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Harnessing Lymphocyte-Cytokine Networks to Disrupt Current Paradigms in Childhood Nephrotic Syndrome Management: A Systematic Evidence Synthesis

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Abstract

Background and Objectives: Pediatric nephrotic syndrome (NS) is characterized by immune dysregulation, with steroid resistance posing a significant therapeutic challenge. This systematic review examines the cytokine and lymphocyte profile in NS to support novel immunotherapies.

Method: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched PubMed, Scopus, and Web of Science (2014-2024) for studies on laboratory-measured serum immune mediators in children (<15 years old) with NS after undergoing steroid treatment. Studies that reported genetic polymorphisms were excluded from the review. Data regarding cytokines, lymphocytes, and immunoglobulins were reviewed and synthesized from 18 human studies.

Results and Limitations: There were elevated levels of pro-inflammatory cytokines (IL-1β, IL-2, IL-5, IL-6, IL-7, IL-8, IL-17A, IL-18, IL-23, TNF-α, IFN-γ) in active NS compared to the down-regulated anti-inflammatory cytokine, IL-10, and regulatory T cells (Treg). The Th17/Treg imbalance was prominent in the pathology of NS and a distinguishing feature of steroid-resistant nephrotic syndrome (SRNS). Results on IL-4 and IL-13 showed differing patterns. Limitations of this review are the human study focus which may exclude a more multifactorial cytokine network.

Conclusion: Targeting the Th17/Treg axis and pro-inflammatory cytokines in NS may represent a feasible adjunct or alternative to steroids, especially in SRNS, and would benefit from further clinical trials.

Key Words: Immunotherapy; Lymphocyte; Nephrotic syndrome; Pediatric.

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1- INTRODUCTION

Pediatric nephrotic syndrome (NS) is defined as having proteinuria, hypoalbuminemia, edema, and hyperlipidemia and has an incidence of 1.15–16.9 per 100,000 children with long-term adverse outcomes, including renal failure in some cases (1,2). Glucocorticoids are the most common treatment for NS and achieve substantial remission in many patients, generally within four weeks (3). Steroid-resistant nephrotic syndrome (SRNS) represents a clinical dilemma as inflammation continues despite immunosuppression, indicating a treatment gap (4). Therapies such as rituximab and some chemotherapy options show some efficacy, but many do not result in remission of NS, suggesting that existing therapies do not sufficiently address some of the underlying mechanisms of the disease (5, 6).

The presence of a circulating immune mediator attracts the attention of treatment (7, 8), NS is driven by a pronounced elevation of interleukinsIL-6, IL-18, and othersworking alongside CD4+ T lymphocytes to sustain chronic glomerular inflammation (9, 10). Emerging insights highlight altered interleukin receptor genes (such as IL-2), amplified JAK/STAT signaling, and disrupted IL-10 responses in podocytes as critical yet under addressed contributors (11, 12). Current treatments, constrained by their inability to fully counter these immune dynamics, underscore the demand for innovative strategies grounded in a deeper immune understanding.

The fragmented cytokine landscape in childhood NS motivated this systematic synthesis of a cohesive profile. This review delineates the cytokine framework of NS, advocating for a pivot toward precision immune-targeted therapies.

2- MATERIALS AND METHODS

2-1. Protocol and Registration

The systematic review was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Along the lines of methodological rigor and reducing bias, we adopted the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, which requires assessing all clinical studies on area of allocation concealment, blinding of participants and personnel, and outcome assessors. The question was framed according to PICO (Population, Intervention, Comparison, Outcomes), which narrowed the scope of the research. The work was prospectively registered with the Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42025640192 to promote transparency and reproducibility.

2-2. Eligibility Criteria and Search Strategy

A systematic review of articles published from January 2014 through January 2024 in the Web of Science, PubMed, and Scopus databases was carried out because of their extensive biomedical literature coverage. NS was defined following the National Institute of Diabetes and Digestive and Kidney Diseases (13), consistent with International Classification of Diseases 11th Revision (ICD-11: Code GB41), characterized by four diagnostic hallmarks:

- Proteinuria (excessive urinary protein)
- Hypoalbuminemia (low serum albumin)
- Edema (swelling of the body)
- Hyperlipidemia (high blood lipids)

This review is aimed at compiling data that will give an immunotherapy-based profile of the pediatric NS, in terms of cytokines, lymphocytes, chemokines, and inflammatory mediators. Rigorous inclusion criteria applied:

• Only English language original research articles were included; reviews, case reports, and editorials were excluded.

• Priority was given to studies that measured inflammatory mediators at the onset of NS, excluding studies with coexisting disorders.

• Studies that assessed genetic polymorphisms of inflammatory mediator-encoding genes to evaluate changes driven by NS immune were excluded.

• Studies measuring serum levels of immune components following steroid treatment were included to evaluate treatment effects.

Terms such as "nephrotic syndrome," "children, " "cytokines," and "lymphocytes" were optimized using the MeSH database. Two independent teams of two researchers conducted parallel searches, beginning with Web of Science, followed by PubMed and Scopus. PRISMA guidelines were followed to eliminate duplicates and non-English records, and titles and abstracts were screened collaboratively. Eligible articles were subjected to aggregation co-authored with subscription barriers solved under the first author's supervision. This process yielded a final collection of 18 studies with no further inclusions from manual citation searches. To put this in context, we cross-referenced our title in the Cochrane Database and found no systematic reviews that directly overlapped with it.

2-3. Data Extraction, Study Selection and Methodological Quality Assessment

The corresponding and first authors created a structured summary table and assessed study quality using the Cochrane Risk of Bias 2 (RoB 2) tool (14), which provided a robust appraisal of methodological quality. Data extraction was undertaken by three authors independently and without collusion. They extracted data on NS subtype, interleukin/cytokine profiles, immune changes, mean age/sex of the populations studied, and assessment methodologies/tools. The corresponding and first authors then synthesized the extracted data, consistently following Cochrane guidelines to minimize bias and maximize accuracy. Given some degree of heterogeneity present in the data-sets across the 18 studies, a standardized extraction tool/template was utilized, formulated and cross-verified by the authors, and we presented the outcomes with a PRISMA flow chart so that visual mapping of studies in the resultant synthesis would enhance transparency and report development alongside wider, concerted immunological efforts to understand immune-mediated conditions for a wider audience.

3- RESULTS

3-1. Study Selection

Initially, review articles, case reports, and letters to the editor identified in the PubMed, Scopus, and Web of Science databases during the preliminary search were excluded. Subsequently, a pair of authors eliminated duplicate titles and evaluated the abstracts of the remaining studies. Studies exploring genetic polymorphisms in NS, as well as those examining the influence of additional disorders alongside NS, were excluded following abstract screening. After filtering out non-English studies, 22 articles underwent full-text review by two authors independently, resulting in the selection of 18 studies that addressed our research question (15-32) (Figure 1).

To maintain impartiality, a double-blind review process was implemented by the two authors. They cross-checked the safety parameters extracted from the articles against the databases using the keyword “nephrotic syndrome.” Any studies potentially overlooked or erroneously excluded at various stages were re-

assessed. Ultimately, no additional studies required re-evaluation or inclusion.

Increased levels of pro-inflammatory interleukins and cytokines lead to kidney tissue damage

Levels of IL-7, IL-5, IL-1β, IL-2, IL-6, and IL-8 were increased in children with NS. This pattern was maintained in steroid-sensitive nephrotic syndrome (SSNS) compared to SRNS. Cytokines were higher during relapse than remission. One study denied a decrease in IL-8 in remission, but others agreed. Additionally, one study reported that there was no difference in levels of IL-2 in remission compared to SSNS, but its levels were increased in NS.

Higher levels of IL-18 were associated with higher levels of glomerulonephritis and renal tissue damage, which, with levamisole showing a higher induction of this cytokine, produced a relapse-free period of 3 months. Another study in NS children compared IL-18 with healthy children, which was significantly higher in the control group, and this was the only study with the opposite result. However, it confirmed that its levels were higher in steroid-sensitive children than in children resistant to these drugs, meaning that steroid resistance was associated with its reduction.

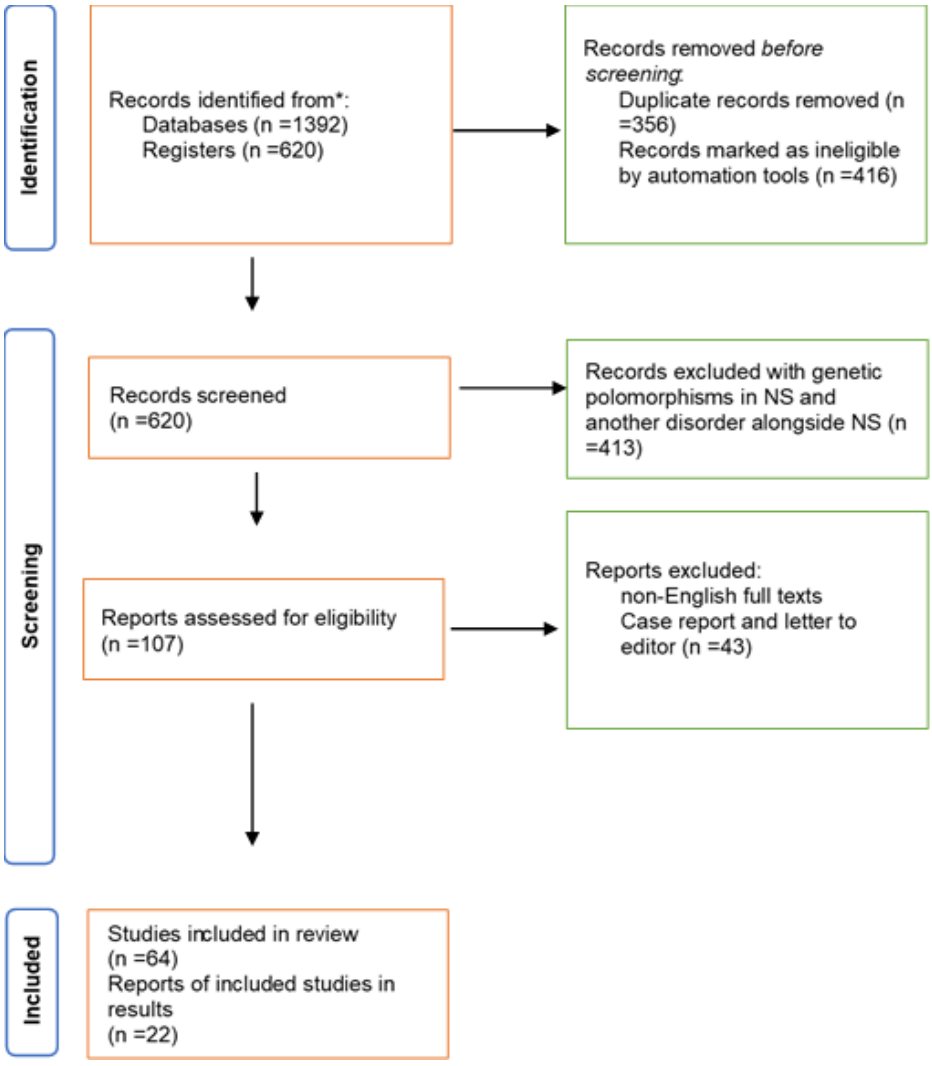

Figure-1: PRISMA flow diagram for systematic reviews which included searches of databases and registers only.

IL-4 and IL-13 levels were significantly reduced during the recovery period of SSNS and were increased in patients with NS. Only one study reported that the levels of these two interleukins were higher in the healthy children group, but it reported that SSNS showed higher levels than the SRNS group. The role of these two interleukins in the recovery of NS in the other four studies is definitely in their reduced levels.

Regarding inflammatory mediators such as TNF and interferon gamma, all studies presented the same results, which showed that NS treatment in the remission phase was associated with their reduction, and that the increase in these mediators is considered to be the main pathology of NS.

One study reported that there was no difference in IL-2 levels during remission compared to the SSNS group, but its levels were increased in NS. Children with primary nephrotic syndrome showed increased levels of IL-6, IL-17A, IL-23p19, and IL-1β, and this increase was also observed in interleukins 15 and 10. IL-23 and IL-17 might have been involved in disrupting the balance of Th lymphocytes.

3-2. Lymphocytes Lose their Inhibitors and Regulators

The NS course was accompanied by a fundamental change in the process of activation and control of lymphocytes, which might have been due to changes in the genetic pattern of interleukins and other mediators. In non-genetic cases, these lymphocytes play a major role in the pathology of NS. Th17 showed a higher level in NS patients compared to the recovery phase, while Treg showed a significant decrease. This condition creates an autoimmune state and interleukins such as IL-17 and IL-23 play a role in it. With the increase of these two interleukins we see an increase in Th17 and these interleukin, changes originate from γδ T cells. One article stated that the level of CD3+ and CD4+ in SSNSpatients is significantly lower than the control group, but the urinary dose of CD80 is significantly higher. However, CD 4+IL-17A was associated with an increase in another study. This increase is also evident in T-cell helper receptors, with TLR8 being significantly expressed on B and CD4+ T cells, but this study found no increase in TLR3. CD86 on B cells and ICOS on THF were increased in NS patients. These T cells carry large amounts of CD40s and are effective in regulating B lymphocyte responses and immunoglobulins, including TH1, TH2 and TH17 cell subsets. Although this study found no increase in these lymphocytes and only reported an increase, another study found an increase in Th2-related interleukins as a cause of NS pathology. It should be mentioned that the immunoglobulin profile of NS included increased IgA, IgM, and C3 and decreased IgG, and IgG/IgM, based on our studies.

In general, T lymphocytes continue to attack the inflammatory response by losing their regulators, and B lymphocytes produce more immunoglobulins and have more active responses in NS against kidney cells. The increase in receptors and the decrease in regulators, especially the Treg/Th17 ratio, on which all studies were based, are key to the pathology of NS.

3-3. Treatment Modulated Changes

The studies available to us show that higher levels of IL-18 are beneficial for NS, and that treatment with immunosuppressive drugs reduces it, but its increase is the key to treatment with levamisole in SSNS. Children with NS and steroid-sensitive patients showed higher levels of IL-18 after treatment with levamisole, an antiparasitic drug that reduces glomerular inflammation by

stimulating the immune system and improving Th 1 and Th 2 function.

Table-1. Data extraction from articles. Terms were defined in Abbreviation part.

Author (Year, DOI)	Upregulated Cytokines	Downregulated Cytokines	Variable Cytokines
Doaa Mohammed Youssef (15) (2015, PMID: 26174457)	IL-4, IL-13 (in SSNS)	None reported	IL-2 (no difference)
A Jamin (16) (2015, DOI: 10.1111/cei.12659)	None reported	None reported	None reported
Amal A Al-Eisa (17) (2017, DOI: 10.2147/JIR.S124947)	None reported	IL-1β, IL-6, IL-8 (in remission)	None reported
Doaa Mohammed Youssef (18) (2018, DOI: 10.4103/1319-2442.235173)	IL-18 (post-levamisole)	None reported	None reported
L Zhang (19) (2018, DOI: 10.1111/sji.12629)	IL-23, IL-17	None reported	None reported
Jiayun Zhou (20) (2018, DOI: 10.3892/etm.2018.5923)	IL-18 (before treatment)	IL-18 (after treatment)	None reported
Xia Yang (21) (2019, DOI: 10.1016/j.molimm.2019.07.001)	None reported	None reported	None reported
Azar Nickavar (22) (2020, DOI: 10.18502/ijaai.v19i6.4932)	IL-1β, IL-2, IL-6, IL-8 (in NS); IL-13, IL-18 (in controls)	IL-1β, IL-6, IL-8 (in SRNS)	None reported
Shipra Agrawal (23) (2021, DOI: 10.1016/j.ekir.2020.12.027)	IFN-γ, IL-5, IL-7, IL-17A, MIP-1β (in SRNS)	IFN-γ, TNF-α, IL-7, IL-13, IL-5 (post-glucocorticoids)	None reported
Shulian Chen (24) (2021, PMCID: PMC8014369)	IL-6 (in SDNS/FRNS, SSNS)	None reported	None reported
Fen-fen Ni (25) (2021, DOI: 10.3389/fped.2021.651544)	IL-4, IL-13 (in AA, ANA groups)	None reported	None reported
Neus Roca (26) (2021, DOI: 10.1093/ckj/sfaa247)	IL-6, TNF-α (in MCD vs. MN, healthy)	None reported	IFN-γ (no difference)
Jessica Forero-Delgadillo (27) (2022, DOI: 10.1371/journal.pone.0277800)	None reported	None reported	None reported
Andrzej Badeński (28) (2023, DOI: 10.3390/ijms24086993)	IL-15 (in urine, serum)	None reported	None reported
Eglal Aly Hassan (29) (2024, DOI: 10.61186/rbmb.13.1.67)	TNF-α, IL-18	None reported	None reported
Asmaa A Elsehmawy (30) (2024, DOI: 10.33393/jcb.2024.2689)	IL-13	None reported	None reported
Wanyu Jia (31) (2024, DOI: 10.1038/s41390-023-02830-9)	IL-6, CRP, PCT (in bacterial infection)	None reported	None reported
Xiaolong Ma (32) (2024, DOI: 10.1186/s12866-024-03667-w)	IL-1β, IL-6, IL-10, IL-17A, IL-23p19	None reported	None reported

4- DISCUSSION

4-1. Key Immunological Insights

NS has very close connections with primary immunological changes, and appropriate understanding of such changes can serve as a foundation for augmenting immunosuppressive therapy, particularly in the SRNS. Our research has revealed that physiological corrections in interleukin levels, as well as pro-inflammatory mediators such as TNF and

IFN, are accountable for stabilizing the pathology of NS, to cause effective modulations in the activity of lymphocyte subsets. Increased levels of significant inflammatory interleukins in blood and urine are associated with a dramatic decrease in established Treg cells, proposing that the interference with such immunological determinants could be key to SRNS therapies.

Th17 cells were increased, while Treg cells were reduced, disrupting the Th17/Treg axis. Elevated pro-inflammatory cytokines, such as IL-6 and IL-18, contributed to glomerular damage in SRNS (12, 33). The identified shift is accountable for a Th17-induced elevation of interleukins, IL-17 and IL-6 in podocytes, which causes increased stress to the glomerulus (34). A higher serum level of IL-6 and IL-2, indicators of Th2 reactions, was clearly seen in children with NS-associated glomerulonephritis (24), Furthermore, the increased renal expression of IFN-γ and TNF-α, pro-inflammatory mediators of Th1, resulted in podocyte inflammation (35).

IL-18 is of particular interest as an early cytokine mediating IFN-γ production and functionally augmenting naïve T cell conversions to Th1, which in turn produces additional related interleukins (36). These Th1 and Th2 subsets also secrete IL-13, regulating glomerular permeability like IL-4both capable of inducing IgE in NS while TCD4+ lymphocytes enhance IL-13 secretion. Our findings confirm elevated IL-4, IL-13, IL-7, IL-5, IL-1β, IL-2, and IL-6, correlated with increased Th lymphocyte activity, providing a fertile chemotherapeutic ground for SRNS.

4-2. Therapeutic Implications

A growing collection of inhibitors is increasingly taking precedence over standard immunosuppressants in NS while narrowing in on Th17 hyperactivity, Treg reestablishment, and Th1 and Th2 stabilization (37,38). Clostridium butyricum is a microbial regulator that decreases IL-10 and adjusts the Th17/Treg ratio. Our findings implicate this imbalance as a central pathology in NS (39), There should be increased emphasis on these natural agents with specificity to interleukins and low resistance, suggesting a transition to more efficient treatments. Icariin inhibits IL-1β, IL-18, and TGF-β, is equivalent to prednisone, and creates a superior control of creatinine when compared to doxorubicin (40, 41). All of these observations from preclinical models exhibit a subgroup of patients with NS for which pharmacological chemotherapy would yield the most utility.

Rituximab, an essential component in the management of NS; inhibits B lymphocytes and modifies IgA and IgM, thereby restoring defects in T-B lymphocyte interaction (42), resulting in the lowest reported rates of relapse following treatment in children with NS (43). However, the efficacy of Rituximab monotherapy is inferior when compared to multi-therapies incorporating other immunosuppressants, a fact that still looms in SRNS (44), Obinutuzumab, meanwhile, in conjunction with supportive therapies following Rituximab, has shown to deplete IgG to near complete, while facilitating recovery of B-cells, and to significantly decrease relapses in children with NS (45). The benefits of multi-therapy in regard to SRNS presents a convincing argument for its clinical use and may change the course of illness for these children.

In distilling these insights, we have delineated an interleukin profile for NS that consistently identifies increased inflammatory cytokines and decreased regulatory lymphocytes, despite variability among studies. The imbalance in these components is, most significantly, the Th17/Treg imbalance and this, coupled with natural and chemical products likely

able to combat immunosuppressants, aims to refine therapeutic targets for steroid resistance.

4-3. Limitations and Future Research

It is necessary to acknowledge limitations. First, as indicated in the inclusion criteria, we only considered studies involving human beings and did not take broader cytokine combinations or mechanistic information from animal studies into account, which would potentially contribute to our understanding of NS pathophysiology. Secondly, there was heterogeneity in the types of studies, as there were differences in study designs with respect to definitions of NS subtypes (SSNS and SRNS), sample size, and measurement type used, making it difficult to achieve consistent findings across studies. For instance, differences in IL-4 and IL-13 levels may be attributable to differences in drug assay sensitivity or variation in the patient population. Thirdly, we did not include any studies on genetic polymorphisms of inflammatory mediators which could further enhance our understanding of the relationship between genetics and various immune system factors in NS. Fourthly, the review focused on just a sub-population of cytokines, and lymphocyte subsets and therefore might not have captured other immune mediators that could characterize NS pathogenesis more thoroughly.

5- CONCLUSION

Nephrotic syndrome is associated with cytokine and lymphocyte changes, and we see an increase in pro-inflammatory cytokines and lymphocyte imbalance during it. Targeting inflammatory lymphocytes may represent a promising complementary or alternative option to steroids in the management of NS, especially in steroid-resistant cases where modulation of the Th17/Treg balance may be associated with better clinical outcomes. We hope that the results of this study can be useful in shaping future trials in steroid-resistant nephrotic syndrome.

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8- ETHICAL CONSIDERATIONS AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not include any studies involving animals conducted by any of the authors.

9- AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

10- CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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