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Infections in children with acute leukemia

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Major advances have been made in the management of childhood leukemias in recent years.[1-3] With better understanding of cell kinetics, development of newer chemotherapeutic agents, modern combination chemotherapy and prophylactic therapy of central nervous system, the five year survival rate in patients with acute lymphatic leukemia has considerably improved. However, infections still remain the leading proximate cause of morbidity and mortality in patients with leukemia.[4-7] About 45 to 100 per cent of children with leukemia die of infection,[4,5] Although fever may not manifest in a compromised host especially while receiving costicosteroid therapy yet 51 to 73 per cent of febrile episodes in patients with leukemia, are secondary to infections.[8-10]

The predisposing factors for infections during the induction and remission phases are different. Therefore, these two phases are discussed separately.

Infections during induction phase

During the initial phase of chemotherapy, infection is the major cause of morbidity and mortality. Most of the infections occur during the first two weeks. In the next two weeks, the infection rate is low and serious infections are uncommon. This is secondary to improvement in host resistance following chemotherapy. Infections are less frequent in patients with acute lymphatic leukemia as compared to those with nonlymphocytic leukemias. Patients with acute lymphatic leukemia, who do not achieve remission repidly and require further intensive therapy, have similar rate of infections as patients with acute myelomonocytic leukemia.

1. Predisposing factors to infections

Neutropenia (count less than 500 cumm) is the most important factor responsible for infection. The frequency and severity of infections is inversely related to granulocyte count.[8,10-12] As remission occurs, the neutrophil count increases and incidence of infection decreases.[8,13] Lower incidence of infections in acute lymphatic leukemia is due to higher granulocyte count at the time of diagnosis, less toxic induction chemotherapy and less prolonged granulocytopenia following chemotherapy. Neutrophil function may also be impaired-inability to migrate to the site of infection in acute myelocytic leukemia[14] and decreased phagocytic and bactericidal activities during relapses.[15,16] Corticosteroids per se reduce phagocytosis,[17] retard migration of neutrophils[14], alter the flora of gastrointestinal tract[18] and depresses the T & B lymphocyte functions.[7]

Bleeding sites in mucosa and skin permit direct entry of microbes, indwelling intravenous and urinary catheters are

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potential sources of infections.[19,20] Scalp vein needle left for more than 48 hours may predispose to infection. Contaminated intravenous fluids, parenteral hyperalimentation and blood component therapy are other sources of infections.[21,22] Nutritional status and serum immunoglobulin levels at the beginning of therapy in majority of these cases are normal.[10] However, in the developing countries protein energy malnutrition is common and this is generally associated with increased susceptibility to infections.[23] Prolonged hospitalization of these children increases the risk of nosocomial infections.

2. Bacterial infections

(a) *Pseudomonas aeruginosa* is prevalent in both endogenous and exogenous flora of man. It is a common contaminant of hospital environment.[10] Pseudomonas infection produces vasculitis leading to extensive hemorrhagic necrosis of the tissue.[24] Skin lesion starts as an erythematous maculopapule which soon becomes vesicular. Subsequently, it becomes a gangrenous ulcer with a crust. Manifestations of pseudomanas infections other than skin lesions do not differ from other bacterial infections, Sepsis is accompanied by fever, and prostration. Showers of petechiae may appear over the skin with erythematous haloes, indicating a grave prognosis. Pneumonia, enteritis, meningitis and peritonitis, have no characteristic features. Isolation of *Pseudomonas aeruginosa* from blood, spinal fluid, bone marrow, skin or urine along with the clinical manifestations establishes the diagnosis. The organism is usually sensitive to gentamicin, polymyxin B and carbenicillin. Combination of carbenicillin and gentamicin is usually preferred.[25,26]

(b) *Proteus mirabilis* causes urinary tract infection, sepsis, cellulitis and menigitis. Kanamycin is effective against most strains.

(c) *Escherichia coli* is normal inhabitant of the intestine. In addition to this endogenous source, the organism may enter iatrogenically. Septicemia is the most frequent. However, pneumonia, peritonitis, meningitis, urinary tract infection and endocarditis may occur. Ther are no specific clinical features to suggest *E. coli* infection. Gentamicin is the drug of choice.

(d) *Klebsiella sp.* is normally present in the nose, mouth and intestinal flora. Infection is usually from endogenous sources but cross infection may occur through hospital personnel. Pneumonia, sepsis and urinary tract infection are common. Meningitis, osteomyelitis, pyelonephritis and cellulitis are less frequent.

(e) *Staphylococcus aureus* and *S. albus* are present in the nose, mouth, skin and vagina. Pyoderma, sepsis, pneumonia, cellulitis are the common form of infections. Meningitis, pyelonephritis, and osteomyelitis occur infrequently.

(f) *Other infections* may be secondary to *Haemophillus influenzae*, salmonella. dipptheroids and bacteroides.[27]

3. Fungal infections

These are commonly secondary to invasive fungi like candida spores, aspergillus, and phycomycetes.[24] Most of these systemic fungal infections occur 24-72 hours before death. Local

candida infection (mouth and pharynx) should be treated promptly to prevent its spread to the lower respiratory or or gastrointestestinal tract. Adequate systemic antifungal therapy should be started at the earliest evidence of systemic infection. (Amphotericin 0.3-0.6 mg/Kg/day).[29]

4. **Viral infections**

Viral infections occur more frequently during remission phase and are discussed later.

B. **Infections during remission phase**

Infections are also the major cause of death during this phase. Common infections are viral, fungal and protozoal.[30] Infections are secondary to lymphopenia.[11] Bacterial infections occur less frequently. Less frequent occurrence of streptococcal pharingitis is possibly due to bactericidal effect of methotrexate.[31]

1. **Predisposing factors**

Granulocyte count from children with acute lymphatic leukemia during remission are normal. These cells have normal phagocytic activity but their bactericidal capacity is reduced. Radiotherapy induces transient leucopenia and reduction in bactericidal function.[32] Infections are generally more common, three months following craniospinal irradiation.[33]

Chemotherapy lowers host resistance by causing (i) leucopenia [34] (ii) depression of humoral and cell mediated immunity[35] and (iii) toxic ulceration of gut which permits the entry of various microbes. Chemotherapeutic agents used during maintenance phase cause lymphopenia and more suppression of B than T cell functions. Primary immunoglobulin response is also reduced (IgG synthesis is more affected than IgM antibodies).[7,36]

Cell mediated immune functions are reduced because of (i) lymphopenia (T cell destruction) (ii) reduced lymphoblast transformation (iii) diminished delayed hypersensitivity responses.[7] Since the cell mediated immune responses are more depressed during the maintenance phase, so the viral, protozoal and fungal infections are more common. Infections are more frequent in children on continuous chemotherapy as compared to those on intermittent maintenance therapy.[37] It has been postulated that partial recovery of immune system occurs during the intermittent therapy.

2. **Viral infections**

(a) *Varicella* is a highly contagious and potentially fatal infection in leukemic patients. Lesions start as macules and progress through papular to vesicular stage. They may become hemorrhagic in children with thrombocytopenia. Corticosteroids affect the outcome adversely.[38] Dissemination to visceral organs occurs in the first week. Tachypnea and heavy nodular opacities are suggesstive of varicella pneumonitis. Meningoencephalitis and pancreatitis are other complications. Diagnosis is based on history of exposure, presence of typical lesions and demonstration of herpes virus. There is no specific therapy. Mortality is higher in children with varicella pneumonitis.[39] Zoster immune globulin is effective in preventing and modifying the course of varicella if administered soon after the exposure. Antiviral drugs like cytosine arabinoside[40] and Idoxuridine [41] have limited efficacy.

(b) *Herpes zoster* infection occurs in 10% of children with A.L.L. [42] Lesions

similar to varicella involve some dermatome preceded by pain and continue to appear for 5 to 7 days. Infection may spread to cause varicella pneumonia, meningoencephalitis, hepatitis, iritis etc. Management is directed towards the prevention of secondary infection. Antiviral agents may be used if systemic complications develop.

(c) *Herpes simplex* lesions often involve mucous membrane of oral cavity and genitalia. Infrequently, it may spread to cause pneumonitis, encephalitis, hepatitis etc. Local treatment is not very effective and systemic antiviral agents are indicated in presence of systemic complications.

(d) *Cytomegalic inclusion disease* has a variable prevalence. Henson et al[43] reported an incidence of 27.3%. Its mode of transmission is not known. The virus can be isolated in numerous body fluids. The common manifestations are pneumonitis, hepatitis, enteritis, and chorioretinitis. Pneumonitis is most frequent. Virus may be isolated for a longer duration than the active disease. Diagnosis is based on isolation of virus and demonstration of a fourfold rise in antibody titre. Death usually occurs from secondary bacterial or fungal infections.[44]

(e) *Vaccinia* may present as a localized or generalized disease. The disease is fatal if left untreated. It may be acquired following vaccination or by autoinoculation. Hyperimmune globulin against vaccinia has been used extensively to treat such cases.[45]

(f) *Measles* follows the same pattern as in normal children but the rash becomes petechial or purpuric in presence of thrombocytopenia. Acute hepatitis, pneumonitis (Hecht's pneumonia), encephalitis, or subacute sclerosing panencephalitis may occur in children with leukemia. Passive immunization within 24-48 hours after exposure is effective in preventing the disease.

(g) *Infectious mononucleosis* also manifests as in normal children but it occurs more frequently. Diagnosis is difficult because of altered lymphoid response.

(h) *Mumps* persists for a longer time in such children though clinical presentation is not different. Management is mainly supportive.

3. Fungal infections

Prevalence of fungal infections has increased in the recent past. This is attributable to prolonged survival and higher cure rates.[46]

(a) *Candida albicans* is the common candida infection. It is a normal inhabitant of the gastriontestinal tract. It may spread from the gut or by the direct inoculation of intravenous catheters. Oral candidiasis, (thrush) is most frequent. Lesions may occur in the esophagus, anal region and vagina. Serious infections like endocarditis, penumonitis. meningitis and peritonitis, may occur. A maculonodular rash with generalized candidiasis has been described.[47] Positive cultures from the concerned specimen along with precipitin titers to cytoplasmic candidal extracts are diagnostic. Localized and intestinal candida infection responds to mycostatin while amphotericin B is used for systemic infection.

(b) *Aspergillosis* is caused by inhalation of spores. Outbreaks of aspergillo-

sis in children with acute leukemia have been reported.[48] Infection occurs most often in the lungs.[49]

Other sites involved are heart, kidney, gastrointestinal tract etc. Pulmonary lesions present as lobar infiltrates, solitary lesions or bronchopneumonic like picture. Demonstration of fungus from infected tissue is diagnostic. Amphotericin may be used with some benefit.

(c) *Cryptococcosis* is an acute or chronic pulmonary, meningeal or disseminated mycosis. It occurs more frequently in patients with chronic lymphatic leukemia. Portal of entry is through respiratory tract. Pulmonary infection may mimic tuberculosis. Diagnosis depends on positive culture. Amphotericin B is the drug of choice.

(d) *Histoplasmosis* usually starts as acute or chronic pulmonary infection but it may spread to other organs.[50] Diagnosis is made on isolation of fungus. Blood and bone marrow caltures may be positive. Amphotericin B is used for its treatment.

4. Protozoal infections

(a) *Toxoplasmosis* in children with leukemia, produces disseminated infection often involving heart, liver and brain.[51] Encephalitis is often associated with sensorial disburbances, cranial nerve palsies and motor paresis. Fever, pneumonitis, hepatosplenomegaly and lymphadenopathy are present but are nonspecific Diagnosis is based on demonstration of rising antibody titer or histological changes in lymphnodes.[52] Toxoplasmosis is treated by pyrimethamine and sulfadiazine combination.

(b) *Pneumocystis carinii* is most frequent cause of pneumonia in children with leukemia. It occurs in 15-17% of children.[53] It is more often seen in children who have been given intrathecal methotrexate for CNS prophylaxsis [53] or on withdrawal of corticosteriods. It starts as coryza and is soon followed by fever, nonproductive cough, tachypnea and mild cyanosis. Roentgenogram of chest shows bilateral interstitial pneumonia. If untreated the condition is usually fatal. Diagnosis is made by the histological evidence of the agent from infected tissue. High index of suspicion, early diagnosis and prompt treatment is the hallmark of successful therapy. Pentamidine isothionate is the drug of choice (dose 4 mg/Kg for 14 days) [39] Recently there are reports of successful prevention of pneumocystis carini pneumonia by continuous administration of sulphamethoxyzol and trimethoprim combination in smaller doses.[54]

5. Bacterial infections

Bacterial infections described during induction. phase, do occur during maintenence phase but the frequency is less. Tuberculosis occurs predominantly during the maintenence phase, and is described in detail elsewhere.[55]

Some comments on therapy

The main principles of management are a high index of suspicion, knowledge of various infections during different phases of disease, prompt diagnosis and appropriate treatment. Since the frequency of infections at the time of diagnosis is so high, every child is con sidered infective till proved otherwise. Infections are caused both by the endogenous microflora and exogenous pathogens. Systemic antibiotics in combination

with topical antibiotics have been used to control endogenous microflora. Plastic isolates and laminar air-flow rooms have been used to prevent the exogenous pathogens.[56] A multicentric study conducted by European Organization for Research and Treatment of Cancer (EORTC) have used three randomized treatment schedules; carbenicillin plus gentamycin, carbenicillin plus cephalothins and cephalothins plus gentamycin. Overall success rate was 70%.[26] In another study by the same group, it was observed that the frequency of serious infections was not reduced by isolation.[57] Recently continuous chemoprophylaxis has been useful in preventing some infections.[54]

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Successful bone narrow transplantation for infantile malignant osteopetrosis

Infantile malignant osteopetrosis (Albers-Schonberg syndrome) is a rare autosomal recessive disorder characterised by dense, sclerotic, fragile radioopaque bones and associated hematologic and neurologic abnormalities. A five-month old girl with this disorder received a bone narrow transplant from her 5-year-old HLA—MLC identical brother after preparation with cyclophosphamide and total body irradiation. Anemia, thrombocytopenia, and leukoerythroblastosis corrected within 12 weeks of transplantation. Low serum calcium, and elevated serum alkaline and acid phosphatase became normal. Osteoclastic activity resorbed bone, and medullary cavity contained normal bone narrow. Vision, hearing, growth, and development were progressively improving 16 months after transplantation. Allogenic bone narrow transplantation offers good prospect of treatment in this fatal disorder

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