# Immune Reconstitution After Peripheral Blood Hematopoietic Stem Cell Transplantation From Matched Sibling Donor

Essay Submitted for Partial Fulfillment of Master Degree in Pediatrics

By

#### **Manar Saad Wahbah Mohammed**

M.B.B.Ch - Ain Shams University December 2005

Under Supervision Of

#### Prof. Dr. Wafaa Ezzat Ibrahim

Professor of Pediatrics
Faculty of Medicine – Ain Shams University

#### Dr. Jounier Hussein Abd El Kafy

Lecturer of Pediatrics

Faculty of Medicine – Ain Shams University

Faculty of Medicine Ain Shams University 2012

#### دراسة إعادة بناء جهاز المناعة بعد زراعة الخلايا الجذعية المكونة للدم من متبرع متطابق من العائلة

مقالة توطئة للحصول على درجة الماجيستير في طب الأطفال

مقدمة من الطبيبة / منار سعد وهبه محمد بكالوريوس الطب والجراحة – جامعة عين شمس ديسمبر ٢٠٠٥

تحت إشراف الأستاذة الدكتورة/ وفاء عزت إبراهيم

> أستاذ طب الأطفال كلية الطب \_ جامعة عين شمس

الدكتورة / جونير حسين عبد الكافي

مدرس طب الأطفال كلية الطب ـ جامعة عين شمس

> كلية الطب جامعة عين شمس ٢٠١٢

#### **Summary and Conclusions**

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many disorders, such as hematologic and oncologic malignancies as well as immunologic and metabolic disorders.

Unfortunately, cure is often hampered by some complications such as relapse of the underlying disease, graft-versus-host disease, or severe opportunistic infections, which account for the majority of deaths after HSCT.

Despite considerable progress in the management of these complications, infections remain an important cause of post-transplant morbidity and mortality, mainly after allogeneic HSCT.

Specific immune defects are associated with each of the different stages of transplantation, which put patients at risk of developing different types of infections.

In the pretransplantation period: baseline host status, medication therapy, pre-existing neutropenia or compromised barrier defences lead to infections at this stage. So before transplantation, screening is needed to identify potential infectious agents that may put the patient at risk following the immunosuppression that precedes the transplantation.

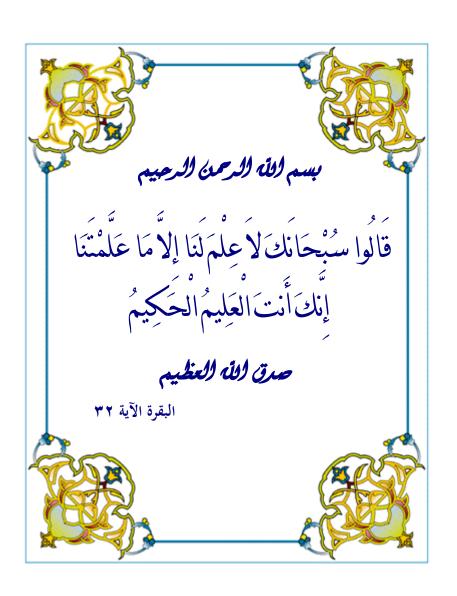


First great thanks to "Allah" who gave me the power to complete this work. Without his care nothing could be achieved.

I would like to express my greatest gratitude to **Prof. Dr. Wafaa Ezzat Torahim**, Professor of Pediatrics – Ain Shams University, for her constant encouragement, unlimited help, stimulation, suggestions, excellent advice and constant support.

I am much thankful to **Dr. Jounier Hussein Abd El Kafy,** Lecturer of Pediatrics – Ain Shams University, for her encouragement, support and sincere guidance throughout the work.

Last but not least, sincere gratitude to *My Mother* may God send his mercy upon her sole.



#### **List of Contents**

Title	Page
List of Abbreviations	II
List of Figures	VI
List of Tables	VII
Introduction	1
Overview on the immune system in relation to hematopoietic stem cell transplantation	3
Infections after HSCT	11
Immune reconstitution following HSCT	42
Factors affecting immune reconstitution	52
Assessment of immune reconstitution	68
Clinical Strategies to enhance post- transplant immune reconstitution	81
Summary and Conclusion	105
References	110
Arabic summary	

#### **List of Abbreviations**

αβ T cell	Alpha beta T cell
α4β7 integrin	Alpha 4 beta 7 integrin
ADCC	Antibody-dependent cell-mediated
	cytotoxicity
aGvHD	Acute graft versus host disease
allo-HSCT	Allogeneic hematopoetic stem cell
	Transplantation
allo-SCT	Allogeneic stem cell transplant
APCs	Antigen presenting cells
ATG	Antithymocyte globulin
auto- PBSCT	Autologous – peripheral blood stem cell
	transplantation
BAL	Broncho-alveolar lavage
2-CDA	2-chlorodeoxyadenosine
СВ	Cord blood
CCR5	C-C chemokine receptor type 5
CCR7	C-C chemokine receptor type 7
CDR3	Complementarity determining region 3
Chm	Chimerism
Corynebacterium	Corynebacterium jeikeium
JK	
CpG	Cytosine, phosphodiester, guanine
CTL	Cytotoxic T-lymphocyte

CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CXCR3	Chemokine receptor CXCR3
DCs	Dendritic cells
DLI	Donor lymphocyte infusion
DTH	Delayed type hypersensitivity
EBMT	European Group for Blood and Marrow
	Transplantation
ECIL	(European Conference on Infections in
	Leukaemia)
FAS-L	Fas ligand
Fcg receptors	Fc-gamma receptors
FISH	Fluorescence in situ hybridization
FL	Flt3 ligand
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating
	factor
GVHD	Graft versus host disease
GVL	Graft versus leukaemia
HDM	High density microparticles
НЕРА	High efficiency particle extraction
HLA	Human leukocyte antigen
HSCT	Haematopoietic stem cell Transplantation
HSPs	Heat-shock proteins
HvG	Host versus-graft reaction
IFI	Invasive fungal infection

IFN	Interferon
IFN-α	Interferon alpha
ΙΕΝ-γ	Interferon gamma
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IR	Immune reconstitution
IVIG	Intravenous immunoglobulin
KGF	keratinocyte growth factor
KIR	killer-cell inhibitory receptor
LAK	lymphokine-activated killer
LLME	Lleucyl- L-leucine methyl ester
LPD	Lymphoproliferative disorders
MAbs	monoclonal antibodies
MACS	Magnetic-activated cell sorting
MBL	mannose binding lectin
MPO	Myeloperoxidase
NASBA	nucleic acid sequence-based amplification
NBT	nitroblue tetrazolium reduction test
NST	Non myeloablative stem cell transplant
	regimens
PBMC	peripheral blood monocytes
PRP	polyribosylribitol phosphate
PRRs	pattern recognition receptors

PTLD	post-transplant lymphoproliferative
	disease
RTE	recent thymic emigrants
TBI	total body irradiation
TCD	T-cell depleted
TCR	T-cell receptor
TGF-β	tumour growth factor beta
TK	thymidine kinase
TLR	Toll-like receptor
TREC	T-cell receptor rearrangement excision
	circles
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
VOD	veno-occlusive disease

#### **List of Figures**

Fig. No.	Title	Page No.
1	The innate immune system is derived from myeloid progenitor cells, whereas the adaptive immune system arises from lymphoid progenitor cell.	4
2	Timeline of infections after Hematopoietic stem cell transplantation.	15
3	Factors affecting immune reconstitution.	53

#### List of Tables

Table No.	Title	Page No.
1	The main recommendations for vaccinations after stem cell transplantation.	28
2	Immune function following Hematopoietic stem cell transplantation.: what we know.	50
3	Methodologies for chimerism testing.	70



#### Introduction





#### Chapter (1)

## Overview on the Immune System in Relation to Hematopoietic Stem Cell Transplantation





### Chapter (2) Infections after HSCT

