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Diarrhea in children with acute lymphoblastic Leukemia: A literature review

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Abstract

Acute lymphoblastic leukemia (ALL) in children often leads to gastrointestinal complications such as diarrhea due to chemotherapy, radiation, and immunotherapy treatments. These therapies damage the gut mucosa, disrupt gut microbiota, and increase susceptibility to infections, exacerbating diarrhea. Effective management strategies, including rehydration, probiotics, and selective antibiotics, are essential to mitigate symptoms and prevent complications like dehydration and malnutrition. Long-term approaches focusing on monitoring gut health and dietary interventions, such as prebiotics and probiotics, are crucial for improving the quality of life and supporting recovery in children with ALL.

Keywords: Diarrhea; Acute Lymphoblastic Leukemia; Chemotherapy; Treatment; Management

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer in children. Infants and toddlers under 2 years old undergoing treatment for ALL often exhibit impaired adaptive responses, increasing their susceptibility to infections and prolonged pathogen excretion. This can trigger a series of complications, including malabsorption, failure to thrive, and disruption of chemotherapy, resulting in challenges in managing the condition (1,2). In 2018, with a child population of 79.5 million in Indonesia, the annual incidence of acute lymphoblastic leukemia (ALL) was estimated to be around 3,434 new cases. Globally, the incidence is comparable, though it may be lower in low-income countries. A systematic review reported an incidence rate of 4.32 per 100,000 children . Genetic predispositions, such as Down syndrome and congenital immunodeficiencies like Wiskott-Aldrich syndrome, are linked to a higher risk of developing acute lymphoblastic leukemia (ALL), although most cases have no identifiable cause. The highest incidence of ALL is seen in children aged 1-4 years, with males being more frequently affected than females, with a male-to-female ratio of approximately 1.5:1. While specific environmental risk factors are still under investigation, exposure to certain chemicals or radiation may increase the likelihood of developing leukemia (3).

Several factors contribute to the incidence of diarrhea in children with ALL, including chemotherapy, which can cause gastrointestinal toxicity and damage the intestinal mucosal lining, leading to increased permeability and diarrhea. Neutropenia, which heightens the risk of infections that can cause diarrhea, with studies showing more severe and prolonged neutropenia in patients with neutropenic enterocolitis (4). Infections, particularly gastrointestinal infections like Clostridium difficile, which exacerbate symptoms, and malnutrition, which can compromise the immune system and increase the risk of febrile neutropenia, indirectly contributing to diarrhea (5). According to a study conducted at Prof. R. D. Kandou Hospital in Manado, Indonesia, among 60 pediatric patients with ALL, 28% (17 patients) experienced diarrhea during their treatment from 2011 to 2015. The study noted that diarrhea was more prevalent during the

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induction phase of chemotherapy and typically lasted less than seven days, indicating acute diarrhea rather than chronic forms (6).

2. Review Content

2.1. Pathophysiological Relationship between Diarrhea and Acute Lymphoblastic Leukemia

The treatment of acute lymphoblastic leukemia (ALL) often involves chemotherapy, radiation therapy, and immunotherapy, all of which can significantly disrupt the gastrointestinal (GI) system and lead to diarrhea. Chemotherapy agents, such as methotrexate and 5-fluorouracil, are known to cause mucositis, which is the inflammation and ulceration of the mucosal lining of the GI tract. This damage can result in diarrhea due to impaired absorption and increased intestinal permeability, leading to the passage of fluids into the intestinal lumen (7,8). Additionally, chemotherapy can alter the gut microbiota, disrupting the balance of beneficial bacteria and allowing for opportunistic infections that may exacerbate diarrhea. For instance, patients undergoing treatment may experience an overgrowth of pathogens like “Clostridium difficile”, which is associated with antibiotic use and can cause severe diarrhea (9,10). Radiation therapy, particularly when directed at the abdominal region, can also contribute to GI toxicity by damaging the intestinal mucosa and affecting motility. This damage can lead to symptoms such as diarrhea and abdominal pain due to changes in gut motility and secretion (7). Immunotherapy agents, especially those targeting immune checkpoints like CTLA-4 and PD-1, have been linked to colitis, which manifests as diarrhea along with abdominal discomfort. The incidence of colitis varies depending on the specific immunotherapy used but can be significant enough to require hospitalization in severe cases (8). Moreover, children with ALL are at a heightened risk for secondary infections due to their compromised immune systems from both the disease and its treatments. Viral infections (rotavirus or enterovirus) or bacterial infections can further contribute to gastrointestinal symptoms and diarrhea. The combination of direct effects from cancer treatments on the GI tract and the increased susceptibility to infections creates a complex interplay that often leads to persistent gastrointestinal issues in these patients (8,10).

2.2. Diagnosing Diarrhea in Children with Acute Lymphoblastic Leukemia (ALL)

Diagnosing diarrhea in children with acute lymphoblastic leukemia (ALL) involves a comprehensive approach that includes clinical assessment and laboratory tests. Clinicians start by gathering a detailed medical history and performing a physical examination to assess symptoms such as frequency, consistency of stools, and associated symptoms like fever or abdominal pain. Laboratory tests are critical for identifying the underlying cause of diarrhea. Stool cultures can detect bacterial infections or parasites, while stool evaluations can reveal the presence of blood or fat, indicating malabsorption issues. Additionally, polymerase chain reaction (PCR) tests can identify specific viral pathogens, which is particularly useful in cases where viral gastroenteritis is suspected. Blood tests may also be conducted to evaluate for dehydration or other systemic effects related to diarrhea (11,12,13).

Management of diarrhea in children with ALL requires careful consideration due to their immunocompromised status. Symptomatic treatment primarily focuses on rehydration, which is crucial given the risk of dehydration. Oral rehydration solutions are often recommended, and in severe cases, intravenous fluids may be necessary. Probiotics can be beneficial in restoring gut flora, particularly after antibiotic use. If an infectious cause is identified, appropriate antimicrobial therapy should be initiated. In some instances, modification of the chemotherapy regimen may be warranted if the diarrhea is severe or persistent, as certain treatments can exacerbate gastrointestinal symptoms (14).

Complications arising from diarrhea in children with ALL can significantly impact their health and prognosis. Dehydration is a primary concern, as it can lead to electrolyte imbalances and renal dysfunction if not promptly addressed. Malnutrition may occur due to inadequate nutrient absorption or intake during episodes of diarrhea, further complicating the child’s overall health status. Severe diarrhea can also predispose these patients to more serious infections due to their compromised immune systems, potentially resulting in longer hospital stays and increased morbidity. Thus, effective management of diarrhea not only alleviates immediate symptoms but also plays a critical role in maintaining the child’s overall health and quality of life during treatment for ALL (15).

2.3. Treatments for Diarrhea in Children with Acute Lymphoblastic Leukemia (ALL)

Recent studies have explored innovative approaches to manage diarrhea in children with acute lymphoblastic leukemia (ALL), particularly focusing on the use of probiotics, selective antibiotic therapy, and strategies to restore gut microbiota balance. Probiotics, such as Lactobacillus rhamnosus GG and Saccharomyces boulardii, have shown significant efficacy in reducing the duration and incidence of diarrhea, especially in cases related to antibiotic use. Evidence indicates that probiotics can help maintain gut barrier integrity and restore microbial diversity, which is often disrupted during

antibiotic treatment. Specifically, a meta-analysis highlighted that probiotics could prevent antibiotic-associated diarrhea (AAD) in children, with a notable reduction in incidence rates compared to control groups (16,17).

In addition to probiotics, selective antibiotic therapy has been proposed as a method to minimize disruptions to the gut microbiome while effectively treating infections. This approach emphasizes the importance of using antibiotics judiciously to prevent the overgrowth of pathogenic bacteria that can lead to diarrhea. Furthermore, enhancing dietary strategies that include prebiotics can also support the growth of beneficial gut bacteria, thereby improving overall gut health and potentially reducing the risk of diarrhea during and after cancer treatment (18,19).

For long-term management of diarrhea in children undergoing maintenance therapy or in remission from ALL, it is crucial to adopt a comprehensive approach that includes regular monitoring of gut health and microbiota composition. Strategies may involve ongoing probiotic supplementation, dietary modifications rich in prebiotics, and education for caregivers on recognizing early signs of gastrointestinal disturbances. This proactive management can help mitigate the impact of diarrhea on quality of life and nutritional status during critical periods of treatment and recovery (20).

3. Conclusion

The conclusion of this literature review shows that diarrhea in children with acute lymphoblastic leukemia (ALL) poses significant challenges, complicating treatment and recovery. The gastrointestinal disruptions caused by chemotherapy, radiation, and immunotherapy, along with a weakened immune system, make these children particularly susceptible to infections that exacerbate diarrhea. Effective management strategies, including rehydration, probiotics, and selective antibiotic therapy, are crucial to alleviating symptoms and preventing complications such as dehydration and malnutrition. Proactive approaches, including dietary modifications and regular monitoring, are essential to maintaining overall health and improving the quality of life for children undergoing ALL treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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