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Chapter from the book *Clinical Epidemiology of Acute Lymphoblastic Leukemia - From the Molecules to the Clinic*
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1. Introduction

The role of infection in the etiology of leukemia was revealed for the first time more than ninety years ago through a series of cases reported by Gordon Ward in the year 1917. These cases included 1457 children with acute leukemia, but the results were inconclusive. Later, in another study by Poynton, Thursfield and Paterson, the authors reported that it was not possible to attribute the etiology of leukemia to a single infectious agent and emphasized the importance of host susceptibility in the acquirement of an infection and the development of acute leukemia.[1,2]

In 1937, in a study conducted in England by Kellet, it was mentioned that an infection could be the causative agent for acute leukemia when the infection is widely distributed but has low infectivity. This conclusion was supported by Cooke in 1942 in a study involving 33 pediatric care units in the United States, who found that the peak age of 2 to 5 years in children with acute leukemia correlated with the peak of increased incidence of diseases, such as measles and diphtheria. [3,4]

One of the most important scientific contributions in this regard was made by Kinlen et al., who found a relationship between high incidence rates of acute leukemia and Non-Hodgkin’s lymphoma and infections in children living near rural areas. Kinlen’s findings resulted in the emergence of a hypothesis proposing that leukemia could be caused by exposure to an infectious agent in a susceptible population and, in this case, a mixed population (rural-urban), causing an abnormal immune response that increases the risk of developing the disease. [5,7]
Moreover, Greaves et al. provided a new approach to the hypothesis that had been raised by Kellet, now basing it on biological and epidemiological data on acute leukemia. These authors suggested the hypothesis of late infection, which is explained by two stages: the first stage occurs with a mutation in utero at the same time that precursor B cells are developing and a second stage, during the postnatal period, in which the cell that undergoes a mutation is exposed to a common infection late in the first year of the child’s life. [8-13]

2. Measuring exposure to infection with proxy variables

Over time, in epidemiological studies that have attempted to determine whether an association between early infections and the development of leukemia exists, some indicators have been used to quantify the exposure to infection. These indicators are designated as "proxies" and include socioeconomic status, surgical history, allergic diseases, immunizations, attendance at daycare, breastfeeding, neonatal infections, and prenatal history, among others. [14-25]

2.1. Socioeconomic status

In several epidemiological studies that have assessed infections during the first year of life in children, it was considered to be important to adjust for socioeconomic status because a high socioeconomic status is consistently associated with the development of leukemia and protection against infection. On the contrary, those who have a low socioeconomic status are at a higher risk for the presence of common infections. [26-30] It is important to note, however, that the methods used to measure this variable are not consistent. For example, Steensel-Moll et al. measured socioeconomic status in The Netherlands (1973-1980) according to the parents’ education, while other authors have used, for example, the number of people per room, home ownership, and family income as indicators of socioeconomic status. [15-17,21,22,31-33]

2.2. Prenatal history

The study of prenatal history is interesting as a proxy because it assesses the association between infections and the development of leukemia before birth in an indirect manner, taking into account the fact that, being part of a binomial mother-fetus, the child may have been exposed to infection during the intrauterine period if the mother had an infection during pregnancy. For example, in a study by Fedrick and Alberman in 1972, a positive association was reported between influenza during pregnancy and the development of leukemia and lymphoma, where a RR of 9 (p <0.001) was obtained. Other studies have used other variables associated with pregnancy for the same purpose. For example, whether antimicrobials and/or antiviral drugs were used if the mother had infections was considered. [34] Moreover, the authors of several studies considered a history of antibiotic and/or antiviral use by mothers during pregnancy to reflect the fact that they had been exposed to an infectious process. In this regard, Infante-Rivard et al. noted during 1989 to 1995 that the use of antimicrobials during pregnancy increased the risk of leukemia, with an OR of 1.5 (95% CI:1.02-2.21). When the data were fur-
ther adjusted for the child’s age being <4 years at diagnosis, the OR was 1.78 (95% CI: 1.04-3.04). Furthermore, in 2010, these results were supported by the German study of Kaatsch et al., who reported an OR of 1.47 (95% CI: 1.06-2.04). [33,35] These findings, however, are inconsistent with those reported by other authors. [36-45]

2.3. Neonatal infections

While there are maternal protective barriers during pregnancy that help to prevent infections that may occur in the child at some point after birth, when these barriers cease to exist and the immune system is not well developed, the child is at greater risk for developing infections. Therefore, many epidemiological studies have considered the neonatal period to be a crucial step in the assessment of the relationship between infections and the development of acute leukemia. In 1999, McKinney et al. reported that the presence of neonatal infection was associated with a decreased risk of acute lymphoblastic leukemia (ALL) in Scottish children, with an OR of 0.49 (95% CI: 0.26 to 0.95) being more evident in cases of skin infections, such as omphalitis and/or infection in the skin around the umbilical cord, with an OR of 0.20 (95% CI: 0.05 to 0.87) for all leukemias and for acute lymphoblastic leukemia, regardless of birth type (vaginal or by cesarean section). [46]

2.4. Breastfeeding

Breast milk is considered to be the first vaccine that a child receives during the first months of life, and it protects against infections by stimulating the immune system. There are many mechanisms by which breast milk exerts its antimicrobial and immunological properties. Among the most important mechanisms are the immunoglobulins, interleukins, lactoferrin, mucin, various types of enzymes (e.g., lysozyme and lipases), opsonins, cytokines, prostaglandins and other small peptides. Also involved in these functions are T and B lymphocytes, which are present in breast milk. Thus, the study of breastfeeding as a protective factor against infections during the first year of life has generated scientific interest. [47-50] In most epidemiological studies, it has been documented that breastfeeding favorably influences both the response to infection and the modulation of the child’s immune system. [21,33,51-64]

These factors require further investigation, as there is inconsistency among the epidemiological studies conducted thus far regarding whether a child’s immune system will respond appropriately to an infectious agent after the child has been breastfed for the first six months of life. However, if the child has had recurrent common infections, his/her immune system will have an adequate response to a delayed infection.

2.5. Attendance at daycare

The child’s attendance at daycare also represents a quantifiable index of infection during the first year of life in relation to the development of leukemia. For its implementation in epidemiological studies, investigators have used the age of entry to kindergarten, the hours spent in child care, the number of partners in the nursery, the presence of infection during their stay in
the nursery, the social activities being undertaken by the child during the first year, the type of staff who attended to the child during their stay and the hours they remained at home, among others. There is evidence reported by some studies that there is a dose-response effect with respect to the number of hours that a child remains in a nursery and a lower risk of developing leukemia, and the more a child is in contact with other children, the risk is increased for common and recurring infections, thus favoring a better stimulation and maturation of the immune system. [17,65] In the UK, Gilham et al. also found child attendance at day care during the first year of life to have a protective effect, reporting an OR = 0.69 (95% CI: 0.51 to 0.93, p = 0.02), but this effect was more significant when the child attended during the first 3 months of age, with an OR = 0.52 (95% CI: 0.32 to 0.83, p = 0.007). [66]

2.6. Immunizations

Knowing the vaccination history of children is another important approach to understanding the role of infections in the modern-day development of childhood acute leukemia. This is based on the assumption that vaccines are infectious antigenic stimuli that enable the formation of antibodies and, therefore, a better performance of the immune system. Vaccines could also be the mechanism by which the development of acute leukemia is prevented. [67] Meanwhile, Schüz et al. conducted a study in Germany (1999) and reported that, in children older than 4 years of age, there was an increased risk of developing leukemia in those with a history of fewer than three vaccines, with an OR of 1.8 (95% CI: 1.2-2.7), and a low risk in children with a history of 4-6 shots, with an OR of 1.3 (95% CI:1.0-1.7), which supports the following dose-response relationship: as the number of vaccines given to children increases, the risk of developing acute leukemia decreases. [68] The role of immunization is still controversial, however, because, as mentioned above, while some authors conclude that immunizations provide protection, others have reported the opposite result. [67,69-74]

2.7. Allergic diseases

The role of allergic diseases (e.g., rhinitis, atopic dermatitis, asthma, and urticaria) as a protective factor for the development of leukemia has been controversial in epidemiological reports. Two hypotheses have been proposed to explain the causal relationship between allergic diseases and cancer, including acute leukemia.

The first hypothesis that we will mention is that of “immune surveillance”, which postulates that the immune system can recognize the antigens of malignant cells as foreign and respond to remove them from the body, preventing the potential development of cancer in most cases. Therefore, it is believed that the presence of an allergic disease would increase the surveillance, providing better control and identifying and eliminating any malignant cells, resulting in an increased incidence of malignancy in people who are immunocompromised compared with those with an intact immune system. [75,76]

The second hypothesis refers to a “chronic stimulation of the immune system” that would be conferred by allergens that trigger the carcinogenic potential through both the proliferation
of large numbers of immune cells and the increased likelihood of genetic errors caused by pro-oncogenic mutations, which could not be repaired in subsequent divisions. [77-78]

Linabery et al. conducted a meta-analysis to investigate the relationship between allergic diseases and the development of acute leukemia. Three studies reported a positive association in this regard, with an OR of 1.42 (95% CI: 0.60-3.35). Six studies examined whether there was an association between acute lymphoblastic leukemia (ALL) (OR = 0.69; 95% CI: 0.54 to 0.89) and acute myeloid leukemia (AML) (OR = 0.87; 95% CI: 0.62-1.22), but there was heterogeneity among the results. We also performed such a study in asthmatics, and inverse associations were observed between asthma (OR = 0.79; 95% CI: 0.61-1.02), eczema (OR = 0.74; 95% CI: 0.58-0.96) and hay fever (OR = 0.55, 95% CI: 0.46-0.66) and the development of ALL. [79]

2.8. Surgical history

The individual susceptibility of children who suffer from common diseases and recurrences has been considered to be the main factor leading to surgical interventions that are performed as part of the treatment of these infections. Some examples of these treatments are adenoidectomy, tonsillectomy, interventions for ear surgery, and appendectomy. It is worth noting that these anatomical structures are important parts of the lymphatic tissue and immune system, especially during the first two years of life. Thus, their removal would result in immune dysfunction and an increased risk of infections that occur especially during the first year of life, and this mechanism could be involved in the development of acute leukemia during that time. It is for this reason that epidemiological studies that examine infections as an exposure factor in the development of leukemia are controlled by this variable, but there is no epidemiological evidence that surgical interventions studied as a proxy are associated with the development of childhood acute leukemia. [68]

3. Epidemiological studies

Some types of infections that have been evaluated in most epidemiological studies are respiratory tract infections, gastroenteritis, and those caused by specific infectious agents, such as streptococcus and influenza virus. Other diseases that have been considered are exanthematous diseases, allergic diseases (e.g., asthma, acute rhinitis, and atopic dermatitis) and gastrointestinal diseases because these diseases are recurrent during the first year of life. This recurrence would result in the child's immune system performing better when mature, decreasing the risk of aberrant responses to infections that could result in the development of acute leukemia. [80,81] This finding was consistent with that of Perillat et al., who conducted a study in France in a sample of 280 children with acute leukemia (cases) and 288 healthy children (controls). The authors reported that if the child suffered from recurrent infections before 2 years of age, he/she would be protected from the development of acute leukemia, with an OR = 0.6 (95% CI: 0.4-1.0). These results were statistically significant and consistent with those reported by Neglia et al. [21,22,32,68]
However, Schüz et al. (1999) conducted a case-control study in Germany during 1992-1997. They studied 1184 families of children with acute leukemia (cases) and 2588 families of healthy children (controls) and found no association between common infections and an increased incidence of leukemia. It is notable, however, that they reported that when the children had a history of surgical procedures, such as appendectomy/tonsillectomy, at least once in their life, their risk of developing acute leukemia increased, with an OR of 1.4 (95% CI: 1.0-1.9). These authors also observed a significant association with pneumonia, with an OR of 1.7 (95% CI: 1.2-2.3), whereas bronchitis was not associated with the development of acute leukemia, with an OR of 1.1 (95% CI: 0.9-1.4). Moreover, they observed a moderate risk (OR = 1.3; 95% CI: 1.0-1.7) when the children were breastfed for no more than 1 month, specifically in children diagnosed with common ALL. [68]

Neglia et al. performed a case-control study in children under 15 years of age in the U.S. The cases of newly diagnosed ALL were ascertained from the Children's Cancer Group (CCG), and the controls were randomly selected using a random digit-dialing methodology and individually matched to the cases by age, race and telephone area code and exchange between January 1, 1989, and June 15, 1993. They observed a slight decrease in the risk of developing acute leukemia when the child had repeated ear infections during their first year of life, with ORs of 0.86 (95% CI: 0.61-1.22), 0.83 (95% CI: 0.63-1.09) and 0.71 (95% CI: 0.50-1.01) for 1 episode, 2-4 episodes and 5 or more episodes, respectively, and continuous infections were associated with an OR of 0.69 (95% CI: 0.35-1.37; p = 0.026), but these results were not statistically significant. Moreover, it should be noted that these results are similar to a dose-response gradient, as the risk of developing acute leukemia was decreased with an increasing number of infections in the child during the first year of life. This association was more evident in children aged 2 to 5 years with pre-B ALL who presented with ear infections (between 2 and 4 episodes), with an OR of 0.65 (95% CI: 0.43-1.00). No other factor studied was associated with the development of acute leukemia. Furthermore, no association was observed between day care and the development of common acute lymphoblastic leukemia (ALL), with an OR of 1.05 (95% CI: 0.80-1.37). [32]

Using a design similar to that of Perillat et al. (2002) and Neglia et al. (2000), Jourdan-Da et al. evaluated the role of childhood infections in the risk of developing acute leukemia in France. This study included 473 cases of acute leukemia and 567 population-based controls. They found a strong inverse association between gastrointestinal infections and the need to assist the child in day care, with an OR of 0.6 (95% CI: 0.4-0.8). Additionally, a history of asthma decreases the risk of developing leukemia (OR = 0.5; 95% CI: 0.3-0.9). Breastfeeding was not associated with the development of leukemia, but an increasing order of the child's birth increases the risk of developing acute lymphoblastic leukemia, with an OR of 2.0 (95% CI: 1.1-3.7). [15,16,32]

Meanwhile, Rudant et al., also in France, used a case-control design of a National Register (ESCALE) and included 765 incident cases of acute leukemia and 1,681 controls. They observed positive associations when the child presented with recurrent common infections, a history of asthma or a history of eczema, with ORs of 0.7 (95% CI: 0.6-0.9), 0.7 (95% CI: 0.4-1.0) and 0.7 (95% CI: 0.6 -0.9), respectively. Having regular contact with farm animals
(OR = 0.6; 95% CI: 0.5-0.8) and breastfeeding (OR = 0.7; 95% CI: 0.5-1.0) were found to be protective factors for this disease, as was also found in children who had visited farms often in their first year of life, with an OR of 0.4 (95% CI: 0.3-0.6). No significant association was found for assistance of the child in daycare before one year of age (OR = 0.8; 95% CI: 0.6-1.1).

One can conclude that repeated infections, such as asthma, play an important role in the etiology of leukemia. [82]

Moreover, Urayama et al., in the USA, conducted two epidemiological studies, namely a case-control study and a meta-analysis. The first study showed that in non-Hispanic white children who attended day care before 6 months of age, the risk of developing leukemia was decreased (OR = 0.90; 95% CI: 0.82-1.00), but this association was not observed in the population of Hispanic children. However, Hispanic children who had ear infections were found to have a decreased risk of developing acute leukemia, with an OR of 0.45 (95% CI: 0.25 to 0.79). Did not report any associations for the other variables studied. In the second study (meta-analysis), these authors evaluated the association between daycare attendance during infancy and the risk of developing acute leukemia; specifically, they wanted to assess whether early exposure to infection protected children from the disease. They concluded that the risk of developing acute leukemia was decreased in children who were exposed to common infections in the first year of life (OR = 0.76; 95% CI: 0.67 to 0.87). [24,25] These findings are consistent with the findings of Perillat et al., Jourdan-Da et al., Dockerty et al., and Ma X et al. [15-19,21,22]

In New Zealand, Dockerty et al. conducted a case-control study that included 121 children diagnosed with acute leukemia and 303 controls (with ages less than 14 years in both groups). They found that exposure to the influenza virus is a risk factor for developing leukemia; that is, a child infected with the influenza virus during the first year of life has a 7-fold risk of developing acute leukemia compared with children who had influenza, with an OR of 6.8 (95% CI: 1.8-25.7). [15,32]

Cardwell et al., using a different epidemiological case-control nested design in a cohort, reported positive evidence of upper respiratory tract infections as a risk factor for the development of acute leukemia (OR = 1.56; 95% CI: 1.08-2.27) and acute lymphoblastic leukemia (OR = 1.59; 95% CI: 1.02-2.49). Similarly, in children presenting with an exanthematous disease, namely chicken pox, we obtained ORs of 2.41 (95% CI: 1.14-5.09) and 2.62 (95% CI: 1.12-6.13) for acute leukemia and acute lymphoblastic leukemia, respectively. [83]

MacArthur et al. conducted a study that included 399 cases and 399 controls who were matched for age and gender and lived in the same area. They evaluated the relationship between vaccination, infectious diseases and common infection and use of medications in children, but their results were not statistically significant, as they found no relationship between childhood diseases and acute leukemia.[84]

Chan et al. performed a population-based, case-control study in China and found that the incidence of roseola and/or fever rash in the first year of life is a protective factor for the development of acute leukemia, with an OR of 0.33 (95% CI: 0.16 to 0.68); however, the risk of developing acute leukemia was increased if the child had a history of tonsillitis in
the period 3-12 months before the reference date (OR = 2.56; 95% CI: 1.22-5.38). No association was found between acute leukemia incidence and daycare attendance. In a study similar to that of Chan et al., Roman et al. found that exposure to fungal infections during the first year of life increases the risk of developing acute leukemia, with an OR of 1.4 (95% CI: 1.0-1.9).[14,85]

4. Infections during the first year of life and development of acute leukemia in children with Down syndrome

In the literature, there are few epidemiological studies that have evaluated the effect of early infections and breastfeeding on the development of acute leukemia in children with Down syndrome; however, the results obtained are very interesting. One such study was conducted by Canfield et al. in a population of children diagnosed with acute leukemia between January 1997 and October 2002 (data were obtained from the records of the Children’s Oncology Group). The sample group consisted of 158 children with Down syndrome and leukemia, and the control group consisted of 173 children with Down syndrome, all of whom were randomly selected. The results of this study were that children with Down syndrome who had infections during the first 2 years of life had a lower risk of developing acute leukemia, with an OR of 0.55 (95% CI: 0.33 to 0.92), compared with children with Down syndrome who had not been infected. [86,87]

In another study that was conducted in children with Down syndrome in Mexico City, however, this association could not be verified. That study sought to assess whether breastfeeding and infections during the first year of life were associated with the development of acute leukemia. In that study, both breastfeeding and the development of infections during the first year of life in children with Down syndrome were protective factors for the development of leukemia, with ORs of 0.84 (95% CI: 0.43-1.61) and 1.70 (95% CI: 0.82-3.52), respectively, but the results were not statistically significant. Infections requiring hospitalization were also evaluated, and it was found that children >6 years of age had a higher risk of developing acute leukemia, with an OR of 3.57 (95% CI: 1.59-8.05). Thus, these results do not support those of the previously mentioned study or the hypothesis proposed by Greaves that infections are a protective factor for developing acute leukemia. [88]

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>Design of study</th>
<th>Size of sample</th>
<th>Data collection</th>
</tr>
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<tbody>
<tr>
<td>Van Steenel et al., 1986 (The Netherlands)</td>
<td>Case-control study (1973-1980)</td>
<td>492 cases, 480 controls; Age: 0-14 years</td>
<td>Mailed questionnaire; addressed to the diagnosed</td>
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<tr>
<td>Schüz et al., 1999 (Germany)</td>
<td>Two-part case-control study (1980-1994)</td>
<td>1184 cases, 2588 controls; Age: 0-14 years</td>
<td>Telephone interviews with the parents</td>
</tr>
<tr>
<td>Dockerty et al., 1999 (New Zealand)</td>
<td>Case-control study (1991-1995)</td>
<td>121 cases, 303 controls; Age: 0-14 years</td>
<td>Mothers interviewed at the home; standardized</td>
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</table>
questionnaires and serological tests were conducted

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<thead>
<tr>
<th>Variables</th>
<th>Odds ratios and relevant results</th>
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<tbody>
<tr>
<td>Breastfeeding; birth order; family size; social class; number of rooms in the household; infections; hospitalization or consultation for infections; primary infections (measles, chicken pox, mumps, or rubella); periods of fever</td>
<td>Common colds (RR: 0.8, 95% CI: 0.6-1.0); periods of fever (RR: 0.9, 95% CI: 0.7-1.2); and primary infections (RR: 0.8; 95% CI: 0.4-2.0). These variables were adjusted for birth order, family size, social class, and residential space. Infectious diseases requiring hospitalization (RR: 0.6; 95% IC: 0.4-1.0).</td>
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<tr>
<td>First-born child; duration of breastfeeding; deficit in social contacts; routine immunizations; infections; tonsillectomy or appendectomy; allergies of the child; allergies of the mother</td>
<td>Routine immunizations between 0-3 years of age and having had a tonsillectomy or appendectomy increased the child's risk of developing leukemia (OR: 3.2; 95% CI: 2.3-4.6 and OR: 1.4; 95% CI: 1.1-1.9, respectively), whereas allergies showed a protective effect (OR: 0.6; 95% IC: 0.5-0.8).</td>
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<td>Social class; marital status; ethnic group; educational level of the parent; home ownership; length of gestation; age of the mother at the child's birth; weight of the child at birth; exposure of the mother to X-rays during the first trimester; exposure of the child to X-rays or radiotherapy before onset of the illness; tobacco smoking by the mother in the first trimester or before the pregnancy</td>
<td>A positive association was found between infection caused by influenza during the first year of life and the risk of developing leukemia (OR: 6.8; 95% CI: 1.8-25.7). No other variable was related to acute leukemia.</td>
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<tr>
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<tbody>
<tr>
<td>Neglia et al., 2000 (USA)</td>
<td>Case-control study (January 1, 1989-June 15,1993)</td>
<td>1842 cases, 1986 controls; Age: &lt;15 years</td>
<td>Structured interview</td>
<td>Interview of the mother; gender; age; race; educational level of the mother; educational level of the father; family income; immunophenotype class.</td>
</tr>
<tr>
<td>Infante et al., 2000 (Canada)</td>
<td>Case-control study (1989-1995)</td>
<td>491 cases, 491 controls; Age: 0-9 years</td>
<td>Structured questionnaire administered to the mothers by telephone</td>
<td>Educational level of the mother; family income at the time of the child's diagnosis; mother's age; father's age; tobacco use by the mother; infections during the pregnancy; child's birth order; attendance at day care or a nursery; principal feeding method (breast or bottle); length of breastfeeding; history of recurrent infections of the mother; use of antibiotics during pregnancy.</td>
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<td>Rosenbaum et al., 2000 (USA)</td>
<td>Case-control study (1980-1991)</td>
<td>255 cases, 760 controls; Age: 0-14 years; 31 county regions (cases)</td>
<td>Standardized questionnaires mailed to the parents</td>
<td>Gender; race; educational level of the mother; birth order; feeding status at birth (breast, bottle); age at the diagnosis; day care or preschool program; family outcome; maternal employment during the pregnancy.</td>
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Neither attendance at nor time remaining in daycare was associated with the risk of developing leukemia. For children with 1-4 episodes of ear infections or sustained infections, the association between infections and early attendance at daycare or at a nursery and breastfeeding were protective factors against the development of acute leukemia (OR: 0.49; 95% CI: 0.31-0.77 and OR: 0.68; 95% CI: 0.49-0.95, respectively). Children who attended day care for >36 months had a lower risk of developing leukemia (OR: 1.32, 95% CI: 0.70-2.52) than those who attended day care for 1-18 months (OR: 1.74, 95% CI: 0.90-3.36).
the development of acute leukemia was not statistically significant.

0.89-3.42) or for 19-36 months (OR: 1.32; 95% CI: 0.64-2.71).

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<tbody>
<tr>
<td>Perillat et al., 2002 (France)</td>
<td>Case-control study</td>
<td>280 incident cases, 288 hospital controls</td>
<td>Standardized, face-to-face interviews of the mothers</td>
<td>Diagnosed categories (acute leukemia classification and immunophenotype); gender; age; ethnic origin; hospital where the case was identified; educational level of the mother; occupation of the mother at the time of the interview; socio-professional categories; place of residence; birth order; number of siblings; daycare attendance; age at the start of daycare; repeated infections before the age of 2 years; incidence of surgical operation for early ear-nose-throat infections before the age of 2 years; breastfeeding</td>
<td>An inverse association was found between the development of acute leukemia and attendance at daycare (OR: 0.6; 95% CI: 0.4-1.0), repeated (≥4 per year) early common infections before the age of 2 years (OR: 0.6; 95% CI: 0.4-1.0), and surgery for infection of the nose, ear, or throat before the age of 2 years (OR: 0.5; 95% CI: 0.2-1.0). A statistically significant interaction was found between attendance at daycare and repeated common infections.</td>
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<td>Chan et al., 2002 (China)</td>
<td>Population-based, case-control study (November 1994-December 1997)</td>
<td>116 cases, 788 controls; Age: 2-14 years; the Hong Kong Pediatric Hematology and Oncology Study Group</td>
<td>Standardized, face-to-face interviews</td>
<td>Medical history (infectious illnesses in the first year of life; breastfeeding; daycare/social contacts of the index patient and siblings; household environment; community environment</td>
<td>If the child had rubella and/or fever during the first year of life, the risk was lowered (OR: 0.33; 95% CI: 0.16-0.68). A change of residence during the first year of life presented a lower risk of the child developing leukemia (OR: 0.47; 95% CI: 0.23-0.98), whereas with such a change during the second year, the risk increased (OR: 3.92; 95% CI: 1.47-10.46).</td>
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<tr>
<td>Jourdan-Da et al., 2004 (France)</td>
<td>Case-control study (1995-1998)</td>
<td>473 cases, 567 population-based controls</td>
<td>Questionnaire</td>
<td>Gender; age at the time of diagnosis; region of the residence at the time of diagnosis; socio-professional categories; educational level of the mother; educational level of the father; birth weight; term of pregnancy; birth order; mother’s age at birth; Down syndrome; breastfeeding; infections in the first year of life</td>
<td>A strong association was found between childhood gastrointestinal illnesses and attendance at daycare and a lowered risk of developing leukemia (OR: 0.6; 95% CI: 0.4-0.8); however, no association was found for breastfeeding. Birth order (4th or later) showed a significant association with an increased risk of acute lymphoblastic leukemia (OR: 2.0; 95% CI: 1.1-3.7), while prior episodes of asthma were associated with a lower risk of developing acute lymphoblastic leukemia (OR: 0.5; 95% CI: 0.3-0.9).</td>
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<td>Ma et al., 2005 (USA)</td>
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<tr>
<td>Roman et al., 2007 (United Kingdom)</td>
<td>Population-based, case-control study (1991-1996)</td>
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<tr>
<td>Size of sample</td>
<td>255 cases, 760 controls; Age: 0-14 years</td>
<td>294 incident cases, 376 controls; Age: 0-14 years</td>
<td>455 cases, 1031 controls; Age: 0-14 years</td>
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<tr>
<td>Data collection</td>
<td>Questionnaire</td>
<td>Personal interview of the parents</td>
<td>Interview of the parents</td>
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<tr>
<td>Variables</td>
<td>Gender; race; birth year; mother's educational level; family income; maternal smoking status; infant feeding at birth; birth order; attendance at daycare before 25 months of age; year of diagnosis of leukemia; age at diagnosis of leukemia; allergies; history of allergies; common infections (e.g., colds, otitis media, influenza, croup, bronchitis, pneumonia, vomiting, diarrhea)</td>
<td>Age; gender; household income; mother's educational level; mother's age at birth; birth weight; birth order; duration of breastfeeding; day care attendance; infections during infancy</td>
<td>Gender; age; diagnosis of an infectious disease</td>
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<tr>
<td>Odds ratios and relevant results</td>
<td>The results showed that infection late in the first year of the child's life was associated with an increase in the risk of developing leukemia.</td>
<td>Attendance at daycare and infections during infancy were associated with a decrease in the risk of developing acute lymphoblastic leukemia within the white, Hispanic population (OR: 0.42; 95% CI: 0.18-0.99 and OR: 0.32; 95% CI: 0.14-0.74, respectively); corresponding data for the Hispanic population, even for those living in the same area, did not agree.</td>
<td>The cases had more episodes of infection than did the controls, which was more notable in the neonatal period (&lt;1 month): 18% of the controls and 24% of the cases with leukemia were diagnosed with an average of &lt;1 infection (OR: 1.4; 95% CI: 1.1-1.9; p &lt; 0.05). The cases with ≥1 episodes of infection in the neonatal period tended to be diagnosed with acute lymphoblastic leukemia at a relatively young age.</td>
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</table>

**Author, Year (Country)**

| MacArthur et al., 2007 (Canada) | Cardwell et al., 2008 (United Kingdom) | Urayama et al., 2010 (USA) |

**Design of study**


**Size of sample**

| 399 cases, 399 controls; Age: 0-14 years | 62 cases, 2215 matched controls | 669 cases, 977 controls; Age: 1-14 years |

**Data collection**

| Standardized personal interviews in the child's home | Data-based |

**Variables**

| Gender; age; mother’s age; father’s age; numbers of live births; annual household income; mother’s education; father’s education; ethnicity; vaccinations; illness and infections; breastfeeding; allergies; immunosuppressant medication for the child; vitamins; antibiotics for the child | Gender; age; consultations; number of consultations; antibiotic prescriptions; common infections | Gender; mother’s age at the child’s birth; mother’s educational level; annual household income; birth weight; breastfeeding; mother’s tobacco use; daycare attendance; history of common infections in the child; ethnicity |

**Odds ratio and relevant results**

| No association was found between early infections and acute leukemia; however, vitamin use was associated with a risk of developing acute leukemia (OR: 1.66; 95% CI: 1.18-2.33); the use of | One or more infections in the first year of life reduced the risk of leukemia (OR: 10.5; 95% CI: 0.69-1.59); | When variables were evaluated separately, both attendance at daycare at 6 months of age and birth order reduced the risk of leukemia (OR: 0.90; 95% CI: |
immunosuppressants by the child decreased the risk of leukemia (OR: 0.37; 95% CI: 0.16-0.84); breastfeeding for >6 months had a protective effect against the development of leukemia (p < 0.05). p = 0.83) and of acute lymphoblastic leukemia (OR: 1.05; 95% CI: 0.64-1.74; p = 0.84).

- 0.82-1.00 and OR: 0.68; 95% CI: 0.50-0.92, respectively) in a white, non-Hispanic population, but not in a Hispanic population; however, if these children had ear infections, the risk of developing acute leukemia was reduced (OR: 0.45, 95% CI: 0.25-0.79).

<table>
<thead>
<tr>
<th>Author, Year (Country)</th>
<th>Design of study</th>
<th>Size of sample</th>
<th>Data collection</th>
<th>Variables</th>
<th>Odds ratios and relevant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudant J et al., 2010 (France)</td>
<td>National registry-based, case-control study ESCALE (2003-2004)</td>
<td>765 incident cases, 1,681 controls.</td>
<td>Questionnaire, interviews by telephone</td>
<td>Mother’s educational level; parental professional category; place of residence at the time of diagnosis; mother’s age at the child’s birth; number of children age &lt;15 years in the household; birth order; breastfeeding; duration of breastfeeding; early common infections; surgical operation for ear, nose, or throat infections; history of allergies; contact with animals; farm visits before the age of 2 years</td>
<td>Negative associations were found for children with repeated common infections (OR: 0.7; 95% CI: 0.6-0.9); with a history of asthma or eczema (OR: 0.7; 95% CI: 0.4-1.0 and OR: 0.7; 95% CI: 0.6-0.9, respectively); with attendance at daycare before 1 year of age (OR: 0.8; 95% CI: 0.6-1.1); and with prolonged breastfeeding (OR: 0.7; 95% CI: 0.5-1.0).</td>
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<tr>
<td>Urayama et al., 2011 (USA)</td>
<td>Observational studies (1993-2008)</td>
<td>14 case-control study</td>
<td>Searches of the PubMed database and bibliographies of the publications</td>
<td>N/A</td>
<td>Attendance at daycare is associated with a reduced risk of acute lymphoblastic leukemia (OR: 0.76; 95% CI: 0.67-0.87).</td>
</tr>
</tbody>
</table>

Table 1. Summary of reviewed articles concerning the epidemiology of early infection and acute childhood leukemia.

5. Conclusions

The vast majority of the epidemiological studies conducted thus far on the association between infection during the first year of life and the development of acute leukemia in children have corresponding case-control designs. Additionally, the results of these studies appear to suggest a lower risk of developing acute leukemia among children who were ex-
posed to early infections compared with those who were not exposed. No such association, however, has been reported by other authors; therefore, infections that occur during the first year of life are still considered to be a controversial exposure factor. To achieve better epidemiological evidence, the consistent study of proxy variables in different studies should be performed to enable a better quantification of exposure.

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