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# Chronic Neutropenia in Children: A Single-Center Experience

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**Abstract**

**Objective.** To analyze the characteristics, etiology, diagnostic evaluation, management, follow-up, and outcomes of children with chronic neutropenia treated at a tertiary care pediatric hospital in Croatia. **Materials and Methods.** We retrospectively reviewed the demographic, clinical, and laboratory data of 48 children (23 males and 25 females; median age 7.75 months [IQR 5.13–11.75]) diagnosed with chronic neutropenia between 2013 and 2021. **Results.** The median absolute neutrophil count (ANC) at presentation was 487/μL (IQR 198.5–837.5), and 52% of the patients had severe neutropenia. Autoimmune neutropenia (AIN) was diagnosed in 21 cases, chronic idiopathic neutropenia (CIN) in 26 cases, and neutropenia in the context of a genetic syndrome in one case. Antineutrophil antibodies were detected in 47% of the children tested. During follow-up, 23% received granulocyte-colony-stimulating factor (G-CSF), and 21% received antibiotics. The median follow-up duration was 21 months (IQR 12–32.75), during which 83% achieved spontaneous remission, with a median time to remission of 13.5 months. Lower ANC at diagnosis was associated with more frequent rehospitalizations, longer time to remission, and longer follow-up. No significant differences were found between AIN and CIN in terms of age, ANC at diagnosis, time to referral, or time to remission, although AIN cases were followed for a longer period. **Conclusion.** Pediatric chronic isolated neutropenia, including AIN and CIN, generally follows a mild clinical course with a low incidence of severe infection. Most children achieve spontaneous remission within one year. Comprehensive genetic testing is essential in children with suspected congenital neutropenia and those with features suggestive of an underlying genetic syndrome. Adherence to European guidelines supports standardized diagnosis, follow-up, and management, thereby improving patient care.

**Key Words:** Neutropenia ▪ Chronic ▪ Children ▪ Etiology ▪ Prognosis.

## Introduction

Neutropenia is defined as a reduction in the number of neutrophils circulating in the blood, with an absolute neutrophil count (ANC) below the lower limit of the normal range for age and ethnic origin. The widely accepted cutoff level for neutropenia in Caucasians is $1.0 \times 10^9$/L (1000/μL) up to the age of 1 year and $1.5 \times 10^9$/L (1500/μL) from the age of 1 year to adulthood (1, 2). Neutropenia can be classified according to severity (based on ANC), duration, and pathogenesis. Based on severity, neutropenia in individuals older than 1 year is classified as mild (ANC 1000-1500/μL), moderate (ANC 500-1000/μL), and severe (ANC <500/μL). Agranulocytosis denotes a profound degree of neutropenia, defined as an ANC <200/μL. Neutropenia is classified as acute (lasting <3 months) or chronic (>3 months). In a pathogenesis-based framework, neutropenias are categorized as congenital, acquired, and likely acquired, with respective subcategories (1, 3, 4). Neutropenia is a common reason for referral to pediatric hematologists. Until recently, limited data were available on the management and outcomes of children with prolonged isolated neutropenia outside the setting of febrile neutropenia in children with cancer.

This study aimed to examine the etiology, clinical course, interventions, and outcomes of children with chronic neutropenia admitted to a tertiary care pediatric hospital in Croatia.

## Materials and Methods

### *Study Population*

Fifty-seven children with neutropenia who were consecutively admitted to the day hospital or inpatient unit at the Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Center Rijeka, Croatia, between January 1, 2013, and December 31, 2021, were enrolled. Patients with chemotherapy-induced febrile neutropenia were excluded from the study. Of the 57 subjects, children with acute neutropenia (ANC recovered to ≥1500/μL within three months) were further excluded. Additionally, two patients with chronic neutropenia were lost to follow-up. After these exclusions, data from 48 children (23 males and 25 females), all of Caucasian origin, were included in the final analysis. The median age at diagnosis was 7.75 months (IQR 5.125–11.75). Thirteen (27%) patients were younger than 6 months, 30 (63%) were between 6 months and 5 years of age, and 5 (10%) were older than 5 years of age. These age categories were defined based on recognized differences in the etiology and clinical course of childhood neutropenia according to the age at onset, rather than on developmental pediatric classifications.

### *Data Collection*

Data were obtained from both paper-based and electronic hospital records. The following variables were collected: (a) Clinical data: sex, ethnic origin, age at presentation, findings from full clinical examination including anthropometry, evidence of recent infection (type and site of infection), history of drug intake and vaccination, comorbidities, family history suggestive of neutropenia and autoimmune disorders, treatment, need for repeated hospitalizations, and duration of follow-up; (b) Laboratory investigations: complete blood count with differential (at diagnosis and throughout follow-up until recovery or for a minimum of 3 months), antineutrophil antibodies, immunoglobulins (IgG, IgM, and IgA), antiglobulin test, viral screening for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), antinuclear antibodies (ANA), vitamin B12, folic acid, vitamin D, bone marrow aspirate with cytological examination, genetic testing for *ELANE* and *HAX-1*, microbiological investigations (pharyngeal swab, urine culture, blood culture) and other investigations in case of findings suggestive of associated diseases (e.g., human herpesvirus 6 [HHV-6] for roseola, peripheral blood flow cytometry for suspected immunodeficiency, chest X-ray for the diagnosis of lower respiratory tract infection, additional bone marrow evaluation – immunophenotype and cytogenetics – in case of signs suspected for malignancy). Antineutrophil antibody detection was performed using the monoclonal antibody immobilization of granulocyte antigen (MAIGA) assay. Targeted genetic testing of the *ELANE* and *HAX1* genes was performed using a next-generation sequencing (NGS) panel. Neutropenia was classified as mild, moderate, or severe based on the ANC, as previously described.

### *Ethics Statement*

The study was approved by the Ethics Committee of the Clinical Hospital Center, Rijeka, Croatia (No. 2170-29-02/1-22-2; May 26, 2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

### *Statistical Analysis*

Frequencies and percentages were used for descriptive statistics. As most variables deviated from the normal distribution, nonparametric tests were applied. The median and interquartile range (IQR) were used as measures of the central tendency. Spearman's correlation coefficient was employed to examine the relationship between two continuous variables, Pearson's chi-square test between two nominal variables, and point-biserial correlation between binomial and continuous variables. The Mann–Whitney U test was used to test the differences between the two

groups. Data were processed using the IBM® SPSS® Statistics Version 25 software package.

## Results

### *Patient Referral and Clinical Presentation*

The median time from the first documented neutropenia to referral to a hematologist was 1 month (IQR 0.23–2.50). Referral time was not influenced by neutropenia severity. The median number of blood counts performed prior to the clinic visit was 3 (IQR 2-4). Neutropenia associated with fever was the reason for referral in 25 (52%) participants, most commonly due to fever of unknown origin (N=13, 5%), followed by unspecified respiratory tract infections (N=6, 24%), pneumonia (N=3, 12%), otitis (N=2, 8%), and urinary tract infection (N=1, 4%). In 23 (48%) participants, neutropenia was an incidental finding during routine checkups (N=18), assessment of atopic dermatitis (N=2), evaluation of nonspecific rash (N=2), or poor weight gain (N=1).

Five out of 48 children had comorbidities in their medical history: two had atopic dermatitis, while allergic rhinitis, hypogammaglobulinemia, and failure to thrive were present in one child each. Eighteen (38%) children received antibiotics prior to referral, and none had received any other drugs known to cause neutropenia or any vaccinations. Family history of neutropenia and autoimmune disorders was positive in three children, all reported in mothers: one case of neutropenia, autoimmune thyroiditis, and celiac disease; one case of autoimmune thyroiditis; and one case of rheumatoid arthritis.

On clinical examination, two children had atopic dermatitis, and a one-month-old infant showed poor growth and hypotonia. In all other cases, the clinical findings were normal, except for the signs of infection. The median ANC at diagnosis was 487/μL (IQR 198.5-837.5). According to the severity of neutropenia, 10 (21%) patients had mild neutropenia, 13 (27%) had moderate neutropenia, and 25 (52%) had severe neutropenia. The main characteristics of the children with chronic isolated neutropenia are shown in Table 1.

Table 1. Main Characteristics of Children With Isolated Chronic Neutropenia. Data Is Shown as Either Number of Cases and Percentage or Median and Inter-Quartile Range

| Baseline characteristics | |
|---|---|
| Gender | |
| Female | 25 (52%) |
| Male | 23 (48%) |
| Median age (IQR) at onset of neutropenia (months) | 7.75 (5.125–11.75) |
| Age group | |
| ≤ 6 months | 13 (27%) |
| 6 months – 5 years | 30 (63%) |
| > 5 years | 5 (10%) |
| Reason for CBC at diagnosis | |
| Fever/infection | 25 (52%) |
| Incidental finding | 23 (48%) |
| Prior antibiotics | |
| Yes | 18 (38%) |
| No | 30 (62%) |
| Outcome characteristics | |
| Median ANC (IQR) at diagnosis (μL) | 487 (198.5-837.5) |
| Severity of neutropenia | |
| Mild | 10 (21%) |
| Moderate | 13 (27%) |
| Severe | 25 (52%) |
| Indirect antineutrophil antibodies | |
| Positive | 21 (47%) |
| Negative | 24 (53%) |
| Not performed | 3 |
| Rehospitalizations | |
| Yes | 15 (31%) |
| No | 33 (69%) |
| Treatment during neutropenia | |
| G-CSF | 11 (23%) |
| Antibiotics for infection | 10 (21%) |
| None | 27 (56%) |
| Etiology-based group | |
| Chronic idiopathic neutropenia | 26 (54%) |
| Autoimmune neutropenia | 21 (44%) |
| Other/complex genetic syndrome | 1 (2%) |
| Median time (IQR) to remission (months) | 13.5 (9.00-18.00) |
| Median follow-up time (IQR) (months) | 21 (12.00-32.75) |

CBC=Complete blood count; G-CSF=Granulocyte-colony stimulating factor; IQR= interquartile range.

Autoimmune neutropenia (AIN) was diagnosed upon detection of positive indirect antineutrophil antibodies, while chronic idiopathic neutropenia (CIN) was diagnosed by exclusion, following normal results of all investigations. In the patient with AIN and vitamin B12 deficiency, supplementation was administered without a significant response. In one patient, neutropenia occurred in the context of a genetic syndrome associated with a *MAGEL2* variant, accompanied by failure to thrive and hypotonia. The patient did not experience spontaneous recovery during the follow-up period and was subsequently managed by another subspecialist. Another patient, initially diagnosed with neonatal alloimmune neutropenia (NAN) and showing spontaneous ANC recovery after six weeks, subsequently developed mild neutropenia at 7 months of age. This persisted until 24 months, leading to a revised diagnosis of CIN.

### *Laboratory Investigations*

The MAIGA test for the detection of antineutrophil antibodies was performed in 45 (94%) children. Positive indirect antineutrophil antibodies were found in 21 (47%) cases. The antiglobulin test was performed in 29 (59%) children, and all the results were negative. Ig levels were measured in 43 (90%) children; IgG was below the age-adjusted reference range in one case, and IgM in two cases. In these children, flow cytometric analysis of peripheral blood lymphocyte subsets revealed no abnormalities. Among the children tested, CMV IgM was positive in 1 of 28, and EBV viral capsid antigen (VCA) IgM was positive in 1 of 25. HHV-6 serology was performed in two children with roseola and neutropenia, and both had positive IgM and IgG. ANA testing was performed in six cases, with one positive result. Vitamin B12 was measured in 17 children and was below the lower limit in one previously described case, while folic acid levels were normal in all 16 children tested. Vitamin D levels were determined in 12 children, and were low in two. However, neutropenia did not resolve after the infection cleared or following vitamin B12 and D supplementation; therefore, these conditions were not considered etiological factors for chronic neutropenia.

### *Genetic and Bone Marrow Findings*

Genetic testing for *ELANE* and *HAX-1* was performed in 7 children with severe neutropenia. No pathogenic variants were identified in either gene. Bone marrow aspiration with cytomorphology, performed as part of the initial investigations, was carried out in 32 (67%) children, with 1 sample being inadequate for analysis. This relatively high percentage reflects pre-guideline clinical practice, when indications for bone marrow evaluation in chronic neutropenia were less clearly standardized and largely dependent on individual clinical judgment, and were generally performed to exclude underlying hematologic disease or in cases of severe neutropenia, particularly when congenital neutropenia or bone marrow failure was part of the differential diagnosis. In 7 of 22 (32%) children with AIN, the bone marrow was hypercellular with myeloid hyperplasia; in 2 of 22 (9%), it was hypocellular with myeloid hypoplasia, and in the remaining cases, it was normal. Among the 25 children with CIN, three had hypocellular marrow with myeloid hypoplasia, while the remaining cases demonstrated normal cellularity and myelopoiesis. A 5-year-old boy with isolated severe neutropenia and positive indirect antineutrophil antibodies developed mild bicytopenia (neutropenia and normocytic anemia) during follow-up. Eight months after the initial presentation, bone marrow aspiration revealed acute lymphoblastic leukemia (5).

### *Microbiological and Radiological Assessments*

During the initial diagnostic workup, regardless of prior antimicrobial therapy, pharyngeal swabs were obtained from 46 (96%) children, of whom 37/46 (80%) were negative. The most common isolates were *Streptococcus pneumoniae* (N=3) and *Enterobacter cloacae* (N=2). Urine cultures were obtained from 30 (63%) participants and were positive in three cases (two *E. coli* and one *Klebsiella oxytoca*). Blood cultures were obtained from 7

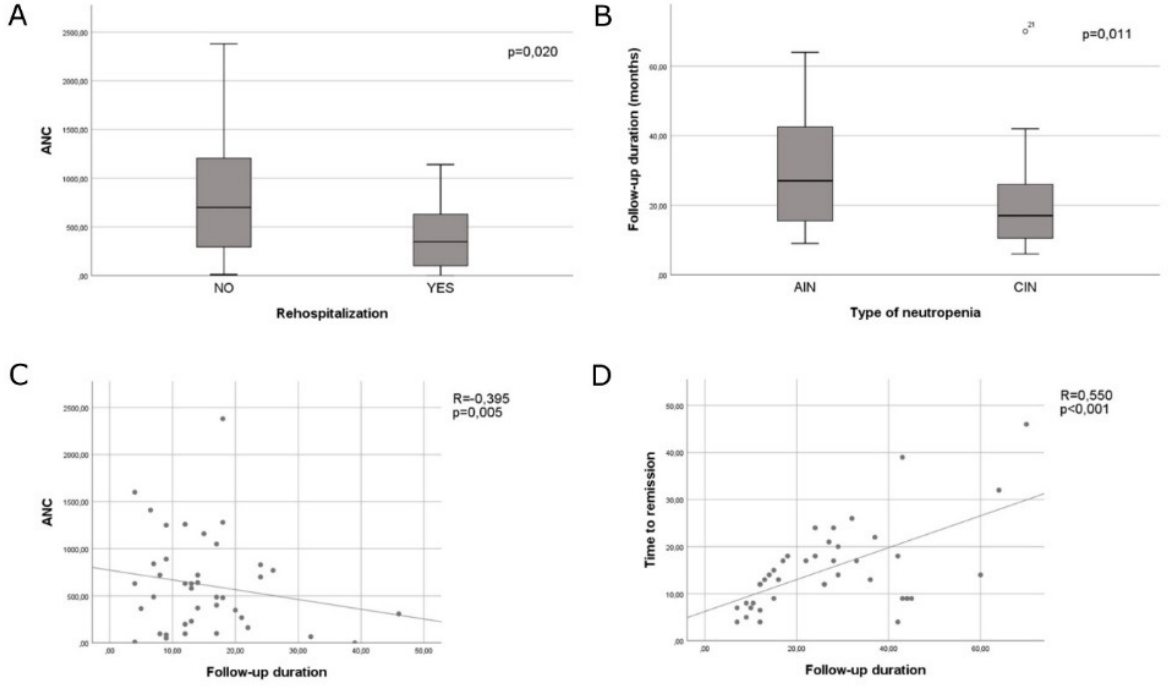
children, and all were negative. Radiological assessments were performed in 20 cases, and pneumonia was diagnosed in three cases.

### *Follow-up and Clinical Outcomes*

The median follow-up time was 21 months (IQR 12.00–32.75). During the neutropenia period, rehospitalization occurred in 15 (31%) participants for a total of 27 admissions: eight were hospitalized once, four twice, one three times, and two four times. The most common reasons for readmission were high fever (N=11), followed by unspecified respiratory infections (N=6), otitis (N=4), gastroenteritis (N=2), pneumonia (N=1), cellulitis (N=1), Covid 19 (N=1), and suspected mastocytosis (N=1). Initial ANC was significantly negatively correlated with repeated admissions, time to remission, and total follow-up duration, whereas no relationship was observed between ANC and age (Supplementary Tables 1 and 2). Scatterplots were generated to depict the relationships between continuous variables and highlight statistically significant associations (Figure 1).

G-CSF therapy was administered in 11 (23%) children during 17 hospitalizations, with an average duration of 2.8 days (IQR 2.00-3.00), and resulted in a significant increase in ANC in all cases. In selected patients, G-CSF was used primarily as a functional test of bone marrow reserve and neutrophil response, in addition to its occasional therapeutic use during clinically significant infectious episodes. The decision was based on individual clinical judgment in the pre-guideline era, when standardized protocols for its use had not yet been established. Antibiotic therapy was administered to 10 (21%) children for 12 episodes of infection. None of the children received prophylactic antibiotics.

Forty participants (83%) achieved spontaneous remission, with a median time to remission of 13.5 months (IQR 9.00-18.00). To further characterize the disease pattern, we compared the main clinical and laboratory features of AIN and CIN. The Mann–Whitney U test demonstrated a statistically




AIN=Autoimmune neutropenia; ANC=Absolute neutrophil count; CIN=Chronic idiopathic neutropenia.

Figure 1. A. Median absolute neutrophil count at diagnosis according to rehospitalization status; B. Median follow-up duration (months) for cases with autoimmune and chronic idiopathic neutropenia; C. Relationship between absolute neutrophil count at diagnosis and follow-up duration; D. Relationship between time to remission and follow-up duration.

Table 2. Clinical and Laboratory Comparison of Cases With Autoimmune Neutropenia and Chronic Idiopathic Neutropenia

| Variable | Type of neutropenia | N | C (25-75) | Mann–Whitney U test | P |
|---|---|---|---|---|---|
| Median age (IQR) at onset of neutropenia (months) | AIN | 22 | 8 (5.375-19.50) | 245.00 | 0.522 |
| | CIN | 25 | 8 (4.665-11.00) | | |
| Median time (IQR) to referral (months) | AIN | 21 | 1.23 (0.185-4.00) | 210.50 | 0.250 |
| | CIN | 25 | 0.50 (0.23-1.58) | | |
| Median ANC (IQR) at diagnosis (μL) | AIN | 22 | 374 (82.25-832.50) | 224.00 | 0.277 |
| | CIN | 25 | 488 (279.50-830.00) | | |
| Median time (IQR) to remission (months) | AIN | 20 | 14 (9.00-19.50) | 176.50 | 0.524 |
| | CIN | 20 | 12 (8.00-18.00) | | |
| Median (IQR) follow-up duration (months) | AIN | 22 | 27.5 (15.75-43.00) | 156.50 | 0.011* |
| | CIN | 25 | 17 (9.75-27.00) | | |

ANC=Absolute neutrophil count; AIN=Autoimmune neutropenia; CIN=Chronic idiopathic neutropenia; IQR=Interquartile range; N=Number; C (25–75)=Median (25th–75th percentile); P=Statistical significance (*P<0.05; **P<0.01; ***P<0.001).

significantly longer follow-up period for AIN cases than for CIN cases (Figure 1B). No significant differences were observed between the groups in terms of age and ANC at diagnosis, time to referral to a hematologist, or time to remission (Table 2).

## Discussion

Childhood chronic neutropenia represents a heterogeneous clinical entity and is a frequent indication for pediatric hematology referral (6). Recent expert recommendations have aimed to standardize its diagnostic evaluation and management (7–10).

This study aimed to present institutional experience with the diagnostic work-up, management strategies, and follow-up of children with chronic neutropenia. Because the European guidelines were published only in April 2023 and adequate follow-up of our cases required a defined observation period, we concluded the study at the end of 2021. The retrospective cohort comprised 48 children who were consecutively treated at a tertiary care pediatric hospital. The sex distribution was approximately equal. The median age at presentation was 7.75 months, and 90% were younger than 5 years. This notably early age presentation is consistent with the findings of Angelino et al., who reported that 72% of cases occurred in children under 2 years of age (11). In our study, the median time from the first detection of neutropenia to referral to a hematologist was short (1 month) and was not influenced by the severity of neutropenia, reflecting the preferences and experience of the primary care pediatrician in most cases. In contrast, Nagalapuran et al. (12) reported a short median referral time of 2 months, which was inversely correlated with the severity of neutropenia.

The median ANC at diagnosis was below 500/μL (487/μL), with the majority of children presenting with severe neutropenia (52%), followed by moderate (27%) and mild (21%) forms. The median ANC in similar published studies varies from 314/μL for AIN and 518/μL for CIN (11), to 600/μL (13), 732/μL (14), and 827/μL (15). The proportion of children with mild neutropenia varies across these studies, ranging from 12% (11), 25.5% (13), 26.1% (14), and 29% (12) to 45% (15). The presence of comorbidities or a positive family history was infrequent in the present study. No drug or vaccine was identified as the etiological cause. In 52% of our cases, neutropenia was accompanied by fever or infection, whereas in the remaining cases, it was detected incidentally. The reported frequencies of post-infectious neutropenia vary widely in the literature, ranging from 33.3% (10), 53.9% (14), and 58.5% (13) to 96.5% (15). However, most of these studies included children with both acute and chronic neutropenia,

making it difficult to compare the overall results. The only small-scale study on chronic neutropenia comparable to ours evaluated 29 children (16), including 15 with CIN, 7 with AIN, and 7 with congenital neutropenic syndromes. Among these, 5 of the 7 patients with AIN (71%) and 10 of the 15 patients with CIN (67%) experienced infections requiring hospitalization. The mean age at onset, mean ANC at presentation (0.77 vs. 0.99 years; 291/μL vs. 549/μL, respectively), and mean duration of neutropenia did not differ significantly between AIN and CIN. Infections were more frequent in patients with CIN, who also had a longer average follow-up.

In our cohort of 22 AIN and 25 CIN cases, age at presentation, ANC at onset, and duration of neutropenia did not differ significantly between the groups. Although AIN cases were followed for a longer period, no notable differences were observed in the frequency of infections or rehospitalizations.

Overall, comparison with previously published cohorts reveals several similarities and differences. The median age at presentation in our study was consistent with reports indicating that chronic neutropenia predominantly affects infants and young children. Similarly, the overall benign clinical course and high rate of spontaneous remission are in agreement with prior studies of both AIN and CIN. However, the proportion of patients presenting with severe neutropenia in our cohort was higher than in some reports, which may reflect referral bias to a tertiary care center and the inclusion of more clinically significant cases. Reported infection rates and causes of neutropenia also vary widely in the literature. While some studies describe a predominance of post-infectious cases, particularly when acute and chronic neutropenia are combined, cohorts focusing exclusively on chronic neutropenia, such as ours, generally report lower rates of severe infectious complications. The differences across studies are likely influenced by variability in inclusion criteria, definitions of chronicity, and referral practices.

AIN has a heterogeneous etiology and may present as an isolated condition (primary AIN) or in association with other autoimmune disorders, infection, drug exposure, malignancy, or occasionally, vaccination (secondary AIN) (1, 17). Primary AIN is the most clinically significant form of acquired neutropenia in children. It typically presents during the first years of life and is driven by autoantibodies directed against human neutrophil antigens (HNA), leading to neutrophil destruction through complement-mediated lysis or splenic phagocytosis of antibody-coated neutrophils (17). The clinical course is largely benign, with few infections, and spontaneous resolution occurs in approximately 90% of affected children within a few years (18). Positive indirect antibody identification supports the diagnosis of AIN in appropriately aged children with a typical clinical history. Antineutrophil antibodies can be detected in 52% to 74% of suspected AIN patients at the first screening and 84% with repeated antibody tests (17, 19).

We identified antineutrophil antibodies in 47% of the cases tested. This slightly lower rate may reflect the use of the MAIGA assay, which has been reported to be less sensitive than the indirect granulocyte immunofluorescence test (GIFT). As GIFT remains the most widely used and validated method for antineutrophil antibody detection, repeated testing in a reference laboratory is recommended when AIN is suspected despite initial negative results (1). Importantly, the limited sensitivity of available assays introduces diagnostic uncertainty and raises the possibility of misclassification between AIN and CIN in antibody-negative cases. This distinction is further complicated by evidence suggesting that AIN and CIN may represent a continuum of the same underlying disorder rather than strictly separate entities. In this context, some patients classified as CIN may represent cases of AIN with undetectable antineutrophil antibodies. Therefore, our findings comparing AIN and CIN should be interpreted with caution, as overlap between these groups cannot be excluded.

As part of the initial diagnostic workup, we performed bone marrow aspiration in 67% of the children. In most cases, the bone marrow

was normocellular, with an adequate reserve of mature neutrophils, and no pattern specifically associated with AIN or CIN was observed. It is well established that bone marrow findings are not diagnostic for AIN. The marrow may be hypercellular or normocellular with myeloid hyperplasia, but it can also appear completely normal. In clinically severe cases, evidence of maturation arrest may be observed (20). Prior to the European guidelines, there was often uncertainty about whether a bone marrow evaluation was necessary. Currently, bone marrow examination is reserved for second-line assessment. Bone marrow aspiration with morphology, flow cytometry, and cytogenetics should be performed in pediatric patients with severe or moderate chronic neutropenia, except in primary AIN with positive antineutrophil antibodies or drug-induced neutropenia; in suspected AIN with negative antibody tests accompanied by recurrent infections; and before the initiation of G-CSF therapy (1).

Congenital neutropenia is a rare cause of isolated neutropenia and is typically associated with impaired production and/or release of neutrophils from the bone marrow. It may occur as an isolated defect or in combination with extra-hematologic manifestations or underlying immunodeficiency/immune dysregulation (1, 21). Many germline forms carry an increased predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Clinically, congenital neutropenia often presents with severe, recurrent bacterial infections beginning in early infancy (4, 22, 23). Genetic testing is essential to confirm the diagnosis, assess the risk for MDS/AML, and provide appropriate genetic counseling to the family (1).

In our study, genetic testing was performed in a limited number of patients (n=7) and was restricted to *ELANE* and *HAX1* genes because broader genetic panels were not available at the time, which may have led to underdiagnosis of congenital neutropenia. Current European guidelines recommend comprehensive genetic testing, including NGS panels, particularly when second-level investigations are inconclusive. Furthermore, in young children with a family history of severe neutropenia, typical congenital anomalies, or recurrent severe infections, genetic testing should be expedited and performed after first-level investigations (1). However, the likelihood of a substantial number of undiagnosed congenital cases in our cohort is low, given that 83% of children achieved spontaneous remission during follow-up.

We identified one patient with a genetic syndrome associated with a *MAGEL2* variant and neutropenia present from the age of one month. *MAGEL2* variants have not been reported to be associated with neutropenia; therefore, a causal relationship cannot be established in this case. This finding nonetheless highlights the importance of broad genetic evaluation in patients with suspected congenital neutropenia, particularly when clinical features suggest an underlying syndromic condition.

In terms of clinical course, 31% of cases with chronic neutropenia experienced rehospitalizations, and only 21% required antibiotic therapy. Since these children were under regular clinical supervision and instructed to contact their hematologist for any episode of fever, it is unlikely that febrile events or infections were unrecorded. Short G-CSF therapy was administered in 23% of the cases. None of the children received prophylactic antibiotics or prolonged G-CSF treatment. This observation of a mild clinical course in pediatric AIN/CIN is consistent with previous reports, which similarly described severe infections as uncommon (13, 16, 18). The low incidence of serious infections in these children may be explained by their preserved bone marrow reserves. During a median follow-up of 21 months, 83% of the patients in the present study achieved spontaneous remission, with a median time to remission of 13.5 months. Patients with a lower ANC at diagnosis experienced a longer time to remission than those with a higher ANC.

Our study has several limitations. First, the relatively small sample size limits the statistical power and restricts the ability to detect smaller differences between subgroups. Second, the retrospective design carries the risk of both selection bias and information bias, as the data were dependent on

the completeness and accuracy of medical records. Furthermore, outpatient cases were excluded due to highly heterogeneous approaches in primary care, lack of structured follow-up, and absence of essential clinical data; this may have introduced additional selection bias and limited the external validity and generalizability of our findings. As a result, most analyses are descriptive, and caution is warranted when extrapolating these findings to larger populations. Therefore, comparisons with published studies were used to provide context and highlight trends without overinterpretation. Despite these limitations, our findings underscore the need for standardized guidelines for children with chronic neutropenia. A national study is currently underway to compare clinical practice before and after the publication and broader implementation of consensus-based European guidelines.

## Conclusion

Chronic isolated neutropenia in children, including AIN and CIN, generally follows a mild clinical course, with severe infections being uncommon. Most children achieve spontaneous remission within 13.5 months. Lower ANC at diagnosis is associated with more frequent rehospitalizations, longer time to remission, and longer follow-up. The recent European guidelines provide standardized recommendations for the diagnosis and management of pediatric neutropenia, helping to harmonize care and reduce variability in clinical practice.

**What is Already Known on This Topic:**

*Chronic isolated neutropenia typically presents during early childhood. Severe infections are uncommon due to preserved bone marrow reserves, and most children achieve spontaneous remission within 1–2 years. Congenital forms of isolated neutropenia can be associated with syndromes and an increased risk of hematologic malignancies. Until the recent European guidelines, clinical approaches to children with neutropenia were heterogeneous and often guided by individual physician experience.*

**What This Study Adds:**

*This is a rare study on pediatric chronic neutropenia that provides a direct comparison of AIN and CIN. It showed similar age at presentation, ANC at diagnosis, and time to remission between the two groups, while a lower ANC predicted more frequent rehospitalizations, longer time to remission, and longer follow-up. The study highlights the importance of the European guidelines in standardizing the diagnosis, follow-up, and management of children with neutropenia.*

**Authors' Contributions**: Conception and design: JR; Acquisition, analysis and interpretation of data: MA, AĐ, and SŠ; Drafting the article: JR and AĐ; Revising it critically for important intellectual content: JR and SŠ; Approved final version of the manuscript: JR, MA, AĐ, and SŠ.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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## Supplementary Material

Supplementary Table 1. Correlations Between Age at Diagnosis, Absolute Neutrophil Count at Diagnosis, Time to Remission, and Follow-up Duration

| Variable | Age | ANC | Time to remission | Follow-up duration |
|---|---|---|---|---|
| Age | 1.000 | $r_s$=0.091<br>P=0.539 | $r_s$=0.171<br>P=0.290 | $r_s$=0.139<br>P=0.346 |
| ANC | - | 1.000 | $r_s$=-0,112<br>P=0.492 | $r_s$=-0.395**<br>P=0.005 |
| Time to remission | - | - | 1,000 | $r_s$=0.550***<br>P<0.001 |
| Follow-up duration | - | - | - | 1.000 |

ANC=Absolute neutrophil count; $r_s$ =Spearman's correlation coefficient; P=Statistical significance (*P<0.05; ** P<0.01; ***P<0.001).

Supplementary Table 2. Differences in Absolute Neutrophil Count Between Groups According to Rehospitalization

| Variable | Rehospitalization | N | C (25-75) | Test | P |
|---|---|---|---|---|---|
| ANC | No | 27 | 700 (280-1250) | 171.500 | 0.020* |
| | Yes | 21 | 348 (98.5-630) | | |

ANC=Absolute neutrophil count; N=Number; C (25–75)=Median (25th–75th percentile); Mann-Whitney U test; P=Statistical significance (*P<0.05; **P<0.01;***P<0.001).