are among the other common adverse events associated with MMF. The onset of these reactions varies widely, ranging from 1 month to 10 years. The condition is more closely associated with non-enteric-coated formulations, concomitant administration of CNIs, and increased MMF exposure, and it is more prevalent among females.

BM suppression caused by MMF is reversible and most commonly manifests as anemia, thrombocytopenia, or leukopenia. Severe neutropenia may increase the risk of infections. These complications typically have a delayed onset and are associated with increased drug exposure and the concomitant use of other agents that cause BM suppression.

Lymphoproliferative disorders and neoplasms may occur with MMF therapy, with a delayed onset ranging from months to years after initiation. The highest probability is within the first year post-transplant due to intense immunosuppression. The risk is also higher in pediatric transplant recipients, as they are more likely to be Epstein–Barr virus (EBV) seronegative at the time of transplantation. Other risk factors include concomitant immunosuppression (due to other medications or preexisting impairments), pre-transplant malignancies, less HLA matching, a history of rejection, and age <25 or >60 years. Skin carcinoma is also associated with ultraviolet (UV) exposure.

PRCA is a type of anemia with a wide range of severity and has been reported in patients receiving concomitant MMF and other immunosuppressive agents. PRCA has a delayed onset and is characterized by fatigue, lethargy, and pallor.

MMF-induced AIS is reversible and characterized by fever, arthralgia, myalgia, and increased inflammatory markers. The onset of AIS varies from weeks to months after therapy initiation or dose increases and typically improves within 24 to 48 hours of discontinuing the drug.

MMF toxicity may result in hematologic adverse events, and dose interruption or reduction should be considered in cases of anemia or an absolute neutrophil count (ANC) $<1.3 \times 10^3/\mu L$.

### Dose Modification

- **Renal Impairment**

  Reports in pediatric patients are limited to kidney transplantation, which suggests avoiding doses >1000 mg/dose twice daily in cases of severe chronic renal impairment with a GFR <25 mL/min/1.73m², particularly with non-enteric-coated formulations. Dose modification is not required for GFR ≥25 mL/min/1.73m² or with enteric-coated formulations. Based on adult considerations, no dose modifications are recommended during the immediate post-transplant period, as this may increase the risk of GVHD or rejection.

  MMF is not removed by hemodialysis and supplemental doses are not required in hemodialysis and peritoneal dialysis.

- **Hepatic Impairment**

  An increased free fraction of MPA may result from displacement in cases of hyperbilirubinemia and/or hypoalbuminemia and should therefore be monitored. However, dose modifications are not recommended (39)

- **Obesity**

  No specific dose adjustment is available.

## T-Cell Depletion

Given that acute GVHD is primarily mediated by effector T-lymphocytes, prophylactic strategies have concentrated on suppressing T-cell activity in the recipient.

T-cell depletion (TCD) or modulation in vivo has formed the foundation for several innovative GVHD prophylaxis strategies. An effective TCD of the graft could potentially prevent both acute and chronic GVHD, even in cases where the donor/recipient pair differs at more than two major HLA loci.

### Ex-Vivo T-Cell Depletion/Modulation

Recent advances in ex vivo techniques for T-cell removal have progressed from selecting CD34+ hematopoietic stem cell (HSC) progenitors (using megadoses of CD34+ cells) to depleting CD3+ cells, CD3+/CD19+ cells, and more recently, CD3+T-cell receptor (TCR)-αβ and naïve (CD45RA+) T-cells **(Table 4)** (34, 35, 37, 38). While the risk of GVHD decreases with commonly used graft manipulation methods such as CD34+ selection, concerns about delayed immune recovery and viral clearance persist (39-42). Newer approaches, such as TCR-αβ TCD, have been shown to reduce GVHD while preserving γδ T cells in the graft, which may facilitate early immune reconstitution and enhance viral or tumor clearance following transplantation. Recent studies have demonstrated the beneficial effects of this strategy in both malignant and non-malignant disorders (43).

**Table 4.** Cellular Composition of Unmanipulated and Different Types of Manipulated Hematopoietic Stem Cell Grafts

| Graft Type | CD34+ HSC | CD14+ DC | CD14+CD16+ MN Cell | CD64+ NK Cell | CD3+TCRγδ+ T Cell | CD3+TCRαβ+ CD45RO+ T Cell | CD3+TCRαβ+ CD45RA+ T Cell | CD19+ B Cell |
|---|---|---|---|---|---|---|---|---|
| Unmanipulated HSC Graft | + | + | + | + | + | + | + | + |
| CD3+/CD19+ Depleted HSC | + | + | + | + | | | | |
| TCRαβ+/CD19+ Depleted Graft | + | + | + | + | + | | | |
| CD45RA+/CD19+ Depleted Graft | + | + | + | + | + | + | | |

*B: B-Lymphocyte, DC: Dendritic cell, HSC: hematopoietic stem cell, MN: Monocyte, NK: Natural killer, T: T-Lymphocyte, TCR: T-cell receptor*

## In-Vivo T-Cell Depletion/Modulation

Novel GVHD prophylaxis strategies have emerged by integrating in vivo depletion techniques into regimens that combine CNIs with monoclonal antibodies, such as anti-thymocyte globulin (ATG) or alemtuzumab, which directly target T cells within the body.

# Rabbit-Derived Anti-Thymocyte Globulin

**Mechanism of Action:** ATG is a polyclonal antibody that induces immunosuppression by clearing T cells from circulation. It acts on surface antigens, leading to activation-induced apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). ATG also modulates T-cell activation, homing, and cytotoxicity (42-46). Among the two commercially available polyclonal antibodies—equine-derived and rabbit-derived—which exhibit different biological activities, the rabbit-derived antibody has demonstrated optimal effects at lower doses, higher specificity for human T lymphocytes, and a considerably longer half-life (47).

**Dosage Forms:** ATG is available as a reconstituted solution for IV administration. Dosing may vary among different rabbit-derived products. Additionally, rabbit-derived and equine-derived products are not interchangeable (48).

**Dosing:** Due to the high incidence of serious infusion reactions, premedication is required 1 hour before administration. Corticosteroids, acetaminophen, and/or an antihistamine are being used as pretreatment. For infants, children, and adolescents, protocols variable and a dose range of 4.5-15 mg/kg is reported as the total dose which is divided into 3 to 5 once-daily and consecutive pre-HSCT doses. A 2.5 mg/kg once-daily dose is generally initiated and differs in the total number of doses upon protocol variations due to the type of HSCT, underlying disease, and source of transplant (49-55). ***[Supplement 10]***

**Therapeutic Drug Monitoring:** This is not needed.

**Pharmacokinetics:** Based on adult data, T-cell depletion is expected within 24 hours. Antithymocyte globulin (rabbit derived) has 2-3 days half-life of elimination and the lymphopenia might continue for up to 1 year (56). Two phases of clearance were observed in pediatrics for both the total and active form of the drug (47).

**Toxicity:** Hematologic and laboratory abnormalities (including increased potassium levels, and lower WBC and platelets counts), urinary tract infection, gastrointestinal adverse events (including abdominal pain, constipation, diarrhea, and nausea), cardiovascular effects (including hyper- or hypotension, peripheral edema, and tachycardia), neuromuscular symptoms (e.g., Arthralgia/myalgia, asthenia, and back pain), nervous system reactions (including headache, anxiety, chills, malaise, insomnia, and pain), respiratory side effects (including dyspnea and upper and lower respiratory tract infections), as well as fever and infections (i.e., cytomegalovirus reactivations and sepsis) are among the most common adverse reactions of the rabbit derived antithymocyte globulin (42, 48).

Not very common, but serum sickness may also occur with arthralgia/myalgia, lymphadenopathy, proteinuria, and decreased oxygen saturation in the 5 to 15 days after the

antithymocyte globulin administration. Corticosteroid treatment resolves the symptoms (42).

Serious hypersensitivity reactions (i.e., anaphylaxis) are probable with antithymocyte globulin and lead to discontinuation of therapy.

Infusion reactions are common due to cytokine release. The first dose should be infused over 6 hours, and subsequent doses may be administered over 4 hours. All infusions should be delivered through a high-flow vein via a central line, using an in-line 0.22-micron filter, and accompanied by premedication. In cases of mild to moderate infusion reactions, the infusion rate should be reduced (48).

Overdose may result in leukopenia and/or thrombocytopenia and is managed through dose reduction (42).

### Dose Modification

- **Renal Impairment**
  No specific dose adjustment is available.
- **Hepatic Impairment**
  No specific dose adjustment is available.
- **Obesity**
  No specific dose adjustment is available.

## Alemtuzumab

**Mechanism of Action:** Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen on T cells, thereby inducing cell death through CDC, ADCC, or apoptosis (57).

**Dosage Forms:** Alemtuzumab is available as a solution for IV administration. The product may contain edetate disodium dihydrate and polysorbate 80. Thrombocytopenia, ascites, pulmonary deterioration, and hepatic or renal impairment have been reported following IV administration of products containing polysorbate 80 in premature neonates (58). Hypersensitivity reactions have also been associated with polysorbate 80 (59-61).

**Dosing:** Alemtuzumab is used off-label for the treatment of acute, steroid-refractory GVHD. It is administered intravenously over 2 hours at a dose of 10 mg once daily for 5 consecutive days, followed by 10 mg weekly on days +8, +15, and +22 (62); alternatively, 10 mg may be administered weekly until symptoms resolve (63). Alemtuzumab-containing regimens are associated with a moderate emetic risk, and therefore, proper prophylaxis is recommended. Alemtuzumab may also cause severe infusion reactions; thus, premedication with 500–1000 mg acetaminophen and 50 mg diphenhydramine 30 minutes before initiating the infusion is advised. IV glucocorticoids may also be added to prevent severe reactions (64).

**Therapeutic Drug Monitoring:** This is not needed.

**Pharmacokinetics:** Based on data from adult studies, alemtuzumab clearance decrea-

ses with repeated dosing, and its elimination half-life varies depending on the dosing protocol and product. For 30 mg doses of Campath®, the half-life is approximately 11 hours (range: 2–23 hours) after the first dose and 6 days (range: 1–14 days) after the last dose. For Lemtrada®, the elimination half-life is approximately 2 weeks (64). The potential effects of preexisting renal or hepatic impairment on alemtuzumab and its metabolic pathways have not yet been studied.

**Toxicity:** Alemtuzumab can cause autoimmune encephalitis (symptoms include altered mental status, neurological findings, psychiatric symptoms, and seizures), BM suppression (including severe and prolonged myelosuppression), immune-mediated severe acute colitis, hemophagocytic lymphohistiocytosis (HLH), acquired hemophilia A, autoimmune hepatitis, infections, pneumonitis, stroke, cervicocephalic arterial dissection, thrombotic thrombocytopenic purpura (TTP), and infusion reactions. Other reported adverse reactions are primarily associated with its use in multiple sclerosis treatment.

In cases of BM suppression with alemtuzumab, patients should only receive irradiated blood products to prevent transfusion-associated GVHD.

Among GI side effects, alemtuzumab commonly induces immune-mediated colitis with an acute onset. However, the onset of this drug-induced colitis typically ranges from months to years and may require hospitalization and systemic corticosteroid therapy.

HLH may occur with a reported onset of up to 33 months after initiating alemtuzumab. It presents with symptoms of extreme systemic inflammation and is considered a life-threatening adverse event.

Autoimmune hepatitis is a potential adverse effect of alemtuzumab and may result in severe hepatic injury, potentially requiring transplantation. Serum transaminases and total bilirubin should be monitored at baseline, during therapy, and for up to 48 months after the last dose.

Alemtuzumab may cause severe and prolonged lymphopenia, thereby increasing the risk of infections. Delaying the initiation of therapy should be considered in cases of active infections until they are controlled. Screening for latent infections, such as hepatitis and tuberculosis, should also be considered in high-risk populations. Alemtuzumab is contraindicated in patients with positive human immunodeficiency virus (HIV) infection, active tuberculosis disease or infection, or severe active infections. It is also contraindicated in patients with active malignancies, a history of PML, stroke, arterial dissection of cervicocephalic arteries, angina or myocardial infarction, uncontrolled hypertension, or known coagulopathy.

Fatal infusion reactions have been reported with alemtuzumab. All patients should be closely monitored for at least 2 hours after administration. Therapy may be withheld in cases of severe reactions (grade 3 or 4).

Alemtuzumab may cause stroke or cervicocephalic arterial dissection. Stroke most commonly occurs within the first day following administration, while cervicocephalic arterial dissection typically occurs within 3 days (64).

### Dose Modification

- **Renal Impairment**
  No specific dose adjustment is available.
- **Hepatic Impairment**
  No specific dose adjustment is recommended for pre-existing hepatic impairment. However, therapy interruption or discontinuation may be necessary in cases of hepatic impairment that develop during treatment.
- **Obesity**
  Flat dosing is recommended for obese patients with a BMI ≥30 kg/m$^2$ (64).

## Post-Transplant Cyclophosphamide

Post-transplant cyclophosphamide (PTCY), first pioneered at Johns Hopkins, is one of the most groundbreaking approaches in GVHD prophylaxis, especially in T-cell-replete haploidentical transplant settings. This innovative strategy selectively induces apoptosis in activated T cells while preserving the viability of resting T cells. By specifically targeting the alloreactive T cells responsible for GVHD, PTCY effectively reduces the risk of GVHD without compromising overall immune reconstitution (45). The success of PTCY in haploidentical transplants has paved the way for its broader application in other transplant settings, including matched-related and unrelated donor transplants, contributing to lower exposure to immunosuppressive drugs after HSCT (46).

## New Immunosuppressive Regimens for GVHD Prophylaxis

### Sirolimus

**Mechanism of Action:** Sirolimus (SIR) has unique immunosuppressive properties and is used for both the prevention and treatment of GVHD. It binds to an intracellular protein called FKBP-12, forming a complex that inhibits the mechanistic target of rapamycin (mTOR) regulatory kinase, thereby suppressing T-lymphocyte proliferation (65).

**Dosage Forms:** Systemic SIR is available in both oral formulations (tablets and oral solutions) with conventional formulations and as nab-sirolimus for IV administration. Conventional oral products are primarily used for GVHD. SIR tablets and oral solutions are not bioequivalent and, therefore, are not interchangeable at doses greater than 2 mg. Oral solutions may contain alcohol, polysorbate 80, propylene glycol, and glycine soja (extracted from soybean). Thrombocytopenia, ascites, pulmonary deterioration, and hepatic or renal impairment have been reported following IV administration of products containing polysorbate 80 in premature neonates. Hypersensitivity reactions have also been reported. Large amounts of propylene glycol (e.g., >3000 mg/day) are associated with potentially fatal toxicities in neonates (23).

**Dosing:** For GVHD prevention, SIR may be initiated either as a fixed dose of 2 mg once daily [TBW] or as a 12 mg loading dose followed by 4 mg once daily (in combination with TAC) (66-68). Doses are adjusted based on TDM using whole blood samples to achieve appropriate $C_0$. The timing of initiation may vary depending on the protocol (data from adult populations).

For the treatment of acute and chronic GVHD, SIR may be administered as a 6 mg loading dose followed by 2 mg once daily as a maintenance dose, adjusted based on TDM (data from adult populations) (69, 70).

**Therapeutic Drug Monitoring:** Samples should be collected 24 hours after the administered dose and immediately before the next dose at steady state, as this is the accepted method for TDM. For optimal GVHD prophylaxis, the target $C_0$ should be maintained within the range of 3 to 12 ng/mL during the first 150 days (66). In the absence of GVHD, the target concentration is tapered over 365 days post-HSCT (71).

If acute GVHD occurs, the target trough level may be adjusted to a range of 10 to 14 ng/mL until GVHD resolves. Subsequently, the dose should be titrated to achieve a goal range of 5 to 10 ng/mL for at least 56 days, followed by a taper over 3 months until discontinuation (69).

In cases of chronic GVHD, the target trough level may be adjusted to a range of 7 to 12 ng/mL for 6 to 9 months. All data are derived from adult populations (70).

**Pharmacokinetics:** SIR is rapidly absorbed, with peak concentrations occurring within 1 to 3 hours for the oral solution and within 6 hours for the tablet. These two oral formulations are not bioequivalent, and tablets are reported to have higher bioavailability compared to oral solutions (27% vs. 14%). SIR has a high protein-binding capacity of approximately 92%. The elimination half-life is 13.7 ± 6.2 hours and is shorter in children. The drug is extensively metabolized by both P-glycoprotein/ABCB1 (in the intestinal wall) and cytochrome P450 3A4 in the liver, with the majority excreted in feces. All grades of hepatic impairment may result in a decreased half-life and increased SIR clearance. Clearance also varies by sex, being approximately 12% lower in males, leading to a prolonged elimination half-life (72 hours in men versus 61 hours in women).

**Toxicity:** SIR is potentially associated with hypersensitivity reactions, including anaphylaxis, hypersensitivity angiitis, exfoliative dermatitis, hypersensitivity vasculitis, and angioedema. Angioedema is more commonly associated with elevated SIR levels and the coadministration of other drugs known to cause this condition. It generally resolves with dose reduction or discontinuation of therapy.

SIR increases the risk of infections due to its immunosuppressive effects. Prophylaxis for Pneumocystis jirovecii pneumonia (PJP) should be administered for at least 1 year to all patients receiving SIR, and CMV prophylaxis should be given for 3 months post-HSCT. Patients should also be monitored for central nervous system (CNS) symptoms of JC virus infection, and immunosuppression may need to be reduced in cases of CNS infections. Additionally, the use of live vaccines should be avoided during SIR therapy.

Higher trough levels of SIR may also lead to pulmonary hypertension, potentially resulting in fatal interstitial lung disease (ILD). This condition typically resolves with dose

reduction or discontinuation of therapy.

SIR may also cause hyperlipidemia, which is often resistant to pharmacologic therapies and should be managed through non-pharmacologic interventions, such as lifestyle modifications.

SIR may be nephrotoxic and can elevate serum creatinine levels, particularly when used concomitantly with other nephrotoxic agents, such as CSA. It may also reactivate the BK virus, leading to nephropathy.

Fluid accumulation has been associated with SIR and may present as peripheral edema, ascites, and pleural or pericardial effusion. Patients with preexisting cardiovascular or pulmonary disease are at higher risk for these adverse events.

SIR is associated with an increased risk of lymphoma and other malignancies. Exposure to UV light should be limited in patients receiving SIR due to the elevated risk of skin cancers. Impaired wound healing has been reported with SIR use, particularly in obese patients (72). Growth failure has been rarely reported in children receiving SIR (73).

### Dose Modification

- **Renal Impairment**
  Dose adjustment is not necessary.
- **Hepatic Impairment**
  No specific dose adjustment is required for the loading dose. However, the maintenance dose may be reduced by 33% in cases of mild to moderate hepatic impairment and by 50% in cases of severe hepatic impairment.
- **Obesity**
  No specific dose adjustment is available.

The side effects of immunosuppressive medications commonly used in pediatric HSCT are varied and can range from mild to severe. As shown in **Table 5**, these medications may cause a wide range of toxicities, including nephrotoxicity, neurotoxicity, GI disturbances, hematologic complications, and increased susceptibility to infections. Management strategies typically include dose adjustments, discontinuation of therapy, supportive care, and prophylactic treatments to mitigate the risks associated with these adverse effects. It is crucial for healthcare providers to closely monitor patients for these potential side effects to ensure timely intervention and improve patient outcomes.

**Table 5.** Common and Serious Side Effects of Immunosuppressive Medications Used in Hematopoietic Stem Cell Transplantation and Their Management Strategies

| Drug | Common Side Effects | Serious/Severe Side Effects | Management Strategies |
|---|---|---|---|
| **Cyclosporine** | - Hypertension<br>- Hyperkalemia<br>- Gingival overgrowth | - Nephrotoxicity (acute & chronic)<br>- Hepatotoxicity<br>- Neurotoxicity, PRES<br>- TMA<br>- Malignancies | - Monitor renal & liver function<br>- Adjust dose for renal function<br>- Blood pressure management<br>- Regular dental care<br>- Monitor for signs of malignancy |
| **Tacrolimus** | - Hypertension<br>- Hyperkalemia<br>- Gingival overgrowth | - Nephrotoxicity (acute & chronic)<br>- Hepatotoxicity<br>- Neurotoxicity, PRES<br>- TMA<br>- Malignancies<br>- Overdose risk | - Monitor renal & liver function<br>- Adjust dose for renal function<br>- Regular blood pressure checks<br>- Monitor for signs of malignancy |
| **Methotrexate** | -Nausea/vomiting<br>- Mucositis<br>- Fatigue | - High-dose toxicity<br>- BM suppression<br>- GI complications | - Folic acid supplementation<br>- Monitor for GI symptoms |
| **Mycophenolate Mofetil** | - Diarrhea<br>- Nausea<br>- Abdominal pain<br>- Fatigue | - BM suppression<br>- Lymphoproliferative disorders<br>- Infections (bacterial, viral, fungal)<br>- Reactivation of hepatitis | - Monitor liver function in hepatitis patients |
| **Alemtuzumab** | - Fatigue<br>- Headache<br>- Rash | - Autoimmune encephalitis<br>- HLH<br>- Autoimmune diseases (hemophilia, hepatitis)<br>- Pneumonitis<br>- Stroke<br>- Infusion reactions | - Pre-medicate with antihistamines and steroids<br>- Monitor for autoimmune reactions<br>- Manage infections proactively<br>- Monitor neurological signs |
| **Sirolimus** | - Hyperlipidemia<br>- Anorexia<br>- Fatigue | - Pulmonary hypertension<br>- ILD<br>- Nephrotoxicity<br>- Lymphoma<br>- Wound healing impairment | - Monitor cholesterol & triglycerides levels<br>- Monitor pulmonary function<br>- Adjust dose for renal function<br>- Regular screening for lymphoma |

*BM: bone marrow, GI: gastrointestinal, HLH: hemophagocytic lymphohistiocytosis, ILD: interstitial lung disease, PRES: posterior reversible encephalopathy syndrome, TMA: thrombotic microangiopathy*

# SINUSOIDAL OBSTRUCTION SYNDROME PROPHYLAXIS

# 3

Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is a life-threatening complication that may arise after hematopoietic stem cell transplantation (HSCT), particularly after myeloablative conditioning (MAC) regimens. This condition primarily affects pediatric patients, with an incidence rate of 15-20%, which can increase to as high as 80% in high-risk individuals. Additionally, the incidence of severe anicteric SOS/VOD accompanied by multi-organ dysfunction is notably higher in children compared to adults, with rates of 74% versus 59%, respectively (74).

In the pediatric setting, there are no distinctions regarding the time of onset, and no time limitations are specified. The pediatric European Society for Blood and Marrow Transplantation (EBMT) criteria for diagnosis require the presence of at least two of the following indicators:

- Unexplained consumptive and transfusion-refractory thrombocytopenia
- An otherwise unexplained weight gain over three consecutive days despite diuretic use, or a weight gain of 5% above baseline
- Hepatomegaly (preferably confirmed by imaging) above baseline levels
- Ascites (preferably confirmed by imaging) above baseline levels
- Rising bilirubin levels from baseline over three consecutive days, or bilirubin levels ≥2 mg/dL within 72 hours

Several pharmacological strategies have been explored to prevent SOS/VOD, with ursodeoxycholic acid (UDCA) and defibrotide (DF) being two of the most notable options.

A meta-analysis of three trials comparing UDCA to placebo suggested a potential benefit of UDCA in preventing SOS/VOD (75).

Regarding DF, a phase III randomized trial demonstrated that prophylactic DF significantly reduced the incidence of SOS/VOD in high-risk pediatric patients, with rates of

12% in the DF group compared to 20% in the control group (P= 0.048) (76).

Based on these findings, the British Committee for Standards in Hematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMTCT) recommend DF use for preventing SOS/VOD in pediatric patients undergoing HSCT who have at least one risk factor for SOS/VOD (77).

Risk factors include pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin (GO), diagnosis of primary hemophagocytic lymphohistiocytosis (HLH), adrenoleukodystrophy (ALD) or osteopetrosis.

However, the HARMONY trial, which included both pediatric and adult patients, found no significant benefit of DF for SOS/VOD prevention compared to best supportive care. As a result, while DF shows promise in specific populations, its overall efficacy as a prophylactic agent continues to be investigated (78).

Currently, the Pediatric Diseases Working Party (PDWP) of the EBMT does not recommend DF as routine prophylaxis for SOS/VOD due to limited availability and high cost. Given these constraints, DF prophylaxis is only recommended for very high-risk patients (previous treatment with GO or inotuzumab, history of prior MAC-HSCT, and infants below 12 months of age) who are planned to receive a MAC regimen containing two or more alkylating agents (79).

**UDCA:** 6 mg/kg twice a day (max: 900 mg/day or 300 mg/dose); from initiation of conditioning until day +90 after transplantation

**DF:** 6.25 mg/kg intravenously four times daily; from initiation of conditioning until neutrophil engraftment or discharge, and for at least 14 days

# STEM CELLS MOBILIZATION AND APHERESIS POLICIES

# 4

The mobilization of hematopoietic stem cells (HSCs) from bone marrow (BM) to peripheral blood (PB) and their subsequent collection are essential aspects of hematopoietic stem cell transplantation (HSCT) programs (80, 81). Although peripheral blood stem cells (PBSCs) are widely utilized, achieving a consensus on the optimal growth factor and its dosage, the most effective chemotherapy type and dosage, methods for identifying patients with poor mobilization, and the best timing for initiating leukapheresis remain challenging (82). Currently, many transplantation centers have developed their own strategies based on individual priorities and available resources, resulting in a lack of uniformity in approaches among institutions.

## Granulocyte-Colony Stimulating Factor (G-CSF) Dosage Recommendation for Allogeneic HSCT in Adults (83-88)

### 1. The recommended dose for sibling donors

- Split dose (5μg/kg twice daily) or 10 μg/kg (per day) as a single dose is advised.
- Aministering a higher split dose of 12 μg/kg twice daily leads to greater collection yields and reduces the time required for collection.

### 2. The recommended dose for unrelated donors based on the National Marrow Donor Program (NMDP) is as follows

- G-CSF should be given for 4 or 5 consecutive days at a daily dose of 10 μg/kg daily.
- During the PBSCs collection, the total processed blood volume should not exceed 24 liters and should be collected during one or two consecutive days.

# Target Stem Cells Dose Collection for Allogeneic HSCT in Adults (81, 88-95)

### 1. HSCT from sibling donors

- Minimum Cell Dose: The commonly accepted minimum dose of CD34+ cells for sibling donor HSCT is $2 \times 10^6$ cells/kg.
- Engraftment Success: Successful engraftment has been reported with doses as low as $0.75 \times 10^6$ CD34+ cells/kg; however, this often results in delayed neutrophil and platelet engraftment, necessitating additional transfusions of blood components.
- Optimal CD34+ Cell Dose: Based on available data, a CD34+ cell dose between 4 and $5 \times 10^6$ cells/kg appears to be the most reasonable target for allogeneic transplantation in adults.
- Impact of Higher Doses: Several studies indicate that higher doses of CD34+ cell infusion are associated with more rapid engraftment.
- Risks of Excessive Dosing: Doses exceeding $8 \times 10^6$ cells/kg may increase the risk of severe chronic graft-versus-host disease (GVHD) without improving patient survival.

### 2. Transplantation from match unrelated donors

- Doses of CD34+ cells greater than $9 \times 10^6$ cells/kg do not provide any additional survival benefits.
- Higher cell doses have not been linked to an increased severity of GVHD.

### 3. Transplantation from haploidentical donors

- Administering mega doses of CD34+ cells, specifically between 8 and $12 \times 10^6$ cells/kg, has been associated with improved survival outcomes in haploidentical transplantation.

# G-CSF Dosage Recommendation for Allogeneic HSCT in Pediatrics (96-98)

- The most common approach for administering G-CSF is 10 µg/kg, given either as a single dose or divided into two semi-doses daily.

# Target Stem Cells Dose Collection for Allogeneic HSCT in Pediatrics (99-101)

- The Minimum amount of collected CD34+ cells are $2.4 \times 10^6$ CD34+ cells/kg.
- Higher doses of CD34+ cell (greater than $4\text{-}5 \times 10^6$ cells/kg) have been associated with faster engraftment; however, these higher doses do not significantly affect overall survival (OS) or the risk of developing GVHD.

# Strategies of Autologous Stem Cell Mobilization

## Mobilization without chemotherapy ("Steady State")

With this approach, HSCs are mobilized using cytokines exclusively. The only approved cytokine for this purpose is G-CSF. Administering G-CSF at a dosage of 10 µg/kg/day or 12 µg/kg given twice daily, with leukapheresis starting on the fifth day of G-CSF treatment, can lead to successful mobilization within a single day (102, 103).

# Target Stem Cells Dose Collection for Autologous HSCT (104-108)

- A minimum dose of $2 \times 10^6$ CD34+ cells/kg is generally accepted as a safe threshold for a single transplant. Lower doses may increase the risk of delayed neutrophil and platelet engraftment.
- The optimal number of collected cells is often considered to be greater than $5 \times 10^6$ CD34+ cells/kg.
- Higher cell counts from individuals identified as "super-mobilizers" have been linked to faster hematopoietic recovery, enhanced long-term platelet recovery, and improved OS.
- CD34+ cell doses exceeding $6 \times 10^6$ cells/kg have been associated with better long-term platelet recovery and a reduced need for blood transfusions; however, there was no significant difference observed in the time required to reach a platelet count of $20 \times 10^9$/L.

# Special Considerations for Obese Patients (109, 110)

A single daily dose of 14 µg/kg/day or a split dose of 2 × 7 µg/kg/day is recommended. When patients were categorized based on body mass index (BMI; <25 or >25 kg/m²), in patients with a BMI greater than 25 kg/m², once-daily dosing led to a higher yield of CD34+ cells.

# Apheresis Procedure in Pediatric Patients with Low Weight (96, 111)

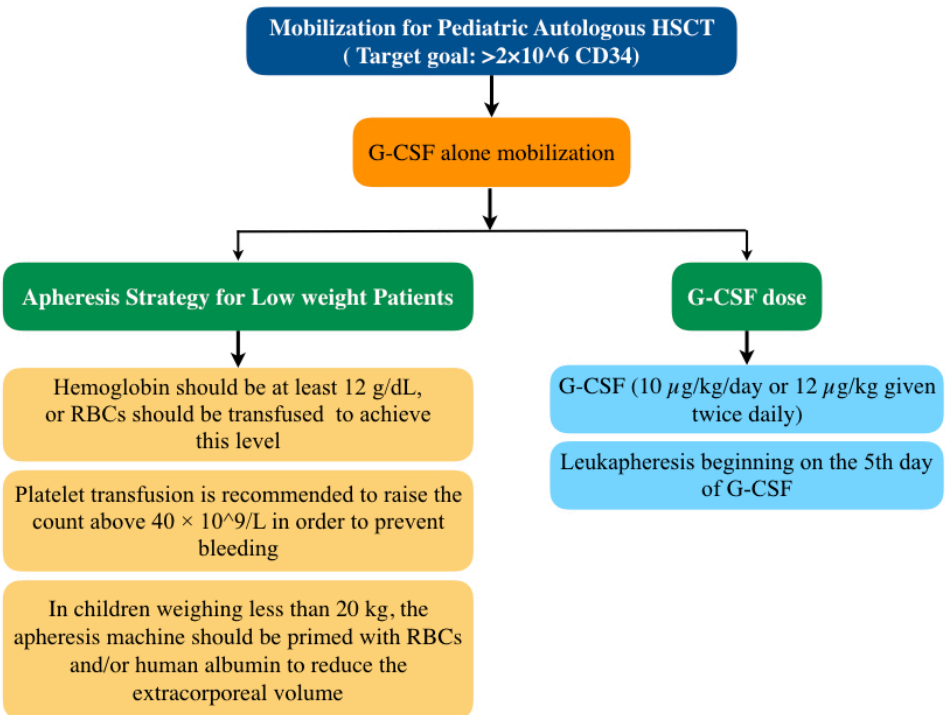
Pediatric patients with low weight should have a hemoglobin (Hb) level of at least 12 g/dL. If this level is not met, it should be achieved through red blood cell (RBC) transfusion.

In cases of severe thrombocytopenia, platelet transfusions should be administered to raise the platelet count above $40 \times 10^9$/L to prevent bleeding complications.

For children weighing less than 20 kg, the apheresis machine should be primed with RBCs and/or human albumin to minimize the extracorporeal volume.

A summary of stem cell mobilization and apheresis strategies, along with target cell doses for autologous stem cell transplantation in pediatric patients, is presented in ***Figure 1*** (112).

**Figure 1.** Stem Cell Mobilization and Apheresis for Autologous Stem Cell Transplantation in Pediatric Patients




## Monitoring of Peripheral Blood CD34+ Cell Counts in Autologous HSCT (113-122)

### 1. Reasons for selecting G-CSF alone strategy

- CD34+ cell counts typically peak in the blood between the fourth and sixth days of therapy.
- Monitoring of CD34+ cells should commence on either day 4 or day 5.

### 2. Plerixafor plus G-CSF mobilization strategy

- CD34+ cell counts should be assessed on days 4 and 5 of G-CSF administration.

### 3. Mobilization with chemotherapy

- CD34+ cell counts generally begin to be monitored 8 to 10 days after chemotherapy administration.

## Best Time to Initiate Leukapheresis (114, 115, 123)

- In regimens involving G-CSF alone or G-CSF combined with plerixafor, leukapheresis is most commonly initiated on day 5.
- In chemotherapy mobilization strategies, the timing for starting leukapheresis is typically based on a threshold of CD34+ cell counts. There is no consensus on the optimal threshold; therefore, institutional practices and local guidelines may vary, with minimal CD34+ counts ranging from 5 to 20 cells/μL.

## Prediction of High-Risk Patients for Stem Cell Mobilization Failure (2, 123-129)

Poor mobilizers are defined as patients who collect fewer than $2 \times 10^6$ CD34+ cells/kg or those who mobilize less than 20 CD34+ cells/μL into the peripheral blood. Generally, poor mobilizers can be categorized into two groups: predicted poor mobilizers and proven poor mobilizers (130).

### Proven Poor Mobilizers

A "proven poor mobilizer" is defined as a patient who fails to achieve sufficient circulating CD34+ cell counts after undergoing adequate mobilization efforts (such as G-CSF administration). Specifically, this designation applies to patients who have received 10 μg/kg of G-CSF alone or at least 5 μg/kg after chemotherapy, yet their peak circulating CD34+ cell count remains below 20/μL. Additionally, if these patients collect fewer than $2 \times 10^6$ CD34+ cells/kg during the first mobilization attempt, they are classified as proven poor mobilizers (131).

### Predicted Poor Mobilizers

Predicted poor mobilizers are patients identified as having a high risk of inadequate stem cell mobilization based on patient or disease characteristics such as:

- Refractory or advanced stage of disease
- High number of prior treatment line (≥2 lines of chemotherapy)
- Extensive BM involvement or cellularity <30% at the time of mobilization
- Age greater than 60 years
- Prior exposure to alkylating agents

- Prior radiation
- Prior treatment with lenalidomide, fludarabine, daratumomab, and melphalan
- Low CD34+ cell count before apheresis
- Platelet count below $100 \times 10^9$ /L
- Previous autologous HSCT
- Low Hb level and white blood cell (WBC) count before mobilization

This definition aims to help clinicians identify patients who may benefit from early intervention with alternative mobilization strategies.

## Prediction of Mobilization Failure Based on CD34+ Cells Yield (114, 115, 132)

### 1. Prior to apheresis

- **Borderline poor mobilizers:** Patients with 11–19 CD34+ cells/μL at maximum stimulation in PB may yield approximately 1.5–2 × $10^6$/kg CD34+ cells after apheresis.
- **Relatively poor mobilizers:** Patients with 6–10 CD34+cells/μL at maximum stimulation in PB are likely to yield less than 1 × $10^6$/kg CD34+ cells after apheresis.
- **Absolute poor mobilizers:** Patients with ≤5 CD34+ cells/μL at maximum stimulation in PB may yield between 0.75 and 1.25 × $10^6$/kg CD34+ cells after apheresis.

### 2. After apheresis

- **Optimal collection:** When pre-apheresis CD34+ cell counts exceed 20 cells/μL, a yield of ≥5 × $10^6$ CD34+ cells/kg may be achieved.
- **Low collection:** A yield ranging from ≥2 to <5 × $10^6$ CD34+ cells/kg is considered low.
- **Poor collection:** A yield of less than 2 × $10^6$ CD34+ cells/kg is classified as poor.
- **Failed collection:** Apheresis is deemed impossible due to insufficient peripheral blood CD34+ cell counts.

## Strategies for Management of Poor Mobilizes in Autologous HSCT (133-139)

### Borderline Poor Mobilizers

#### 1. Large-volume leukapheresis

- This strategy involves considering 4.0–5.3 times the patient's total blood volume as the target PB volume for leukapheresis.
- No significant difference in CD34+ cell viability was observed when compared to normal-volume apheresis, which typically uses 2.7–3.5 times the patient's total blood volume.
- Large-volume leukapheresis is indicated for relatively poor mobilizers or patients with a high individual CD34+ cell collection goal (≥3 transplants).

### 2. Plerixafor addition

The addition of plerixafor to standard mobilization strategies should be considered for patients who continue to mobilize poorly even with larger-volume approaches.

### 3. Rest period

A rest period of 2 to 4 weeks is recommended for patients who fail their initial mobilization attempt.

### 4. Plerixafor plus G-CSF with or without chemotherapy

The addition of plerixafor to G-CSF alone or to G-CSF combined with chemotherapy results in:

- Increased mobilization of CD34+ cells
- Increased proportion of more primitive HSC subsets
- A positive correlation between the number of reinfused natural killer (NK) cells and early absolute lymphocyte recovery following autologous HSCT

### 5. Preemptive intervention

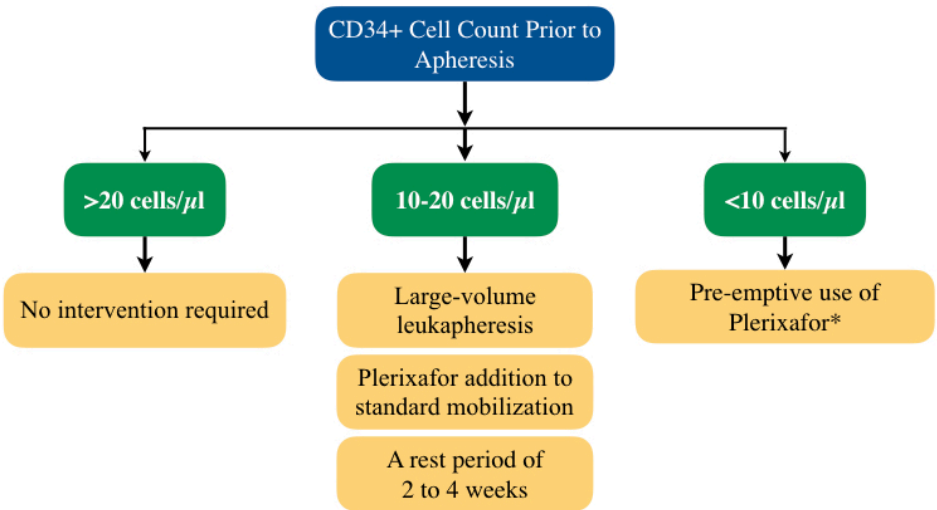
Preemptive intervention with plerixafor should be considered for at-risk patients.

## Relatively poor and poor mobilizers

Preemptive use of plerixafor should be considered.

A summary of apheresis and mobilization strategies based on CD34+ cell counts prior to apheresis for poor mobilizers in autologous HSCT is displayed in ***Figure 2***.

**Figure 2.** Apheresis and Mobilization Strategies Based on CD34+ Cell Counts Prior to Apheresis




*Plerixafor: 240 μg/kg/ 8–12 h before apheresis by subcutaneous injection

## Threshold of Leukocytosis for Holding Growth Factor (140-142)

- In one-third of patients, WBC counts exceeded $50 \times 10^9$/L, while less than 1% had WBC counts greater than $75 \times 10^9$/L.
- During G-CSF mobilization, a significant increase in spleen size was observed. The median spleen volume increased by 1.47-fold on the first day of leukapheresis but returned to near pretreatment size after 7 days of leukapheresis.
  No cases of splenic rupture or thrombosis were reported.
  Only 9% of patients experienced an increase in splenic volume of more than two-fold.
  There was no correlation found between changes in spleen volume, G-CSF dosage, peak absolute neutrophil count (ANC), CD34+ cell yield, or donor weight.

Although there is no documented evidence linking hematological parameters to splenic enlargement or the risk of splenic rupture, current data suggest that G-CSF administration should be withheld when WBC counts exceed $100 \times 10^9$/L, and plerixafor should be withheld when WBC counts exceed $75 \times 10^9$/L.

## Mobilization Failure in Allogeneic HSC Donors

In healthy donors, the failure to mobilize stem cells using G-CSF is relatively rare, with an estimated incidence rate of 5% to 10%. While plerixafor is not currently approved for use in allogeneic HSCT, two case series have demonstrated the feasibility and safety of combining plerixafor with G-CSF. This combination has been shown to successfully mobilize a sufficient number of HSCs in healthy pediatric haploidentical and genoidentical donors who did not respond adequately to G-CSF alone (143, 144).

# BLOOD PRODUCTS TRANSFUSION 5

Blood products transfusion support is a crucial aspect of care for patients undergoing stem cell transplantation. Ensuring the availability of safe and effective blood products during the pre-, peri-, and post-transplantation phases is vital for optimizing overall survival and improving outcomes in this patient population. Effective transfusion support helps manage complications such as anemia, thrombocytopenia, and coagulopathy, ultimately contributing to better recovery and quality of life for these individuals (145).

Hematopoietic stem cell transplantation (HSCT) recipients are at risk of transfusion-associated graft-versus-host disease (GVHD) and should receive irradiated cellular blood products (146). According to the European Committee on Blood Transfusion, it is recommended that no part of the blood component receive a dose less than 25 Gy and greater than 50 Gy during irradiation (147).

There is no universal consensus on the duration of using irradiated blood products in HSCT recipients. However, standard practice is:

- For autologous HSCT, irradiated blood products should be given starting at least 2 weeks prior to stem cell collection until at least 3 months after HSCT (6 months if total body irradiation (TBI) has been used in conditioning). Patients diagnosed with Hodgkin lymphoma or those who have received purine analog treatment should receive irradiated blood products indefinitely.
- For allogeneic HSCT, irradiated blood products should be given starting at the latest with the conditioning regimen. The recommended duration of irradiated blood product use is based on the recovery of the recipient's immune system, as indicated by a lymphocyte count above $1 \times 10^9$/L, absence of active chronic GVHD, and discontinuation of all immunosuppressive medications.

Additionally, allogeneic cellular blood components transfused to hematopoietic stem cell (HSC) donors within 7 days before or during the harvest should also be irradiated to prevent transfusion-associated GVHD in the transplant recipient (148, 149).

Additionally, recipients of HSCT should receive leukocyte-reduced red blood cells (RBCs), platelet concentrates (PCs), and fresh frozen plasma (FFP) to minimize the risk

of febrile non-hemolytic transfusion reactions, reduce the incidence of alloimmunization to leukocyte antigens, and lower the risk of cytomegalovirus (CMV) transmission (2).

## Red Blood Cell Concentrates

The Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) recommends a hemoglobin (Hb) concentration threshold of 7-8 g/dL for considering RBC transfusion in children undergoing HSCT who are critically ill or at risk for critical illness, provided they are hemodynamically stable (150). The volume of RBC should be calculated using the following formula:

> Volume (mL RBC): Target Hb after transfusion (g/dL) – pretransfusion Hb (g/dL) × 4 × weight (kg)

## Platelet Concentrates (PCs)

In non-febrile patients without active bleeding, prophylactic platelet transfusions should be considered to maintain a platelet count at or above $10 \times 10^9$/L. For patients experiencing active bleeding, febrile conditions, or active infections, prophylactic PC transfusions should be administered at a threshold of $20 \times 10^9$/L. In circumstances such as acute GVHD, mucositis, hemorrhagic cystitis, or diffuse alveolar hemorrhage, which may elevate the risk of bleeding, the threshold should be raised to $20 \times 10^9$/L or even higher. depending on clinical judgment (151).

Current recommendations for platelet transfusion volume are 10 to 20 mL/kg of body weight for children <15 kg, or a single pack for children ≥15 kg, with a maximum volume of one pack (152).

## Transfusion in ABO- or RhD-Incompatible HSCT

Approximately 50% of transplants are ABO incompatible; however, this is not a barrier to HSCT. Nonetheless, immunohematological issues may arise, and specific precautions must be implemented to ensure a safe HSCT procedure. There are three types of ABO incompatibility:

- Major Incompatibility (20-25% of HSCTs): In cases of major incompatibility, the recipient's plasma contains isohemagglutinins. To manage the potential risk of hemolysis, the erythrocyte content of the peripheral blood stem cells collected via apheresis should be less than 20 mL (or hematocrit <2%).
- Minor Incompatibility (20-25% of HSCTs): In cases of minor incompatibility, the donor's plasma contains isohemagglutinins (≥1/256) and immune cells. To prevent severe hemolysis during transplantation, plasma reduction in the stem cell product is recommended. It is important to note that plasma reduction does not decrease the content of B lymphocytes; therefore, it does not affect the occurrence of passenger lymphocyte syndrome or delayed hemolysis.

- Bidirectional Incompatibility (up to 5% of HSCTs): In cases of bidirectional incompatibility, both the donor and recipient have plasma containing isohemagglutinins and immune cells. In such situations, both RBC and plasma depletion should be considered if isohemagglutinins are greater than 1/128 and hematocrit exceeds 2% (153, 154).

During the HSCT process, it is essential to consider the blood types and immune systems of both the donor and recipient, with a preference for using products that are compatible with both parties **(Table 6)** (145).

**Table 6.** RBC, Platelet, and Plasma Transfusion Support for Patients Undergoing ABO-Incompatible HSCT

| | | | Phase I* | Phase II and Phase III** | | | | |
|---|---|---|---|---|---|---|---|---|
| ABO Incompatibility | Recipient | Donor | All Products | RBC | Platelets | | Plasma | |
| | | | | Choice | First choice | Second choice | First choice | Second choice |
| Major | O | A | Recipient | O | A | AB, B, O | A | AB |
| | O | B | Recipient | O | B | AB, A, O | B | AB |
| | O | AB | Recipient | O | AB | A, B, O | AB | - |
| | A | AB | Recipient | A, O | AB | A, B, O | AB | - |
| | B | AB | Recipient | B, O | AB | B, A, O | AB | - |
| Minor | A | O | Recipient | O | A | AB, B, O | A | AB |
| | B | O | Recipient | O | B | AB, A, O | B | AB |
| | AB | O | Recipient | O | AB | A, B, O | AB | - |
| | AB | A | Recipient | A, O | AB | A, B, O | AB | - |
| | AB | B | Recipient | B, O | AB | B, A, O | AB | - |
| Bidirectional | A | B | Recipient | O | AB | B, A, O | AB | - |
| | B | A | Recipient | O | AB | A, B, O | AB | - |

*RBC: red blood cell*
**Phase I until preparative regimen **Phase II until complete engraftment, Phase III after complete engraftment*

RhD incompatibility is an important consideration in HSCT for both genders. This issue is particularly relevant for RhD-negative female recipients receiving transplants from RhD-positive donors. RhD-negative female recipients should receive RhD-negative RBCs, while the use of RhD-negative platelet units is less critical. Due to the intense immunosuppression resulting from the conditioning regimen and the minimal amount of RBCs in single and random donor platelet units, anti-D antibodies are unlikely to develop, making RhD-incompatible platelet products generally safe. Given the minimal risk of D alloimmunization from red cells present in RhD-positive platelet units, selecting RhD-negative platelets is not mandatory (155, 156). Currently, there are no consensus recommendations regarding RhD immunoglobulin prophylaxis for HSCT in these patients (157). After erythroid engraftment—indicated by the appearance of RhD-positive RBCs—transfusions of RBCs and platelet components can be switched to RhD-positive products for RhD-negative recipients (158).

# PHARMACEUTICAL MICROBIAL PROPHYLAXIS

# 6

Antimicrobial prophylaxis is an essential component of care during and after hematopoietic stem cell transplantation (HSCT), as exposure to infectious pathogens is unavoidable in this patient population. It is crucial to tailor antimicrobial prophylaxis based on local epidemiology, resistance patterns, and individual patient factors to optimize the prevention of infections and minimize the development of antimicrobial resistance in HSCT recipients.

## Antibacterial Prophylaxis

Systemic antibacterial prophylaxis is not recommended during the neutropenic period following the conditioning regimen, nor during the pre-engraftment or post-engraftment periods for patients without acute or chronic graft-versus-host disease (GVHD) (159-162). However, late infection prevention (beyond 100 days post-transplant) targeting mainly encapsulated bacteria (Streptococcus pneumoniae and Haemophilus influenzae), is advised for patients who are undergoing immunosuppressive (IS) therapy for GVHD and for those with severe hypogammaglobulinemia (serum IgG levels <400 mg/dL) who are receiving immunoglobulin replacement therapy (163-165).

## Antiviral Prophylaxis

Antiviral prophylaxis is an essential component of care for patients undergoing HSCT to prevent viral infections, particularly those caused by herpesviruses such as herpes zoster (HZ), cytomegalovirus (CMV), and varicella-zoster virus (VZV).

The choice of antiviral agent, duration of prophylaxis, and dosing regimens should be tailored to individual patient risk factors and local practices to optimize outcomes and prevent viral infections in HSCT recipients. Our recommendation for antiviral prophlaxis, are summarized in **Table 7** (10, 166-169).

**Table 7.** Antiviral Prophylaxis for HSCT in Pediatrics

| Virus | Serostatus | Prophylaxis Recommendation |
|---|---|---|
| Herpes Simplex Virus (HSV) | Seropositive recipients | Acyclovir: 250 mg/m$^2$ or 5 mg/kg q12h; start from day +1 until neutrophil engraftment or mucosal recovery (at least 4 weeks after HSCT in VZV-seronegative recipients) |
| | Seronegative recipients | Not recommended |
| Varicella-Zoster Virus (VZV) | Seropositive recipients | Acyclovir: 20 mg/kg q12h; for at least 12 months or up to the end of IS therapy |
| | Seronegative recipients | Post-exposure prophylaxis with anti-VZV-immunoglobulins (within 96 hours) and acyclovir/valaciclovir is recommended for seronegative patients exposed to VZV. Prophylaxis should begin as soon as possible and continued until 21 days after exposure. |
| Cytomegalovirus (CMV) | Seropositive recipients | Letermovir may be an option for seropositive children in an off-label setting; given for 3 months after HSCT |
| | Seronegative recipients & seropositive donors | Has not been adequately studied after HSCT. |

*HSCT: hematopoietic stem cell transplantation, IS: immunosuppressive*

* *CMV is a latent virus belonging to the herpesvirus family. It is one of the most common viral pathogens that can reactivate after HSCT during T-cell deficiency or dysfunction periods. It remains a significant and potentially life-threatening infectious complication following allogeneic HSCT (170-174). In addition to prophylactic strategies, preemptive antiviral treatment guided by surveillance through quantitative polymerase chain reaction (PCR) assays is crucial for the early detection of CMV reactivation, ideally before any clinical symptoms arise (175, 176).* ***Figure 3*** *presents the threshold of CMV viral load for initiating preemptive therapy (177), which is further detailed in the preemptive treatment regimen outlined in* **Table 8** *(178, 179).*

**Figure 3.** Threshold of CMV Viral Load for Preemptive Therapy

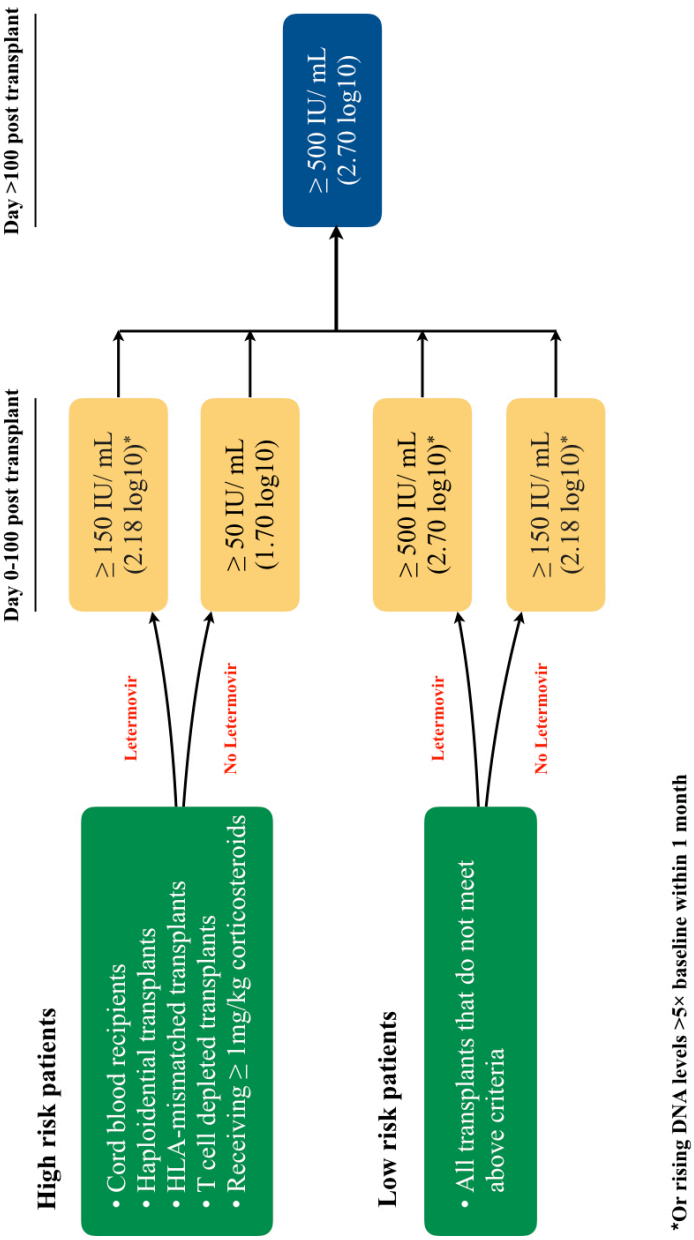


**Table 8.** Preemptive Treatment Regimen for CMV Reactivation

| Time | | Induction (Preferred) | Induction (Alternative) | Maintenance (Preferred) | Maintenance (Alter native) |
|---|---|---|---|---|---|
| Pretrans-plant | Through day -2 | Valganciclovir*<br>Adults and Pediatrics >50 kg: 900 mg PO q12h<br><br>Pediatrics ≥ 40 to <50kg: 675 mg PO q12h<br>Pediatrics ≥ 30 to <40kg: 450 mg PO q12h<br>Pediatrics ≥20 to <30 kg: 450 mg PO q12h or Liquid 14 mg/kg q12h<br>Pediatrics ≥15 to <20 kg: 225 mg PO q12h (= ½ pill) or Liquid 14 mg/kg q12h<br>Pediatrics ≥10 to <15 kg: Liquid 14 mg/kg q12h<br><br>OR<br>Ganciclovir**<br>5 mg/kg IV q12h | Foscarnet** 90 mg/kg IV q12h | Valganciclovir*<br>Adults and Pediatrics >50 kg: 900 mg PO daily<br><br>Pediatrics ≥40 to <50kg: 675 mg PO daily<br>Pediatrics ≥30 to <40kg: 450 mg PO daily<br>Pediatrics ≥20 to <30 kg: 450 mg PO daily or Liquid 14 mg/kg daily<br>Pediatrics ≥15 to <20 kg: 225 mg PO daily (= ½ pill) or Liquid 14 mg/kg daily<br>Pediatrics ≥10 to <15 kg: Liquid 14 mg/kg daily<br><br>OR<br>Ganciclovir**<br>5 mg/kg IV daily | Foscarnet** 90 mg/kg IV daily |
| | After day -2 Through day 0 | Foscarnet** 90 mg/kg IV q12h | | Foscarnet** 90 mg/kg IV daily | |
| Post-trans-plant | Pre-engraft-ment | Foscarnet** 90 mg/kg IV q12h | | Foscarnet** 90 mg/kg IV daily | |
| | Post-engraft-ment | Valganciclovir*<br>Adults and Pediatrics >50 kg: 900 mg PO q12h<br>Pediatrics ≥40 to <50kg: 675 mg PO q12h<br>Pediatrics ≥ 30 to < 40kg: 450 mg PO q12h<br>Pediatrics ≥20 to < 30 kg: 450 mg PO q12h or Liquid 14 mg/kg q12h<br>Pediatrics ≥15 to <20 kg: 225 mg PO q12h (= ½ pill) or Liquid 14 mg/kg q12h<br>Pediatrics ≥10 to <15 kg: Liquid 14 mg/kg q12h<br><br>OR<br>Ganciclovir**<br>5 mg/kg IV q12h | Foscarnet** 90 mg/kg IV q12h | Valganciclovir*<br>Adults and Pediatrics >50 kg: 900 mg PO daily<br><br>Pediatrics ≥40 to <50kg: 675 mg PO daily<br>Pediatrics ≥30 to <40kg: 450 mg PO daily<br>Pediatrics ≥20 to <30 kg: 450 mg PO daily or Liquid 14 mg/kg daily<br>Pediatrics ≥15 to <20 kg: 225 mg PO daily (= ½ pill) or Liquid 14 mg/kg daily<br>Pediatrics ≥10 to <15 kg: Liquid 14 mg/kg daily<br><br>OR<br>Ganciclovir**<br>5 mg/kg IV daily | Foscarnet** 90 mg/kg IV daily |

*IV: intravenously, PO: per os*
**Oral valganciclovir induction and/or maintenance therapy should be considered only for patients with good oral intake, no active severe GI GVHD, no significant liver disease, and no severe diarrhea.*
***Use actual weight unless the actual weight is above 150% of the ideal weight. For patients whose actual weight is >150% of the ideal body weight, the weight used should be capped at 150% of the ideal body weight.*

**Duration of Induction:**

- For Non-Cord blood (CB) transplant, a switch to maintenance dosing may be made if CMV DNA levels are declining (at least 1-log reduction) after 7 days; if not declining at day 7 of treatment, continue twice daily induction dosing until CMV DNA levels have decreased over the course of 1 week; at which point transition to maintenance dosing can occur.
- For CB transplant, CMV DNA levels must be negative at one week in order to transition to maintenance dosing. Otherwise, continue induction dosing until CMV DNA levels are negative at which point a transition to maintenance is appropriate.
- All patients failing induction should be considered to switch therapy and do UL97/UL54 resistance testing.

**Duration of Maintenance Therapy:**

- Maintenance therapy should be given for at least 2 weeks after induction therapy has been completed.
- Preemptive therapy may be discontinued when the surveillance test is negative after a minimum of 3 weeks of therapy (at least 1 week induction). Shorter courses may be appropriate for subsequent episodes of CMV reactivation.

## Antifungal Prophylaxis

**Primary antifungal chemoprophylaxis:** Despite advances in the treatment of invasive fungal infections (IFIs) due to the availability of new antifungal drugs, IFIs continue to be a significant cause of morbidity and mortality following HSCT (165). According to the guidelines from the 8th European Conference on Infections in Leukemia (ECIL-8), primary antifungal chemoprophylaxis is strongly recommended for patients undergoing allogeneic HSCT during both the pre-engraftment and post-engraftment phases until immune reconstitution occurs. This recommendation also applies to patients receiving immunosuppressive treatment for GVHD (162). Our recommendations, based on the ECIL-8 guidelines, are summarized in **Table 9**.

**Table 9.** Antifungal Prophylaxis for HSCT in Pediatrics

| Antifungal Drug | Dose and Administration Route |
|---|---|
| Fluconazole | Single dose of 8–12 mg/kg (max 400 mg)/day IV or PO (in the pre-engraftment phase) |
| Itraconazole | Patients aged 2 years or older: 5 mg/kg/day PO in two divided doses |
| Caspofungin | 50 mg/m²/day (70 mg/m² on day 1) IV in a single dose |
| Liposomal Amphotericin B | 1 mg/kg every other day IV OR<br>2.5 mg/kg twice per week IV |
| Posaconazole | Patients aged 13 years or older: Delayed-release tablets, 300 mg in a single daily dose (2 × 300 mg on day 1)<br>Patients aged 1 month to 12 years: Oral suspension, starting dose 6 mg/kg three times daily |
| Voriconazole | Patients aged 2–12 years, or aged 12–14 years weighing <50 kg: 8 mg/kg (9 mg/kg on day 1) twice a day IV or 9 mg/kg twice a day PO<br>Patients aged 12–14 years weighing ≥50 kg, or patients aged 15 years and older: 4 mg/kg (6 mg/kg on day 1) twice a day IV or 200 mg twice a day PO |

*IV: intravenously, PO: per os*

**Secondary antifungal chemoprophylaxis:** Secondary antifungal prophylaxis is strongly recommended for patients with a history of IFI prior to undergoing allogeneic HSCT. This approach is a critical strategy to mitigate the risk of post-transplant IFI recurrence.

## High-risk patients for invasive fungal infection (IFI) recurrence after HSCT

- Hematologic malignancy not in complete remission (CR)
- High-risk allogeneic HSCT
  - Matched unrelated donor (MUD)
  - CB transplant
  - T-cell depleted

  - Haploidentical transplant
  - Chronic lymphocytic leukemia (CLL)
  - Mismatched transplant
- Multi-drug resistant (MDR) fungus
- Disseminated or multifocal lung IFI (especially mold disease)
- Severe comorbidities (e.g., liver/kidney impairment)
- <4 weeks of antifungal treatment

## Recommendations for peritransplantation management of high-risk patients for invasive fungal infection (IFI) Recurrence

- Continue antifungal treatment pre-HSCT at least 4 weeks and until polymorphonuclear (PMN) leukocyte recovery and objective signs of response by symptoms and follow-up computed tomography (CT) scan, then switch to secondary antifungal prophylaxis.
- Consider reduced-intensity conditioning (RIC) regimen.
- Secondary prophylaxis with mold-active triazole
  - The duration of secondary antifungal prophylaxis is individualized; consider stopping after up to 1-year post-HSCT (carefully evaluating for acute and chronic toxicities from antifungals) if the patient is in CR, has PMN leukocyte count >1000 cells/$mm^3$, and no signs or symptoms of active IFI.
  - Resume mold-active prophylaxis if GVHD develops—whether acute or chronic—and requires systemic IS therapy.
- Consider therapeutic drug monitoring (TDM) and close coordination with the HSCT clinical pharmacist for managing drug interactions.
- *Triazole antifungal should be administered with a conditioning regimen (eg, busulfan, cyclophosphamide) or calcineurin inhibitors (CNIs) and sirolimus.*
- Consider infectious diseases consult, fungal biomarkers testing, CT imaging, and prompt bronchoscopy, with any signs or symptoms consistent with IFI relapse.
  - The role of surveillance with fungal biomarkers in asymptomatic patients receiving mold-active prophylaxis is unproven.

## Low-risk patients for invasive fungal infection (IFI) recurrence after HSCT

- Hematologic malignancy in remission
- Standard-risk allogeneic HSCT
  - Low-risk MUD
  - Chronic myelogenous leukemia (CML), multiple myeloma, aplastic anemia
- Prior candidemia but not disseminated candidiasis

- Appropriate antifungal treatment >4 weeks
- Objective response >70% by CT for invasive mold disease
- Low risk according to hematopoietic cell transplantation comorbidity index (HCT-CI)

## Recommendations for peritransplantation management of low-risk patients for IFI recurrence

- Consider a full-intensity conditioning regimen if indicated.
- Secondary prophylaxis with mold-active triazoles with TDM or echinocandin
  - The duration of secondary antifungal prophylaxis is individualized; consider stopping after up to 6 months post-HSCT (carefully evaluating for acute and chronic toxicities from antifungals) if the patient is in CR, has PMN leukocyte count >1000 cells/mm3, and no signs or symptoms of active IFI.
  - Resume mold-active prophylaxis if GVHD develops—whether acute or chronic—and requires systemic IS therapy.
- Consider bridging with intravenous (IV) echinocandin (history of prior Candida spp.) or liposomal amphotericin B (invasive mold disease or endemic fungus) until PMN leukocyte recovery if severe mucositis is expected and IV triazole cannot be administered due to conditioning regimen.
  - Triazole antifungal should be administered with a conditioning regimen (eg, busulfan, cyclophosphamide) or CNIs and sirolimus.
- Consider infectious diseases consult and repeat fungal biomarkers with CT imaging for any signs or symptoms of relapse.
  - The role of surveillance with fungal biomarkers in asymptomatic patients receiving mold-active prophylaxis is unproven.

### Prophylaxis Against Pneumocystis Jirovecii Pneumonia

Pneumocystis jirovecii pneumonia (PJP) is a serious infectious complication of HSCT with a high early mortality rate. Several risk factors have been identified for the development of PJP after transplantation, including GVHD and/or its treatment with IS therapy, lymphopenia, GVHD prophylaxis containing alemtuzumab or rabbit anti-thymocyte globulin (ATG), and peripheral blood stem cell source (180).

Prophylaxis is recommended from the time of engraftment until at least 6 months post-transplant, or longer for patients who continue to receive immunosuppressive drugs and/or have chronic GVHD. Trimethoprim/sulfamethoxazole is the drug of choice for primary prophylaxis against PJP, with a recommended dose of 150 mg/m$^2$ per day of the trimethoprim component, administered either in 1 or 2 doses per day or the same dose given 2 to 3 times per week (181).

# SUPPORTIVE CARE 7

## Nutritional Support

Enteral nutrition (EN) is preferred over total parenteral nutrition (TPN) for all patients due to its beneficial effects on gastrointestinal (GI) integrity and the microbiome.

## Total Parenteral Nutrition

Indications for the use of TPN during hematopoietic stem cell transplantation (HSCT):

- Contraindications for EN
- Severe malnutrition at admission (serum albumin <3 g/dL or body mass index (BMI) <18.5 kg/m$^2$).
- A prolonged period (1-3 days in infants and 4-5 days in children and adolescents) of minimal oral intake (failure to meet 60–70% of requirements with EN)
- Clinical weight loss of >10% during treatment
- Oral feeding impractical; severe mucositis (grade 4)

TPN should be reduced promptly, and it should be completely discontinued as soon as the patient is able to meet at least 50% of their daily energy requirements through oral intake (79, 182).

Recommended daily parenteral nutrient requirements for children, based on the American Academy of Pediatrics (AAP) nutrition guidelines, are outlined in **Table 10**. These dosages are designed for patients with normal fluid losses and without any organ failure.

**Table 10.** Daily Parenteral Nutrient Requirements

| Nutrient | Weight/Age | Requirement |
|---|---|---|
| Fluid | >1.5 kg | 150 mL/kg |
| | 1.5–2.5 kg | 120 mL/kg |
| | 2.5–10 kg | 100 mL/kg |
| | 10–20 kg | 1000 mL + 50 mL/kg for each kg >10 kg |
| | >20 kg | 1500 mL + 20 mL/kg for each kg >20 kg |
| Calories | Up to 10 kg | 100 kcal/kg |
| | >10–20 kg | 1000 kcal + 50 kcal/kg for each kg >10 kg |
| | >20 kg | 1500 kcal + 20 kcal/kg for each kg >20 kg |
| Protein | Preterm infants (<1 year) | 3–4 g/kg |
| | Term infants (<1 year) | 2.5–3 g/kg |
| | Older children (1–10 years) | 1.5–2.5 g/kg |
| | Adolescents (>10 years) | 0.8–2 g/kg |
| Fat | Infants (<1 year) | Initially 0.5–1 g/kg, advance by 0.5–1 g/kg to a goal of 3 g/kg |
| | Children (1–10 years) | Initially 1 g/kg, advance by 1 g/kg to a goal of 1–2 g/kg |
| | Adolescents (>10 years) | Initially 1 g/kg, advance by 1 g/kg to a goal of 1–2 g/kg |
| Dextrose | Infants (<1 year) | Initially 6–8 mg/kg/minute, advance by 1–2 mg/kg/minute to a goal of 10–14 mg/kg/minute (max 18 mg/kg/minute) |
| | Children (1–10 years) | Initially 3–6 mg/kg/minute, advance by 1–2 mg/kg/minute to a goal of 8–10 mg/kg/minute |
| | Adolescents (>10 years) | Initially 2.5–3 mg/kg/minute, advance by 1–2 mg/kg/minute to a goal of 5–6 mg/kg/minute |

| Nutrient | Weight/Age | Requirement |
|---|---|---|
| **Electrolytes and Minerals** | | |
| Sodium | Infants and children | 2–5 mEq/kg |
| | Adolescents and children (>50 kg) | 1–2 mEq/kg |
| Potassium | Infants and children | 2–4 mEq/kg |
| | Adolescents and children (>50 kg) | 1–2 mEq/kg |
| Chloride and acetate | Infants and children | As needed to maintain acid–base balance |
| Calcium | Preterm neonates | 2–4 mEq/kg |
| | Infants and children | 0.5–4 mEq/kg |
| | Adolescents and children (>50 kg) | 10–20 mEq |
| Phosphorus | Preterm neonates | 1–2 mmol/kg |
| | Infants and children | 0.5–2 mmol/kg |
| | Adolescents and children (>50 kg) | 10–40 mmol |
| Magnesium | Infants and children | 0.3–0.5 mEq/kg |
| | Adolescents and children (>50 kg) | 10–30 mEq |
| **Trace Elements** | | |
| Zinc | Preterm neonates | 400 µg/kg |
| | Term neonates (3–10 kg) | 250 µg/kg |
| | Children (10–40 kg) | 50 µg/kg (up to 5 mg) |
| | Adolescents (>40 kg) | 2–5 mg |
| Copper | Infants and children (≤40 kg) | 20 µg/kg (up to 500 µg) |
| | Adolescents (>40 kg) | 200–500 µg |
| Manganese | Infants and children (≤40 kg) | 1 µg/kg (up to 55 µg) |
| | Adolescents (>40 kg) | 40–100 µg |

| Nutrient | Weight/Age | Requirement |
|---|---|---|
| Chromium | Preterm neonates | 0.05–0.3 µg/kg |
| | Term neonates and children (≤40 kg) | 0.2 µg/kg (up to 5 µg) |
| | Adolescents (>40 kg) | 5–15 µg |
| Selenium | Infants and children (≤40 kg) | 2 µg/kg (up to 100 µg) |
| | Adolescents (>40 kg) | 40–60 µg |

Nutritional assessments for patients receiving EN or TPN during stem cell transplantation are summarized in **Table 11**.

**Table 11.** Monitoring of Nutritional Parameters

| Parameter | Monitoring Frequency |
|---|---|
| Weight | Daily |
| Serum Albumin | Weekly |
| Sodium, Potassium, Creatinine | Daily |
| Calcium, Magnesium, Phosphate, Liver Function Tests | Twice weekly |
| INR, quick | Twice weekly |
| Glucose | 3–6x daily if TPN or preexisting diabetes mellitus; otherwise, twice weekly |
| Triglycerides | Twice weekly (if TPN) |
| Vitamin D, Vitamin B12 | At admission |

*INR: international normalized ratio, TPN: total parenteral nutrition*

# Vitamins supplementation

## Vitamin K supplementation

| | | |
|---|---|---|
| 1-3 years old: 30 µg/day | 9-13 years old: 60 µg/day | **Once or twice weekly** |
| 4-8 years old: 55 µg/day | 14-18 years old: 75 µg/day | |

## Bone Health: Calcium/Vitamin D3

Consider calcium and vitamin D supplementation according to serum vitamin D3 level and also for patients on steroids.

- Serum 25-OH-vitamin D3 levels: <30 ng/mL: 50,000 units weekly for 8 weeks, followed by 1000–2000 units/day.
- Serum 25-OH-vitamin D3 levels: <10 ng/mL: 50,000 units weekly for 12 weeks, followed by 1000–2000 units/day.
- Extra calcium during corticosteroid therapy: 1500 mg/day for older children, 1000–1200 mg/day for younger children (calcium carbonate or citrate).

## Water-soluble vitamins (values per day) (183)

| Age | Vitamin B12 | Vitamin B6 | Vitamin B9 | Vitamin C |
|---|---|---|---|---|
| **0-6 months** | 0.4 µg | 0.1 mg | 65 µg | 40 mg |
| **7 months** | 0.5 µg | 0.3 mg | 80 µg | 50 mg |
| **1-3 years** | 0.9 µg | 0.5 mg | 150 µg | 15 mg |
| **4-8 years** | 1.2 µg | 0.6 mg | 200 µg | 25 mg |
| **9-13 years** | 1.8 µg | 1.0 mg | 300 µg | 45 mg |
| **14-18 years** | 2.4 µg | 1.2 mg | 400 µg | 75 mg |

# Mouthcare

The oral cavity should be evaluated before initiating the conditioning regimen and monitored daily, as oral mucositis (OM) is one of the most debilitating complications associated with HSCT (79). The World Health Organization (WHO) scale integrates subjective and objective criteria to assess the severity of OM (184).

| |
|---|
| **Grade 0** = No oral mucositis |
| **Grade 1** = Erythema/soreness |
| **Grade 2** = Erythema/soreness, ulcers, able to eat solids |
| **Grade 3** = Erythema/soreness, ulcers, requires a liquid diet (due to mucositis) |
| **Grade 4** = Erythema/soreness, ulcers, alimentation not possible (due to mucositis) |

Several risk factors contribute to the development of OM, including specific chemotherapy agents such as high-dose melphalan, etoposide, and low-dose methotrexate (185). Additionally, certain underlying conditions like Fanconi anemia, dyskeratosis congenita, and myelodysplastic syndrome (MDS) can increase susceptibility (79).

To effectively prevent OM, maintaining excellent oral hygiene is crucial. This includes

brushing teeth two to three times a day with a soft nylon toothbrush and adhering to a non-cariogenic diet that limits highly fermentable carbohydrates and sticky foods, such as those high in sugar and starch. It is also advisable to rinse the mouth with non-medicated oral rinses -0.9% saline- or medical agents like Nystatin every four hours (186, 187).

### Nystatin (oral drop)

Infants: 200,000 units (2 mL) PO every 4 hours**,** Children: 400,000-600,000 (4-6 mL) units; PO every 4 hours, should be swished and retained in the mouth for as long as possible before swallowing.

Oral cryotherapy, which involves applying ice chips to the buccal mucosa during chemotherapy treatment, is also a practical and cost-effective approach to preventing OM in patients undergoing HSCT (188).

## Anaphylactic Reactions

### Epinephrine

**Intramuscular epinephrine (1 mg/mL preparation);** Epinephrine 0.01 mg/kg should be injected intramuscularly (IM) in the mid-outer thigh. For larger children (>50 kg), the maximum is 0.5 mg per dose. If there is no response or the response is inadequate, the injection may be repeated in 5 to 15 minutes (or more frequently). If epinephrine is injected promptly IM, patients respond to 1, 2, or, at most, 3 injections. If signs of poor perfusion are present or symptoms are not responding to epinephrine injections, prepare intravenous (IV) epinephrine for infusion.

**Epinephrine infusion;** For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at **0.1 µg/kg/minute** by infusion pump.

**Intravenous epinephrine;** In an adult or adolescent, this is accomplished by administration of a 50 to 100 µg (0.05 to 0.1 mg) IV bolus of epinephrine by slow push of 0.5 to 1 mL of 0.1 mg/mL epinephrine solution over 1 to 10 minutes. In pediatric patients, 0.1 mL/kg IV; not to exceed 1 mg/dose; may repeat every 3-5 minutes.

### H1 antihistamine

Consider giving diphenhydramine 1 mg/kg (max 50 mg IV, over 5 minutes).

### H2 antihistamine

Consider giving famotidine 0.25 mg/kg (max 20 mg IV, over at least 2 minutes).

### Glucocorticoid

Consider giving methylprednisolone 1 mg/kg (max 125 mg IV).

Premedication of Stem Cells Infusion

| Medication | | Dosage and Administration Route |
|---|---|---|
| Antihistamines | Diphenhydramine Hydrochloride | 0.5–1 mg/kg/dose/PO or IV/q6h PRN (max 50 mg/day) |
| | Promethazine (≥2 years) | 0.25–1 mg/kg/dose/PO/q4-6h PRN (max 25 mg) |
| Corticosteroids: Hydrocortisone | | 2 mg/kg (max 100 mg) |
| Antipyretics: Acetaminophen | | 10 mg/kg |
| Antiemetics: Granisetron | | 0.01 mg/kg (max 3 mg) |
| Calcium Gluconate 10% | | 5 mL to 10 mL, over 10–15 minutes |

*IV: intravenously, PO: per os, PRN: pro re nata*

Antiemetics during conditioning regimen (should be administered 30 min before chemotherapy)

| Medication | Dosage and Administration Route |
|---|---|
| Granisetron | 0.04 mg/kg IV |
| Ondansetron | 0.15 mg/kg once daily IV on days of chemotherapy |
| Dexamethasone | 10 mg/m² once daily IV on days of chemotherapy |
| Aprepitant | For children ≥30 kg: 125 mg PO 1 hour before chemotherapy on day -1, followed by 80 mg PO once daily on days 2 and 3<br>For children <30 kg: 3 mg/kg PO 1 hour before chemotherapy on day -1, followed by 2 mg/kg PO once daily on days 2 and 3 |

*IV: intravenously, PO: per os*

## Cardiac monitoring

High-dose alkylating agents, such as cyclophosphamide (CY), can result in various cardiovascular complications, including heart failure, atrial arrhythmias, pericardial effusion, and myocarditis. The CY-induced cardiac toxicity is driven by several mechanisms, including inflammation, oxidative stress, disturbances in calcium homeostasis, and the activation of programmed cell death (189). Given the potential severity of these complications, early detection is essential (190).

Echocardiography is one of the most widely used noninvasive techniques for monitoring cardiac toxicity. Early damage from CY contributes to diastolic dysfunction, which is characterized by alterations in the E/A [early (E) and late (A) filling velocity] ratio,

increased thickness of the interventricular septum during diastole, enlargement of the left ventricular diastolic and systolic diameters, and early functional mitral regurgitation (191, 192). Furthermore, hemorrhagic myocarditis associated with CY use is characterized by hypertrophy, increased myocardial echogenicity, decrease in left ventricular ejection fraction, and normal chamber size as observed on echocardiography (193).

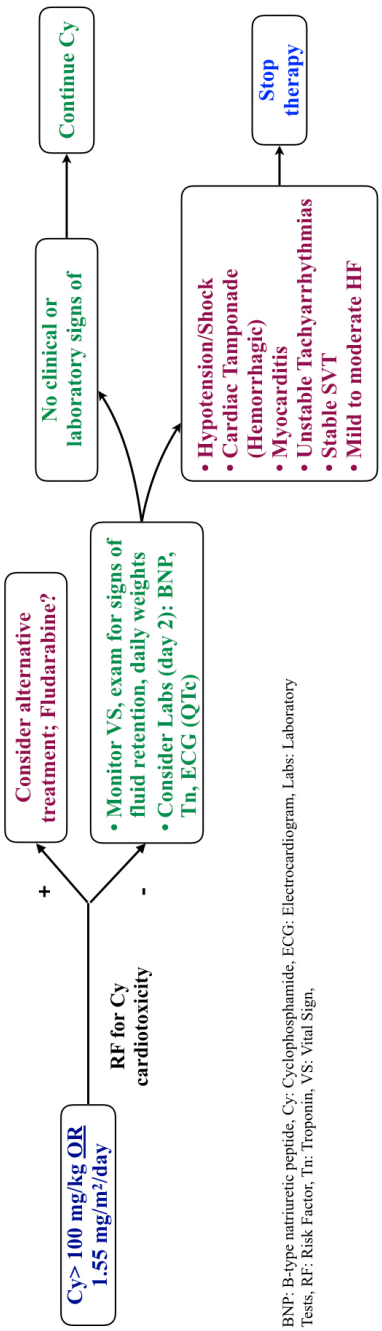
An early sign of CY-induced acute heart failure is a prolonged corrected QT interval (QTc) and increased QTc dispersion, which indicates the difference between the maximum and minimum QTc intervals on a 12-lead electrocardiogram (ECG) (194-196).

In addition to echocardiography, circulating cardiac markers such as B-type natriuretic peptide (BNP) and cardiac troponin T or I can be valuable in predicting early chemotherapy-induced cardiac toxicity. BNP is particularly noteworthy in the context of high-dose CY; it typically increases within the first 24 hours of treatment and may remain elevated for up to a week following the clinical onset of acute heart failure (197-199). Troponin levels are highly sensitive and generally peak between 8 and 15 days after high-dose CY administration, indicating direct myocardial damage (192).

It is important to note that early elevations in troponin levels may occur even in the absence of myocardial damage due to supply-demand mismatch ischemia or renal impairment following CY administration (190).

***Figure 4*** illustrates the baseline and subsequent assessment strategies for patients receiving high-dose CY.

**Figure 4.** Baseline and Subsequent Assessment of Patients Receiving High-Dose Cyclophosphamide




BNP: B-type natriuretic peptide, Cy: Cyclophosphamide, ECG: Electrocardiogram, Labs: Laboratory Tests, RF: Risk Factor, Tn: Troponin, VS: Vital Sign,

## Donor Specific Anti-Human Leukocye Antigen (HLA) Antibodies Desensitization

Donor-specific anti-HLA antibodies (DSAs) are associated with a high incidence of primary graft failure (GF) or delayed engraftment in haploidentical or mismatched HSCT, regardless of the stem cell source, conditioning regimen intensity, or other patient and donor characteristics (200, 201).

The strength of DSAs is determined by mean fluorescence intensity (MFI) values, classified as follows: low (MFI between 1000 and 3000), moderate (MFI between 3000 and 5000), and strong (MFI over 5000). While GF is more common with MFI levels exceeding 5000, rejection can occur at any MFI level. The European Society for Blood and Marrow Transplantation (EBMT) has published consensus guidelines recommending the detection and desensitization of patients with DSAs before HSCT if no other suitable donor is available (202).

The choice of desensitization protocol may vary based on the center's experience, but it typically involves antibody removal through plasmapheresis or immunoabsorption, inhibition of antibody production using monoclonal antibodies targeting CD20+ B lymphocytes (such as rituximab), antibody neutralization with intravenous immunoglobulin (IVIG), and inhibition of the complement cascade (203).

In patients with an MFI greater than 5000, we do not recommend proceeding with HSCT from the identified donor. Instead, we advise searching for a second-degree relative who can be a haploidentical donor or considering a mismatched donor.

For patients with an MFI between 1000 and 5000, and in the absence of a suitable donor, our preferred DSA desensitization algorithm is outlined in **Table 12**. Desensitization aims to reduce the DSA to an MFI of less than 1000 on phenotype panels and achieve a negative flow cross-match.

**Table 12.** Donor-Specific Antibodies Desensitization Algorithm

| Day | Treatment |
|---|---|
| -21 | • Rituximab 375 mg/kg |
| -14 | • Tacrolimus (1 mg, IV/PO per day)<br>• Mycophenolate mofetil (1 g, twice daily)<br>• IVIG 100 mg/kg<br>• TPE: exchanging 1 plasma volume and replacing at 100% volume with 5% albumin |
| -12 | • IVIG 100 mg/kg<br>• TPE: exchanging 1 plasma volume and replacing at 100% volume with 5% albumin |
| -10 | • IVIG 100 mg/kg<br>• Therapeutic Plasma Exchange (TPE): exchanging 1 plasma volume and replacing at 100% volume with 5% albumin |

| Day | Treatment |
|---|---|
| -9 | Check MFI; If MFI >3000, stop HSCT |
| -8 | Start conditioning regimen |
| -1 | Discontinue Tacrolimus & Mycophenolate mofetil |
| 0 | HSCT |
| +1 & +2 | Check MFI<br>If MFI >3000:<br>• VIG 100 mg/kg<br>• TPE: exchanging 1 plasma volume and replacing at 100% volume with 5% albumin |

*HSCT: hematopoietic stem cell transplantation, IVIG: intravenous immunoglobulin, MFI: mean fluorescence intensity, TPE:therapeutic plasma exchange*

# ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

# 8

## Acute Leukemia

### Acute Lymphoblastic Leukemia

With current chemotherapy protocols, the majority of pediatric patients with acute lymphoblastic leukemia (ALL) achieve favorable outcomes. However, for those who experience relapse, the criteria for utilizing hematopoietic stem cell transplantation (HSCT) can differ among various leukemia cooperative groups, such as the Italian Association of Pediatric Hematology-Oncology (AIEOP) and the Berlin-Frankfurt-Munster (BFM) group. The integration of measurable residual disease (MRD) assessment into the treatment of ALL has enhanced risk stratification. Additionally, the emergence of immunotherapy agents like blinatumomab, inotuzumab, and tisagenlecleucel in the upfront treatment of ALL has shifted the indications for HSCT over time. Currently, MRD is regarded as the most significant prognostic factor in childhood ALL, serving as a surrogate marker for leukemia sensitivity to chemotherapy. Several cooperative groups have accepted this to identify candidates for HSCT (204-207).

**Tables 13** & **14**, along with ***Figure 5***, summarize the current indications for HSCT in pediatric ALL based on the AIEOP-BFM ALL 2017, ALLTogether1, and IntReALL 2010 protocols.

**Table 13.** Indications for HSCT in Pediatric Patients with B-Cell ALL in First Complete Remission (CR1)

| Indication | Criteria |
|---|---|
| Infants (<1 year) with KMT2A-rearrangements and one of the following: | • Age <6 months and initial WBC >300,000/μL<br>• Age <6 months and prednisone poor-response<br>• No CR at day 33<br>• MRD at EOC ≥$5 \times 10^{-4}$ |
| TCF3-HLF; t(17;19)(q22;p13) | • HSCT indicated irrespective of MRD results |
| Ph+ ALL and one of the following: | • EOC MRD ≥$5 \times 10^{-4}$ (high positive)<br>• EOC MRD <$5 \times 10^{-4}$ (low positive) and still positive at any level at the end of HR block 3<br>• Uncertain risk factors for Ph+ ALL such as IKZF mutations |
| Positive MRD | • MRD ≥$5 \times 10^{-4}$ at EOC<br>• MRD ≥5% at EOI and ≥$5 \times 10^{-3}$ at mid-consolidation (day 50) |
| Patients ≥16 years | • MRD ≥5% at EOI regardless of subsequent MRD levels<br>• NCI high-risk patients with MRD ≥$1 \times 10^{-4}$ at EOC |
| Extramedullary disease | • Indicated for HSCT if not in CR1 at EOC |
| High-risk features with positive MRD at EOC | • Induction Failure (IF)<br>• hypodiploidy (<44 chromosomes or DNA index <0.8)<br>• KMT2A-AFF1 (previously MLL-AF4)<br>• IKZF1$^{plus}$ |

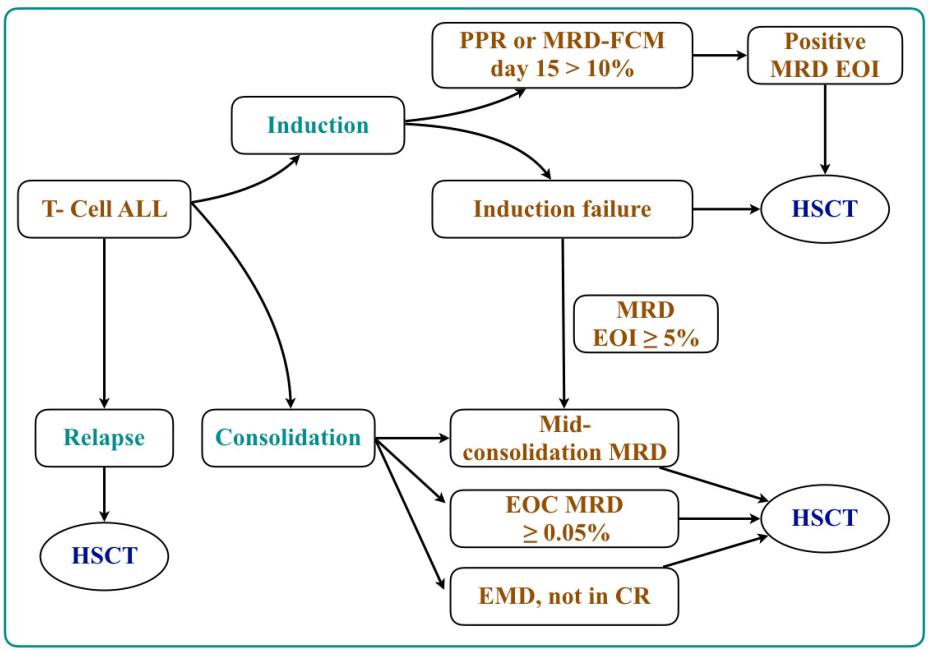
*ALL: acute lymphoblastic leukemia, CR: complete remission, CR1: first complete remission, EOC: end of consolidation, EOI: end of induction, HR: high-risk, MRD: measurable residual disease, NCI: National Cancer Institute, Ph+: Philadelphia-positive, WBC: white blood cell*

**Table 14.** Indications for HSCT in Pediatric Patients with B-Cell ALL in Second Complete Remission (CR2)

| Indication | Criteria |
|---|---|
| All High-Risk Relapses | • All very early relapses (<18 months from diagnosis), irrespective of site<br>• Early B-ALL isolated BM relapses (18 months from diagnosis but <6 months after end of treatment) |
| Standard-Risk Relapses, if Positive MRD at EOI | • Early* and late IEM relapse (18 months from diagnosis)<br>• Late BM relapse (>6 months after end of treatment)<br>• Early/late combined BM and IEM relapse (>18 months from diagnosis) |

*B-ALL: B-cell acute lymphoblastic leukemia, BM: bone marrow, EOI: end of induction, IEM: isolated extramedullary, MRD: measurable residual disease*
**Early isolated EM relapse if HLA-matched donor available*

**Figure 5.** Indications for HSCT in Pediatric Patients with T-Cell ALL




*ALL: Acute Lymphoblastic Leukemia, EOC: End of Consolidation, EOI: End of Induction, FCM: Multicolor flow cytometry, HSCT: Hematopoietic Stem Cell Transplantation, MRD: Measurable Residual Disease, PRP: Poor Prednisolone Response*

* *The conditioning regimen plays a vital role in determining the outcomes of HSCT for patients with hematological malignancies. Total body irradiation (TBI)-based conditioning before allogeneic HSCT is considered the gold standard for children aged 4 years and older with ALL. This method has been linked to improved overall survival (OS) and event-free survival (EFS), as well as a reduced risk of relapse and treatment-related mortality (TRM), compared to patients who undergo myeloablative chemotherapy conditioning regimens. Despite its benefits, long-term sequelae following TBI can include secondary malignancies, as well as neurocognitive, endocrine, and cardiometabolic effects, which are significant drawbacks. Additionally, TBI requires specialized facilities, including sedation or anesthesia for pediatric patients (208-210).*

## Acute Myeloid Leukemia

In contrast to adults, where allogeneic HSCT significantly improves relapse-free survival (RFS) and OS in intermediate- and poor-risk acute myeloid leukemia (AML) during first complete remission (CR1), the role of HSCT as a consolidation treatment for newly diagnosed pediatric AML remains a topic of considerable debate. Currently, there is no consensus on the use of allogeneic HSCT in CR1 for children with AML. Decisions regarding the optimal indication for HSCT are made by carefully weighing the risk of relapse against the risk of non-relapse mortality (NRM) and the potential late effects associated with the procedure (211-214).

**Table 15** presents the current indications for allogeneic HSCT in pediatric patients with AML. These indications reflect the evolving understanding of risk stratification and treatment response in pediatric AML, emphasizing the importance of genetic factors and MRD assessment in determining eligibility for HSCT.

**Table 15.** Indications for HSCT in Pediatric Patients with AML

| Indication | Criteria |
|---|---|
| High-Risk Cytomolecular Abnormalities | • Abnormalities of 3q: inv(3)(q21.3q26.2)/t(3;3)(q21.3q26.2)/RPN1-MECOM, t(3;21)(q26.2;q22)/RUNX1-MECOM, t(3;5)(q25;q34)/NPM1-MLF1<br>• t(6;9)(p22.3;q34.1)/DEK-NUP214<br>• inv(16)(p13.3q24.3)/CBFA2T3-GLIS2<br>• 11p15 rearrangement/NUP98-any partner gene (eg, t(5;11)(q35;p15.5)/NUP98-NSD1, NUP98-KDM5A)<br>• t(4;11)(q21;q23.3)/KMT2A-AFF1 (MLL-MLLT2)<br>• t(6;11)(q27;q23.3)/KMT2A-AFDN (MLL-MLLT4)<br>• t(10;11)(p12.3;q23.3)/KMT2A-MLLT10<br>• t(10;11)(p12.1;q23.3)/KMT2A-ABI1<br>• t(11;19)(q23.3;p13.3)/KMT2A-MLLT1(MLL-ENL)<br>• t(11;12)(p15;p13)/NUP98-KDM5A<br>• t(7;11)(p15.4;p15)/NUP98-HOXA9<br>• t(5;11)(q35;p15)/NUP98-NSD1<br>• t(16;21)(q24;q22)/RUNX1-CBFA2T3<br>• t(7;12)(q36;p13)/MNX1-ETV6<br>• t(16;21)(p11.2;q22.2)/FUS-ERG<br>• Abnormalities of 12p (ETV6): 12p13.2 rearrangement/ETV6-any partner gene, deletions of 12p.13.2/loss of ETV6<br>• Monosomy5/del(5q) to include 5q31, loss of EGR1<br>• Monosomy 7<br>• High allelic ratio FLT3/ITD (allelic ratios cutoffs may vary)<br>• Complex karyotype (≥3 aberrations including at least one structural aberration) |
| Response Risk* | • MRD ≥1% after the first induction course<br>• MRD ≥1 × $10^{-3}$ after the second induction course<br>• Primary induction failure [i.e. patients with ≥25% blasts after the first induction course and ≥5% blasts after the second induction course] |
| Secondary AML | • Therapy-related AML<br>• AML evolving from MDS |
| Second Complete Remission (CR2) and Beyond | • All patients in CR2 and beyond |

*CR2: second complete remission, MDS: myelodysplastic syndrome, MRD: measurable residual disease*

**For patients with favorable-risk AML (NPM1, CEBPA, t(8;21), inv(16)/t(16;16)) who are MRD-positive at first EOI, HSCT consolidation*

*is not required based on this early time point.*

For pediatric patients with AML, the optimal conditioning regimen has yet to be clearly defined. Studies indicate that chemotherapy-based conditioning regimens result in lower NRM and relapse rates than TBI-based regimens (215, 216). The most commonly used chemotherapy regimens for children with AML include BuCy (Busulfan + Cyclophosphamide), BuFlu (Busulfan + Fludarabine), and BuCyMel (Busulfan + Cyclophosphamide + Melphalan).

BuFlu represents a valid myeloablative regimen that can provide lower TRM and reduced rates of acute and chronic graft-versus-host disease (GVHD). This conditioning regimen may serve as an alternative approach for patients at high risk of severe post-transplant complications (217).

BuCyMel has been associated with a significant reduction in relapse incidence compared to BuCy and may be considered a preparative regimen for AML patients at higher risk of relapse, particularly those with high-risk cytogenetics (218).

At RIOHCT, we utilize T-cell-replete peripheral blood stem cells (PBSCs) and chemotherapy-based conditioning regimens for patients with acute leukemia, including:

- **BuCy (Busulfan + Cyclophosphamide)** *[Figure 6,7]*
- **BuFlu (Busulfan + Fludarabine)** *[Figure 8,9]*
- **BuCyMel (Busulfan + Cyclophosphamide + Melphalan)** *[Figure 10]*
- **BuFluCy (Busulfan + Fludarabine + Cyclophosphamide)** *[Figure 11]*
- **TBF (Thiotepa + Busulfan + Fludarabine)** *[Figure 12-14]*

The choice of conditioning regimen depends on several factors:

- Donor source: Matched related donor (MRD), matched unrelated donor (MUD), mismatched related or unrelated donor, or haploidentical donor. Anti-thymocyte globulin (ATG) may be incorporated into the conditioning regimen when using alternative donors to prevent graft rejection and GVHD.
- Stem cell source: PBSCs, bone marrow (BM), or umbilical cord blood (UCB). The stem cell source is particularly important in determining the composition of the preparative regimen before HSCT.

These chemotherapy-based conditioning regimens aim to eradicate residual leukemia cells while providing sufficient immunosuppression to allow engraftment of donor cells. The intensity of the conditioning regimen is tailored to the patient's disease status, comorbidities, and transplant-related factors to optimize outcomes and minimize toxicity.

Whenever possible, the interval between the end of the last chemotherapy and the start of the conditioning *regimen should be 3–6 weeks to reduce the risk of NRM* (2*).*

**Figure 6.** Myeloablative Conditioning (MAC): (BU-CY)
- Acute Leukemia (AL)
- Matched Related Donor (MRD)

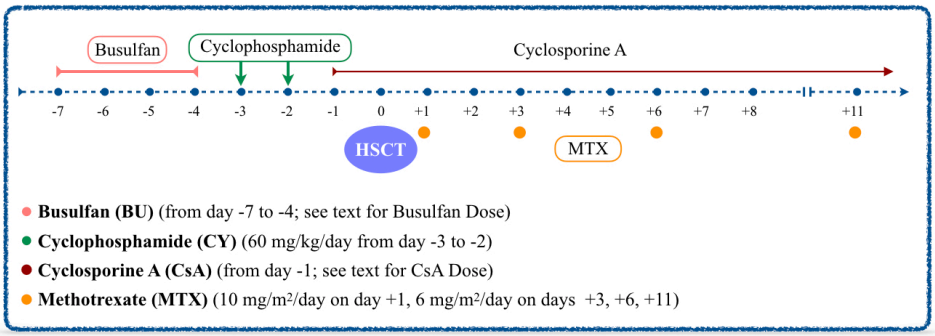
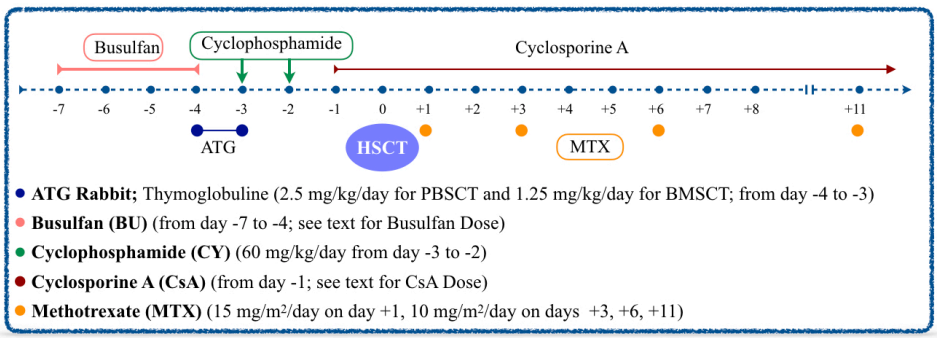



**Figure 7.** Myeloablative Conditioning (MAC): (BU-CY)
- Acute Leukemia (AL)
- Matched Unrelated Donor (MUD)




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

**Figure 8.** Myeloablative Conditioning (MAC): (BU-FLU)
- Acute Myeloid Leukemia (AL)
- Matched Related Donor (MRD)

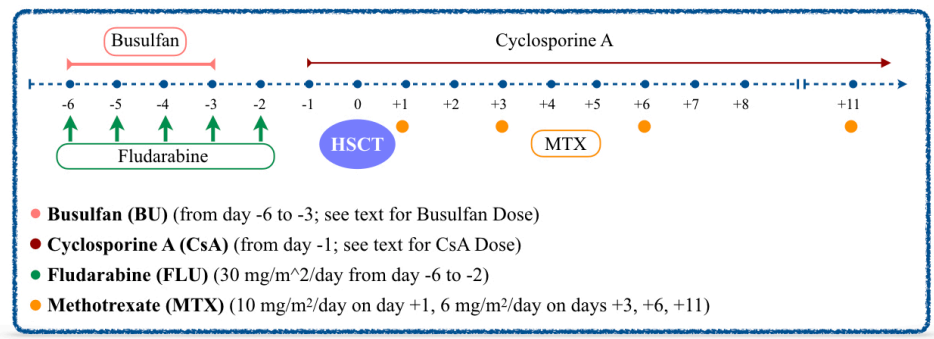
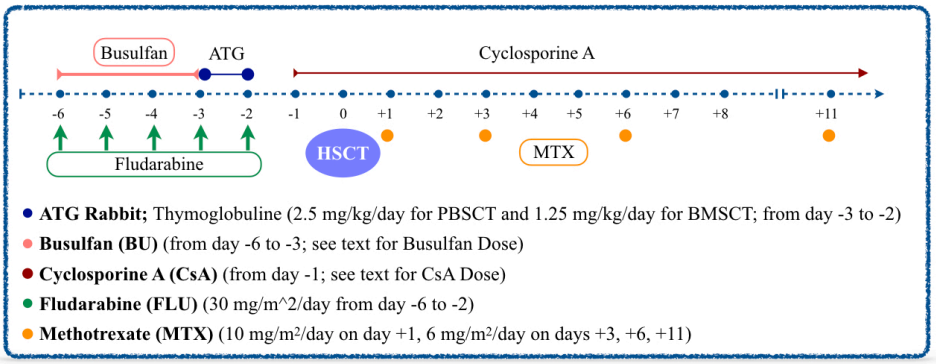


**Figure 9.** Myeloablative Conditioning (MAC): (BU-FLU)
- Acute Myeloid Leukemia (AML)
- Matched Unrelated Donor (MUD)




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

**Figure 10.** Myeloablative Conditioning (MAC): (BU-FLU-MEL)
- Acute Myeloid Leukemia (AML)
- Matched Related Donor (MRD)

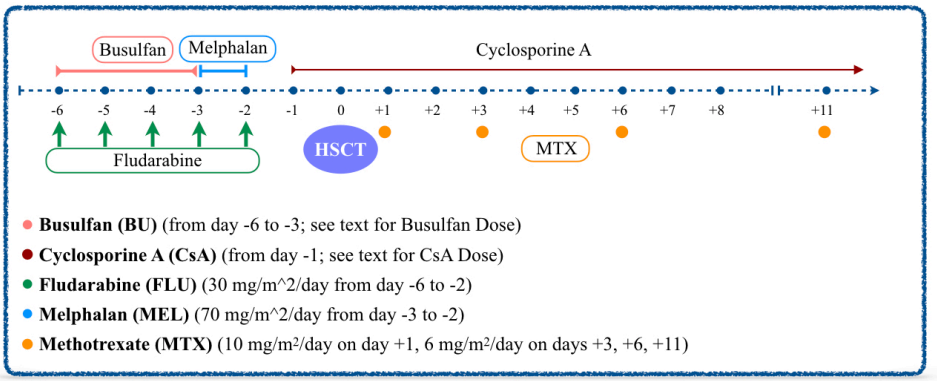



**Figure 11.** Myeloablative Conditioning (MAC): (BU-FLU-CY)
- Acute Leukemia (AL)
- Haploidentical Stem Cell Transplantation

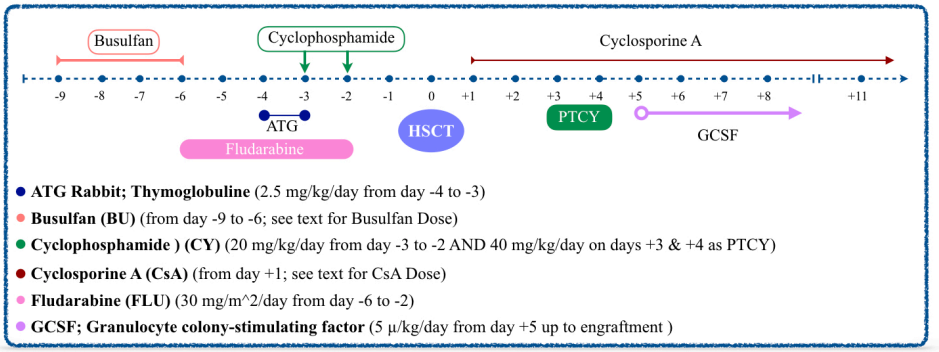


**Figure 12.** Myeloablative Conditioning (MAC): (TT-BU-FLU)
- Acute Lymphoblastic Leukemia (ALL)
- Matched Related Donor (MRD)

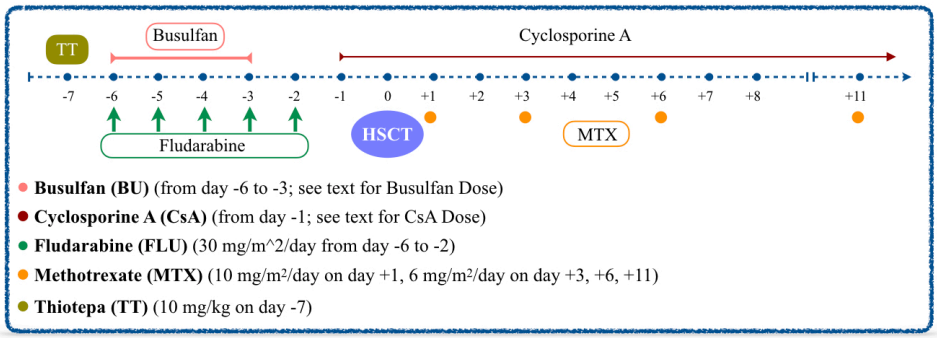
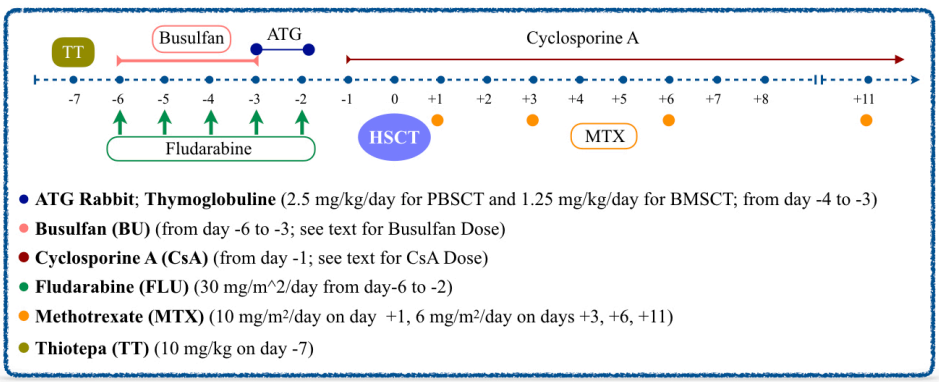
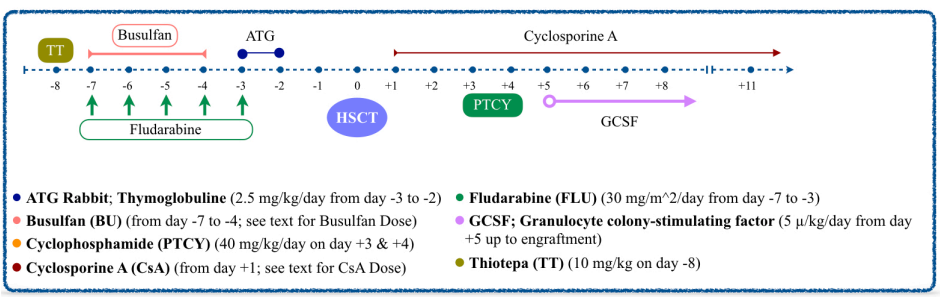



**Figure 13.** Myeloablative Conditioning (MAC): (TT-BU-FLU)
- Acute Lymphoblastic Leukemia (ALL)
- Matched Unrelated Donor (MUD)




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

**Figure 14.** Myeloablative Conditioning (MAC): (TT-BU-FLU)
- Acute Lymphoblastic Leukemia (ALL)
- Haploidentical Stem Cell Transplantation



## Mixed-Phenotype Acute Leukemia

While HSCT has been associated with improved outcomes in adults with mixed phenotype acute leukemia (MPAL) and is recommended during CR1, several pediatric studies suggest that HSCT may not provide significant benefit in CR1, especially for those with favorable characteristics (219). In pediatric patients, HSCT in CR1 is generally considered for those with positive MRD following consolidation, as outlined by the Children's Oncology Group (COG) and BFM-AIEOP protocols (220).

## Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) represents 5% to 7% of all pediatric AMLs and has shown an OS rate of 98.4% and an EFS rate of 89.4% in standard-risk patients, and 84.3% and 74.2% in high-risk patients, respectively (P= 0.002 and P= 0.043). These outcomes were achieved through the International Consortium for Childhood APL (ICC-APL-01) trial, which aimed to reduce anthracycline exposure while increasing the use of all-trans retinoic acid (ATRA) (221).

HSCT is no longer indicated for patients with APL in CR1, except for those who have persistent PML-RARA transcripts at the end of consolidation (<1%). In such cases, salvage therapy followed by allogeneic HSCT is recommended (2).

However, HSCT is crucial for patients who relapse and achieve a second CR (CR2) following salvage chemotherapy. The decision between allogeneic HSCT and autologous HSCT hinges on the understanding that graft-versus leukemia (GVL) effect in allogeneic HSCT may be offset by a higher risk of TRM. Furthermore, patients who relapse after autologous HSCT are more likely to attain a successful second remission through salvage therapy compared to those who relapse following allogeneic HSCT (222-224).

Prognostic factors linked to transplant outcomes in APL during CR2 that negatively affect patient outcomes include a relapse time of less than 18 months from diagnosis, prior treatment with arsenic trioxide (ATO) which may be associated with delayed hematopoietic recovery after transplantation, and the inability to eliminate the PML-RARA transcript (225-227). Based on these recommendations, for children who experience a relapse within 18 months of the initial diagnosis and have either previously received ATO or have not been exposed to it:

- Autologous HSCT is considered if a second complete molecular remission (CMR) is achieved following the induction and consolidation strategy.
- If PML-RARA remains positive at the end of consolidation, allogeneic HSCT is recommended after an additional cycle of intensive therapy.

For children who relapse 18 to 36 months after the initial diagnosis:

- If they have been previously treated with ATO and achieve CMR after four consolidation courses, they may be considered for autologous HSCT. For those who remain positive for the PML-RARA transcript, allogeneic HSCT is planned following additional intensive consolidation chemotherapy.
- In children who have not been previously exposed to ATO, reinduction with ATO-

ATRA and gemtuzumab ozogamicin (GO) is recommended. If CMR is achieved, maintenance therapy with ATO-ATRA is initiated, and if PML-RARA remains persistently positive at the end of consolidation, allogeneic HSCT is considered.

In patients who experience a very late relapse, defined as hematological or molecular relapse occurring more than 36 months after diagnosis, the benefits of consolidation HSCT are uncertain. For these individuals, maintenance therapy with ATO-ATRA may be an option.

### Extramedullary Relapse

Extramedullary relapse in APL can occur in various locations, with the central nervous system (CNS), skin, and external auditory canal being the most common (228, 229). CNS relapse with a very low incidence in children (1.39%) (230) is mostly accompanied by signs of molecular disease in the BM and is significantly associated with elevated white blood cell (WBC) counts and/or intracranial hemorrhage at diagnosis (230, 231). For CNS relapses, intrathecal chemotherapy, with or without ATO-ATRA, has been reported as an effective treatment option (232). Since ATO accumulates in epidermal tissues and can cross the blood-brain barrier, reaching cerebrospinal fluid (CSF) levels that may be up to 50% of serum levels, a therapeutic response at these sites is anticipated (233).

The role of HSCT in isolated CNS relapse remains controversial, although it was recommended by the European Leukemia Network (ELN) in 2009 (234). For patients with concurrent molecular disease in the BM, achieving a CMR is crucial for the successful outcome of autologous HSCT. Some experts recommend allogeneic HSCT for patients with an available human leukocyte antigen (HLA)-identical donor, while others prefer autologous HSCT due to its lower risk of TRM (232).

In terms of the conditioning regimen, there is no universally established best chemotherapy protocol. However, myeloablative conditioning (MAC) regimens, commonly used for AML, have been widely applied for both autologous and allogeneic HSCT (2, 232).

## Hemoglobinopathies

### Thalassemia

Despite progressive improvements in the management of hemoglobinopathies, allogeneic HSCT remains the only potentially curative and widely available option for patients with transfusion-dependent thalassemia (TDT) (235).

According to the 2021 Thalassaemia International Federation (TIF) guidelines, HSCT should be offered to thalassemia patients at an early age, before the development of complications related to iron overload (236).

To predict the outcomes of HSCT, the Pesaro group developed a prognostic score for patients under 17 years of age, stratifying them into three risk groups based on factors such as the adequacy of iron chelation, hepatomegaly, and portal fibrosis (237-239). Another critical factor influencing post-transplant outcomes is the preparatory regimen,

which aims to eliminate the disordered marrow and create a supportive environment for the transplanted marrow to survive and thrive (240). Transplant-related acute and long-term complications primarily arise from the intensity of the conditioning regimen (241).

An optimized conditioning regimen is crucial to maximize outcomes for patients with TDT undergoing HSCT. The conditioning regimens have evolved over time, with myeloablative BuCy being the standard approach due to their effectiveness in heavily transfused patients. However, this regimen is associated with hepatic and cardiac toxicity due to iron overload and the adverse effects of busulfan and cyclophosphamide (238).

One of the most prevalent toxicities associated with conditioning regimens is busulfan-induced veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS), which is dose-dependent (242, 243). Treosulfan, a water-soluble bifunctional alkylating agent with myeloablative and immunosuppressive properties, has demonstrated a reduced risk of hepatic, pulmonary, and neurological toxicity compared to busulfan-based regimens (244).

With the advent of reduced-toxicity, fludarabine-based MAC regimens (245, 246), Treosulfan has emerged as a safe and effective component when used in combination with fludarabine and thiotepa. Studies indicate that treosulfan-based conditioning regimens are associated with significantly reduced incidences of non-hematologic acute toxicities commonly observed in allogeneic HSCT recipients undergoing standard conditioning therapy, allowing for fast and sustained engraftment. Overall, the combination of treosulfan, fludarabine, and thiotepa represents a promising approach to conditioning in HSCT, particularly for patients at high risk of complications (247).

To further reduce the risk of graft failure (GF), several strategies may be considered, including the addition of thiotepa to the conditioning regimen, implementing a pretransplant immune suppression (PTIS) phase with hypertransfusions, and utilizing hydroxyurea and azathioprine before transplantation. The use of ATG or alemtuzumab may also be beneficial (248).

## Haploidentical Hematopoietic Stem Cell Transplantation

Clinical outcomes for children with hematologic malignancies undergoing haploidentical HSCT have shown consistent improvement over time (249-253). However, those with hemoglobinopathies face additional challenges, including hyperplastic BM and frequent alloimmunization from prior transfusions. These issues contribute to a heightened risk of GF and a TRM rate of 30% (248, 254-257).

To mitigate graft rejection in patients with thalassemia major undergoing haploidentical HSCT, innovative strategies have been introduced. One significant approach developed by Anurathapan et al. involves administering two cycles of PTIS using fludarabine and dexamethasone (258). The conditioning regimen used was myeloablative and included ATG, busulfan, fludarabine, cyclophosphamide, and post-transplant cyclophosphamide (PTCY) administered on days +3 and +4, resulting in an engraftment rate of 90%. This protocol demonstrated a low incidence of both acute and chronic GVHD, making

haploidentical HSCT a favorable option for children without appropriately matched donors (258).

Another regimen that incorporates rabbit ATG, thiotepa, fludarabine, cyclophosphamide, and 200 cGy TBI provides adequate immunosuppression to achieve successful engraftment. Furthermore, administering PTCY at a dose of 50 mg/kg per day on days +3 and +4, in conjunction with tacrolimus, ensures effective in vivo T-cell depletion (TCD) in haploidentical HSCT (259).

## Sickle Cell Disease

Allogeneic HSCT is currently regarded as a curative treatment for severe sickle cell disease (SCD) (260). It is most commonly offered to patients with serious SCD-related complications including stroke, recurrent vaso-occlusive crises, episodes of acute chest syndrome (ACS), and other significant organ damages (261-263). **Table 16** outlines the current indications for HSCT based on specific SCD complications and also the type of donor that might be considered (i.e., MRD, haploidentical related donor, or MUD) (264).

**Table 16.** Current Indications for HSCT in Patients with SCD (One or More of the Following Complications)

| Donor | Indications for HSCT |
|---|---|
| MSD | • Stroke or CNS event lasting >24 h<br>• Impaired cognition/neuropsychological function with abnormal cerebral MRI/MRA<br>• Elevated transcranial Doppler velocity<br>• Recurrent ACS<br>• Recurrent pain/VOEs<br>• Red cell alloimmunization<br>• Pulmonary hypertension/TRJV >2.5 m/s<br>• Osteonecrosis/*AVN*<br>• Recurrent priapism<br>• Sickle nephropathy<br>• Sickle retinopathy<br>• Sickle lung disease |
| MUD | • Stroke or CNS event lasting >24 h<br>• Elevated transcranial Doppler velocity unresponsive to hydroxyurea or chronic blood transfusion therapy<br>• Recurrent ACS despite supportive care<br>• Recurrent pain/VOEs despite supportive care<br>• Red cell alloimmunization despite intervention plus established indication for chronic transfusion therapy<br>• Pulmonary hypertension/TRJV >2.5 m/s<br>• Recurrent priapism<br>• Sickle nephropathy<br>• Osteonecrosis /AVN |
| Alternative donor | • Recurrent stroke despite adequate chronic transfusion therapy or progressive CNS changes<br>• Inability to tolerate supportive care though strongly indicated, e.g. red cell alloimmunization, severe VOE and inability to tolerate hydroxyurea |

*ACS: acute chest syndrome, AVN: avascular necrosis, CNS: central nervous system, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging, MSD: matched sibling donor, MUD: matched unrelated donor, TRJV: tricuspid regurgitation jet velocity, VOE: veno-occlusive episode*

Given that there are no randomized clinical trials (RCTs) comparing stem cell transplant with conservative approaches in patients with SCD, a multidisciplinary guideline panel formed by the American Society of Hematology (ASH) addressed eight recommendations with very low certainty in the evidence, focused predominantly on which patients should be considered for HSCT **(Table 17)** (265).

**Table 17.** Summary of American Society of Hematology (ASH) Recommendations for HSCT in Patients with SCD.

| | |
|---|---|
| 1 | The ASH guideline panel suggests HLA-matched related HSCT rather than standard of care (hydroxyurea/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound.<br>When considering transplantation for neurologic injury, children younger than 16 years who receive MSD HSCT have better outcomes than those older than 16 years. |
| 2 | For patients with frequent pain, the ASH guideline panel suggests using matched related allogeneic transplantation rather than standard of care. |
| 3 | For patients with recurrent episodes of ACS, the ASH guideline panel suggests using matched related allogeneic transplantation over standard of care. |
| 4 | For patients with SCD with an indication for HSCT who lack an MSD, the ASH guideline panel suggests using transplants from alternative donors in the context of a clinical trial. |
| 5 | For allogeneic HSCT, the ASH guideline panel *suggests* using either TBI ≤400 cGy or chemotherapy-based conditioning regimens. |
| 6 | For children with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* using MAC over RIC that contains melphalan/fludarabine regimen.<br>For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* NMA conditioning over RIC that contains melphalan/fludarabine regimens. |
| 7 | In patients with an indication for HSCT, the ASH guideline panel *suggests* using allogeneic transplantation at an earlier age rather than an older age. |
| 8 | The ASH guideline panel *suggests* the use of HLA-identical sibling UCB when available (with an adequate cell dose and good viability) over BM. |

*ACS: acute chest syndrome, BM: bone marrow, CB: cord blood HLA: human leukocyte antigen, HSCT: hematopoietic stem cell transplantation, MAC: myeloablative conditioning, MSD: matched sibling donor; NMA: non-myeloablative conditioning, RIC: reduced intensity conditioning, SCD: sickle cell disease, TBI: total body irradiation, UCB: umbilical cord blood*

Modifications to traditional MAC regimens, which typically involve busulfan in combination with high doses of cyclophosphamide and the addition of ATG to mitigate the risk of graft rejection, have enhanced the outcomes of HSCT in pediatric patients with SCD. However, adult patients may face significant toxicity from MAC regimens due to accumulated end-organ damage (266).

To address these concerns, reduced-intensity conditioning (RIC) regimens have been developed, incorporating fludarabine, melphalan, and thiotepa or total lymphoid irradiation. These RIC regimens are designed to minimize the toxicities associated with MAC,

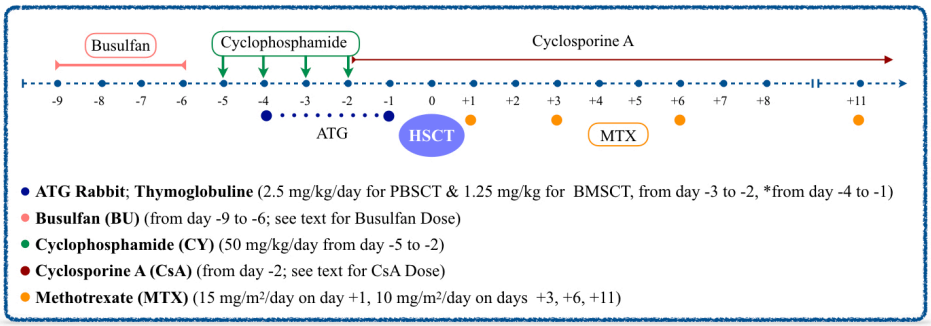
making HSCT more acceptable and better tolerated for patients with SCD (267).

Furthermore, non-myeloablative (NMA) conditioning regimens, which are associated with lower rates of GVHD and HSCT-related toxicity, have proven to be safe, feasible, and effective in reducing complications related to SCD in severely affected adults (268, 269).

In the pediatric cell therapy unit of RIOHCT, the conditioning regimen for TDT patients is tailored based on the Pesaro (Locarelli) risk classification (LRC). For patients classified as LRC I and II, the myeloablative BuCy regimen is employed and patients with LRC III are considered for the myeloablative FluBuCy regimen. Additionally, the favorable effects of serotherapy with ATG on engraftment have led to its widespread adoption in our preparative regimens. This approach aims to enhance the likelihood of successful engraftment while minimizing the risks associated with graft rejection. Overall, the combination of risk stratification and the incorporation of effective conditioning regimens, including the use of ATG, reflects our commitment to optimizing outcomes for TDT patients undergoing allogeneic HSCT.

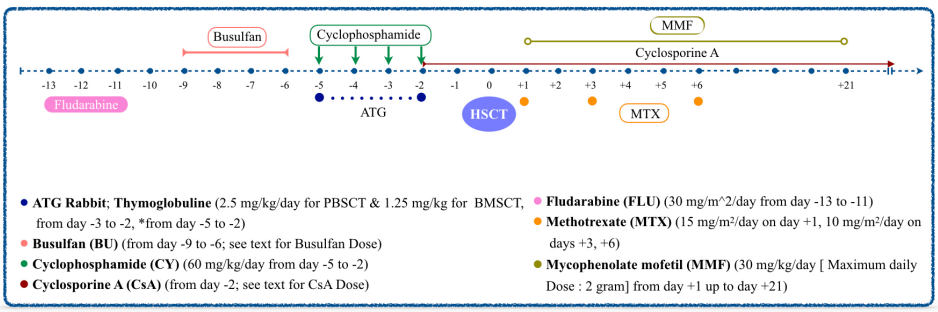
***Figures 15 & 16*** illustrate our conditioning regimens for HSCT in patients with TDT and SCD.

**Figure 15.** Myeloablative Conditioning (MAC): (BU-CY)
- Major Thalassemia LRC I & II / Sickle Cell Disease
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

**Figure 16.** Myeloablative Conditioning (MAC): (BU-FLU-CY)
- Major Thalassemia LRC III / (>15 Years old)
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

## Haploidentical Hematopoietic Stem Cell Transplantation

Finding a suitable HLA-matched related or unrelated donor is possible for only a small percentage of the SCD population. Consequently, there is considerable optimism regarding using haploidentical family members, as this approach could expand access to HSCT for many patients who currently lack viable treatment options for their SCD. However, initial observational studies have indicated a higher incidence of GF and associated complications in haploidentical HSCT than in transplants from sibling donors (270). GF was more common among patients who underwent NMA conditioning with in vitro donor TCD compared to those who received NMA conditioning with PTCY, MAC with in vitro TCD, or MAC with PTCY. However, modifications to the NMA regimens, such as adding thiotepa or increasing TBI dose from 2 Gy to 4 Gy alongside PTCY, significantly improved sustained engraftment rates. Furthermore, while optimized NMA regimens have demonstrated results comparable to MAC regimens, chemotherapy-based MAC regimens utilizing fludarabine and treosulfan have become the most commonly used preparative regimens for haploidentical HSCT in SCD in recent years (271-274).

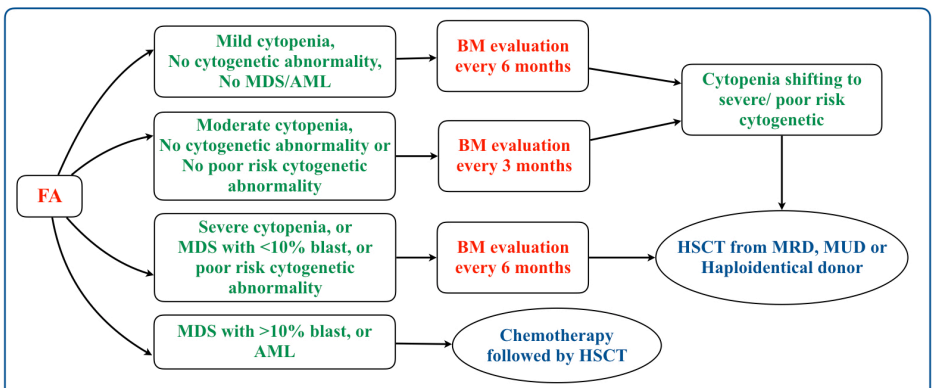
# Fanconi Anemia and Other Hereditary Bone Marrow Failure Syndromes

## Fanconi Anemia

Allogeneic HSCT is currently the only curative option for hematological disorders in patients with Fanconi anemia (FA). This treatment has the potential to address bone marrow failure (BMF) and prevent clonal hematopoietic disorders associated with FA (275, 276).

Established indications for HSCT in FA include severe cytopenia, progression of moderate cytopenia, poor prognosis cytogenetic abnormalities, and the presence of overt myelodysplastic syndrome (MDS) or AML. ***Figure17*** illustrates the hematologic monitoring and decision-making process for patients with FA following diagnosis (277).

**Figure 17.** Decision-making process for patients with Fanconi anemia




AML: Acute Myeloid Leukemia, BM: Bone Marrow, FA: Fanconi Anemia, HSCT: Hematopoietic Stem Cell Transplant, IST: Immunosuppressive Therapy, MDS: Myelodysplastic Syndrome, MRD: Matched Related Donor, MUD: Matched Unrelated Donor

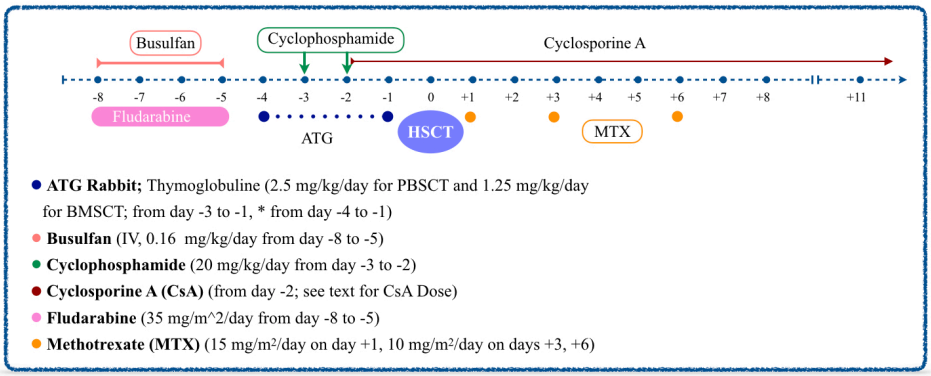
The initial conditioning regimens for FA included high doses of cyclophosphamide and TBI (278). However, due to the hypersensitivity of FA cells to high doses of cyclophosphamide and radiation (279), reducing these doses has helped decrease TRM, but it has also led to poor engraftment and graft function (280). As an alternative, fludarabine, an antimetabolite with strong immunosuppressive properties, has been incorporated into conditioning regimens. Fludarabine does not have DNA cross-linking properties, which helps reduce the incidence of toxicity and GVHD in patients with FA (281). Fludarabine is known for its immunosuppressive effects and is often used in conditioning regimens prior to allogeneic HSCT due to its ability to minimize toxicity while effectively suppressing the immune response. In the context of treating hematological malignancies, fludarabine has demonstrated efficacy in various settings, including its incorporation into regimens with RIC. This approach allows for better tolerance in patients with compromised BM function, such as those with FA, while leveraging the immunosuppressive properties of fludarabine to facilitate successful engraftment and enhance the effectiveness of the transplant.

Our main preparative regimen for HSCT in FA patients is a radiation-free, fludarabine-based conditioning consisting of fludarabine, intravenous (IV) busulfan, reduced dose of cyclophosphamide, and ATG ***[Figure 18].***

As mentioned, patients with FA have a DNA repair defect and consequently are more sensitive to DNA cross-linking agents like busulfan. Due to the narrow therapeutic index of busulfan, it is recommended to dose using therapeutic drug monitoring (TDM) to decrease toxicity and prevent graft rejection. Precision dosing of busulfan is usually reflected by measuring the area under the plasma concentration-time curve (AUC) or concentration at steady state (Css). However, this approach is not routinely used in FA patients, and data about pharmacokinetics (PKs)-guided busulfan dosing in patients with FA is scarce. In a study by Mehta et al., an optimal busulfan Css level of ≤350 ng/mL has been proposed (282).

The incorporation of TDM for busulfan dosing aims to further optimize the balance between efficacy and safety. However, the lack of robust data on PK-guided busulfan dosing in FA patients highlights the need for additional research to establish optimal dosing strategies and improve outcomes for these high-risk individuals.

**Figure 18.** Myeloablative Conditioning (MAC): (BU-FLU-CY)
- Fanconi Anemia (FA)
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

## Haploidentical Hematopoietic Stem Cell Transplantation

In the absence of a well-matched unaffected related donor, and considering that many patients lack a suitable MUD, patients may be candidates for alternative donor transplantation. This is especially pertinent for those experiencing disease progression or clonal evolution. Haploidentical HSCT combined with low-dose PTCY (25 mg/kg on days +3 and +4) offers an immediately available option for nearly all patients. It has been reported as a well-tolerated and effective approach for individuals with FA, demonstrating promising engraftment rates and a manageable risk of GVHD (283, 284).

The most commonly used conditioning regimen for patients with FA undergoing haploidentical HSCT includes fludarabine, cyclophosphamide, and TBI, followed by the administration of ATG (285). Additionally, studies utilizing radiation-free preparative regimens with moderate-dose alkylating agents have demonstrated promising engraftment and survival rates. However, these regimens have been associated with a notably higher incidence of severe acute GVHD compared to TBI-containing regimens, whether or not they include low-dose alkylating agents (286-288).

Furthermore, serotherapy with ATG has been linked to a significant reduction in GVHD incidence and an increase in OS without any effect on GF (289).

Graft manipulation techniques that focus on the selective depletion of T-cell receptor (TCR)-αβ and CD19+ lymphocytes have been also employed in haploidentical HSCT for patients with FA. These methods have resulted in good engraftment rates, a low incidence of post-HSCT complications, and excellent survival outcomes (275).

## Diamond-Blackfan Anemia

Diamond-Blackfan anemia (DBA) is a congenital disorder characterized by pure red cell aplasia (PRCA), associated with constitutional abnormalities and an increased risk of de-

veloping hematologic malignancies such as AML/MDS, as well as non-hematologic cancers like osteosarcoma and colon cancer. HSCT is currently the only curative treatment option for patients with hematological manifestations of DBA (290-292). The indications for HSCT include (293):

- Steroid-unresponsive, defined as no increase in reticulocyte count at a dose of at least 1 mg/kg/day prednisone
- Steroid-responsive but requires more than 0.3–0.5 mg/kg/day prednisone to maintain acceptable hemoglobin (Hb) levels
- Growth impairment or other unacceptable toxic effects of steroids, even on low doses, including weight gain, irritability, insomnia, hypertension, hyperglycemia, osteoporosis, and skin alterations
- Transfusion dependency
- Clonal evolution or myelodysplasia or clinically relevant thrombocytopenia or neutropenia

MAC using busulfan (and more recently treosulfan) combined with fludarabine is currently recommended as the standard regimen. Due to the need for multiple transfusions and to prevent GF, ATG is included in the conditioning protocol. It is important to note that TBI should be avoided, as patients with DBA are already at an increased risk of developing malignancies (293).

Our conditioning regimen for these patients consists of busulfan and cyclophosphamide (Bu-Cy), with an alternative option being busulfan, fludarabine, and thiotepa (Bu-Flu-Thiotepa), plus ATG.

## Congenital Amegakaryocytic Thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare inherited BMF syndrome (IBMFS) that carries an increased risk of progressing to trilineage BM aplasia within the first decade of life, as well as developing myeloid malignancies. Although HSCT is the only curative treatment available, the optimal timing for HSCT remains uncertain; it is unclear whether transplantation should occur at the time of diagnosis when the patient requires transfusion support, or upon the progression of BM aplasia or clonal evolution (294, 295).

MAC is the preferred preparative regimen. However, in patients who develop severely hypocellular BM, and in the absence of clonal aberrations and alloimmunization to platelet transfusions, RIC may be considered.

At the Pediatric Cell Therapy Unit of RIOHCT, we utilize a fludarabine-based MAC regimen. Since these patients are often multiply transfused, ATG is also included in the conditioning protocol.

# Acquired Bone Marrow Failure: Severe Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria

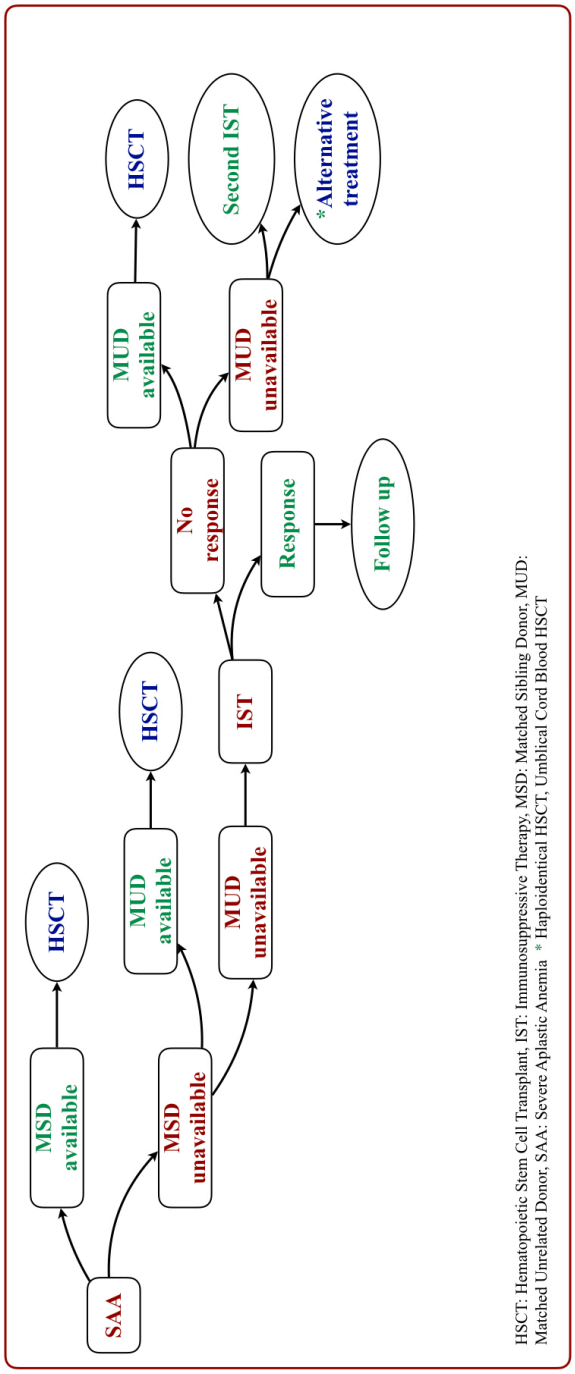
## Severe Aplastic Anemia

Severe aplastic anemia (SAA) is an immune-mediated BMF disorder characterized by destruction of hematopoietic progenitor cells (HPCs) due to a cytotoxic T-cell-mediated autoimmune response, resulting in pancytopenia. For children with SAA, allogeneic HSCT from a matched sibling donor (MSD) is the recommended first-line treatment, with survival rates ranging from 85% to 97%. This strategy has demonstrated superior outcomes in patients who undergo upfront transplantation compared to those who receive immunosuppressive (IS) therapy (296-298).

In a study conducted by the UK Pediatric Bone Marrow Transplantation (BMT) Working Party, the Pediatric Diseases Working Party, and the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT), the evaluation of upfront MUD stem cell transplant in pediatric patients with SAA revealed outcomes comparable to HSCT from MSDs. Furthermore, MUD HSCT demonstrated better results than IS therapy and was superior to unrelated donor HSCT following IS therapy failure. The study recommends considering upfront MUD HSCT as a first-line therapy for pediatric patients who do not have an MSD (299).

Currently, many centers utilize a 10/10 MUD as a frontline treatment option for young patients when an MSD is unavailable and when HSCT from a suitable MUD donor can be performed within 2-3 months of diagnosis. ***Figure 19*** illustrates the hierarchical management approach for children with SAA.

**Figure 19.** Management of severe aplastic anemia (SAA) in pediatrics



The NMA reduced-toxicity conditioning regimen consisting of fludarabine (30 mg/m²/day for 4 days) and cyclophosphamide (25 mg/kg/day for 4 days) is recommended by the European Working Group (EWOG) of MDS and SAA as the chemotherapy backbone for allogeneic HSCT in pediatric patients with SAA (300). This regimen has demonstrated favorable outcomes in retrospective studies (301-303).

The incorporation of serotherapy with rabbit or horse ATG (rATG/hATG) or alemtuzumab has improved outcomes of HSCT in SAA (304, 305). While rATG is associated with a lower risk of acute and chronic GVHD, it also presents a higher incidence of opportunistic infections and mixed chimerism compared to hATG (306, 307). The cumulative doses of rATG for children undergoing HSCT vary based on donor type and graft source, typically ranging from 40 to 60 mg/kg for Grafalon and 8 to 10 mg/kg for Thymoglobulin (300).

Alemtuzumab has also been shown to reduce both acute and chronic GVHD; however, it is associated with a higher rate of GF.

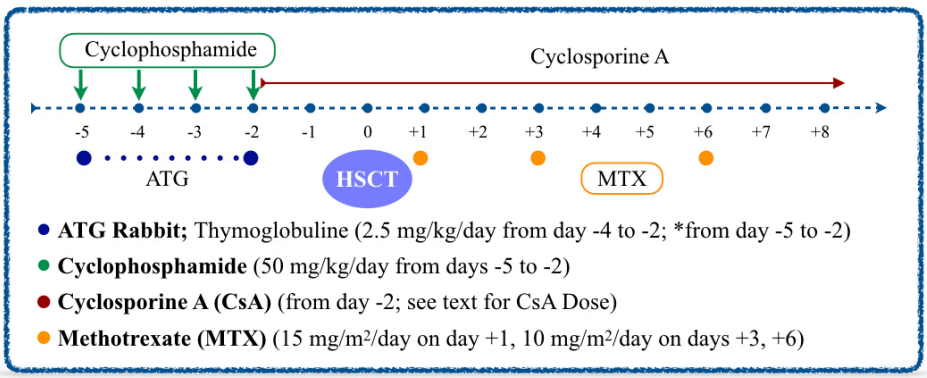
Overall, the choice between rATG, hATG, and alemtuzumab should be tailored to individual patient factors, including donor availability and specific clinical circumstances (308, 309).

## Hematopoietic Stem Cell Transplantation from Alternative Donor

According to the treatment algorithm for SAA, stem cell transplantation from alternative donors, such as haploidentical or UCB donors, may be considered as salvage for patients who do not have an MSD or MUD and fail to respond to IS therapy. Although haploidentical HSCT offers donor availability for nearly all patients, it is associated with significant challenges, including a high rate of GF, GVHD, delayed immune recovery, and severe infections, which can hinder successful outcomes (310-313). Ex vivo TCD grafts utilizing CD34+ cell enrichment and the infusion of large doses of CD34+ cells from mobilized peripheral blood (PB) have demonstrated rapid engraftment; however, this approach has also been linked to an increased incidence of infectious complications due to delayed immune recovery (314). To address the infectious complications stemming from delayed immune recovery, strategies such as the selective elimination of αβ+ T cells—while preserving natural killer (NK) cells and γδ+ T cells in the graft—have been evaluated. Additionally, a novel approach aims to remove naïve T cells responsible for GVHD while preserving CD34+ progenitor cells and CD45RA− memory T cells that are specific for opportunistic pathogens (315, 316).

At RIOHCT, if HSCT from BM as a graft source is not feasible, we utilize in vivo T-cell depleted PBSC transplantation. Our preferred conditioning regimen consists of cyclophosphamide and ATG when HSCT is performed using an MRD or MUD ***[Figure 20]***.

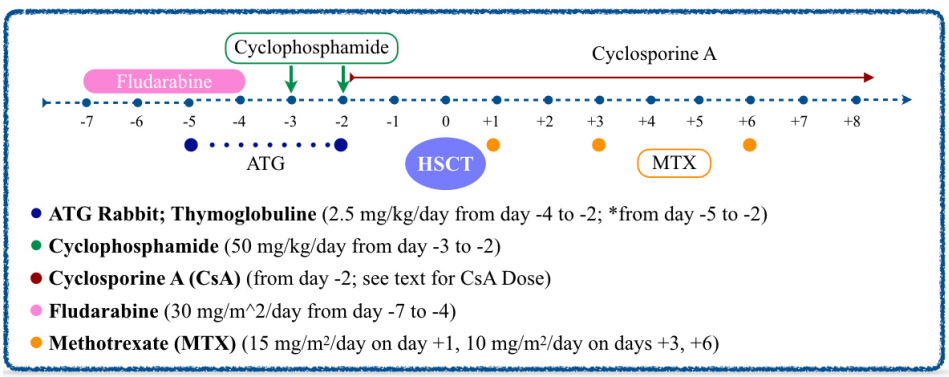
**Figure 20.** Myeloablative Conditioning (MAC): (CY-ATG)
- Severe Aplastic Anemia (SAA)
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

Given the risk of cyclophosphamide-induced cardiotoxicity, it is crucial to exercise caution when increasing the cumulative dose of cyclophosphamide used in the conditioning regimen and in PTCY for GVHD prophylaxis. For patients at significant risk of developing cardiotoxicity, a conditioning regimen based on fludarabine and cyclophosphamide, with a reduced PTCY dose lowered from 100 mg/kg to 80 mg/kg, is a viable alternative ***[Figure 21]*** (317, 318).

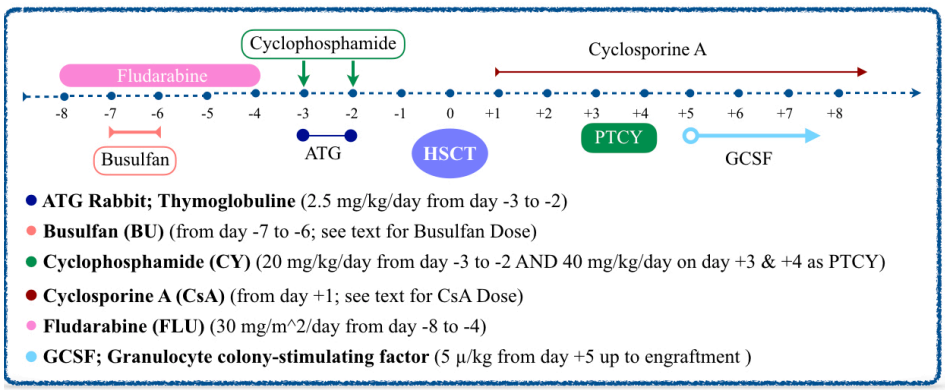
**Figure 21.** Myeloablative Conditioning (MAC): (FLU-CY-ATG)
- Severe Aplastic Anemia (SAA)
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

Additionally, due to the late toxicity associated with radiation in pediatric patients, we continue to use a chemotherapy-based preparative regimen that includes in vivo TCD with ATG for haploidentical HSCT in these patients [Figure 22].

**Figure 22.** Myeloablative Conditioning (MAC): (BU-FLU-CY-ATG)
- Severe Aplastic Anemia (SAA)
- Haploidentical Stem Cell Transplantation




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

## Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of hematopoietic stem cells (HSCs) due to loss of expression of the CD55 and CD59 proteins, marked by uncontrolled activation of the terminal complement system on blood cell surfaces. This disorder can result in symptoms like intravascular hemolysis, thrombosis, and BMF. However, in pediatric patients, the most significant manifestation is usually BMF, rather than the typical symptoms seen in adults with PNH (319, 320).

While HSCT remains the only curative treatment for patients with PNH (312, 321), the emergence of terminal complement component 5 (C5) inhibitors like eculizumab and ravulizumab has limited the criteria for HSCT. Currently, HSCT is primarily reserved for patients who experience BMF, refractory transfusion-dependent hemolytic anemia, disease transformation to MDS/AML, or recurrent thromboembolic events that do not respond to C5 inhibitors (322-328).

Regarding the conditioning regimen, both MAC and RIC can effectively eradicate the PNH clone (320). However, due to the advantages of RIC in preserving fertility and the increased NRM associated with MAC, there has been a shift in preference toward RIC.

Pantin et al. reported long-term survival in 15 out of 17 PNH patients who underwent MRD transplantation using a fludarabine/cyclophosphamide ± ATG-based regimen

(329). In another study, the RIC regimen eradicated the PNH clone within two months post-transplant, with donor-type engraftment persisting six months after the procedure (330).

Nevertheless, further research is needed to establish the benefits of RIC over MAC in reducing TRM and achieving a cure for PNH.

Our preferred preparative regimen for patients with PNH at the Pediatric Cell Therapy Unit of RIOHCT is the RIC regimen using fludarabine/cyclophosphamide ± ATG for MRDs and a combination of busulfan/cyclophosphamide + ATG for MUDs ***[Figures 23, 24]***.

**Figure 23.** Non-myeloablative Conditioning (NMA): (FLU-CY)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Matched Related Donor (MRD)

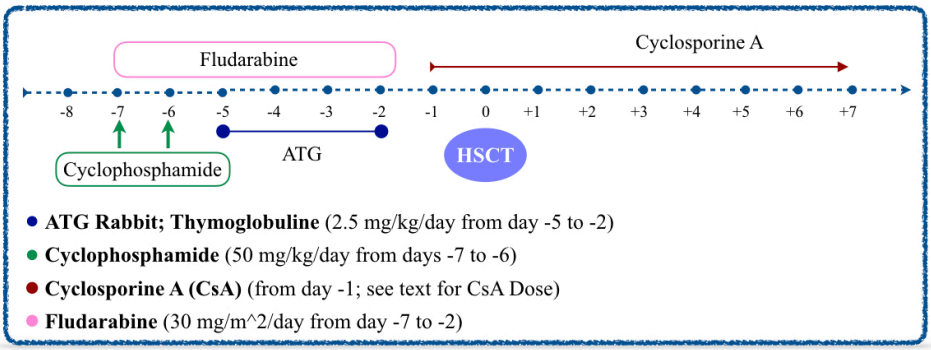
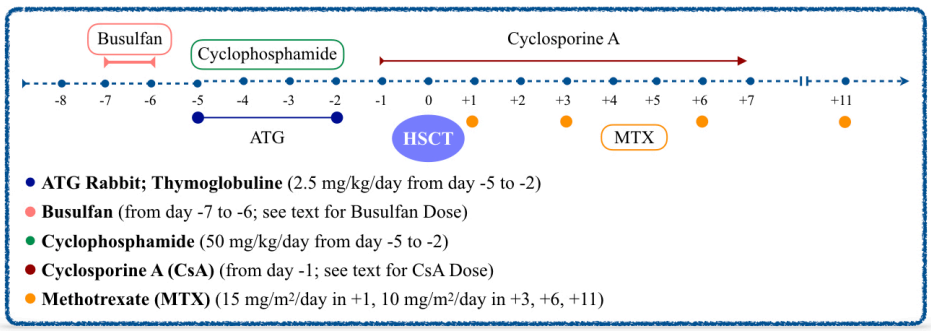



**Figure 23.** Reduced Intensity Conditioning (RIC): (BU-CY)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Matched Unrelated Donor (MUD)



## Pediatric Myelodysplastic Syndromes Including Refractory Cytopenia and Juvenile Myelomonocytic Leukemia

Pediatric MDS represents a varied group of clonal disorders, accounting for less than 5% of hematologic malignancies in children. These syndromes frequently manifest alongside IBMFSs (331). Allogeneic HSCT is the standard treatment for many children with MDS and is typically offered to those with MDS characterized by excess blasts, those with MDS secondary to previous chemoradiotherapy, and those with refractory cytopenia of childhood (RCC) associated with monosomy 7, complex karyotypes, severe neutropenia, or dependence on transfusions (332, 333). Approximately 30% of pediatric MDS patients may progress to acute leukemia, typically within two years of diagnosis (334). Studies show that following HSCT in pediatric MDS, approximately 20% of patients relapse, while 21–35% experience NRM (335-337). Studies from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT have shown comparable OS probabilities of around 35% for both pediatric and adult patients undergoing allogeneic HSCT for MDS (338, 339). While the stem cell source and the donor type seem to have minimal effect on transplant outcomes in these patients (340, 341), modifying the conditioning regimen and modulating the recipient's immune system are being explored. The intensity of the conditioning regimen, particularly concerning the alkylating agent busulfan, has been scrutinized in numerous studies, which have produced mixed findings. Retrospective studies evaluating RIC versus MAC in patients with MDS indicate that RIC leads to lower TRM, but a higher cumulative incidence of relapse (CIR), resulting in similar OS rates between the two approaches (342-345). Meanwhile, PK-guided IV administration of busulfan has not shown any variation in OS between RIC and MAC (346). Notably, in a cohort study by Kobos et al., implementation of a busulfan-based conditioning regimen, with the majority of patients receiving a TCD allograft, a 5-year OS probability was 61% (347). In contrast, a study by Maher et al. involving patients with therapy-related myelodysplastic syndromes (t-MDS), found a 5-year OS probability of 36%, with a significant non-response rate (348).

Treatment with treosulfan plus fludarabine has had encouraging results in a retrospective real-world multicenter study conducted by the EBMT (349). Importantly, the RIC using treosulfan and fludarabine appears to maintain a myeloablative effect while minimizing extra hematological toxicity. To mitigate the severity of acute GVHD, prophylaxis should incorporate in vivo TCD (such as ATG or anti-T-lymphocyte globulin (ATLG)) along with a regimen of cyclosporine A (CSA) and methotrexate, similar to the recommendations for MAC (350). The inclusion of thiotepa in preparative regimens for allogeneic HSCT in patients with MDS was studied across various graft sources following MAC, with disappointing outcomes due to a high incidence of TRM (351).

Haploidentical HSCT with the preconditioning regimen including a combination of cytarabine, busulfan, cyclophosphamide, simustine, and rATG led to 2-year OS and DFS

of 76.0% (352). Results of a T-cell replete haploidentical HSCT with ATG, CSA, mycophenolate mofetil (MMF), and short-term methotrexate, in a cohort of 27 children with MDS, at a median follow-up of 24.1 months, showed a 3-year OS of 81.9% and CIR and NRM of 7.4%. Additionally, 52.6% of patients experienced grade II-IV acute GVHD, while 42.3% developed overall chronic GVHD over three years (353). In a retrospective cohort of pediatric patients with MDS who underwent decitabine-containing and Bu/Cy-based MAC, 65.4% of patients developed grade II-IV acute GVHD within 100 days, 38.5% developed chronic GVHD and the OS rate at three years was 84.8% (354).

In conclusion, the success of allogeneic HSCT in MDS is influenced by the conditioning regimen. While MAC lowers relapse rates, it also poses a higher risk of toxicity, making it more appropriate for younger patients with less comorbidity. Although RIC has been investigated, its effectiveness for MDS remains uncertain. Our preferred preparative regimen is MAC, which consists of busulfan, cyclophosphamide, and ATG.

## Juvenile Myelomonocytic Leukemia

Allogeneic HSCT remains the only established curative approach for most pediatric patients with juvenile myelomonocytic leukemia (JMML), resulting in a cure rate of over 50%. However, a small proportion of patients may experience spontaneous clinical remissions and survive for extended periods without the need for HSCT (355, 356).

Cumulative evidence indicates a relationship between specific genetic mutations and clinical outcomes, highlighting the importance of a genotype-based management approach. Research on genotype-phenotype correlations suggests that children with JMML who have NF1, somatic PTPN11, or KRAS mutations, as well as a significant proportion of those with somatic NRAS mutations, should be promptly considered for allogeneic HSCT **(Table 18)**. In contrast, children with germline CBL mutations, who frequently experience spontaneous disease regression, should not undergo HSCT immediately after diagnosis; instead, a "watch and wait" strategy should be adopted (355, 357).

**Table 18.** Indications for HSCT in Pediatric Patients with JMML Based on Genetic Subgroups

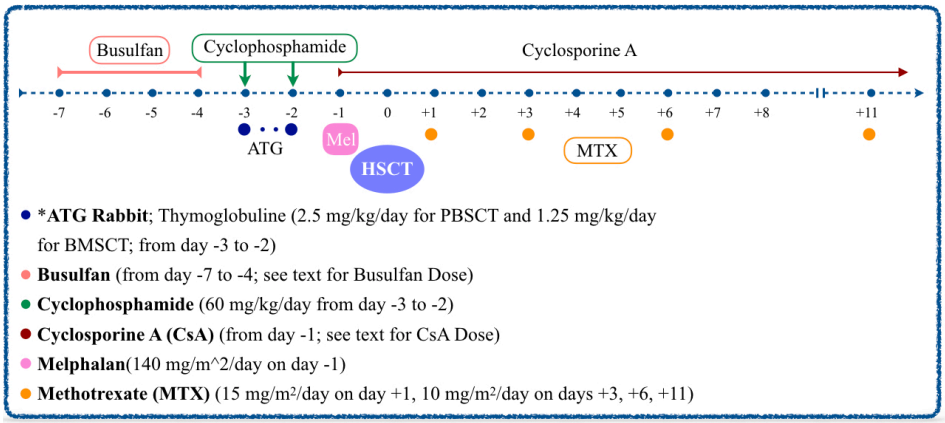
| Genetic Subgroup | Indication for HSCT |
|---|---|
| Somatic NRAS | Low HbF and high platelet count: "watch and wait" strategy<br>Disease progression: Swift HSCT (+ pretransplant azacitidine) with low-intensity GVHD prophylaxis |
| Somatic KRAS | HSCT with high-intensity GVHD prophylaxis |
| Somatic PTPN11, Germline NF1, Normal finding | Swift HSCT (+ pretransplant azacitidine) with low-intensity GVHD prophylaxis |
| Germline CBL | A "watch and wait" strategy<br>HSCT in cases of disease progression |

*GVHD: graft-versus-host disease, HbF: fetal hemoglobin, HSCT: hematopoietic stem cell trans-*

*plantation*

The standard conditioning regimen for HSCT in pediatric patients with JMML, as recommended by the EWOG-MDS, consists of a three-alkylator combination of busulfan, cyclophosphamide, and melphalan (335, 358). This regimen is also utilized at RIOHCT ***[Figure 25]***.

**Figure 25.** Myeloablative Conditioning (MAC): (BU-CY-MEL)
- Juvenile Myelomonocytic Leukemia (JMML)
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




## Inborn Errors of Immunity

Inborn errors of immunity (IEIs) or in other words, primary immunodeficiency disorders (PIDs) include a diverse and extensive collection of disorders caused by defects in the development and/or function of the immune system and HSCT is a recognized curative option for children suffering from IEIs.

Historically, transplantation in patients with IEIs relied on a combination of the alkylating agents busulfan and cyclophosphamide. However, due to the significance of IEI-related comorbidities, these standard myeloablative preparative regimens led to considerable toxicity, a high rate of TRM, and long-term complications. Although initial outcomes may have been satisfactory, increased awareness of acute conditioning toxicities and the recognition of long-term effects have led to a decline in the use of conventional myeloablative preparative regimens at most centers. Most of these regimens included cyclophosphamide with a total dose of 200 mg/kg and the reported OS by their patients was around 50% (359-361). The use of conditioning regimens with lower toxicity is now typically favored for patients with IEIs because there is no malignant disease to eliminate, stable mixed chimerism can lead to cure for various conditions, and many patients undergoing HSCT have chronic infections and existing organ-related health issues (362). These regimens are almost all, fludarabine-based and have led to very high survival rates, reaching

a 90-100% OS (363-366). treosulfan in combination with either cyclophosphamide or fludarabine has been reported to achieve an OS of 81% (367). A more recent retrospective study of 160 consecutive patients with IEIs who underwent HSCT with treosulfan, fludarabine, and alemtuzumab, showed an OS of 83% (368). In a prospective multicenter study, an RIC regimen including high-dose fludarabine, serotherapy, and low-dose or targeted busulfan for chronic granulomatous disease (CGD) patients achieved a 93% OS after a median follow-up of 21 months (363). In patients with severe combined immunodeficiency (SCID) using low-exposure busulfan (cumulative area under the concentration-time curve (AUC) of 30 mg×h/L), with a median follow-up of 4.5 years, resulted in the survival of all patients (369). In hemophagocytic lymphohistiocytosis (HLH), an RIC using melphalan, fludarabine, and intermediate-timing alemtuzumab, achieved a 1-year OS of 80.4% (365). In children transplanted from a haploidentical family donor with a MAC regimen and PTCY for an IEI, after a median follow-up of 25.6 months, the 2-year OS rate was 77.7% (370). In another cohort of patients with IEIs undergone haploidentical HSCT with mostly busulfan, fludarabine, and PTCY, after a median follow-up of 2 years, the overall 2-year survival rate was 66%, slightly varying between SCID (64%) and non-SCID (65%) patients and the study noted a 33% rate of grade II-IV acute GVHD and a 14% rate of grade III-IV (371). A clinical trial evaluating a novel radiation-free and serotherapy-free RIC, using pentostatin, low-dose cyclophosphamide, and busulfan, along with PTCY in patients with IEIs, after a median follow-up of 1.9 years, reported a 1-year OS rate of 90%, with 80% of patients free from grade III-IV acute GVHD and GF at 180 days post-transplant (372).

In conclusion, the integration of RIC in HSCT for PID patients represents a significant advancement, likely improving survival while reducing early toxicities. As gene therapy becomes mainstream, non-toxic conditioning followed by autologous gene-corrected stem cell procedures could greatly minimize treatment-related complications for IEI patients. Future conditioning strategies appear promising, with potential advancements in treatment protocols.

## T-Cell Depletion

While ex vivo TCD grafts enriched with CD34+ cells and infused with high doses of CD34+ cells from mobilized PB have demonstrated rapid engraftment, they were also linked to an increased incidence of infectious complications due to delayed immune reconstitution (316).

To address infectious complications arising from delayed immune recovery, new strategies have been developed to selectively eliminate TCR-αβ+ T cells while preserving NK cells and TCR-γδ+ T cells in the graft. Additionally, a novel approach has been explored that removes naïve T cells responsible for GVHD while retaining CD34+ progenitor cells and CD45RA− memory T cells specific for opportunistic pathogens (315, 316).

Recent studies have demonstrated the beneficial effects of this approach in both malignant and non-malignant disorders. The outcomes of haploidentical or mismatched unrelated HSCT using CD3+ TCR-αβ+/CD19+ depleted grafts have been evaluated in

patients with IEIs. After a median follow-up of 20.8 months, the OS and EFS rates at three years were found to be 83.9% and 80.4%, respectively. The cumulative incidence of grade II-IV acute GVHD was 22% ± 8.7%, with no instances of chronic GVHD reported. Furthermore, the cumulative incidences of GF, cytomegalovirus (CMV) and adenoviral infections, and TRM at one year were 4.2% ± 4.1%, 58.8% ± 9.8%, and 16.1% ± 7.4%, respectively (373).

## Severe Combined Immunodeficiency

SCID is a diverse group of IEIs characterized by impaired T-lymphocyte differentiation and proliferation, leading to the absence of autologous T lymphocytes. However, B-lymphocytes and NK cells may also be impacted. Nearly 20 different types of SCID have been identified. Some of the more commonly recognized types are classified based on their genetic mutations and the presence of T cells, B cells, and NK cells (374).

Once the diagnosis of SCID is confirmed, it is crucial to urgently identify a suitable donor. While HSCT from a matched sibling or related donor is considered the gold standard, alternative options should be pursued in the absence of such a donor. These alternatives include 10/10 MUD, haploidentical family donors, or mismatched unrelated CB (375).

The selection of a conditioning regimen is determined by the donor type and the SCID phenotype, as well as the genotype when it is available. A preparative regimen prior to HSCT from an MSD is not recommended for patients with the following genotypes:

- JAK3, IL2Rγ (TB+ NK-)
- IL7Rα, CD3 δ, ε, ζ, CD45 (T- , B+, NK+)
- ADA

Although achieving full myeloid chimerism is not essential, obtaining some level of myeloid engraftment is advantageous for promoting B cell reconstitution and sustaining long-term thymic output. Patients who do not achieve sufficient myeloid engraftment or who have a declining naïve T-cell compartment may experience significant complications. Therefore, if feasible for the patient, conditioning is recommended for all SCID patients to ensure optimal clinical and immunological outcomes (375, 376).

## Non-SCID Inborn Errors of Immunity

### • Hemophagocytic Lymphohistiocytosis

HLH is a serious hyperinflammatory condition marked by the uncontrolled accumulation of macrophages and lymphocytes resulting in excessive cytokine production. It is classified into two forms: primary (genetic) and secondary (acquired).

Primary HLH encompasses familial HLH (FHL), which is the most prevalent form, as well as X-linked lymphoproliferative disease (XLP), Griscelli syndrome type 2 (GS2), and Chediak-Higashi syndrome (CHS) (377).

Given the high risk of reactivation in patients with primary HLH, stem cell transplantation is currently regarded as the only curative option for replacing the defective immune system (378).

Since not all genetic causes are clearly defined, a significantly reduced expression of relevant proteins, diminished lymphocyte degranulation, a positive family history, or persistent/recurrent disease may be enough to diagnose primary HLH. Identifying likely pathogenic germline variants in HLH-related genes alone is insufficient for diagnosing primary HLH without additional supporting evidence from functional assays or prior patient reports. Specifically, the presence of a heterozygous or homozygous A91V perforin variant in a patient with HLH does not automatically indicate the need for HSCT unless it is accompanied by a "severe" mutation (379, 380).

* *In asymptomatic carriers of biallelic HLH-associated mutations who has a familiy history of HLH in infancy, early HSCT should strongly be considered (378).*

For patients with secondary HLH who do not have germline mutations, allogeneic HSCT is typically not recommended. However, if these patients show a suboptimal response to the treatment of the underlying disease, allogeneic HSCT may be considered as a therapeutic option.

At present, there is no evidence to suggest that heterozygous siblings or parents of a homozygous or compound heterozygous index patient face an elevated risk of developing HLH that could be passed on to the transplant recipient. Therefore, heterozygous mutation carriers can be considered as potential donors (378).

* *It is important to note that active HLH at the time of HSCT is linked to a poorer outcome.*

### • Chronic Granulomatous Disease

CGD is an inherited IEI characterized by X-linked and autosomal recessive patterns of inheritance that impairs neutrophils, monocytes, and macrophages' production of superoxide anions and other reactive oxygen species. This deficiency results in compromised microbial killing, leading to life-threatening bacterial and fungal infections, immune dysregulation, and hyperinflammation (381). HSCT should be regarded as the main curative treatment for all genetic forms of CGD, including the rare variant caused by mutations in CYBC1 (382, 383). It is advisable to pursue transplantation as early as possible, before the onset of disease-related organ damage (384).

While stable donor myeloid chimerism of over 15–20% is adequate to reduce the risk of infections, ideally, a high level of donor myeloid chimerism exceeding 80% will be achieved. Additionally, the decision to consider retransplantation is typically based on the patient's symptom history rather than chimerism levels alone (385).

* *Optimal management of autoinflammation, such as colitis, is recommended before HSCT; however, this is not always feasible.*

In X-linked CGD, female carriers who are family donors may exhibit inflammatory and autoimmune symptoms. Generally, they should be avoided as potential HSC donors; however, in the absence of suitable alternatives, they may be considered after thorough evaluation, including dihydrorhodamine (DHR) flow cytometry analysis (385-387).

### • Leukocyte Adhesion Deficiency

Leukocyte adhesion deficiency (LAD) syndromes are a group of rare autosomal recessive

IEIs marked by the inability of leukocytes to adhere to the endothelial lining of blood vessels, which hinders their migration to extravascular spaces (388, 389). Most individuals affected by LAD-I and LAD-III experience significantly reduced life expectancy, with a mortality rate exceeding 75% by the age of two (390). Successful allogeneic HSCT can restore leukocyte function in patients with LAD-I and LAD-III, eliminating the need for additional treatments (391).

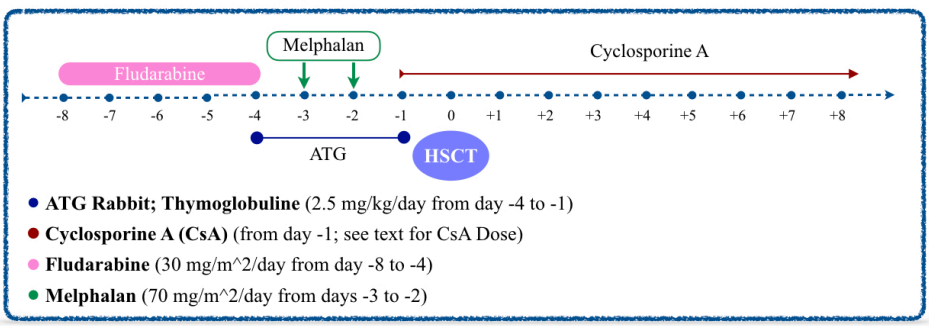
### • Combined Immunodeficiency

Combined immunodeficiency (CID) is a subtype of SCID characterized by a less severe quantitative or functional defect in T cells, often accompanied by a B cell deficiency. CID can manifest as an isolated immune disorder, such as CD40 ligand deficiency, Bare lymphocyte syndrome, CD27-CD70 deficiency, or DOCK8 deficiency. It may also occur as part of a syndrome, such as Wiskott-Aldrich syndrome (WAS) or autosomal dominant anhidrotic ectodermal dysplasia with immune deficiency (AD EDA-ID) (392-396).

Special attention should be given to the conditioning regimen in certain subgroups of CIDs, where mixed chimerism is linked to poorer outcomes, such as in WAS. In these cases, MAC regimens are typically favored to ensure sustainable donor stem cell engraftment (392, 394, 397).

At RIOHCT, our preferred conditioning regimen for patients with IEIs is a RIC protocol that includes fludarabine, melphalan, and serotherapy ***[Figure 26]***. However, for conditions like WAS, we typically utilize a MAC regimen consisting of busulfan and fludarabine.

**Figure 26.** Figure | Reduced Intensity Conditioning (RIC): (Flu-Mel)
• Inborn Error of Immunity (IEI)



# Inborn Errors of Metabolism and Osteopetrosis

HSCT is an effective therapeutic strategy for certain inborn errors of metabolism (IEMs), particularly in preventing disease progression rather than reversing established manifestations. Timely HSCT is crucial for stabilizing the clinical situation and significantly improving long-term outcomes for patients with IEMs (398).

## Lysosomal Storage Diseases

Lysosomal Storage Diseases (LSDs) are characterized by genetic defects in specific proteins involved in lysosomal pathways (399). HSCT leads to the continuous secretion of enzymes by donor-derived myeloid cells, which are then absorbed by enzyme-deficient host cells (400).

In contrast to enzyme replacement therapy (ERT), donor-derived cells can migrate through the blood-brain barrier (BBB) and differentiate into microglia, which secrete the deficient enzyme into the CNS, thereby enhancing neurocognitive outcomes (401). However, the engraftment of donor myeloid cells in the brain occurs gradually, taking up to one year. This delay may not keep pace with neurological disease progression, which can result in some patients experiencing slow improvement or even deterioration of CNS function after HSCT (402, 403).

RIC and ex vivo TCD have been linked to high GF rates. Therefore, a MAC regimen that includes fludarabine and busulfan is recommended for patients with LSDs (404).

### • Mucopolysaccharidoses

Allogeneic HSCT, combined with pretransplant or peritransplant ERT, is considered the standard treatment for Hurler Syndrome, the most severe phenotype of Mucopolysaccharidosis Type I (MPS IH) (405).

For other types of MPS, including Hunter syndrome (MPS-II), Maroteaux-Lamy syndrome (MPS-VI), and Sly syndrome (MPS-VII), HSCT is considered an optional treatment approach.

### • Sphingolipidoses

***1. Metachromatic Leukodystrophy***

Metachromatic Leukodystrophy (MLD) is characterized by widespread demyelination of the central and peripheral nervous systems (406, 407) and is classified into three subtypes based on the age at presentation: late-infantile (up to 30 months), juvenile (30 months to 15 years), and adult (over 15 years) (408).

Both HSCT and hematopoietic stem cell gene therapy (HSCGT) are effective for enzyme replacement in the nervous system when administered early in the disease course or before symptoms appear (409-412). However, HSCT is generally reserved for the attenuated forms of the disease, specifically juvenile and adult types (411, 413, 414).

Late-infantile MLD, which is the most common and severe form, is typically not considered for allogeneic HSCT because it cannot prevent the progression of early-onset

disease (415, 416).

***2. Acid Sphingomyelinase Deficiency***

Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease (NPD), is an ultra-rare multisystem genetic disorder characterized by the accumulation of lipid substrates in the lysosomes of the liver, brain, spleen, lungs, and BM cells. ASMD is classified into three subtypes: Type A, which represents the infantile neurovisceral form; Type B, known as the chronic visceral form; and Type A/B, which is referred to as the chronic neurovisceral type (417, 418).

HSCT can help correct metabolic defects, improve blood counts, and decrease enlarged liver and spleen volumes; however, it does not address neurological issues, and the reversal of growth retardation remains uncertain. Consequently, attempts to perform HSCT in individuals with clinically apparent neurological disease should be regarded as experimental, as this treatment does not correct or stabilize neurological conditions (418).

## Peroxisomal Diseases

### • X-Linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is caused by the absence of the adrenoleukodystrophy protein, which impairs the transport of very long-chain fatty acids to the peroxisome for oxidative degradation. This deficiency leads to the accumulation of these fatty acids in the CNS and adrenal tissues (419). ALD is categorized into four types: asymptomatic, adrenal failure, adrenomyeloneuropathy, and inflammatory cerebral disease (420).

The most severe form is childhood cerebral ALD (CCALD), which is the only indication for stem cell transplant. HSCT has shown effectiveness in early cerebral inflammatory disease, particularly when early magnetic resonance imaging (MRI) changes show demyelination, as measured by the Loes score (2, 421). The Loes score, derived from MRI scans, assists in making therapeutic decisions regarding HSCT. A score of less than 4 indicates a very early stage, 4 to 8 indicates an early stage, 9 to 13 indicates a late stage and a score above 13 indicates an advanced stage (422). Patients with a Loes score below 9, especially those with scores under 4, are considered suitable candidates for HSCT (423, 424). However, for advanced cerebral ALD, HSCT is contraindicated as the disease will likely progress despite the transplant.

It is important to note that HSCT does not impact adrenal insufficiency or the later development of myeloneuropathy in the spinal cord (2).

## Mitochondrial Diseases

### • Mitochondrial Neurogastrointestinal Encephalomyopathy

Mitochondrial neuro gastrointestinal encephalomyopathy (MNGIE) is an ultra-rare and progressive autosomal recessive disorder presents with GI dysmotility, ptosis, peripheral neuropathy, and white matter changes visible on brain MRI (425).

Pathogenic mutations in the thymidine phosphorylase (TYMP) gene lead to a deficiency of thymidine phosphorylase, resulting in the toxic accumulation of plasma nucleosi-

des, particularly thymidine, and deoxyuridine, which contribute to mitochondrial DNA (mtDNA) instability (426, 427).

Currently, allogeneic HSCT is the only effective treatment that restores thymidine phosphorylase activity and eliminates toxic levels of thymidine and deoxyuridine from circulation. HSCT should be considered for younger patients and before severe GI dysmotility develops. For those with advanced disease, HSCT is generally not recommended (428-430).

## Osteopetrosis

Osteopetrosis (OPT), resulting from defects in osteoclast differentiation or function, has two patterns of inheritance: autosomal recessive osteopetrosis (ARO) and autosomal dominant osteopetrosis (ADO). ARO, also known as infantile malignant OPT, represents the most severe form of the disorder. In contrast, ADO is characterized by adult onset and is generally a more benign form of the condition (431).

Since osteoclasts originate from HSCs, the only curative and sustainable treatment for OPT is currently allogeneic HSCT. This intervention is indicated in specific situations, including hematological failure requiring transfusions, impending blindness, and other clinical complications that significantly reduce quality of life or are incompatible with long-term survival (432).

However, HSCT is generally not recommended for patients with the following genetic forms of OPT: (432)

- CAII (Carbonic anhydrases II) – biallelic: Renal tubular acidosis (RTA)
  *In patients experiencing progressive visual and/or hearing loss, along with less severe renal and CNS impairment, HSCT may be considered as a treatment option.*
- CLCN7 – monoallelic: Intermediate or "benign" OPT
- OSTM1 – biallelic: Infantile OPT with neurodegeneration
- PLEKHM1 – biallelic: Intermediate OPT
- RANKL – biallelic: Infantile or intermediate osteoclast-poor OPT

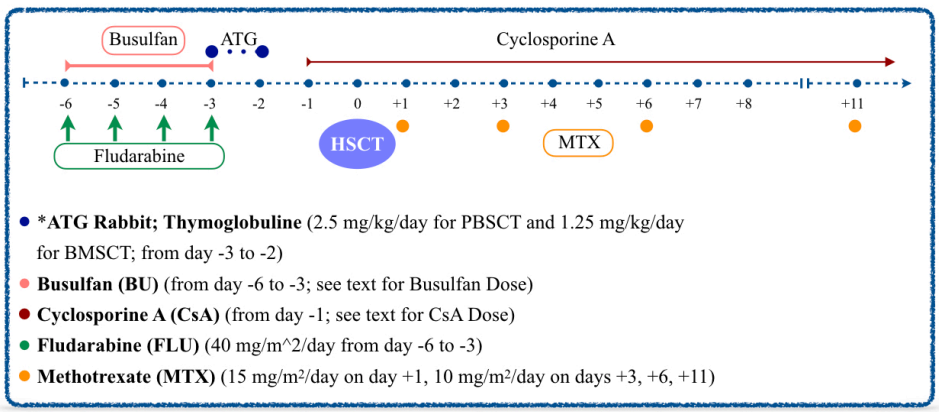
Moreover, HSCT has been demonstrated to be ineffective in cases involving CLCN7 and OSTM1 mutations associated with CNS involvement. However, HSCT is strongly indicated for patients under 1 year of age who exhibit limited disease progression and minimal neurological damage. Therefore, a comprehensive neurological assessment is essential for patients with these mutations (433).

The increased risk of GF due to BM space obliteration and extramedullary hematopoiesis (such as hepatosplenomegaly) necessitates utilizing a MAC regimen to ensure effective donor engraftment. The preferred preparative regimen is a combination of busulfan and fludarabine ***[Figures 27 & 28]***. For patients with advanced disease, an alternative regimen of treosulfan, fludarabine, and thiotepa may be considered (375, 431).

* *Given the high risk of transplant-related complications in patients with OPT, it is recommended that HSCT be performed at experienced centers, especially for recipients of haploidentical transplantations.*

**Figure 27.** Myeloablative Conditioning (MAC): (BU-FLU)

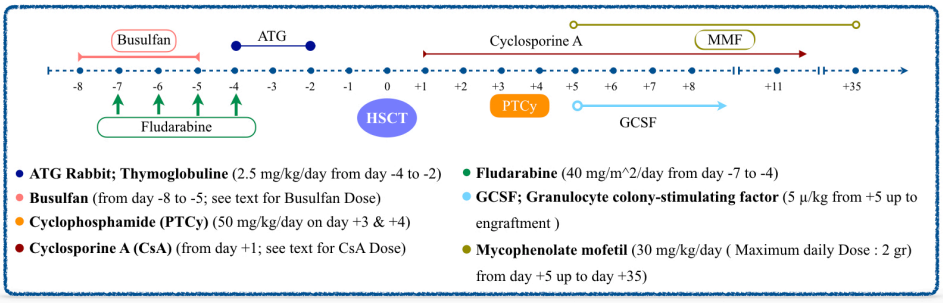
- Osteopetrosis
- Matched Related Donor (MRD) / Matched Unrelated Donor (MUD)*




- ***ATG Rabbit; Thymoglobuline** (2.5 mg/kg/day for PBSCT and 1.25 mg/kg/day for BMSCT; from day -3 to -2)
- **Busulfan (BU)** (from day -6 to -3; see text for Busulfan Dose)
- **Cyclosporine A (CsA)** (from day -1; see text for CsA Dose)
- **Fludarabine (FLU)** (40 mg/m^2/day from day -6 to -3)
- **Methotrexate (MTX)** (15 mg/m²/day on day +1, 10 mg/m²/day on days +3, +6, +11)

**Figure 28.** Myeloablative Conditioning (MAC): (BU-FLU)

- Osteopetrosis
- Haploidentical Stem Cell Transplantation




- **ATG Rabbit; Thymoglobuline** (2.5 mg/kg/day from day -4 to -2)
- **Busulfan** (from day -8 to -5; see text for Busulfan Dose)
- **Cyclophosphamide (PTCy)** (50 mg/kg/day on day +3 & +4)
- **Cyclosporine A (CsA)** (from day +1; see text for CsA Dose)
- **Fludarabine** (40 mg/m^2/day from day -7 to -4)
- **GCSF; Granulocyte colony-stimulating factor** (5 µ/kg from +5 up to engraftment )
- **Mycophenolate mofetil** (30 mg/kg/day ( Maximum daily Dose : 2 gr) from day +5 up to day +35)

# AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

# 9

## Lymphoma

### Lymphoblastic Lymphoma

The use of acute lymphoblastic leukemia (ALL)-type treatment has led to improved outcomes for pediatric patients with T-cell lymphoblastic lymphoma (T-LBL), achieving an event-free survival (EFS) rate of approximately 75-90%. However, patients with relapsed or refractory (R/R) T-LBL face significantly poorer outcomes, with survival rates ranging from 10-30%. Therefore, inducing a second remission through intensive chemotherapy, followed by allogeneic hematopoietic stem cell transplantation (HSCT) and a total body irradiation (TBI)-based conditioning regimen, is recommended (434).

At RIOHCT, our approach for treating R/R T-LBL is to utilize a regimen similar to that used for T-cell ALL, employing a myeloablative conditioning (MAC) regimen followed by allogeneic HSCT.

Research on management strategies for R/R primary B-cell lymphoblastic lymphoma (pB-LBL) is limited due to the small number of affected patients. Nevertheless, considering the poor outcomes linked to this condition, it is recommended to adopt an aggressive reinduction approach followed by consolidation with allogeneic HSCT, similar to the treatment strategy employed for T-LBL (434).

* *Autologous transplantation is not effective for R/R LBL (435).*

## Relapsed/Refractory Mature B-Cell Non-Hodgkin Lymphoma (Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma)

Due to the low incidence of non-Hodgkin lymphoma (NHL) in children, data on the use of HSCT for treating R/R disease is limited, and there are no definitive guidelines for choosing between autologous and allogeneic HSCT, (436) as outcomes for these approaches appear to be similar (437).

In a study conducted by Rigaud et al., no significant difference was observed in the five-year survival rates between patients who received allogeneic HSCT and those who underwent autologous stem cell transplantation (ASCT), with rates of 50% and 54%, respectively (438).

Most pediatric centers typically perform autologous HSCT for most patients, reserving allogeneic HSCT for those with specific NHL histological subtypes, such as lymphoblastic lymphoma (LBL), or patients with higher-risk or refractory disease. Based on adult experience, the higher non-relapse mortality (NRM) associated with allogeneic HSCT compared to autologous HSCT diminishes potential benefits from a lower relapse rate attributed to graft-versus-lymphoma activity (436).

Pediatric patients with primary Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) have excellent outcomes in frontline treatment, achieving five-year EFS rates of nearly 90%. In contrast, those with R/R NHL experience significantly poorer outcomes, with a cure rate of approximately 30% (437, 439-441). For patients with R/R BL, research from the Center for International Blood and Marrow Transplant Research (CIBMTR) found no significant difference in two-year EFS rates between allogeneic HSCT (31%) and autologous HSCT (27%). Similar findings were observed in patients with R/R DLBCL, where the five-year EFS rates were reported at 50% for allogeneic HSCT and 52% for autologous HSCT (442).

At RIOHCT, our approach considers ASCT for patients with R/R BL and DLBCL, utilizing a conditioning regimen similar to that used for Hodgkin lymphoma (HL).

It should be noted that patients with R/R DLBCL often do not benefit from ASCT if they are primary refractory or experience early relapse. In such cases, alternative therapies, including chimeric antigen receptor (CAR) T-cell therapy (if available), may be more appropriate.

In the context of R/R BL, the conditioning regimens can include reduced-intensity conditioning (RIC) to improve engraftment and minimize toxicity. Our strategy aligns with current findings that emphasize the importance of effective reinduction regimens before consolidation with ASCT to enhance survival outcomes. Overall, while ASCT remains a viable option for R/R BL and DLBCL at RIOHCT, carefully considering each patient's unique clinical situation is essential in determining the most appropriate treatment pathway.

## Hodgkin Lymphoma

The need for ASCT in pediatric patients with classical Hodgkin lymphoma (HL) should be assessed through risk stratification, as most studies comparing ASCT and standard-dose chemotherapy (SDCT) have not demonstrated any survival advantage for ASCT in cases of first relapse (443, 444).

In line with European Network-Pediatric Hodgkin Lymphoma (EuroNet-PHL) strategies, most pediatric patients do not receive radiation therapy (RT) as part of their first-line treatment for classical HL. Additionally, the potential toxicities associated with ASCT raise concerns in pediatric populations. Therefore, in the context of relapse, ASCT may be substituted with SDCT combined with RT (445).

Risk stratification at the time of relapse is determined by pre-salvage risk factors, which categorize patients into low and standard-risk groups. For high-risk patients, the classification is defined by the failure to achieve a complete metabolic response on 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) following two lines of salvage SDCT.

The EuroNet guidelines recommend a risk-stratified and response-adapted approach to salvage therapy for pediatric classical HL, reserving ASCT for standard- and high-risk patients while utilizing SDCT plus RT for low-risk patients to minimize toxicity without compromising survival **(Table 19)** (445).

**Table 19.** Risk-Stratified and Response-Adapted Approach to Salvage Therapy for Pediatric Classical HL

| Risk Group | Inclusion Criteria | Treatment Recommendations |
|---|---|---|
| Low Risk | Early relapse after a maximum of 4 cycles of first-line chemotherapy<br>Late relapse after a maximum of 6 cycles of first-line chemotherapy<br>and all of the following:<br>• Stage at relapse is I-III<br>• No prior RT or relapse only outside prior RT field<br>• No excessive RT fields required in salvage | Salvage therapy with SDCT plus RT consolidation only |
| Standard Risk | Any of the following factors:<br>• Primary progressive HL<br>• Early relapse after more than 4 cycles of first-line chemotherapy<br>• Stage IV relapse<br>• Relapse in a prior RT field<br>• Relapse requiring RT in salvage therapy that is considered as having unacceptable toxicity | Salvage therapy with SDCT plus ASCT consolidation<br>In selected standard-risk and/or high-risk patients, consolidation RT is given after ASCT. |

| Risk Group | Inclusion Criteria | Treatment Recommendations |
|---|---|---|
| High Risk | Failure to achieve a negative FDG-PET after 2 lines of salvage SDCT | Conventional ASCT plus additional treatments pre- and/or post-ASCT or experimental strategies |

*ASCT: autologous stem cell transplantation; FDG-PET: 18-fluoro-deoxyglucose positron emission tomography, HL: Hodgkin lymphoma, RT: radiation therapy, SDCT: standard-dose chemotherapy*

Several conditioning regimens have been developed to improve the outcomes of ASCT, with progression-free survival (PFS) and overall survival (OS) rates ranging from 34% to 60% and 26% to 46%, respectively. Until recently, BCNU (1-3-bis(2-chloroethyl)-1-nitrosourea (carmustine))-based regimens, such as BEAM (carmustine, etoposide, cytarabine, and melphalan), have been the most commonly used for R/R lymphoma, demonstrating acceptable ASCT-related mortality rates (446-448). However, the limited availability of BCNU in some countries, along with its association with late pulmonary complications—such as chronic interstitial fibrosis and decreased lung diffusing capacity in 16% to 64% of patients exposed to carmustine—has created a pressing need for alternative conditioning regimens (449, 450). Bendamustine hydrochloride (BEN) is a cytotoxic agent with a unique chemical structure that combines the alkylating properties of a mustard group with the antimetabolite activity of a purine analog. In vitro studies have demonstrated that bendamustine primarily activates apoptotic pathways in multi-drug-resistant malignant lymphoma cell lines that do not respond to other alkylating agents (451-453).

BEAM and BEN-EAM (with bendamustine replacing BCNU) have been compared in ASCT and have demonstrated comparable four-year PFS and OS rates, although acute non-hematological toxicity is more prevalent in BEN-EAM (454).

Busulfan-based conditioning regimens are considered more intensive than BEAM (455, 456). In a retrospective adjusted analysis conducted by Zaucha et al., the BU-MEL-TT (busulfan, melphalan and thiotepa) regimen was utilized in patients with NHL, demonstrating a high complete response rate but similar PFS and OS compared to BEAM (457). Additionally, Shin et al. reported that two-year EFS and OS were superior in busulfan-containing conditioning regimens compared to the BEAM/BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) group (458).

At RIOHCT, we utilize BEN-EAM ***[Figure 29]*** for pediatric patients with relapsed or classical HL, and as an alternative, we employ BEN-BU-MEL (bendamustine, busulfan, and melphalan) ***[Figure 30]***.

**Figure 29.** Autologous Stem Cell Transplant (ASCT): (BEN-EAM)
- Lymphoma (Hodgkin & Non-Hodgkin)

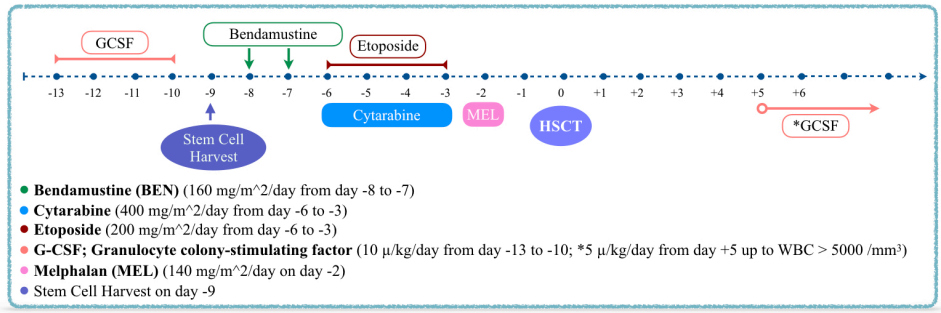
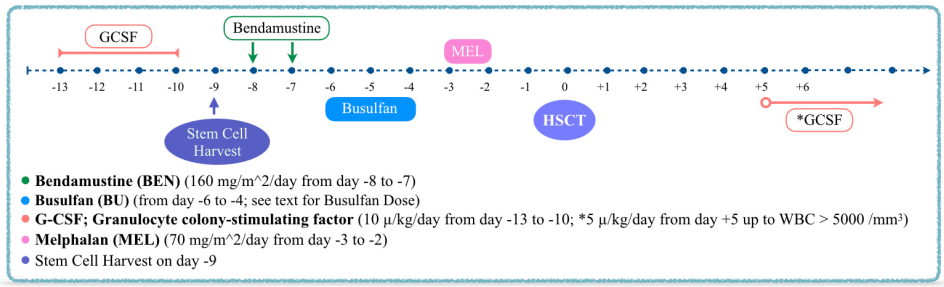



**Figure 30.** Autologous Stem Cell Transplant (ASCT): (BEN-BU-MEL)
- Lymphoma (Hodgkin & Non-Hodgkin)




## Neuroblastoma

For high-risk neuroblastoma (NB), the major international cooperative groups (German Society for Pediatric Oncology and Hematology (GPOH), Children's Oncology Group (COG), and International Society of Pediatric Oncology (SIOP)) use intensive multimodal approaches that include induction with multiagent chemotherapy and surgical resection, consolidation with RT, and myeloablative chemotherapy followed by ASCT, treatment of measurable residual disease (MRD) with retinoids and immunotherapy using a tumor-specific anti-disialoganglioside (GD2) antibody, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin (IL)-2 (381, 382). **Table 20** outlines the indications for ASCT in pediatric patients with NB.

**Table 20.** Indications for ASCT in Pediatric Patients with Neuroblastoma

| Clinical Condition | Indication for ASCT |
|---|---|
| Newly Diagnosed NB | • Age >18 months at diagnosis with widespread metastatic disease (INRG M)<br>• Any age with MYCN amplified tumors with INSS stages 2–4 |
| Relapsed Disease | • Any responding metastatic relapse in patients >18 months<br>• Relapse of MYCN amplified tumors without prior ASCT |

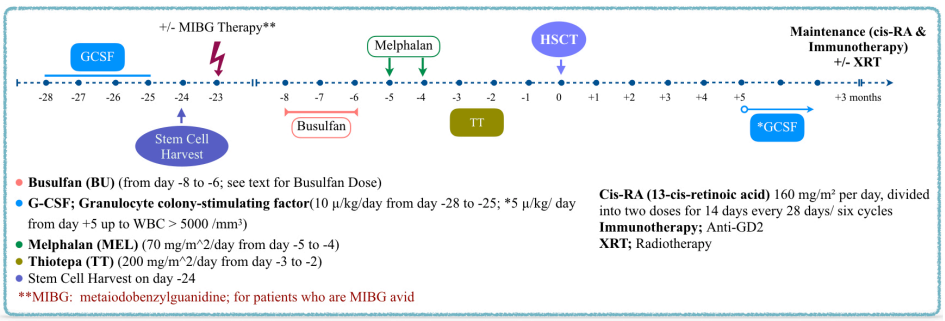
*ASCT: autologous stem cell transplantation, INRG: International Neuroblastoma Risk Group, INSS: International Neuroblastoma Staging System, NB: neuroblastoma*

The International Society of Pediatric Oncology European Neuroblastoma (SIOPEN) conducted a randomized trial and demonstrated the superiority of busulfan and melphalan over CEM (carboplatin, etoposide, and melphalan) as a conditioning regimen for ASCT in pediatric patients with NB (459). Additionally, thiotepa, as an alkylating agent, is widely utilized in conditioning regimens in combination with melphalan for various solid tumors, including high-risk NB and medulloblastoma (460).

Moreover, meta-iodobenzylguanidine (MIBG), a norepinephrine analog that is taken up by 90% of NBs, labeled with iodine-131 ($^{131}$I-MIBG), has been effective against both R/R and newly diagnosed NB. The incorporation of $^{131}$I-MIBG targeted RT in the treatment of R/R NB has resulted in response rates of up to 37%, with dose-limiting hematologic toxicity being managed through the support of ASCT (461, 462).

Considering these factors, at RIOHCT, we employ a combination of busulfan, melphalan, and thiotepa followed by ASCT for high-risk NB patients, along with $^{131}$I-MIBG therapy administered before stem cell harvest in MIBG-avid tumors ***[Figures 31]***.

**Figure 31.** Autologous Stem Cell Transplant (ASCT)
- Neuroblastoma (BU-MEL-TT +/- MIBG)




***13-cis-retinoic acid:*** Due to the high risk of relapse from MRD following ASCT, 13-cis-retinoic acid (cis-RA), a known differentiating agent for NB, is considered a crucial com-

ponent of multimodal therapy aimed at addressing any residual NB that remains after maximal tumor burden reduction through high-dose chemotherapy (HDCT) and stem cell transplantation. The administration schedule consists of six cycles of oral cis-RA at 160 mg/m² per day, divided into two doses for 14 days every 28 days. Dose-limiting toxicities associated with cis-RA treatment may include hepatic dysfunction, hypercalcemia, skin rash, anemia, thrombocytopenia, and vomiting; however, these side effects typically resolve after discontinuation of the medication (463, 464).

***Anti-GD2 immunotherapy:*** Another agent targeting MRD is the anti-GD2 monoclonal antibodies, specifically dinutuximab and naxitamab, which have received Food and Drug Administration (FDA) approval and have been shown to improve EFS and OS when administered after ASCT. Anti-GD2 immunotherapy is now considered the standard of care for all high-risk NB patients in remission following ASCT, significantly enhancing the effectiveness of post-transplant treatment strategies (464, 465).

## Tandem versus Single ASCT

The benefit of tandem myeloablative therapy plus ASCT in NB patients subsequently treated with anti-GD2 immunotherapy, compared to single ASCT, was confirmed in a randomized controlled trial (RCT) by Park et al (466). However, the study indicates that this benefit may not be evident in the subgroup of patients who did not receive anti-GD2 immunotherapy, which is consistent with findings from a retrospective study by Yan et al (467). Overall, data from both randomized and non-randomized controlled trials comparing tandem and single ASCT are heterogeneous, not definitive and subject to bias. The observed effects suggest that in patients who did not receive immunotherapy, tandem ASCT may not offer any additional advantages over single ASCT. Consequently, tandem ASCT is not currently considered the standard of care for NB.

## Allogeneic Hematopoietic Stem Cell Transplantation for Children with High-Risk Neuroblastoma

Given the notable alloreactive effects mediated by the cytotoxic functions of natural killer (NK) cells, combined with advancements in supportive care and the development of reduced-intensity or NMA conditioning regimens, several research groups are reevaluating the use of allogeneic HSCT in NB (468).

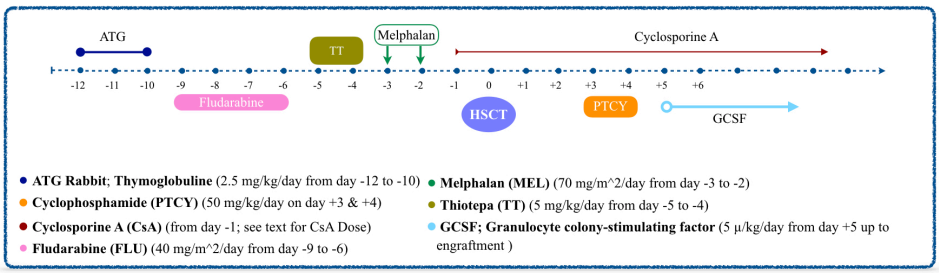
A retrospective analysis from the CIBMTR examined the outcomes of high-risk and refractory NB patients undergoing allogeneic HSCT. The study revealed superior EFS for patients who had not previously undergone ASCT. However, transplant-related mortality (TRM) remains a significant limitation of the procedure's applicability (469).

Haploidentical HSCT is noteworthy due to its association with strong alloreactive NK cell-mediated graft-versus-tumor (GVT) responses. Illhardt et al. indicated that haploidentical HSCT is a feasible treatment option for NB patients, with the potential to induce long-term remission in some cases while causing tolerable side effects. This approach may enable the development of further post-transplantation therapeutic strategies based

on harnessing the donor-derived immune system (470).

At the Pediatric Cell Therapy Unit of RIOHCT, we utilize reduced-intensity haploidentical HSCT for children with NB who experience progression after ASCT ***[Figure 32]***.

**Figure 32.** Reduced Intensity Conditioning (RIC): (FLU-TT-MEL)
- Neuroblastoma
- Haploidentical Stem Cell Transplantation




## Wilms' tumor

The successful application of high-dose chemotherapy combined with stem cell transplantation for treating recurrent Wilms' tumor (WT) has been documented by various research groups, with EFS estimates ranging from 36% to 60% (471-473). However, similar findings have also emerged from non-randomized studies (474, 475). Therefore, conducting a randomized trial comparing maintenance chemotherapy with consolidation against HDCT followed by ASCT is crucial.

Additionally, based on the experiences of the SIOP, GPOH, National Wilms Tumor Study Group (NWTS), and Medical Research Council (MRC) groups, adverse prognostic factors, as summarized in **Table 21**, are regarded as indications for ASCT in pediatric patients with WT (2).

**Table 21.** Indications for ASCT in Wilms' Tumor

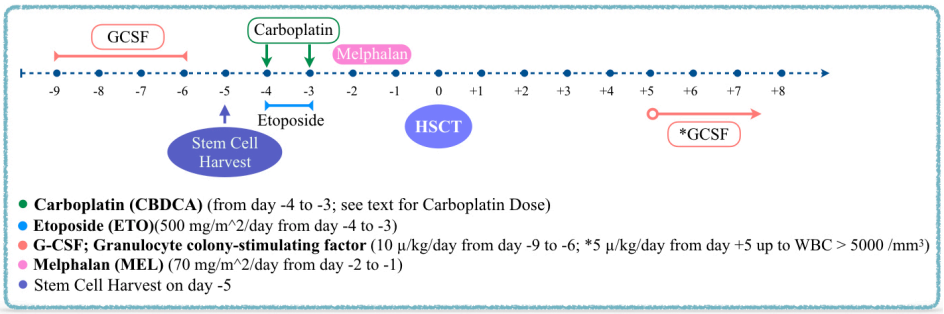
| Clinical Condition | Indication for ASCT |
|---|---|
| Unfavorable Histology and Metastatic Disease | • Diagnosis of Wilms' tumor with unfavorable histology and metastatic disease |
| Relapse with Unfavorable Histology and one of the following criteria: | • Extra-pulmonary relapse or abdominal relapse after RT<br>• Stage IV<br>• More than two drugs in the first-line regimen<br>• Relapse within 1 year |

*RT: radiation therapy*

Melphalan, MEC (melphalan, etoposide, and carboplatin), and CyET (cyclophosphamide, etoposide, and thiothepa) are the most commonly used conditioning regimens for ASCT in WT. However, a study conducted on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Pediatric Diseases Working Party found that the choice of pretransplant regimen—whether melphalan alone or multi-drug combinations—did not significantly affect EFS or OS probabilities after ASCT (476).

At RIOHCT, we utilize the MEC regimen for ASCT in pediatric patients with WT ***[Figure 33]***.

**Figure 33.** Autologous Stem Cell Transplantation (ASCT): (MEL-ETO-CBDCA)
- Wilms Tumor




BMSCT; Bone Marrow Stem Cell Transplantation, PBSCT; Peripheral Blood Stem Cell Transplantation

## Germ Cell Tumors

Pediatric patients with extracranial germ cell tumors (GCTs) typically have excellent outcomes with conventional platinum-based chemotherapy. However, high-risk patients—including non-responders, poor responders, and those who fail to achieve complete remission (CR) after relapse—may require additional treatments such as RT, targeted therapy, or HDCT with ASCT, depending on the patient's clinical and tumor molecular profile.

While previous studies have not definitively shown the benefits of HDCT combined with ASCT as a frontline therapy, several small observational studies suggest that most children with R/R GCTs do benefit from this approach. For the central nervous system (CNS) GCTs, HDCT, and ASCT may be considered for patients under 18 years of age who experience recurrence and insufficient response to primary chemotherapy (2, 476).

Several conditioning regimens have been used for ASCT in patients with R/R GCTs. These regimens include (477, 478):

- **CarboPEC:** carboplatin 250–350 mg/m² for 4 days, etoposide 250–400 mg/m² for 4 days, and cyclophosphamide 1.6 g/m² for 4 days.
- **CE:** carboplatin 250–500 mg/m² for 3–4 days and etoposide 250–400 mg/m² for 3–4 days.

- **TE:** Thiotepa 300 mg/m² for 3 days and etoposide 250-300 mg/m² for 3 days.
- **MEC:** melphalan 140 mg/m² on day -6, etoposide 200 mg/m² on days -6 to -3, and carboplatin 200 mg/m² on days -6 to -3.

Given that carboplatin and etoposide are commonly used in the frontline treatment of children with GCTs, it is advisable to incorporate other chemotherapy agents, such as melphalan or thiotepa, into the conditioning regimen.

At the Pediatric Cell Therapy Unit of RIOHCT, we utilize the CarboPEC conditioning regimen for extracranial GCTs ***[Figure 34]***, while TE conditioning is employed for patients with CNS GCTs ***[Figure 35]***.

**Figure 34.** Autologous Stem Cell Transplantation (ASCT): (CarboPEC)
- Germ Cell Tumor (GCT)

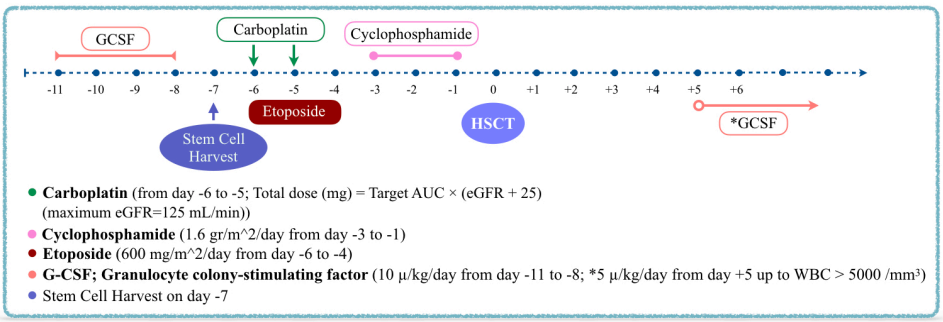
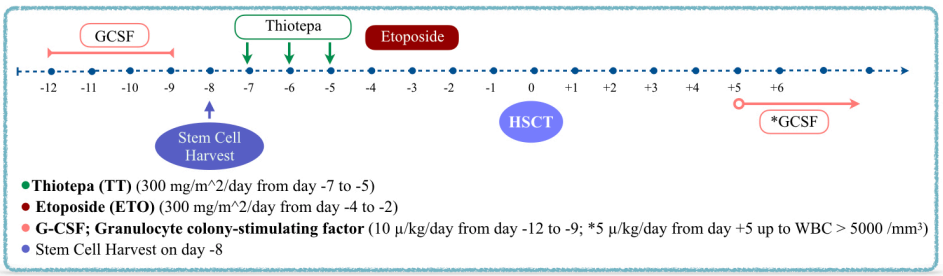



**Figure 35.** Autologous Stem Cell Transplant (ASCT): (TT-ETO)
- Germ Cell Tumor (GCT)



## Ewing Sarcomas

The role of HDCT combined with ASCT in the upfront treatment of newly diagnosed Ewing sarcoma (ES) remains a topic of ongoing debate (479).

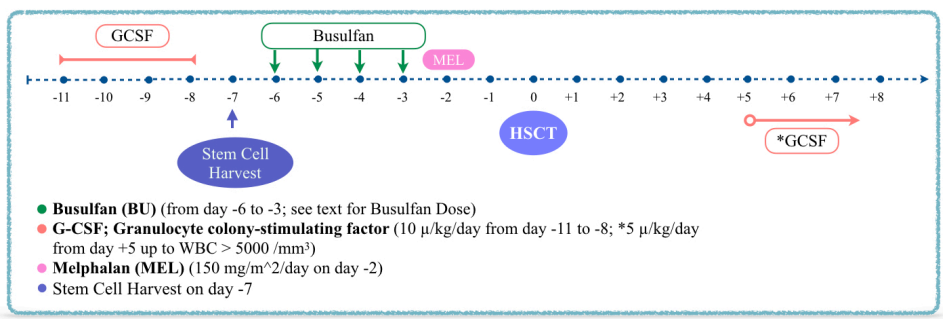
The EURO-EWING 99 study investigated the role of ASCT with a busulfan/melphalan conditioning regimen in newly diagnosed ES patients with localized, high-risk disease as part of the R2Loc trial. High-risk was defined as having a tumor volume greater than 200 milliliters or a poor histological response, indicated by more than 10% viable tumor cells in the resection specimen at the time of local control. The results revealed a statistically significant improvement in OS and EFS for patients who received ASCT (480).

Primary metastasis in ES is recognized as the most significant poor prognostic factor, leading to a five-year survival rate of less than 30%. While there is currently no definitive evidence supporting the effectiveness of ASCT for ES patients with primary metastasis to non-pulmonary sites, the Ewing 2008R3 RCT, which utilized treosulfan and melphalan followed by ASCT, indicated a benefit for children under 14 years old (481). In contrast, the R2PULM trial, which focused solely on patients with pulmonary metastasis, did not demonstrate a clear advantage for the combination of busulfan and melphalan followed by ASCT when compared to conventional chemotherapy and whole lung irradiation (482).

Additionally, ASCT has been investigated as a treatment option for relapsed ES, which is known for its aggressive nature and poor prognosis. Most studies suggest that HDCT combined with ASCT as a consolidation regimen is associated with improved OS and EFS compared to conventional chemotherapy. However, RCTs are necessary to establish the true clinical benefits of ASCT in patients with relapsed ES (483).

The conditioning regimen utilized for ASCT in children and adolescents with ES at the Pediatric Cell Therapy Unit of RIOHCT is busulfan/melphalan, as illustrated in ***Figure 36***.

**Figure 36.** Autologous Stem Cell Transplant (ASCT): (BU-MEL)
- Ewing sarcoma (ES) & Primitive neuroectodermal tumor (PNET)



### Allogeneic Hematopoietic Stem Cell Transplantation for Children with Ewing Sarcoma

Despite intensive treatment, the five-year survival rate for patients with relapsed or refractory Ewing sarcoma family tumors (RR-ESFTs) remains less than 20%. Allogeneic HSCT has emerged as a potential therapeutic option to leverage the graft-versus-ES effect through cellular immunotherapy. This approach is particularly promising with haploidentical HSCT, which is associated with a stronger allogeneic immune response compared to conventional HSCT (484). While there are some reports of using allogeneic HSCT for patients with RR-ESFTs, (485-487) further research is needed to evaluate its efficacy and to understand the mechanisms driving the GVT effect. This knowledge is essential for optimizing treatment strategies for this high-risk patient population.

## Brain Tumors

Over the past several years, researchers have investigated the use of HDCT combined with autologous stem cell rescue for patients with various CNS tumors. The primary objectives are to avoid RT in infants and young children under four years of age, to deliver dose-intensive chemotherapy, and to treat patients with recurrent disease (435).

Indications for ASCT include:

- High-risk medulloblastoma (primary metastases or relapse) in patients older than three years
- CNS GCT
- Metastatic primitive neuroectodermal tumors (PNETs) at diagnosis or those with additional high-risk features such as incomplete resection or young age (under three or five years)
- Young children under four years with malignant brain tumors

The role of ASCT in high-grade gliomas, ependymomas, brain stem gliomas or pineoblastoma remains controversial (2, 435).

Outcomes following ASCT are influenced by the disease status before chemotherapy, as well as tumor histology and location. For instance, patients with medulloblastoma have shown favorable outcomes, with a five-year EFS rate of 52%, while those with supratentorial ependymoma have a three-year EFS rate of 86%. In contrast, patients with infratentorial ependymoma and atypical teratoid/rhabdoid tumors (ATRT) have poorer outcomes, with three-year and two-year EFS rates of 27% and 29%, respectively (488, 489).

The ideal conditioning regimen for ASCT in brain tumors should effectively and rapidly penetrate the CNS (490). Recent conditioning regimens typically incorporate alkylating agents, such as thiotepa, platinum-based drugs, melphalan, and busulfan, often combined with topoisomerase inhibitors. Thiotepa is frequently included due to its ability to achieve similar concentrations in blood and cerebrospinal fluid (CSF) (491). Common conditioning combinations include BU/TT (busulfan/thiotepa), VP/TT/CBDCA (etopo-

side/thiotepa/carboplatin), and tandem approaches like VP16/CBDCA (etoposide/carboplatin)—TTP/L-PAM (thiotepa/melphalan) (2).

At RIOHCT, we utilize the VP/TT/CBDCA regimen for pediatric patients with brain tumors ***[Figure 37]***. For infants and young children under three years old with malignant brain tumors, our preferred conditioning approach is a tandem regimen consisting of etoposide/carboplatin followed by thiotepa/melphalan ***[Figure 38]***.

**Figure 37.** Autologous Stem Cell Transplant (ASCT): (VP/TT/CBDCA)
- Brain Tumor

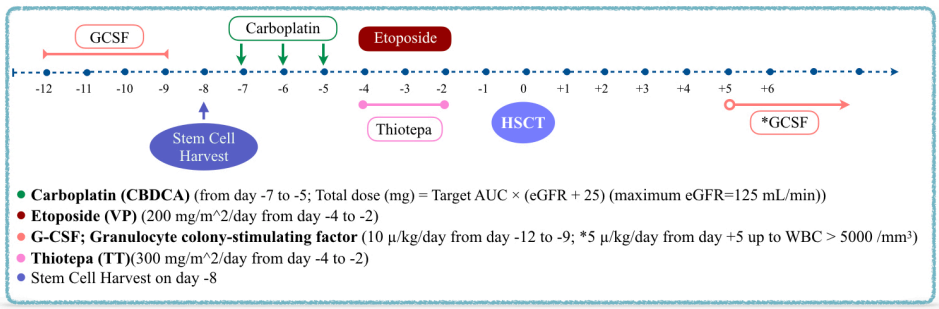
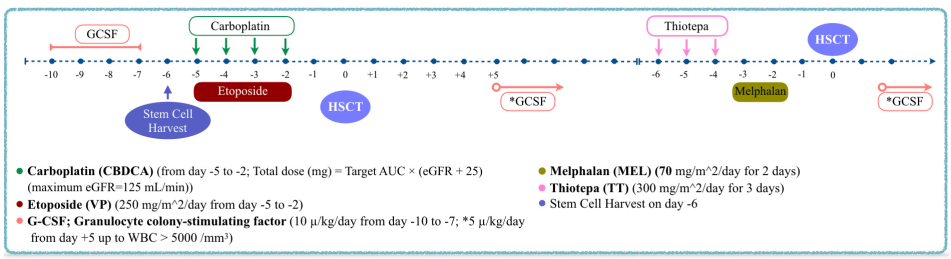



**Figure 38.** Autologous Stem Cell Transplant (ASCT) / Tandem: (VP/CBDCA-TT/Mel)
- Brain Tumor



# Abbreviations - References - Supplements

## Acknowledgments
The authors would like to acknowledge the support of the Research Institute for Oncology, Hematology, and Cell Therapy (RIOHCT).

## Funding
This work was supported by a grant from the Tehran University of Medical Sciences (TUMS).

## Conflict of interest
The authors declare no conflict of interest.

## Abbreviations

### A

| | |
|---|---|
| **ABW** | Adjusted ideal body weight |
| **ACS** | Acute chest syndrome |
| **AD EDA-ID** | Autosomal dominant anhidrotic ectodermal dysplasia with immune deficiency |
| **AIS** | Acute inflammatory syndrome |
| **ALD** | Adrenoleukodystrophy |
| **ALL** | Acute lymphoblastic leukemia |
| **AML** | Acute myeloid leukemia |
| **ANC** | Absolute neutrophil count |
| **APL** | Acute promyelocytic leukemia |

| | |
|---|---|
| **ARO** | Autosomal recessive osteopetrosis |
| **ASCT** | Autologous stem cell transplantation |
| **ASMD** | Acid sphingomyelinase deficiency |
| **ATLG** | Anti-T-lymphocyte globulin |
| **ATO** | Arsenic trioxide |
| **ATRA** | All-trans retinoic acid |
| **ATRT** | Atypical teratoid/rhabdoid tumors |
| **AUC** | Area under the concentration–time curve |

## B

| | |
|---|---|
| **BBB** | Blood-brain barrier |
| **B-CLL** | B-cell chronic lymphocytic leukemia |
| **BEN** | Bendamustine |
| **BL** | Burkitt lymphoma |
| **BM** | Bone marrow |
| **BMF** | Bone marrow failure |
| **BMI** | Body mass index |
| **BMT** | Bone marrow transplantation |
| **BNP** | B-type natriuretic peptide |
| **BU** | Busulfan |

## C

| | |
|---|---|
| **CAII** | Carbonic anhydrases II |
| **CAMT** | Congenital amegakaryocytic thrombocytopenia |
| **CAR** | Chimeric antigen receptor |
| **CB** | Cord blood |
| **CBDCA** | Carboplatin |
| **CCALD** | Childhood Cerebral ALD |
| **CGD** | Chronic granulomatous disease |
| **CHS** | Chediak-Higashi syndrome |
| **CID** | Combined immunodeficiency |
| **CIR** | Cumulative incidence of relapse |
| **cis-RA** | 13-cis-retinoic acid |
| **CMR** | Complete molecular remission |
| **CMV** | Cytomegalovirus |
| **CNI** | Calcineurin inhibitor |
| **CNS** | Central nervous system |
| **COVID-19** | Coronavirus disease 2019 |
| **CrCl** | Creatinine clearance |
| **CR** | Complete remission |
| **CR1** | First complete remission |
| **CRRT** | Continuous renal replacement therapy |

| | |
|---|---|
| **CSA** | Cyclosporine A |
| **CSF** | Cerebrospinal fluid |
| **Css** | Concentration at steady state |
| **CT** | Computed tomography |
| **CY** | Cyclophosphamide |

## D

| | |
|---|---|
| **DBA** | Diamond-Blackfan anemia |
| **DC** | Dendritic cell |
| **DF** | Defibrotide |
| **DHR** | Dihydrorhodamine |
| **DLBCL** | Diffuse large B-cell lymphoma |
| **DSA** | Donor-specific anti-HLA antibody |

## E

| | |
|---|---|
| **EBV** | Epstein–Barr virus |
| **ECG** | Electrocardiogram |
| **EFS** | Event-free survival |
| **EN** | Enteral nutrition |
| **EOC** | End of Consolidation |
| **EOI** | End of Induction |
| **ER** | Extended-release |
| **ERT** | Enzyme replacement therapy |
| **ES** | Ewing sarcoma |
| **ETO** | Etoposide |

## F

| | |
|---|---|
| **FA** | Fanconi anemia |
| **FDA** | Food and Drug Administration |
| **FDG-PET** | 18-Fluoro-deoxyglucose positron emission tomography |
| **FFP** | Fresh frozen plasma |
| **FHL** | Familial HLH |
| **FLU** | Fludarabine |

## G

| | |
|---|---|
| **GCT** | Germ cell tumor |
| **GD2** | Disialoganglioside |
| **GF** | Graft failure |
| **GFR** | Glomerular filtration rate |
| **GI** | Gastrointestinal |
| **GM-CSF** | Granulocyte-macrophage colony–stimulating factor |
| **GO** | Gemtuzumab ozogamicin |

| | |
|---|---|
| **GS2** | Griscelli syndrome type 2 |
| **GVHD** | Graft-versus-host disease |
| **GVL** | Graft-versus-leukemia |
| **GVT** | Graft-versus-tumor |

## H

| | |
|---|---|
| **hATG** | Horse-derived anti-thymocyte globulin |
| **Hb** | Hemoglobin |
| **HBV** | Hepatitis B virus |
| **HCV** | Hepatitis C virus |
| **HDCT** | High-dose chemotherapy |
| **HIV** | Human immunodeficiency virus |
| **HLA** | Human leukocyte antigen |
| **HLH** | Hemophagocytic lymphohistiocytosis |
| **HL** | Hodgkin lymphoma |
| **HPC** | Hematopoietic progenitor cell |
| **HSC** | Hematopoietic stem cell |
| **HSCGT** | Hematopoietic stem cell gene therapy |
| **HSCT** | Hematopoietic stem cell transplantation |
| **HSV** | Herpes Simplex Virus |
| **HZ** | Herpes zoster |

## I

| | |
|---|---|
| **IBW** | Ideal body weight |
| **IBMFS** | Inherited bone marrow failure syndrome |
| **IEI** | Inborn errors of immunity |
| **IEM** | Inborn errors of metabolism |
| **IFI** | Invasive fungal infections |
| **IL** | Interlukin |
| **ILD** | Interstitial lung disease |
| **IM** | Intramuscular |
| **IMPDH** | Inosine-50-monophosphate dehydrogenase |
| **INRG** | International Neuroblastoma Risk Group |
| **INSS** | International Neuroblastoma Staging System |
| **IS** | Immunosuppressive |
| **IVIG** | Intravenous immunoglobulin |
| **IV** | Intravenous |

## J

| | |
|---|---|
| **JMML** | Juvenile myelomonocytic leukemia |

## L

| | |
|---|---|
| **LAD** | Leukocyte adhesion deficiency |
| **LRC** | Locarelli risk classification |
| **LSD** | Lysosomal Storage Diseases |

## M

| | |
|---|---|
| **MAC** | Myeloablative conditioning |
| **MDR** | Multi-drug resistant |
| **MDS** | Myelodysplastic syndrome |
| **MEL** | Melphalan |
| **MFI** | Mean fluorescence intensity |
| **MIBG** | Meta-iodobenzylguanidine |
| **MLD** | Metachromatic Leukodystrophy |
| **MMF** | Mycophenolate mofetil |
| **MNGIE** | Mitochondrial neurogastrointestinal encephalomyopathy |
| **MN** | Monocyte |
| **MPA** | Mycophenolic acid |
| **MPAL** | Mixed phenotype acute leukemia |
| **MPS** | Mucopolysaccharidoses |
| **MRA** | Magnetic resonance angiography |
| **MRC** | Medical Research Council |
| **MRD** | Matched related donor |
| **MRD** | Measurable residual disease |
| **MRI** | Magnetic resonance imaging |
| **MSD** | Matched sibling donor |
| **mtDNA** | Mitochondrial DNA |
| **mTOR** | Mechanistic target of rapamycin |
| **MTX** | Methotrexate |
| **MUD** | Matched unrelated donor |

## N

| | |
|---|---|
| **NB** | Neuroblastoma |
| **NHL** | Non-Hodgkin lymphoma |
| **NK** | Natural killer |
| **NMA** | Non-myeloablative |
| **NPD** | Niemann-Pick disease |
| **NRM** | Non-relapse mortality |
| **NSAID** | Non-steroidal anti-inflammatory drug |

## O

| | |
|---|---|
| **OM** | Oral mucositis |
| **OPT** | Osteopetrosis |
| **OS** | Overall survival |

## P

| | |
|---|---|
| **pB-LBL** | Primary B-cell lymphoblastic lymphoma |
| **PB** | Peripheral blood |
| **PBSC** | Peripheral blood stem cell |
| **PC** | Platelet concentrates |
| **PCR** | Polymerase chain reaction |
| **PFS** | Progression-free survival |
| **PID** | Primary immunodeficiency |
| **PIRRT** | Prolonged intermittent renal replacement therapy |
| **PJP** | Pneumocystis jirovecii pneumonia |
| **PK** | Pharmacokinetics |
| **PML** | Progressive multifocal leukoencephalopathy |
| **PMN** | Polymorphonuclear |
| **PNET** | Primitive neuroectodermal tumors |
| **PNH** | Paroxysmal nocturnal hemoglobinuria |
| **PO** | Per os |
| **PPI** | Proton pump inhibitor |
| **PRCA** | Pure red cell aplasia |
| **PRES** | Posterior reversible encephalopathy syndrome |
| **PRN** | Pro re nata |
| **PTCY** | Post-transplant cyclophosphamide |
| **PTIS** | Pre-transplant immune suppression phase |

## R

| | |
|---|---|
| **rATG** | Rabbit-derived anti-thymocyte globulin |
| **RCC** | Refractory cytopenia of childhood |
| **RCT** | Randomized-controlled trial |
| **RFS** | Relapse-free survival |
| **RIC** | Reduced-intensity conditioning |
| **RR-ESFT** | Relapsed or refractory Ewing sarcoma family tumors |
| **R/R** | Relapsed or refractory |
| **RTA** | Renal tubular acidosis |

## S

| | |
|---|---|
| **SAA** | Severe aplastic anemia |
| **SCD** | Sickle cell disease |
| **SDCT** | Standard-dose chemotherapy |
| **SCID** | Severe combined immunodeficiency |
| **SIR** | Sirolimus |
| **SOS** | Sinusoidal obstruction syndrome |

## T

| | |
|---|---|
| **TT** | Thiotepa |
| **TAC** | Tacrolimus |
| **TBI** | Total body irradiation |
| **TBW** | Total body weight |
| **TCD** | T-cell depletion |
| **TCI** | Transplant conditioning intensity |
| **TCR** | T-cell receptor |
| **TDM** | Therapeutic drug monitoring |
| **TDT** | Transfusion-dependent thalassemia |
| **T-LBL** | T-cell lymphoblastic lymphoma |
| **t-MDS** | Therapy-related myelodysplastic syndrome |
| **TMP** | Trimethoprim |
| **TPE** | Therapeutic plasma exchange |
| **TPN** | Total parenteral nutrition |
| **TRM** | Treatment-related mortality |
| **TTP** | Thrombotic thrombocytopenic purpura |
| **TYMP** | Thymidine phosphorylase |

## U

| | |
|---|---|
| **UCB** | Umbilical cord blood |
| **UDCA** | Ursodeoxycholic acid |
| **UV** | Ultraviolet |

## V

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| **VOD** | Veno-occlusive disease |
| **VZV** | Varicella-zoster virus |

## W

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| **WAS** | Wiskott-Aldrich syndrome |
| **WT** | Wilms' tumor |

## X

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| **XLP** | X-linked lymphoproliferative disease |

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# Supplement 1

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| **Busulfan** | IV infusion | Diluent must be 10 times the volume of Busulfan<br>Dilute in N/S or D/W 5%<br>Infusion over 2 hours via CV-line<br>Flush the line before and after the infusion<br>Concentration to be as close to 0.5 mg/mL as possible | If <60 mg: to the nearest 1.2 mg<br>If >60 mg: to nearest 6 mg | Store intact vials under refregirator at 2 to 8 °C<br>Diluted solution is stable for up to 8 hours at room tempreture (25°C) and 12 hours at the refregirator<br>Busulfan must not be infused concomitantly with another intravenous solution.<br>Anticonvulsant should be administrated 24 h prior to Busulfan up to 24 h after the last dose of Busulfan. |

- **Quantity of Busulfan:**

Y (kg) x D (mg/kg) / 6 (mg/ml) = A ml of Busulfan to be diluted
Y: body weight of the patient in kg (Actual Body Weight)
D: dose of Busulfan

- **Quantity of diluent:**

(A ml Busulfan) x (10) = B ml of diluent

- **Administration dose:**

<9 kg: 1 mg/kg‡ every 6 hours
9-16 kg: 1.2 mg/kg‡ every 6 hours
16-23 kg: 1.1 mg/kg‡ every 6 hours
23-34 kg: 0.95 mg/kg‡ every 6 hours
>34 kg: 0.8 mg/kg‡ every 6 hours
Total of doses: 16 doses
[‡ Bu: ABW25 = IBW + 0.25 (TBW – IBW)]

**Fanconi Anemia:**

IV infusion, 0.16 mg/kg/day, Total of doses: 16 doses [Use IBW (Ideal Body Weight) or TBW (Total Body Weight), whichever is lower. If BMI>35 kg/$m^2$: use AIBW.]

## Therapeutic Drug Monitoring (TDM)

- Sample material: Plasma
- Time of sampling:
  - AUC-based monitoring (Bayesian estimation): It is advised to draw at least 4 samples after the first infusion of busulfan on day 1:
    - S1: 5 minutes after the end of infusion.
    - S2: 1 hour after the end of infusion.
    - S3: 2 hours after the end of infusion.
    - S4: 3 hours after the end of infusion.
  - *Additional sampling:* In case of a dose adjustment ≥25% or in the presence of risk factors for toxicity, TDM on the following day of treatment is advised.
- Target exposure:
- 4-day cumulative AUC ($AUC_{cum\ day\ 0\text{-}4}$) of 80-100 mg×h/L, targeting an $AUC_{cum\ day\ 0\text{-}4}$ of 90 mg×h/L.

## Drug Overdoses

- There is no known antidote to Busulfan other than hematopoietic progenitor cell transplantation.
- Dialysis should be considered.
- The use of NAC and Defibrotide may be helpful.

## Drug interactions

- Avoid paracetamol within 72 h prior to or concurrently with Busulfan.
- Monitor for increased BU concentrations/ toxicity when used concurrently.

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on adjusted ideal body weight 25 (ABW25) should be considered. (ABW25 = IBW + 0.25 (TBW – IBW))

### 2. Renal and Hepatic Impairment

Patients with renal impairment

No dose adjustment (Studies in renally impaired patients have not been conducted, however, as busulfan is moderately excreted in the urine, dose modification is not recommended in these patients. However, caution is recommended).

Patients with hepatic impairment

No dose adjustment (Busilvex as well as busulfan has not been studied in patients with hepatic impairment. Caution is recommended, particularly in those patients with severe hepatic impairment).

## Supportive care

Seizure prophylaxis

Levetiracetam: 10 mg/kg/BD PO or IV (max: 500 mg/dose) from 24 hours before Bu initiation up to 24 hours after the last dose of busulfan.

# Supplement 2

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| **Bendamustine** | IV infusion | Reconstitute 25 mg vial with 5 mL and 100 mg vial with 20 mL of SWFI to a concentration of 5 mg/mL. Within 30 minutes of reconstitution, dilute appropriate dose for infusion in 500 mL NS or D/S to a final concentration of 0.2 to 0.6 mg/mL; mix thoroughly. Infusion over 30-60 min via CV-line | To the nearest 25 mg | Store intact vials up to 25°C; excursions are permitted up to 30°C. Protect from light. The solution in the vial (reconstituted with SWFI) is stable for 30 minutes (transfer to 500 mL infusion bag within that 30 minutes). The solution diluted in 500 mL of NS or D/S for infusion is stable for 24 hours refrigerated or 3 hours at room temperature (15°C to 30°C) and room light. Infusion must be completed within these time frames. |

## Drug Overdoses

- No specific antidote for bendamustine hydrochloride overdose is known.
- Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

## Drug intervals

- No need for additional consideration.

## Drug interactions

- No significant interaction with usual used medications

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on total body weight (TBW) should be considered.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

No dose adjustment

(Some references NOT recommend in eGFR <30 mL/min)

Patients with hepatic impairment

Mild impaiment (Bilirubin <1.7 or AST or ALT less than 1.5 times ULN): No dose adjustment

Moderate impairment (Bilirubin: 1.7- 2.9): 70% of standard dose

Severe impaiment (Bilirubin ≥3): Not recommended

# Supplement 3

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| Cyclophosphamide | IV infusion | Reconstitute with 25 mL N/S or SWFI, then dilute in N/S or D/W<br>Infusion over 2 hours via CV-line | To the nearest 20 mg | Store intact vials at the room temperature (25°C)<br>The reconstituted solution is stable for 24 hours at the 25°C and 6 days at the refigirater<br>IV Mesna should be administarted (see Mesna)<br>Consider hyperhydration (3 L/m2/24 hours of N/S) begining at least 4 hours before Cyclophosphamide and continue at least 24 hours after Cyclophosphamide termination. |

## Drug overdose

- No specific antidote for cyclophosphamide is known.
- Cyclophosphamide is dialyzable.

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on ideal body weight (IBW) should be considered.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

eGFR ≥30 mL/min: No dose adjustment

eGFR 10-29 mL/min: 75% of normal dose

eGFR <10 mL/min: 50% of normal dose

HD: Not recommended; if unavoidable: 50% of normal dose

Patients with hepatic impairment

Serum bilirubin ≤3 mg/dL: No dose adjustment

Serum bilirubin from 3.1 to 5 mg/dL: 75% of normal dose

Serum bilirubin >5 mg/dL: Not recommended

# Supportive care

## Hydration and diuresis

Recommended hydration regimen is 3 L/m$^2$/24 hours of N/S begining at least 4 hours before Cyclophosphamide.

- Continue hydration for at least 24 hours after completion of cyclophosphamide.
- Diuretics may be indicated for positive fluid balance, weight gain or declining urine production, and to maintain urine output >150 mL/h.
  - Furosemide 0.5-1 mg/kg IV PRN should be prescribed.

**Mesna (sodium 2-mercapto ethane sulfonate):** 10% of Cyclophosphamide daily dose 30 minutes before Cyclophosphamide , then 100% of Cyclophosphamide daily dose infusion from the time of Cyclophosphamide initiation until 24 hours.

# Supplement 4

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| **Melphalan** | IV infusion | Reconstitute 50 mg vial initially with 10 mL of supplied diluent to a concentration of 5 mg/mL. Shake immediately and vigorously to dissolve. Immediately dilute dose in N/S to a final concentration ≤0.45 mg/mL. Infusion over 15-20 min (a rate NOT to exceed 10 mg/min) via CV-line<br>* Consider hydration pre- and post-melphalan administration | To the nearest 2 mg | Stability is limited; must be prepared fresh. The time between reconstitution/dilution and administration of must be kept to a minimum (<60 min). Do not refrigerate solution; precipitation occurs if stored at 5°C. |

## Drug Overdoses

- There is no known specific antidote to melphalan.
- Appropriate supportive treatment, such as blood transfusion, antimicrobials and/or hematopoietic growth factors (e.g., G-CSF, GM-CSF) should be instituted if needed.
- This drug is not removed from plasma to any significant degree by haemodialysis or haemoperfusion.
- The blood picture should be closely monitored for at least 4 weeks following overdosage until there is evidence of recovery.

## Drug intervals

- No need for additional consideration.

## Dose modifications

### 1. Obese patients

TBW; if patients weigh >130% of their IBW, BSA better to be calculated using ABW.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

No dose adjustment

Patients with hepatic impairment

No dose adjustment

## Supportive care

### Hydration and diuresis

Pre- and post-hydration should be considered for melphalan (to prevent nephrotoxicity).
N/S 125 mL/m2/h for 2 hours pre-melphalan and 6 hours post-melphalan.
10 mmol Potassium may be added to each 1 L of fluid.

# Supplement 5

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| Thiotepa | IV infusion | Reconstitute each 15 mg vial with 1.5 mL SWFI to a concentration of 10 mg/mL. Gently mix by repeated inversions. Further dilute dose volume of reconstituted solution in N/S to a final concentration of 0.5- 1 mg/mL. Infusion over 2-4 hours through in-line filter with a pore size of 0.22 microns via CV-line. Flush line prior and after infusion with ~5 mL N/S. | To the nearest 5 mg | Store intact vials under refrigeration (2º-8ºC) and protect from light. Reconstituted solution is stable for 8 hours in refrigerator (2º-8ºC). Diluted solution in N/S is stable for 24 hours at refrigerator (2º-8ºC) or 4 hours at room temperature. |

## Drug Overdoses

- There is no known antidote for overdosage with thiotepa.
- Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on adjusted body weight 40 (ABW40) should be considered.

(ABW40 = IBW + 0.4 (TBW – IBW))

### 2. Renal and Hepatic Impairment

Patients with renal impairment

eGFR ≥30 mL/min: No dose adjustment

eGFR <30: 70% of standard dose

HD: 70% of standard dose (Thiotepa is dialyzable)

Patients with hepatic impairment

Serum bilirubin <1.5 × ULN: No dose adjustment

Serum bilirubin 1.5-3 × ULN: Monitor closely (intensify monitoring)

Serum bilirubin >3 × ULN: Not recommended

# Supplement 6

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| Etoposide | IV infusion | Dilute in D/W or N/S to a final concentration of 0.2 to 0.4 mg/mL. Infusion over 60 min through non-PVC (low sorbing) tubing via CV-line ***Etoposide injection contains polysorbate 80 which may cause leaching of DEHP, a plasticizer contained in PVC bags and tubing. | To the nearest 50 mg | Store intact vials at 20°C to 25°C; do not freeze. Diluted solutions have concentration-dependent stability. 0.2 mg/mL reconstitute solution is stable for 96 hours at room temperature and 0.4 mg/mL solution is stable for 24 hours at room temperature (precipitation may occur at concentrations above 0.4 mg/mL). Higher concentrations and longer storage time after preparation in PVC bags may increase DEHP leaching. |

## Drug Overdoses

- No specific antidote for etoposide overdose is known.
- Supportive care should be applied.

## Drug intervals

- No need for additional consideration.

## Drug interactions

- No significant interaction with usual used medications

## Dose modifications

### 1. Obese patients

Actual body weight (TBW) for calculation of BSA for BSA-based dosing and dosing based on adjusted ideal body weight 25 (ABW25) should be considered for mg/kg dosing (ABW25 = IBW + 0.25 (TBW – IBW)).

### 2. Renal and Hepatic Impairment

Patients with renal impairment

eGFR >50 mL/min: No dose adjustment
eGFR 15- 50 mL/min: 75% of standard dose
eGFR <15 mL/min: 50% of standard dose

HD: 50% of standard dose (not dialysed)

Patients with hepatic impairment

Bilirubin <3 mg/dL: No dose adjustment

Bilirubin ≥3 mg/dL: 50% of standard dose

# Supplement 7

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| Cytarabine | IV infusion | Reconstitute with SWFI, then dilute in 250 to 1,000 mL N/S or D/W. Infuse over 1-3 hours | To the nearest 10 mg | Store intact vials of powder for reconstitution at 20°C to 25°C. Store intact vials of solution at 15°C to 30°C. Protect from light. Reconstituted solutions should be stored at room temperature and used within 48 hours. Solutions for IV infusion diluted in D/W or N/S retained 94% to 100% of potency after 8 days when stored at room temperature, although the manufacturer recommends administration as soon as possible after preparation. |

## Drug Overdoses

- No specific antidote for cytarabine overdose is known.
- Supportive care should be applied.

## Drug intervals

- No need for additional consideration.

## Drug interactions

- No significant interaction with usual used medications

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on total body weight (TBW) should be considered.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

No dose adjustment

Patients with hepatic impairment

No dose adjustment

## Supportive care

To prevent a chemical induced conjunctivitis developing with cytarabine, artificial tears may be administered (2 drops per eye 4 hourly) starting 1 day before cytarabine treatment and continuing for 48 hours after last dose of cytarabine as prophylaxis. If patient becomes symptomatic treatment may escalate to corticosteroid eye drops 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered.

# Supplement 8

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| **Fludarabine** | IV infusion | Reconstitute lyophilized powder with 2 mL SWFI to a concentration of 25 mg/mL; then dilute for infusion in 100 mL N/S or D5W to a concentration of 0.25 mg/mL Infusion over 30 min | Fludarabine doses ≤50 mg to the nearest 2.5 mg and doses >50 mg to the nearest 5 mg | Store intact vials under refrigeration (2º-8ºC) and protect from light Reconstituted solution should be used within 8 hours. |

## Drug Overdoses

- There is no known specific antidote for fludarabine over dosage.
- Treatment consists of drug discontinuation and supportive therapy.

## Dose modifications

### 1. Obese patients

For obese patients, dosing based on total body weight (TBW) should be considered.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

eGFR ≥80 mL/min: No dose adjustment
eGFR 50- 79 mL/min: 20 mg/m2
eGFR 30- 49 mL/min: 15 mg/m2
eGFR <30: Not recommended
HD: Not recommended (if unavoidable; 80% of standard dose)

Patients with hepatic impairment

No dose adjustment

# Supplement 9

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| Carboplatin | IV infusion | Solution should be diluted in 100- 250 mL of NS or D/W to concentrations as low as 0.5 mg/mL Infusion over 15-60 min ***Needles or IV administration sets that contain aluminum should NOT be used in the preparation or administration of carboplatin. | To the nearest 10 mg | Store intact vials at room temperature at 25°C; excursions permitted to 15°C to 30°C Protect from light. Diluted solution (0.5 mg/mL) in N/S or D/W is stable at room temperature (25°C) for 8 hours. Diluted solution in PVC bag is stable for 24 hours. Multidose vials are stable for up to 14-15 days after opening when stored at 25°C following multiple needle entries. |

## Drug overdose

- No specific antidote for carboplatin overdose is known.
- Supportive care should be applied.
- The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

## Drug intervals

- No need for additional consideration.

## Drug interactions

- No significant interaction with usual used medications.

## Dose modifications

### 1. Obese patients

TBW (for both BSA- and AUC-based dosing)

### 2. Renal and Hepatic Impairment

Patients with renal impairment

Dose according to the Calvert formula incorporating patient's GFR
ARC (i.e., eGFR >125 mL/min): Consider eGFR=125 (max)
HD: Consider eGFR=0 in the Calvert formula
*** Calvert formula: Total dose (mg) = Target AUC × (eGFR + 25)

Patients with hepatic impairment

No dose adjustment

## Supportive care

*** Desensitization protocol may be required in the case of carboplatin anaphylactic reactions.

# Supplement 10

| Drug | Route of administration | Preparation | Dose rounding | Storage |
|---|---|---|---|---|
| rATG [Anti-thymocyte globulin (Rabbit-derived)] | IV infusion | Allow vials to reach room temperature, then reconstitute each vial of ATG with 5 mL SWFI to a concentration of 5 mg/mL. Rotate vial gently until completely resolved. Then, dilute in N/S or D5W to a concentration of 0.5 mg/mL (each 25 mg vial should be diluted in 50 mL). Mix by gently inverting infusion bag once or twice.<br><br>Infusion over 6-12 hours through in-line filter with pore size of 0.22 microns via CV-line. Subsequent doses can be infused over 4 hours if first dose tolerated.<br>For peripheral administration, dilute in 500 mL N/S with the addition of 1000 units heparin.<br>***Immidiate treatment (SQ epinphrine and corticosteroid) should be available during infusion for the managment of hypersensitivity. | To the nearest 20 mg | Store intact vials in refrigerator at 2°C to 8°C (36°F to 46°F).<br><br>Do not freeze.<br><br>Protect from light<br><br>Reconstituted ATG is stable for up to 24 hours at room temperature. |

## Drug Overdoses:

- No specific antidote for ATG is known.
- Treatment should be symptomatic.

## Drug intervals

- Avoid administration of ATG with other drugs or fluids via Y-site.

## Dose modifications

### 1. Obese patients

ATG [Anti-thymocyte globulin (Rabbit)]: For obese patients, dosing based on total body weight (TBW) should be considered.

### 2. Renal and Hepatic Impairment

Patients with renal impairment

No dose adjustment.

Patients with hepatic impairment

No dose adjustment.

## Supportive Care

Use premedication **1 hour before** infusion:

- Acetaminophen 15 mg/kg (max: 650 mg), IV
- Diphenhydramine 1.25 mg/kg (max: 50 mg), IV
- Methylprednisolone 0.5 mg/kg, IV

Monitoring during the ATG infusion: blood pressure, pulse rate, respiration and temperature at 15, 30 and then 60 minutes intervals. The patient should be monitored closely for adverse events during and for 3 to 4 hours after completion of the infusion; for both initial and subsequent infusions.

If the patient becomes hypotensive or experiences chest or back pain, indicating anaphylaxis reactions, the infusion should be stopped immediately.

Platelets should be $>50 \times 10^9$/L on day 1 of ATG infusion or in the setting of clinically symptomatic bleeding.
If the patient has no reaction to ATG platelets can be maintained at $>30 \times 10^9$/L for the remaining days of ATG administration.