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PULMONARY COMPLICATIONS IN PEDIATRIC PATIENTS WITH HEMATOLOGICAL MALIGNANCY

An Essay
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BY

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This study has been directed for all who are engaged in care of pediatric patients with hematological malignancy. It covers all the important aspects of pulmonary complications, including infectious and noninfectious causes.

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ABSTRACT

Pulmonary complications remain a major cause of both morbidity and mortality in pediatric patients with hematological malignancy. The differential diagnosis of these complications is broad and includes both infectious and noninfectious causes. Infectious etiologies include bacterial, fungal, viral and mycobacterial pathogens. Noninfectious etiologies include disease related and treatment related causes. Thus the diagnosis of specific cause is important to proceed to the specific management. So etiologic factors, disease pattern, up to date management and possible ways of prevention of these complications are discussed aiming at achieving an earlier diagnosis that potentially may improve the mortality rate of these patients.

Key Words:

hematological malignancy, pulmonary complications, infectious, noninfectious, treatment.

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LIST OF ABBREVIATIONS

ABLC : Amphotericin B Lipid Complex
ALL : Acute Lymphoblastic Leukemia
AML : Acute Myelogenous Leukemia
ANC : Absolute Neutrophil Count
A-PLTs : Apheresis Platelet Concentrates
aPTT : Activated Partial Thromboplastin Time
Ara-C : Cytosine Arabinoside
ARDS : Acute Respiratory Distress Syndrome
ASCO : American Society of Clinical Oncology
AsO3 : Arsenic Trioxide
ATRA : All-Transretinoic Acid
BAL : Bronchoalveolar Lavage
BCG : Bacillus Calmette-Guérin
BCNU : Bis-Chlororethyl Nitrosourea
BPT : Bleomycin Pulmonary Toxicity
C.albicans : Candida Albicans
CHF : Congestive Heart Failure
CMI : Cell-Mediated Immunity
CML : Chronic Myelogenous Leukemia
CMV : Cytomegalovirus
CNS : Central Nervous System
CSFs : Colony-Stimulating Factors
CT : Computed Tomography
CVL : Central Venous Lines
DAD : Diffuse Alveolar Damage
DAH : Diffuse Alveolar Hemorrhage
DAH : Diffuse Alveolar Hemorrhage
D-AmB : Deoxycholate Amphotericin B
DLCO : Diffusing Capacity for Carbon Monoxide
EBV : Epstein-Barr Virus
EFS : Event-Free Survival
ELISA : Enzyme-Linked Immunosorbent Assay
FAB : French-American-British
FDA : Food and Drug Administration
FFP : Fresh Frozen Plasma
G-CSF : Granulocyte-Colony Stimulating Factor
GM-CSF : Granulocyte-Macrophage-Csf
GM-EIA : Galactomannan Enzyme Immunoassay

GVHD : Graft Versus Host Disease
HHV-6 : Human Herpes Virus Type 6
HIB : Haemophilus Influenzae Type B
hMPV : Human Metapneumovirus
HSCT : Hematopoietic Stem Cell Transplantation
HSV : Herpes Simplex Virus
IA : Invasive Aspergillosis
ICH : Immunocompromised Host
ICU : Intensive Care Unit
IDSA : Infectious Diseases Society Of America
IFI : Invasive Fungal Infection
IFN-γ : Interferon Gamma
Ig : Immune Globulin
IPA : Invasive Pulmonary Aspergillosis
IPS : Idiopathic Pneumonia Syndrome
IVDR BSIs : Ivd-Related Bloodstream Infections
IVDs : Intravascular Devices
IVIG : Intravenous Immune Globulin
K.pneumoniae: Klebsiella Pneumoniae
L-AmB : Liposomal Amphotericin B
LFAB : Lipid Formulations of Amphotericin B
LPSs : Lipopolysaccharides
LRTI : Lower Respiratory Tract Infection
MDVI : Multidimensional Volumetric Imaging
MICs : Minimum Inhibitory Concentrations
MNCs : Circulating Monocytes
MTX : Methotrexate
NCI : National Cancer Institute
NCPE : Non Cardiogenic Pulmonary Edema
NHL : Non-Hodgkin's Lymphomas
NO : Nitric Oxide
NOC : Nocardiosis
NSIP : Nonspecific Interstitial Pneumonia
OP : Organizing Pneumonia
ORSA : Oxacillin-Resistant S. Aureus
P.aeruginosa: Pseudomonas Aeruginosa
PaO_2 : Partial Pressure of O_2
PCP : Pneumocystis Carinii Pneumonia
PCR : Polymerase Chain Reaction
PIE : Pulmonary Infiltrates and Eosinophilia
PMNs : Polymorphonuclear Cells (Neutrophils)
PRBCs : Packed Red Blood Cells
PT : Prothrombin Time
RAS : Retinoic Acid Syndrome
RCTs : Randomised Controlled Trials

RSV : Respiratory Syncytial Virus
SARS : Severe Acute Respiratory Syndrome
SMS : Superior Mediastinal Syndrome
spp. : Species
SVCS : Superior Vena Cava Syndrome
TB : Tuberculosis
TBI : Total Body Irradiation
TLRs : Toll-Like Receptors
TMP-SMX : Trimethoprim-Sulfamethoxazole
TNF-α : Tumor Necrosis Factor Alpha
TRALI : Transfusion-Associated Lung Injury
VAT : Video-Assisted Thorascopically
VRE : Vancomycin-Resistant Enterococcus
VTE : Venous Thromboembolism
VZIG : Varicella Zoster Immune Globulin
VZV : Varicella Zoster Virus
WBC : White Blood Cell
WB-PLTs : Whole Blood–Derived Platelet Concentrates
WHO : World Health Organization

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INTRODUCTION AND AIM OF THE WORK

Unprecedented gains have been made in the cure rates for childhood cancer during the past four decades. This progress reflects steady improvement in treatment protocols, a multidisciplinary approach to patient care, adequate hospital infrastructure, and psychosocial and economic support for affected families [1].

Patients with hematological malignancies or recipients of hematopoitic stem cell transplants are prone to many complications. Pulmonary complications are of the most important and common complications in these patients. They occur in up to 40 to 60% of patients with hematological disorders during the disease course and considerably influence morbidity and mortality [2].

Patient with hematological malignancies who are treated with chemotherapeutic drugs or recipients of bone marrow or hematopoitic stem cell transplants may develop a wide variety of potentially fatal infectious and non infectious pulmonary complications, which represents a challenge to the pulmonary and critical care practitioner because the diagnosis is complex, and there is little time for diagnosis and treatment. The increased complexity of multimodality treatments and high-dose protocols designed to augment antineoplastic efficacy, and the context of HSCT have increased the incidence of pulmonary complications [3].

Pulmonary disease can be caused by a wide spectrum of pathogenic mechanisms in pediatric patients with hematological malignancies. The causes for respiratory dysfunction are divided into different categories: oncologic emergencies, directly tumor-related pulmonary dysfunction, infectious diseases, iatrogenic causes (medical, irradiation, bone marrow transplantation) [4].

The frequency, range and severity of pulmonary complications are influenced by the intensity and length of immunosuppression and are also dependent on whether the treatment goal is immunosuppression or myeloablation [5].

This work aims at finding a global approach to pulmonary complications in pediatric patients with hematological malignancies and reviewing the etiologic factors, disease pattern and up to date management of these complications.

In the first chapter a global idea about the incidence and the cure rate of different types of hematological malignancies is mentioned to give an idea about these types of malignancies and the impact of preventing such complications on improving their cure rates.

With the introduction of intensive frontline protocols, pediatric oncology patients are threatened by various infectious agents, depending on the degree and type of immunosuppression [4]. Bacterial, fungal, viral, and mycobacterial pathogens may infect the lungs of immunosuppressed patients. Thus the diagnosis of specific cause is important to proceed to the specific management. So, in the second chapter the differential diagnosis to possible causes of pulmonary infection is discussed with methods of diagnosis, management and prevention [4].

Noninfectious etiologies for pulmonary infiltrates in the immunosuppressed host are as diverse as the potential microbiologic etiologies [5]. Pulmonary toxicity caused by antineoplastic agents is being recognized more frequently, and the number of drugs known or suspected to cause lung disease is steadily increasing. Because continuing the offending agent may cause death and because withholding the agent may result in resolution of the pulmonary toxicity, it is important to recognize radiation- and drug-induced pulmonary disease [3]. In the last chapter, parenchymal lung disease caused by irradiation and chemotherapy is discussed. Mechanisms of lung injury, histopathologic findings, clinical and laboratory features, and diagnosis and treatment of the abnormalities produced by these agents are reviewed. Also other non infectious

etiologies including disease related causes and complications caused by transfusion of blood components are discussed in this last chapter.

CHAPTER ONE :

PEDIATRIC HEMATOLOGICAL MALIGNANCIES

Cancer is the second leading cause of death -after accidents- among children aged 6 to 14 years in the United States [6]. In developing regions of Asia, South and Central America, northwest Africa, and the Middle East cancer is emerging as a major cause of childhood death, as a result of reduced mortality from preventable infectious diseases [1].

The most common malignancy found in children are leukemias (in particular, acute lymphocytic leukemia), brain and other nervous system cancers, non-Hodgkin's lymphoma, and soft tissue cancers [6]. Survival for childhood cancers has improved dramatically over the last half century. Before 1950, almost all children who developed cancer died. At present, approximately three out of four children who are diagnosed with cancer can be cured [6]. This progress reflects steady improvement in treatment protocols, a multidisciplinary approach to patient care, adequate hospital infrastructure, and psychosocial and economic support for affected families [1]. Survival rates improved by at least 20% for acute lymphocytic and myeloid leukemias, neuroblastoma, non-Hodgkin's lymphoma, soft tissue cancer, and Wilms' tumor [6].

Hematopoietic neoplasms in the pediatric and adolescent population comprise almost 50% of all cancers, whereas in adults, they comprise only 5%–8% [7]. In addition, the spectrum of hematopoietic malignancies varies significantly between pediatric and adult patients (Figure 1.1) [8].

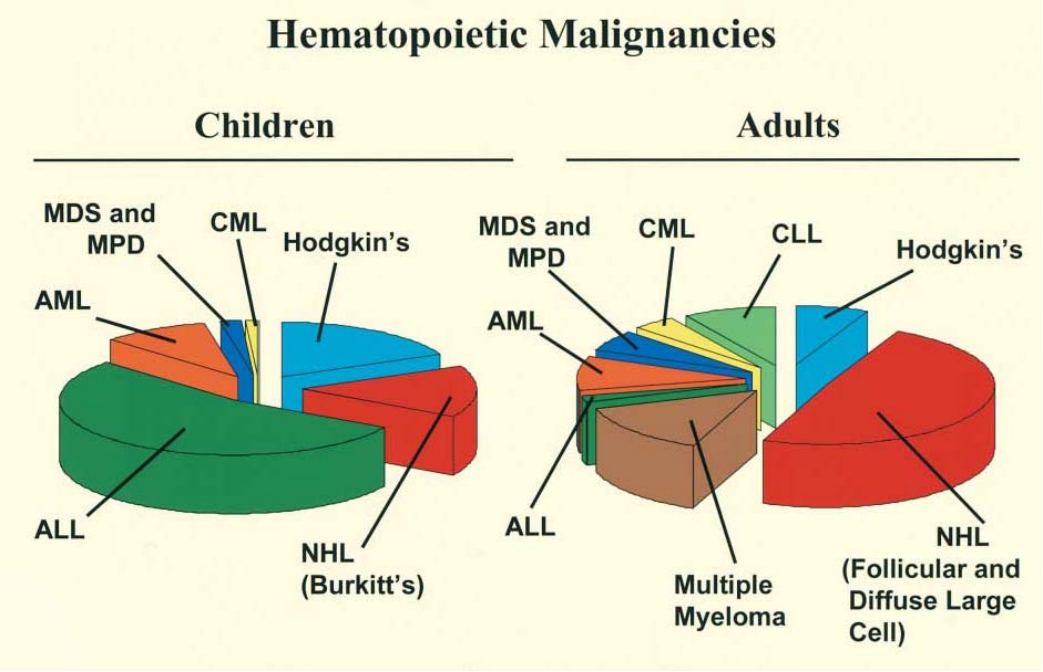

Figure 1.1: Frequency of the Major Subtypes of Hematopoietic Malignancies in Pediatric and Adult Patients. The pie charts show the relative frequency of the major hematopoietic malignancies in children (0 to 19 years) and adults (>19 years). The major leukemia and lymphoma subtypes include chromic myelogenous leukemia (CML), chromic lymphocytic leukemia (CLL), Hodgkin's disease, non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), acute Lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative disease (MPD) [8].

Hematopoiesis (Figure 1.2) is a complex process regulated by the coordinated expression of several transcription factors, which are activated or inhibited as hematopoiesis proceeds. The dysregulated expression of transcription factors and their resulting functional imbalance is believed to be required for malignant transformation [8]. Because hematopoiesis in vertebrates is intensely active during fetal development and the first few years of life, it is not surprising that leukemia is the most common childhood malignancy [9].

Malignancies that arise in the cells of the hematopoietic system are as varied as the individual lineages that comprise this tissue, and can be broadly categorized into acute and chronic leukemias, myelodysplastic and myeloproliferative syndromes, Hodgkin's disease, and the non-Hodgkin's lymphomas. As a result of advances in understanding of both normal hematopoietic development and the molecular pathology of hematopoietic

malignancies, significant improvements have occurred in our ability to accurately diagnose, subclassify, and treat these cancers.

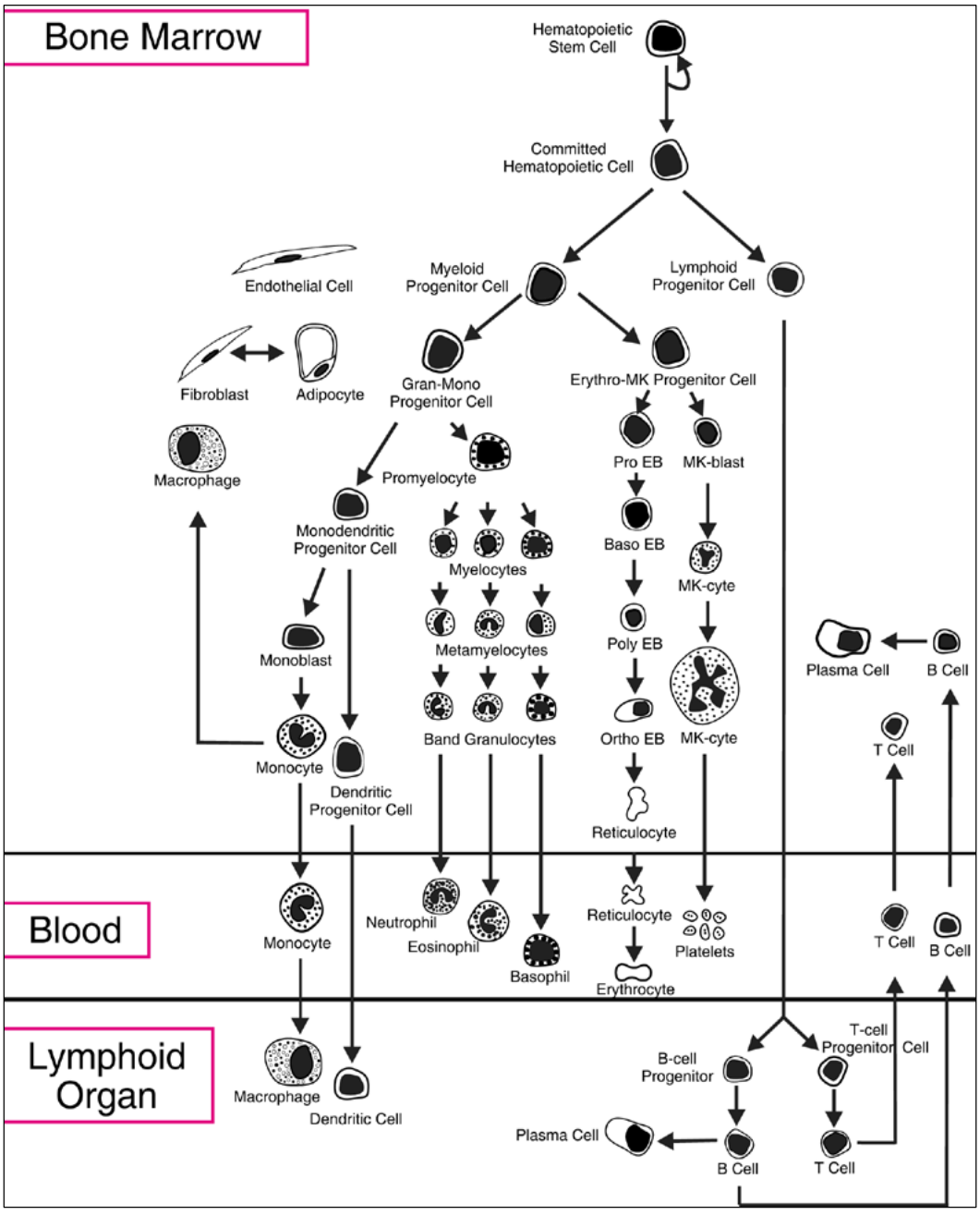

Figure 1.2: Hematopoiesis [10].

Thus the most common pediatric hematological malignancies (incidence, clinical picture, diagnosis and treatment options) are discussed preifly in the following part.