Profile of Infections in Newly Diagnosed Patients With Acute leukemia at the N.C.I of cairo University...

Thesis
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By
SALLY MOHAMED TALAAT KHATAB
(M.B.B.Ch.)

Supervised by
Dr.AHMED KADDAH
Assistant Professor of Pediatrics
Faculty of Medicine
Cairo University

Dr.HANY ABDELRAHMAN
Lecturer of Pediatric Oncology
National Cancer Institute
Cairo University

DR.HEBA ISMAEL
Lecturer of Pediatrics
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2009

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ABSTRACT

BACKGROUND: Newly diagnosed leukemia patients are highly susceptible to various types of infections. Neutropenia has been recognized for many decades as a major risk factor for the development of infections in cancer patients undergoing chemotherapy. Managing infections in neutropenic patients remains a dynamic process, supported by the appearance of new pathogens and the emergence of antibiotic-resistant organisms. The pathogens responsible for initial infections early in the course of fever and neutropenia are primarily bacteria, whereas antibiotic resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections during the course of induction chemotherapy.

METHODS: This is a retrospective study including 100 new cases of acute leukemia admitted to the pediatric department of the NCI, Cairo University in the year 2007 from the period of 1st of January to the end of June. Data collected included the initial evaluation in the form of: history and full clinical examination, complete blood picture (CBC), culture and sensitivity of blood, urine, stool, culture from the removed canula, throat swap and another swap from the wound if present, chest x-ray and x-ray of the sinuses (initially and at the point of re-evaluation) and other imaging and laboratory studies according to the clinical condition. Each infection was categorized as bacteremia, as fever of unknown origin (FUO), as upper respiratory tract infection (URI), like sinusitis, acute otitis media, tonsillitis, laryngitis, and as lower respiratory tract infection (LRI), like pneumonia and bronchopneumonia, based on clinical and radiographic findings. A gastrointestinal tract (GIT) infection was based on clinical, serology, or pathology findings. Genitourinary tract (GUT) infections involved urinary tract infections as well as vaginitis. CNS infections and eye infections were also diagnosed.

RESULTS: In total, 348 infectious episodes were recorded in these patients admitted to the inpatient pediatric unit of the NCI, Cairo University. As a single isolate, Gram-positive cocci were the most frequently observed cause of BSI, accounting for 271 (77.9%) of the total isolates. Gram negative organisms accounted for 66 (18.9%) of the total number of BSI. Mixed infections were detected in 27 (8%) of the total number (348) of BSI. Fungi constituted 24 of the mixed isolates and were obtained from a localized site

in 10 patients (i.e. catheter site sample) and from a peripheral blood sample (i.e fungemia) in 14 patients. The majority of the episodes (n = 208, 58.4%) responded to first-line empirical antibiotic therapy. The two regimens used as first-line empirical antibiotic therapy did not show significant differences with respect to the persistence of fever or the outcome. A more serious BSI in terms of a prolonged episode was encountered in 30.2% of the episodes and was significantly associated with patients being hospitalized, having intensified chemotherapy, polymicrobial and fungal infection, lower respiratory tract infections and persistent neutropenia at day seven.

CONCLUSION: In a large population of children, common clinical and laboratory risk factors were identified that can help predict more serious BSI. These results encourage the possibility of a more selective management strategy for these children.

RECOMMENDATIONS: While overall trends are for an increasing proportion of gram positive bloodstream infections, and a decreasing proportion of gram-negative infection, the emergent and increasing problem of drug resistance is observed for a broad range of infecting organisms.

Control of the transmission of multi-resistant bacteria is therefore required in the haematology population. Universal policies and strategies are required for endemic nosocomial multi-resistant organisms (e.g. MRSA, VRE). There are currently no data reporting the significance or extent of community-acquired MRSA within the haematology population as a cause of bloodstream infection. Future agendas should address the possibilities for earlier targeted antimicrobial therapy for bloodstream infection in this population in order that mortality is reduced.

KEY WORDS: Bloodstream infections; Fungemia; infection episodes; Infections in immunocompromized oncology patients

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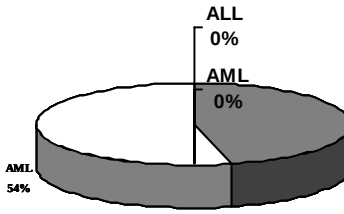

LIST OF ABBREVIATIONS

ADE	Ara-c Doxaurubacine Etoposide
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophillic Count
ANLL	Acute Non Lymphoblastic Leukemia
APL	Acute Promyelocytic Leukemia
Ara-C	Arabinoide-Cytosine
BMT	Bone Marrow Transplant
BSI	Blood Stream Infections
CML	Chronic Myeloid Leukemia
CMV	Cytomegalo Virus
CNS	Central Nervous System
CONS	Coagulase Negative Staph.
CSF	Cerebro Spinal Fliud
CVCs	Central Venous Catheters
DIC	disseminated intravascular coagulation
FAB	French American British
FUO	Fever of Unknown origin
G-CSF	Granulocyte Colony Stimulating Factor
GIT	Gastero Intestinal Tract
GVHD	graft-versus-host disease
HIB	Heamophilles Infleuanza- B
HSCT	Heamatopoietic Stem Cell Transplant
HSV	Herpes Simplex Virus
ICA	Intercellular adhesion
IFN-γ	InterFeron gamma
IgA	Immunoglobulin A
IL-1	InterLeukine 1
iNOS	inducible Oxide Synthase
IT	Intra Thecal
IVDs	Intra Vascular Devices
IVDR-BSI	Intra Vascular Devices Related Blood Stream Infections
LPSs	LypoPolySaccharides
MDS	Myelo Dysplastic Syndrome

MODS	Multiorgan dysfunction syndrome
MNCs	Monocytes
mRNA	massanger RNA
MRSA	Methecillin resistant Staph.aureues
NCCN	National Cancer Comprehensive Network
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NK	Natural Killer cells
NF-kB	Nuclear Factor kB
PCP	Pneumocystis jiroveci (formerly Carinii) pneumonia
PCR	Polymerase Chain Reaction
PIA	Polysaccharide intercellular adhesion
PMNS	Poly Morphnucleutide Neutrophils
SIRS	Systemic inflammatory response syndrome
SMX\TMP	Sulfamethoxazole/trimethoprim
TDN-AML	True De Nevo- Acute Myeloid Leukemia
TCRs	T-Cell Receeptors
TNF- α	Tumour Necrosis Factor alpha
TLRs	Toll-Like Receptors
VADs	Venous Access Devices
VGS	Viridans group of streptococci
VRE	Vancomycin-resistant enterococci
VSSS	Viridans-related septic shock syndrome

INTRODUCTION AND AIM OF THE WORK

Acute leukemia is the most common pediatric malignancy. The current cure rate of childhood ALL is more than 80%. Survival has improved significantly; infectious complication mortality rate has declined overtime (Papadakis V, et al; 2003)

Despite the significant progress in the treatment of infectious complications in immunosuppressed patients, infection-related morbidity and mortality continue to be of great importance. However, the type and incidence of any infection during treatment other than induction i.e., maintenance, are not well known (Lex C, et al; 2001)

Bacteremia, respiratory tract infection, and pneumonia are the most frequent infectious complications in febrile patients with acute leukemia (Hughes WT, Armstrong D, Bodey GP et al; 1997). The widespread use of indwelling vascular catheters has altered the type of bacteremia seen overtime. Furthermore, prompt initiation of the appropriate empiric antibiotic treatment has improved infection outcome (Pizzo PA, et al; 1991)

Limited is the number of reports entertaining the incidence and the kind of infections during the entire course of chemotherapy in pediatric patients with ALL Thus, the true incidence of otitis, gastroenteritis, eye infections, or central nervous system (CNS) infections has not been well documented (Rahiala J, et al ;1998) .

The aim of the present study is to assess the type, frequency, and severity of all types of infectious complications in a pediatric patient, also identify factors affecting bloodstream infections in cohort with newly diagnosed ALL and AML during the induction phase of treatment.

All infectious episodes were analyzed by the treatment element and the degree of neutropenia while they occurred. Finally, the outcomes of the infectious complications as well as the changing epidemiological pattern over the years ; thus more tailored policies for the treatment of patients with

fever and neutropenia during the induction chemotherapy can then be created.

PEDIATRIC LEUKEMIA :

Leukemia is the most common malignancy that affects children, accounting for approximately a third of cancer diagnoses. It may be defined as a neoplastic disease that involves the blood-forming tissues of the bone marrow, lymph nodes, and spleen.

Normal hematopoiesis occurs in these blood forming tissues; the development of blood cells is shown in Fig. 1.1(D.Tomlinson et al; 2002).

A range of extra cellular protein factors regulates the growth and differentiation of pathways of developing cells. This ensures that the mature blood cell types are produced in appropriate proportions.

Leukemia is a clonal disease that is due to genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell during hematopoiesis. The type of leukemia that results is therefore dependent on the cell lineage that is affected by the mutation. Table 1.1(D.Tomlinson et al; 2002) shows the blood cells that can be affected from either stem cell lineage. In leukemia, there is an overproduction of immature white blood cells that cannot function effectively. These immature white blood cells, such as the myeloblasts, lymphoblasts, and monoblasts, are commonly called “blasts.” An abnormal population of immature white blood cells decreases the space available for the production of other healthy blood cells produced by the bone marrow. The blast cells may then enter the blood and may also infiltrate the central nervous system (CNS) (D.Tomlinson et al; 2002)

The two broad classifications of leukemia are acute and chronic. The most common types of leukemia are:

— Acute lymphoblastic leukemia (ALL), which accounts for 75–80 % of childhood leukemia.

— Acute myeloid leukemia (AML), also known as Acute nonlymphoblastic leukemia (ANLL), which accounts for 20–25 % of childhood leukemia.

The most common type of chronic leukemia is chronic myeloid (or myelocytic) leukemia (CML), which accounts for less than 5 % of childhood leukemia

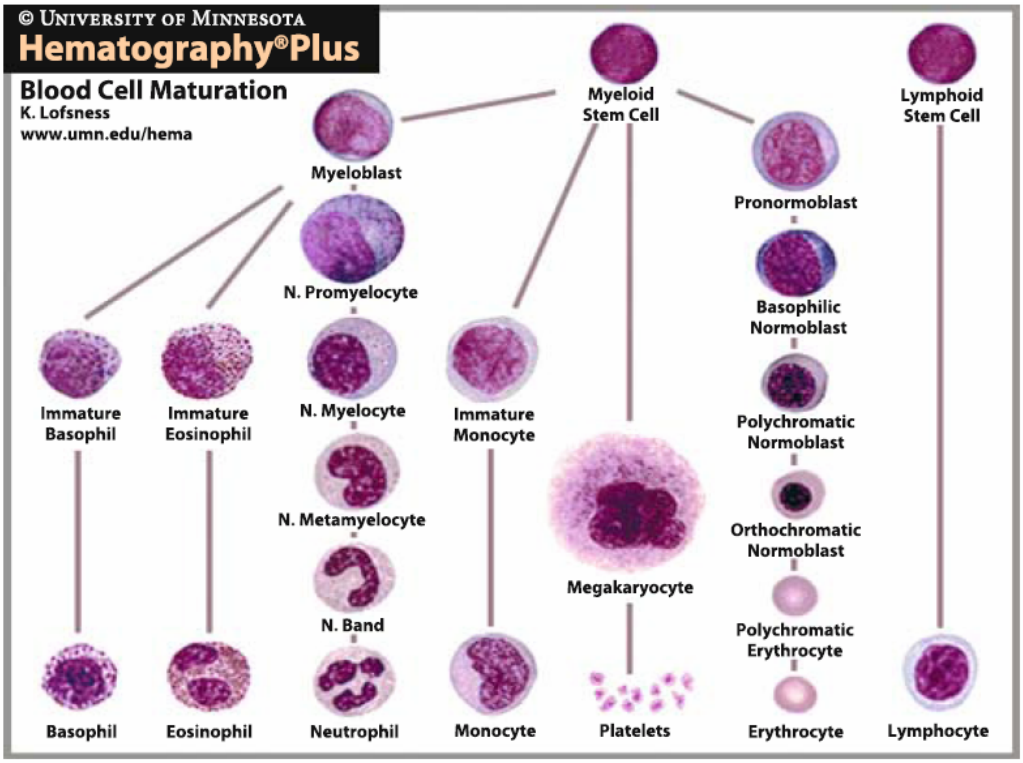

Figure 1.1

Hemopoiesis: The lymphoid stem cell differentiates into T-lymphocytes and B-lymphocytes. Natural Killer (NK) cells are also thought to derive from the lymphocyte stem cell. Image credit: K. Lofsness, University of Minnesota