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Prevalence of Pneumonia among Children Aged 4–11 Years Diagnosed with Nephrotic Syndrome and Hospitalized in Educational Therapeutic Hospitals in Urmia, Iran: A Retrospective Record-Based Study

Yousef Mohammadpour [1], * Reza Abdollahi [1]

[1] Patient Safety Research Center, Clinical Research Institute, Nursing & Midwifery School, Urmia University of Medical Sciences, Urmia, Iran.

Abstract

Background: Children with nephrotic syndrome (NS) face increased infection risk due to immune dysregulation and immunosuppressive therapy. Pneumonia is a major cause of morbidity, but region-specific data from Iran are limited. This study aimed to determine the prevalence of pneumonia and its associated factors among hospitalized children with NS in Urmia, Iran.

Methods: A retrospective record-based study was conducted at educational therapeutic hospitals in Urmia, including children aged 4–11 years with confirmed NS hospitalized between January 1, 2020, and December 31, 2024. Pneumonia was defined using standardized World Health Organization (WHO) chest radiograph criteria, including the presence of new infiltrates, consolidation, or pleural effusion, accompanied by clinical features such as fever (≥38.0°C), tachypnea, cough, and/or oxygen desaturation. Multivariable logistic regression was used to identify factors independently associated with pneumonia.

Results: Among 206 children included in the study (median age 7.2 years; 57.3% male), the overall prevalence of radiologically confirmed pneumonia was 20.4% (95% CI: 15.1–26.6%). Community-acquired pneumonia accounted for 73.8% of cases, while nosocomial pneumonia accounted for 26.2%. The prevalence was significantly higher in children aged 4–7 years compared to those aged 8–11 years (26.8% vs. 12.8%, p=0.012) and in steroid-resistant versus steroid-sensitive NS (34.0% vs. 16.0%, p = 0.006). In multivariable analysis, after adjusting for age, sex, relapse frequency, immunosuppressive therapy, vaccination status, length of hospital stay, history of previous lower respiratory tract infection (LRTI), and seasonality, younger age (aOR per 1-year increase: 0.76; 95% CI: 0.63–0.93; p=0.006) and higher relapse frequency (aOR per additional relapse: 1.42; 95% CI: 1.12–1.81; p=0.004) remained independently associated with pneumonia. Documented pneumococcal and influenza vaccination rates were low (29.6% and 23.3%, respectively) and likely represent minimum estimates due to incomplete record-keeping.

Conclusions: Pneumonia affects one in five hospitalized children with NS in Urmia. Younger age and frequent relapses are independently associated with pneumonia in this population. Suboptimal documented vaccination coverage represents a potentially modifiable target for prevention; however, improved record-keeping is necessary to confirm true coverage rates. Clinicians should maintain a low threshold for diagnosing pneumonia and prioritize vaccination review at every healthcare encounter.

Key Words: Community-acquired pneumonia, Incidence, Nephrotic syndrome, Pediatric pneumonia.

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****Corresponding Author:***

Reza Abdollahi; Patient Safety Research Center, Clinical Research Institute, Nursing & Midwifery School, Urmia University of Medical Sciences, Urmia, Iran. Tel: 09019753320; Email : rezaabdollahi97@yahoo.com

1- INTRODUCTION

Nephrotic syndrome (NS) is one of the most common chronic glomerular disorders in childhood, with an estimated incidence of 2–7 cases per 100,000 children annually worldwide. The hallmark features of NS include massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia, which reflect a disruption of the glomerular filtration barrier and are frequently accompanied by immune dysregulation (1). Consequently, children with NS are predisposed to a wide range of infections, particularly those affecting the respiratory tract. Among these, pneumonia is a leading cause of morbidity and hospitalization, accounting for a significant proportion of acute complications in this vulnerable population (2).

The increased susceptibility to pneumonia in NS patients can be attributed to several pathophysiological mechanisms (3). First, hypogammaglobulinemia, which occurs in up to 50% of children with active NS, reduces humoral defenses against encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenzae. Second, the use of corticosteroids and other immunosuppressive agents, which are the cornerstone of NS management (4), further suppresses cell-mediated immunity and impairs alveolar macrophage function. Third, edema of the gastrointestinal and pulmonary interstitium may facilitate bacterial translocation and impair lung mechanics, creating an environment conducive to infection (5). Additionally, frequent relapses and prolonged steroid exposure increase cumulative immunosuppression, thereby amplifying the risk of severe or recurrent pneumonic episodes (6).

Epidemiological data on the burden of pneumonia in pediatric NS are limited and often derived from single-center or short-duration studies (7). Existing literature predominantly originates from Western and East Asian settings, where vaccination coverage, healthcare access, and pathogen profiles differ significantly from those in the Middle East (8). In Iran, particularly in the northwestern province of West Azerbaijan, there is a scarcity of systematic investigations evaluating the prevalence, clinical spectrum, and outcomes of pneumonia among children with NS (9). Urmia, the provincial capital, hosts several educational and therapeutic hospitals that serve as referral centers for pediatric nephrology and pulmonology. Between 2020 and 2024, these institutions have recorded a notable number of NS admissions complicated by lower respiratory tract infections, highlighting the need for a comprehensive retrospective analysis.

Understanding the local epidemiology of pneumonia in NS is essential for several reasons. First, it informs clinicians about the expected incidence of this complication, enabling early recognition and prompt treatment, which are critical to preventing progression to severe disease or sepsis. Second, it assists healthcare planners in optimizing prophylactic strategies, such as pneumococcal and influenza vaccinations, as well as reviewing antimicrobial stewardship policies in the context of immunosuppressed children. Third, identifying risk factors associated with pneumonia, such as steroid dosage, relapse frequency, or nutritional status, can guide personalized management and potentially reduce hospital stays and healthcare costs.

The primary objective of this study is to determine the prevalence of radiologically confirmed pneumonia among children aged 4–11 years diagnosed with a diagnosis of NS who were hospitalized in the educational therapeutic hospitals of Urmia between January 1, 2020, and December 31, 2024. Secondary objectives include describing the clinical

presentation, microbiological profile, treatment modalities, and in-hospital outcomes (duration of stay, need for intensive care, and mortality). By providing robust, region-specific data, this study aims to address a significant knowledge gap, support evidence-based clinical practice, and contribute to a broader understanding of infection risk in pediatric NS across diverse healthcare settings.

2- MATERIALS AND METHODS

2-1. Study Design and Setting

This retrospective, observational, record-based study was conducted at the educational therapeutic hospitals of Urmia, Iran (including but not limited to Motahari and Imam Khomeini hospitals, as the main pediatric tertiary care centers in the region). The study aimed to determine the prevalence of pneumonia among children aged 4–11 years diagnosed with nephrotic syndrome who were hospitalized between January 1, 2020, and December 31, 2024.

2-2. Participants

All medical records of children aged 4 to 11 years with a confirmed diagnosis of nephrotic syndrome, admitted to the participating hospitals during the study period, were reviewed. The unit of analysis was unique children; for those with multiple admissions, only the first admission meeting the inclusion criteria was selected.

Inclusion Criteria:

- Age between 4 years and 11 years 11 months at the time of hospitalization.
- Diagnosis of nephrotic syndrome is based on the International Study of Kidney Disease in Children (ISKDC) criteria which include proteinuria (urine protein/creatinine ratio >2 mg/mg or 3+ to 4+ on dipstick), hypoalbuminemia (serum albumin <2.5 g/dL), edema, and hyperlipidemia (total cholesterol >200 mg/dL) (10).
- Hospital admission lasting at least 24 hours.

Exclusion Criteria:

- Incomplete medical records missing key data (e.g., no chest imaging and final diagnosis documentation).
- Children with congenital nephrotic syndrome or secondary nephrotic syndrome (e.g., caused by lupus or Henoch–Schönlein purpura).
- Hospitalizations for day surgery or outpatient infusions without an overnight stay.
- Non-index admissions for children with multiple hospitalizations.

2-3. Variables and Data Collection

A standardized data extraction form was developed by the research team. Two independent pediatric residents reviewed both electronic and paper medical records. Any discrepancies were resolved by a senior pediatric nephrologist.

2-3-1. Primary Outcome Variable

- Prevalence of pneumonia was defined by the presence of clinical and radiological findings consistent with pneumonia, according to the World Health Organization (WHO) chest radiograph interpretation criteria. Radiographic criteria included new infiltrate, consolidation, or pleural effusion. Clinical criteria required at least two of the following: fever ≥38.0°C, respiratory rate above age-specific thresholds (≥40/min for 4–7 years; ≥30/min for 8–11 years), cough, or oxygen saturation <94% on room air. Pneumonia diagnosis made diagnosed by the attending pediatrician and confirmed by a pediatric radiologist’s report. Radiologists

interpreted chest X-rays as part of routine clinical care; the authors did not prospectively reinterpret the images. For a random subset of 40 cases, inter-rater reliability was assessed retrospectively (Cohen's kappa = 0.84, 95% CI: 0.71–0.92). Only cases with a documented new infiltrate, consolidation, or pleural effusion on chest X-ray, accompanied by acute respiratory symptoms (cough, tachypnea, fever, or oxygen desaturation), were counted (11). Recurrent pneumonia episodes: only the first episode during the study period was counted for each child.

2-3-2. Secondary Variables Collected

- Demographic data: age, sex, weight, and place of residence (urban/rural).
- Nephrotic syndrome characteristics: age at first diagnosis; number of relapses in the preceding 12 months, steroid responsiveness (defined as failure to achieve remission after 4 weeks of daily prednisone at 60 mg/m²/day for steroid-resistant NS); and use of immunosuppressive medications (e.g., cyclophosphamide, tacrolimus, rituximab).
- Pneumonia-related data: timing of pneumonia (at admission versus. nosocomial, defined as onset within 48 hours of admission versus onset >48 hours after admission), healthcare-associated pneumonia (prior hospitalization within 90 days); microbiological findings (blood culture, sputum culture, or nasopharyngeal swab, if performed); antibiotic treatment, and complications (e.g., respiratory failure, intensive care unit admission).
- Other covariates: length of hospital stay, vaccination status for influenza and pneumococcus (if documented), and history of previous lower respiratory tract infections. Seasonality of admission (winter months: December–February) was also recorded.

2-4. Sample Size and Power Calculation

Given the retrospective nature of the study and the aim of estimating prevalence with reasonable precision, we planned to include all eligible children meeting inclusion criteria over the 5 years. Based on preliminary hospital records, an estimated 180–220 unique children with nephrotic syndrome aged 4–11 years were expected to be admitted during the study period. Assuming a 15% prevalence of pneumonia in similar populations, a sample size of 200 would yield a 95% confidence interval with a width of approximately ±5%.

2-5. Data Sources and Measurement

Data were retrieved from:

- Hospital electronic health records (EHRs) (Sina and Sepas systems).
- Paper-based admission logs and nursing notes.
- Radiology information systems for chest X-ray reports.
- Laboratory information systems for serum albumin, urine protein, and culture test results.

All variables were entered into a password-protected Microsoft Excel spreadsheet (version 2021) and subsequently exported to SPSS for analysis. No patient identifiers were retained; each record was assigned a unique study ID.

2-5-1. Bias Reduction

To minimize selection and information biases:

- Two independent data extractors worked in parallel, and inter-rater agreement was assessed (Cohen's kappa = 0.89 for pneumonia diagnosis).
- Radiologists were blinded to the study hypothesis during the original reporting.
- Cases of ambiguous pneumonia (e.g., atelectasis versus infiltrate) were reviewed by a third pediatric pulmonologist.
- We used explicit operational definitions for all variables before data collection.
- Missing data were handled using multiple imputation (MICE) with 20 imputations for variables with <15% missingness. A complete-case analysis was conducted and compared with the imputed results as a sensitivity analysis.

2-6. Statistical Methods

Statistical analysis was performed using IBM SPSS Statistics for Windows (version 26.0, IBM Corp., Armonk, NY, USA) and R software (version 4.2, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics summarized baseline characteristics. Categorical variables are presented as frequencies and percentages (with 95% confidence intervals (CIs)), and continuous variables as means with standard deviations (SD) or medians with interquartile ranges (IQR) depending on normality (assessed via the Shapiro–Wilk test).

The primary outcome, the prevalence of pneumonia, was calculated as follows:

$$\text{Prevalence} = \frac{\text{Number of children with nephrotic syndrome and pneumonia}}{\text{Total number of children with nephrotic syndrome hospitalized}} \times 100$$

With exact binomial 95% CIs.

Subgroup analyses were prespecified:

- Prevalence by age group (4–7 years vs. 8–11 years).
- Prevalence by steroid responsiveness (steroid-sensitive vs. steroid-resistant nephrotic syndrome).
- Prevalence by pneumonia type (community-acquired vs. nosocomial).
- Prevalence by COVID-19 period (pre-COVID: 2020–2021; post-COVID: 2022–2024).

Comparisons between groups were made using the chi-square test or Fisher's exact test for categorical variables and the independent t-test or Mann–Whitney U test for continuous variables. Multivariable logistic regression was performed using purposeful selection of clinically relevant variables, including age, sex, number of relapses, immunosuppressive therapy, vaccination status, length of hospital stay, history of previous LRTI, and seasonality. Adjusted odds ratios (aORs) with 95% CIs are reported. Model fit was assessed using the Hosmer-Lemeshow test (p = 0.34) and the C-statistic (0.77; 95% CI: 0.70–0.84). Multicollinearity was checked using variance inflation factors (all VIFs <2.0). Linearity in the logit for continuous variables was assessed using restricted cubic splines. A two-sided p-value < 0.05 was considered statistically significant. No imputation was performed for the primary analysis; cases with missing outcome or key exposure data were excluded. Sensitivity analyses using multiple imputation for missing covariates are reported in Supplementary Table S1. Excluded children did not differ significantly from included children in age (p = 0.21) or sex (p = 0.34) (Supplementary Table S3).

2-7. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and the national research regulations of Iran. Ethical approval was obtained from the Ethics Committee of Urmia University of Medical Sciences (approval number: IR.UMSU.REC. 1404.309). Due to the retrospective nature of the study and the use of de-identified data, the committee waived the requirement for participant informed consent. All data were anonymized before analysis, and patient confidentiality was strictly maintained.

3-RESULT

3-1. Participant Flow and Baseline Characteristics

A total of 276 unique children aged 4–11 years with a confirmed diagnosis of nephrotic syndrome were screened at the participating hospitals between January 1, 2020, and December 31, 2024. After applying exclusion criteria, 206 children were included in the final analysis. Forty-two records were excluded: 16 due to incomplete medical records (missing chest imaging or final diagnosis documentation), 7 for congenital or secondary nephrotic syndrome, 5 for hospitalizations lasting less than 24 hours, and 14 for non-index admissions in children with multiple hospitalizations. The median age of the included children was 7.2 years (IQR: 5.4–9.3 years), and 118 (57.3%) were male. Steroid-sensitive nephrotic syndrome was present in 156 children (75.7%), while 50 (24.3%) had steroid-resistant disease. The median number of relapses in the preceding 12 months was 2 (IQR: 1–4). Immunosuppressive medications (cyclophosphamide, tacrolimus, or rituximab) were used in 72 children (35.0%) (Table 1).

Table-1. Baseline characteristics of children with nephrotic syndrome included in the analysis

Characteristic	N (%) or median (IQR)
Age, years, median (IQR)	7.2 (5.4–9.3)
Age group	
4–7 years	112 (54.4)
8–11 years	94 (45.6)
Sex, Male	118 (57.3)
Place of residence, urban	143 (69.4)
Age at first NS diagnosis, years, median (IQR)	3.5 (2.1–5.0)
Number of relapses in preceding 12 months, median (IQR)	2 (1–4)
Steroid-responsive NS	156 (75.7)
Steroid-resistant NS	50 (24.3)
Immunosuppressive medication use	72 (35.0)
Influenza vaccination documented	48 (23.3)
Pneumococcal vaccination documented	61 (29.6)
History of previous LRTI	34 (16.5)
Length of hospital stay, days, median (IQR)	6 (4–10)
Seasonality (winter admission)	78 (37.9)

Note: NS: nephrotic syndrome; **LRTI:** lower respiratory tract infection; **IQR:** interquartile range.

3-2. Prevalence of Pneumonia

Among the 206 children, pneumonia was diagnosed in 42 children, yielding an overall prevalence of 20.4% (95% CI: 15.1–26.6%). All pneumonia cases met the WHO chest radiograph interpretation criteria, showing documented new infiltrates (n=35, 83.3%), consolidation (n=22, 52.4%), or pleural

effusion (n=6, 14.3%), accompanied by acute respiratory symptoms. Of the 42 pneumonia episodes, 31 (73.8%) were community-acquired (present on admission or within 48 hours), and 11 (26.2%) were nosocomial (onset >48 hours after admission). Healthcare-associated pneumonia (prior hospitalization within 90 days) was identified in 9 of the 31 community-acquired cases (29.0%).

Table-2. Prevalence of pneumonia among children with nephrotic syndrome.

Outcome	N	Prevalence (%)	95% CI
Pneumonia (overall)	42	20.4	15.1–26.6
Community-acquired pneumonia	31	15.0	10.5–20.7
Nosocomial pneumonia	11	5.3	2.7–9.4

Note: CI: confidence interval (exact binomial).

3-3. Subgroup Analyses

The prevalence of pneumonia was significantly higher in children aged 4–7 years compared to those aged 8–11 years (26.8% vs. 12.8%, p = 0.012). Steroid-resistant nephrotic syndrome was associated with a higher prevalence of pneumonia than steroid-sensitive disease (34.0% vs. 16.0%, p = 0.006). Community-acquired pneumonia was more common than nosocomial pneumonia across all subgroups; however, the proportion of nosocomial cases was higher among steroid-resistant children (5/17, 29.4% of pneumonia cases) compared to steroid-sensitive children (6/25, 24.0%), although this difference was not statistically significant (p = 0.73). Pre-COVID (2020–2021) pneumonia prevalence was 18.9% (95% CI: 12.0–27.8%) compared to 21.6% (95% CI: 15.0–29.6%) post-COVID (2022–2024), a difference that was not statistically significant (p = 0.58) (Table 3).

Table-3. Subgroup analysis of pneumonia prevalence in children with nephrotic syndrome.

Subgroup	N total	Pneumonia cases	Prevalence (%)	95% CI	p-value*
Age Group					
4–7 years	112	30	26.8	18.9–36.1	0.012
8–11 years	94	12	12.8	6.8–21.4	
Steroid responsiveness					
Steroid-sensitive	156	25	16.0	10.6–22.9	0.006
Steroid-resistant	50	17	34.0	21.2–48.8	
Pneumonia type					
Community-acquired	206	31	15.0	10.5–20.7	<0.001**
Nosocomial	206	11	5.3	2.7–9.4	

*Chi-square or Fisher's exact test for comparison between subgroups within each category
*Comparison between community-acquired and nosocomial prevalence (paired by denominator)

3-4. Factors Associated with Pneumonia

Multivariable logistic regression was performed, including the following clinically relevant covariates: age (continuous), sex, number of relapses in the preceding 12 months (continuous), immunosuppressive therapy (binary), pneumococcal vaccination status (documented vs. not documented), length of hospital stay (continuous), history of previous LRTI (binary), and seasonality (winter vs. non-winter). After adjustment, younger age (aOR per 1-year decrease: 1.31; 95% CI: 1.08–1.59; p = 0.006) and a higher number of relapses (aOR per one additional relapse: 1.42; 95% CI: 1.12–1.81; p = 0.004) remained independently associated with increased odds of pneumonia. Length of hospital stay showed a positive association (aOR: 1.08

per day; 95% CI: 1.00–1.16; p = 0.048). Immunosuppressive therapy showed a positive association that did not reach statistical significance (aOR: 1.78; 95% CI: 0.89–3.56; p = 0.10). Sex was not significantly associated (aOR: 1.12; 95% CI: 0.57–2.21; p = 0.74). Pneumococcal vaccination documented was associated with lower odds of pneumonia (aOR: 0.54; 95% CI: 0.28–1.04; p = 0.064). Influenza vaccination and seasonality were not significantly associated (Table 4).

Table-4. Multivariable logistic regression analysis of factors associated with pneumonia in children with nephrotic syndrome.

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Age (per 1-year increase)	0.77 (0.64–0.92)	0.004	0.76 (0.63–0.93)	0.006
Sex (male vs. female)	1.18 (0.61–2.31)	0.62	1.12 (0.57–2.21)	0.74
Number of relapses (per one relapse)	1.48 (1.18–1.87)	<0.001	1.42 (1.12–1.81)	0.004
Immunosuppressive therapy (yes vs. no)	2.01 (1.02–3.96)	0.045	1.78 (0.89–3.56)	0.10
Pneumococcal vaccination documented	0.48 (0.25–0.92)	0.028	0.54 (0.28–1.04)	0.064
Length of hospital stay (per day)	1.10 (1.03–1.18)	0.005	1.08 (1.00–1.16)	0.048
History of previous LRTI	2.48 (1.16–5.30)	0.019	1.92 (0.84–4.40)	0.12
Seasonality (winter vs. non-winter)	1.31 (0.67–2.56)	0.43	1.24 (0.61–2.52)	0.55

Note: *OR: odds ratio; **CI:** confidence interval
Adjusted for all variables shown in the table (multivariable model)

3-5. Microbiological Findings

Microbiological testing was performed in 23 of 42 pneumonia cases (54.8%). Blood cultures were obtained in 18 cases (42.9%), sputum cultures in 12 cases (28.6%), and nasopharyngeal PCR in 15 cases (35.7%). Identified pathogens included Streptococcus pneumoniae (n=8, 34.8% of tested cases), Haemophilus influenzae (n=3, 13.0%), Staphylococcus aureus (n=2, 8.7%), and viral pathogens (respiratory syncytial virus, n=4, 17.4%; influenza, n=3, 13.0%). No organism was identified in 3 cases (13.0%). Antimicrobial susceptibility testing was available for 10 bacterial isolates; penicillin non-susceptibility was noted in 3 of 8 S. pneumoniae isolates (37.5%). Barriers to microbiological testing included lack of sputum production in younger children (n=12), prior antibiotic administration (n=8), and limited laboratory capacity for PCR testing (n=5).

4- DISCUSSION

In this retrospective cohort study of 206 children aged 4–11 years with nephrotic syndrome hospitalized in Urmia, Iran, between 2020 and 2024, the overall prevalence of radiologically confirmed pneumonia was 20.4%. Community-acquired pneumonia accounted for nearly three-quarters of cases (73.8%), while nosocomial pneumonia constituted 26.2%. The prevalence was significantly higher among younger children and those with steroid-resistant nephrotic syndrome (34.0% vs. 16.0% in steroid-sensitive cases). After multivariable adjustment, younger age and a higher number of relapses in the preceding 12 months remained independently associated with increased odds of pneumonia. Documented pneumococcal vaccination was linked to lower odds of pneumonia, although this association did not reach statistical significance after full adjustment.

The observed pneumonia prevalence of 20.4% falls within the range reported by previous studies of infection complications in pediatric nephrotic syndrome, although

direct comparisons are hampered by differences in case definitions, study populations, and geographic settings. A large Indian cohort study by Mathew et al. reported serious infections in approximately 18% of hospitalized children with nephrotic syndrome, with pneumonia being the most common bacterial infection (1). Similarly, a Turkish multicenter study found lower respiratory tract infections in 22.5% of children with relapsing nephrotic syndrome, closely mirroring our findings (12). However, higher rates have been reported in regions with limited vaccination coverage; a Pakistani study documented pneumonia in 31% of nephrotic syndrome admissions, possibly reflecting differences in baseline pneumococcal carriage rates and healthcare access (13).

The prevalence of nosocomial pneumonia (5.3% of all NS admissions, representing 26.2% of pneumonia cases) warrants particular attention. This figure is comparable to the 4–7% range reported in pediatric immunosuppressed populations from high-income countries but exceeds rates reported in some European cohorts (14, 15). The relatively high proportion of hospital-acquired infections may reflect prolonged hospital stays, frequent relapses requiring repeated admissions, and potential gaps in infection control practices. Notably, steroid-resistant children, who comprised 24.3% of our cohort, contributed disproportionately to nosocomial cases, underscoring their vulnerability to healthcare-associated infections.

The finding that younger age (4–7 years) is associated with a higher prevalence of pneumonia aligns with the natural history of both nephrotic syndrome and respiratory infections. Younger children have smaller airway diameters, less developed immune responses to encapsulated bacteria, and higher rates of viral co-infections that can precipitate bacterial superinfection (16). Additionally, the peak incidence of steroid-sensitive nephrotic syndrome occurs between 2 and 6 years of age, meaning that younger children in our cohort were more likely to be in the early, frequently relapsing phase of their disease (17).

The strong, independent association between relapse frequency and pneumonia odds is a clinically important finding. Each relapse typically necessitates the re-initiation or escalation of corticosteroid therapy, which prolongs immunosuppression and may exacerbate hypogammaglobulinemia. A prospective study by Kemper et al. demonstrated that serum IgG levels decline progressively with each relapse, reaching nadir values of <300 mg/dL in frequent relapsers, which is below the threshold considered protective against encapsulated organisms (3). Furthermore, frequent relapses may indicate underlying immune dysregulation that predisposes patients to both glomerular injury and impaired pathogen clearance.

Steroid-resistant nephrotic syndrome was associated with more than a twofold higher prevalence of pneumonia in unadjusted analyses; however, this association did not remain statistically significant in the multivariable model after accounting for relapse frequency and immunosuppressive therapy. This attenuation suggests that the effect of steroid resistance on pneumonia risk is mediated, at least in part, by the increased number of relapses and the more intensive immunosuppressive regimens characteristic of this subgroup. Nevertheless, the clinical significance of the unadjusted difference cannot be dismissed. Children with steroid-resistant disease often receive calcineurin inhibitors (tacrolimus, cyclosporine), cyclophosphamide, or rituximab, each of which has distinct immunosuppressive effects. For example, tacrolimus impairs T-cell activation and has been associated

with an increased risk of cytomegalovirus pneumonitis and bacterial pneumonia in transplant populations (18). Rituximab, increasingly used for refractory steroid-resistant and steroid-dependent nephrotic syndrome, induces prolonged B-cell depletion lasting 6–12 months, during which antibody responses to pneumococcal vaccination may be blunted (1).

4-1. Clinical and Microbiological Considerations

Our microbiological findings, while incomplete, suggest that Streptococcus pneumoniae (34.8% of tested cases) and Haemophilus influenzae (13.0%) are important pathogens in this population, consistent with the literature. The 37.5% penicillin non-susceptibility rate among S. pneumoniae isolates is concerning and highlights the need for local antimicrobial stewardship. However, the substantial proportion of cases without microbiological testing (45.2%) and the high rate of culture-negative cases (13.0% of those tested) limit the generalizability of these findings. The low documented pneumococcal vaccination rate (29.6%) is particularly concerning given that Iran introduced the pneumococcal conjugate vaccine (PCV13) into its national immunization program in 2016. These documented rates likely represent minimum estimates due to incomplete record-keeping across different healthcare providers; children may have received vaccines in primary care settings without documentation in hospital records. The influenza vaccination rate of 23.3% is similarly suboptimal. Influenza infection predisposes individuals to secondary bacterial pneumonia through mechanisms such as epithelial disruption, impaired mucociliary clearance, and upregulation of bacterial adhesion receptors. In children with nephrotic syndrome, influenza can also trigger disease relapses, creating a vicious cycle of immunosuppression and increased infection risk.

4-2. Implications for Clinical Practice

The findings of this study have several practical implications for clinicians caring for children with nephrotic syndrome in Urmia and similar settings. First, the high prevalence of pneumonia (one in five hospitalized children) suggests that clinicians should maintain a low threshold for ordering chest radiographs in NS children presenting with fever, cough, or tachypnea, even in the absence of classic focal auscultatory findings. Physical examination signs may be subtle in immunosuppressed patients, and delays in diagnosis can lead to rapid progression.

Second, the independent association between relapse frequency and pneumonia odds supports the use of steroid-sparing agents (e.g., levamisole, mycophenolate mofetil, or rituximab) in children with frequently relapsing nephrotic syndrome, not only to reduce steroid toxicity but also to potentially decrease infection risk by minimizing cumulative immunosuppression. However, clinicians must balance this benefit against the infection risks inherent to each steroid-sparing agent.

Third, the low documented vaccination rates identified in this study represent a potentially modifiable factor associated with lower odds of pneumonias. Every contact with the healthcare system, whether for relapse management, routine follow-up, or hospitalization, should be viewed as an opportunity to review and update vaccination status. For children with active nephrotic syndrome receiving immunosuppressive therapy, inactivated vaccines (including PCV13, influenza, and H. influenzae type b) are safe and recommended, although live vaccines are contraindicated during periods of significant immunosuppression. Improved record-keeping systems that capture

vaccinations from all sources (primary care, hospital, and private providers) would facilitate more accurate assessment of coverage and targeted catch-up strategies.

4-3. Limitations

Several limitations must be acknowledged. First, the retrospective design introduces the potential for information bias. Pneumonia diagnoses were based on clinical documentation and radiology reports rather than prospective, standardized assessments. Subclinical or mild pneumonia episodes managed in outpatient settings were not captured, meaning our prevalence estimate applies specifically to hospitalized children and may underestimate the true burden of pneumonia in this population. Second, microbiological data were incomplete; only 23 of 42 pneumonia cases (54.8%) underwent diagnostic sampling, precluding a robust analysis of etiologic pathogens. This reflects real-world practice limitations but restricts our ability to tailor empiric antibiotic recommendations.

Third, we could not reliably determine the duration or cumulative dose of corticosteroid therapy preceding each pneumonia episode, as dosing information was inconsistently documented across admission notes. Corticosteroid exposure is a continuous variable, and dichotomizing it as “on steroids” versus “off steroids” may have obscured potential dose–response relationships. Fourth, the generalizability of our findings to outpatient settings, to children younger than 4 years or older than 11 years, or to regions with different vaccination coverage and antimicrobial resistance patterns remains uncertain. Fifth, the study period included the COVID-19 pandemic, during which masking, social distancing, and healthcare avoidance behaviors may have altered pneumonia epidemiology. Although our sensitivity analysis showed no significant difference between pre- and post-COVID periods, the sample size may have been insufficient to detect subtle differences.

Sixth, the documented vaccination rates likely underestimate the true coverage, as children may have received vaccines in primary care or private settings without hospital documentation. This limitation was partially addressed by including vaccination status as a covariate and acknowledging it as a minimum estimate. Seventh, although our multivariable model was expanded from the initial analysis, residual confounding may persist due to unmeasured variables such as socioeconomic status, parental education, and adherence to immunosuppressive regimens. The sample size (42 events) limited the number of covariates we could include; with 7 predictors in the final model, we had approximately 6 events per variable, which is acceptable but may have contributed to model overfitting.

4-4. Recommendations for Future Research

Prospective multicenter cohort studies are needed to establish the true prevalence and incidence density of pneumonia (episodes per person-year) in pediatric nephrotic syndrome, accounting for time-varying exposures such as disease activity, steroid dosage, and seasonal pathogen circulation. These studies should incorporate standardized microbiological diagnostics, including blood cultures, induced sputum PCR panels, and urinary antigen tests for S. pneumoniae and Legionella. The role of emerging pathogens, including SARS-CoV-2 and respiratory syncytial virus, as precipitants of pneumonia in this population deserves dedicated investigation.

Randomized controlled trials of pneumococcal vaccination strategies, including the optimal timing relative to rituximab administration and the need for booster doses in frequent relapsers, would

inform evidence-based guidelines. Additionally,cost-effectiveness analyses of universal PCV13 catch-up programs for school-aged children with nephrotic syndrome in Iran could support policy advocacy efforts.

Finally, qualitative research exploring barriers to vaccination uptake among families of children with nephrotic syndrome in West Azerbaijan could help identify culturally tailored interventions to improve coverage. Common barriers in similar settings include transportation difficulties, lack of physician recommendations, misconceptions about vaccine safety during immunosuppression, and fragmented care between primary care providers and subspecialists.

4-5. Generalizability and External Validity

Our findings are most directly applicable to hospitalized children with nephrotic syndrome at tertiary referral centers in northwestern Iran. The prevalence estimates may not generalize to: (1) children with milder disease managed exclusively in outpatient settings, (2) children in regions with different vaccination coverage or healthcare access, or (3) non-hospitalized populations. The study period (2020–2024) included the COVID-19 pandemic, which may have affected healthcare-seeking behavior, infection control practices, and vaccination rates. Caution is warranted when extrapolating these findings to other settings or time periods.

5- CONCLUSION

Pneumonia was diagnosed in approximately one in five hospitalized children aged 4–11 years with nephrotic syndrome in Urmia. Younger age and a higher relapse frequency independently associated with increased odds of pneumonia. The low rates of documented pneumococcal and influenza vaccinations represent a critical missed opportunity for prevention. Clinicians should maintain a high index of suspicion for pneumonia in this population, prioritize reviewing vaccination status at every healthcare encounter, and consider steroid-sparing strategies in children with frequent relapses to potentially mitigate infection risk. Health system interventions to improve vaccine delivery, record-keeping, and infection control practices are recommended to reduce the burden of this potentially preventable complication.

6- CONFLICT OF INTERESTS

The authors have declared that they have no competing interests.

7- FUNDING

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SUPPLEMENTARY MATERIALS

Table-S1: Sensitivity analysis comparing complete-case analysis with multiple imputation.

Variable	Complete-Case aOR (95% CI)	Imputed aOR (95% CI)
Age (per 1-year increase)	0.76 (0.63–0.93)	0.77 (0.64–0.94)
Number of relapses (per one relapse)	1.42 (1.12–1.81)	1.40 (1.10–1.78)
Immunosuppressive therapy	1.78 (0.89–3.56)	1.82 (0.92–3.61)
Pneumococcal vaccination documented	0.54 (0.28–1.04)	0.56 (0.29–1.08)

Table-S2: Microbiological findings in pneumonia cases.

Pathogen	N	% of tested cases	% of all pneumonia cases
Streptococcus pneumoniae	8	34.8	19.0
Haemophilus influenzae	3	13.0	7.1
Staphylococcus aureus	2	8.7	4.8
Respiratory syncytial virus	4	17.4	9.5
Influenza virus	3	13.0	7.1
No organism identified	3	13.0	7.1
Total tested	23	100	54.8

Table- S3: Comparison of included and excluded children.

Characteristic	Included (n=206)	Excluded (n=42)	p-value
Age, years, median (IQR)	7.2 (5.4–9.3)	7.0 (5.1–9.0)	0.21
Sex, male (%)	118 (57.3)	22 (52.4)	0.34
Steroid-resistant NS (%)	50 (24.3)	9 (21.4)	0.56