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Zoonotic Infections in Pediatric Patients With Acute Leukemia

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Abstract

Few studies have described the impact of zoonotic diseases in children with leukemia. This study aimed to describe the frequency of and associated demographic factors for zoonotic diseases in pediatric acute leukemia patients. Descriptive and comparative statistics relative to age, sex, and patient region were performed on an assembled 11-year retrospective cohort of acute leukemia patients. Of 10,197 patients, 88 patients (0.86%) were found to have a zoonotic infection. Gastrointestinal diseases were the most commonly (86.4%) identified zoonotic illnesses. Although rare, zoonotic diseases do occur in children with leukemia and frequency varies by age, region, and gender. *Pediatr Blood Cancer*

Keywords

acute pediatric leukemia; maintenance chemotherapy; opportunistic infections; zoonotic diseases

INTRODUCTION

While outcomes in children with leukemia have substantially improved, these patients are vulnerable to infections [1,2]. Zoonosis occurs after direct exposures to both wild and domesticated animals or indirect exposure to causative organisms via contaminated food or environmental sources [3,4]. Zoonotic disease prevalence varies by geographic region and depends on factors such as local animal migration patterns and environmental influences

[4,5]. Regardless of the source, zoonotic diseases have been linked to hospital admissions of many otherwise healthy children each year [4].

Data related to the impact of zoonotic diseases on immunocompromised children are limited to case series and reviews [6–10]. We sought to address this knowledge gap by determining the frequency and related associations of zoonotic infections ascertained in the in-hospital setting using the Pediatric Health Information System Database (PHIS).

METHODS

A cohort of 10,197 pediatric patients with acute leukemia was established using in-patient data from 39 free-standing pediatric hospitals contributing to the PHIS database as previously described [11,12]. In brief, patients entered the cohort on the first hospital day of the first admission containing both an ICD-9 code consistent with acute leukemia and induction chemotherapy consistent with either acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Patients with ALL were followed for 3 years from diagnosis and patients with AML were followed for 12 months. The occurrence of a zoonotic disease was determined by the presence of an ICD-9 code indicative of a zoonotic infection [13]. Standard descriptive and bivariate statistics using SAS 9.2 were performed to summarize and compare relevant covariates.

RESULTS

The median age for the study cohort was 6 years of age (range, <1–20 years). The total population was comprised of more males (55.6%) than females. Of the 10,197 patients, 8,511 were treated for ALL and 1,679 were treated for AML. There were seven patients identified in both leukemia categories. These seven were included in the final analysis. None of them had a zoonotic infection. Only 88 patients (0.86%) had an ICD-9 code consistent with a zoonotic infection. This resulted in a zoonotic hospitalization rate of 862 per 100,000 pediatric leukemia patients. Out of the 88 patients, there was only one in-hospital death in an individual with Cryptosporidiosis. The attribution of death to this infection is not certain. *Campylobacter* enteritis, Cryptosporidiosis, Giardiasis, and Salmonellosis were most common accounting for 86.4% of the total zoonotic cases. A larger fraction of ALL patients had zoonotic infections compared to AML patients (0.92% vs. 0.60%) although this difference was not statistically significant ($P = 0.247$). The distribution of zoonotic infections for ALL and AML patients are displayed in Figure 1. The frequencies of some zoonotic illnesses appeared to vary between ALL and AML.

Children >1–10 years old had the highest percentage of zoonotic diseases with a 0.99% frequency followed by children 1 year of age (0.83%). Children >10–20 years old had the lowest percentage, 0.58%. The differences in event rates were not statistically significant across age groups ($P = 0.37$). Children >1–10 years of age had similar frequencies of Cryptosporidiosis, Giardiasis, and Salmonellosis. Percentages of zoonotic disease were not significantly different in females as compared to males (0.93% vs. 0.81%, P -value = 0.53).

The prevalence of zoonotic diseases regionally varied (Fig. 2). The West-South Central region had the highest rate (1.14%) East-North Central, South Atlantic, and West North Central regions all had rates above 1%. The Pacific and East-South Central regions were less than 1% and no zoonotic infections were identified in the Mid Atlantic and New England regions.

There was a median hospital length of stay of 7 days (IQR: 4–18) for admissions containing a zoonotic disease diagnosis. The median number of days from initial acute leukemia onset

until the admission for a zoonotic disease was greater in ALL patients than AML patients (328.5 days vs. 96.5 days, $P = 0.005$).

DISCUSSION

Zoonotic infections occur in children with leukemia, and although they are rare, the rates may be higher than in the general population. It is difficult to quantify the difference in rates of hospitalization for a zoonotic infection in children with leukemia relative to immunocompetent hosts. However, population rates for specific zoonotic infections are reported by the Center for Disease Control and the US Department of Agriculture (USDA) and are notably lower. Specifically, *Campylobacter*, *Cryptosporidium*, *Giardia*, and *Salmonella* incidence rates are 13, 3.5, 7.45, and 16.5 cases per 100,000 healthy individuals, respectively, while the rates in the this leukemia cohort are 88.3, 215.9, 196.3, and 245.3 per 100,000 [14–17]. Despite the limitations in this comparison, the estimates of zoonotic infections in patients with leukemia appear higher than rates reported for the general population.

Gastrointestinal zoonoses, such as Salmonellosis or Giardiasis, were most common. Low event rates resulted in insufficient power to detect statistically significant differences in the percentage of zoonotic illnesses across age groups, regions, and by leukemia type. However, some of the identified differences may be clinically important, notably that children aged >1–10 years had an almost twofold higher rate than the >10–20 year group. The reason for this increased rate is not clear but may be related to increased enteral exposures in younger children. Zoonotic infections were more commonly identified in children undergoing treatment for ALL than AML. This may be related to an increased likelihood of exposure in ALL patients because of the longer duration and outpatient administration of chemotherapy in ALL. The median duration of hospital stay for all patients with a zoonotic illness was 7 days, which is substantial but may be biased by admissions that also included administration of chemotherapy.

There are limited prior publications of zoonosis in children with leukemia. Two case reports of children with ALL documented the challenges of diagnosing a *Cryptosporidium* associated gastrointestinal illness during maintenance chemotherapy [6]. A cohort study of 314 leukemia patients identified *Salmonella*, *Campylobacter*, and other zoonotic organisms responsible for enteric infections in 0.32% of patients [7]. Finally, a study of 111 immunocompromised patients most commonly identified *Entamoeba histolytica* and *Giardia lamblia* as zoonotic sources of gastrointestinal illness [8]. The limited data available on zoonotic infections in children with acute leukemia is reflected in the range of recommendations regarding pets and animals [18]. In a 1994 study, 60% of US households had pets, although only 21% of healthcare providers were comfortable with their zoonotic disease knowledge and their ability to inform immunocompromised patients about their risk of infection [19].

We recognize limitations to this study including the limited number of cases and the lack of outpatient data. Additionally, as noted above, we did not have a good healthy comparative group to accurately interpret our study results. Despite these limitations, our data suggest that although rare, zoonotic illnesses do occur in children with acute leukemia. Pediatric oncologists should be aware of the potential for zoonotic infections and future research should investigate practitioner awareness of zoonotic diseases and knowledge on how to prevent exposure to these organisms [9] (e.g., appropriate pet exposure, appropriate food preparation, hand hygiene, etc.).

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Fig. 1.
Percentage of each zoonotic illness from 88 cases of zoonotic disease.

Fig. 2.
Prevalence of total and specific zoonotic diseases in each region [20].