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Revisiting Chlorambucil: A Pragmatic Approach to Childhood Steroid-Resistant Nephrotic Syndrome with Historical and Contemporary Insights

Aamir Jalal Al-Mosawi*

Advisor Doctor and Expert Trainer, Baghdad Medical City and Iraqi Ministry of Health Baghdad, Iraq

ABSTRACT

Background: Childhood steroid resistant nephrotic syndrome has traditionally relied on renal biopsy for therapy guidance; however, in children under six years old with typical features of idiopathic nephrotic syndrome, the likelihood of minimal change disease is high. This paper discusses the dynamic nature of renal histopathology in steroid resistant nephrotic syndrome, where transitions between minimal change disease, focal segmental glomerulosclerosis, and diffuse mesangial proliferation, are well-documented; suggesting that initial biopsy results may not definitively predict disease progression. Chlorambucil, an alkylating agent introduced in 1955, has shown effectiveness in treating difficult cases of nephrotic syndrome. Several studies from the 1970s demonstrated that chlorambucil, when used in combination with prednisone, provided high rates of sustained remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. However, concerns about its long-term safety, including gonadal toxicity and the potential risk of malignancy, must be considered. This paper aims to examine a pragmatic approach to managing young children with idiopathic steroid-resistant nephrotic syndrome without immediate renal biopsy. The approach leverages the high likelihood of minimal change disease in early childhood and highlights histopathologic variability, particularly the transitions between minimal change disease, focal segmental glomerulosclerosis, and diffuse mesangial proliferation. The paper also presents a representative case treated successfully with chlorambucil and offers expert commentary on its potential relevance in modern clinical settings. **Patients and Methods:** An archival case, seen before 2003, describes a 20-month-old male child with steroid-resistant idiopathic nephrotic syndrome. The patient initially responded to corticosteroid therapy but developed a second episode of nephrotic syndrome at 18 months, which was resistant to corticosteroid therapy. The patient was treated with chlorambucil at a dose of 0.2 mg/kg/day, leading to complete remission within five weeks. No infectious triggers for steroid resistance were identified. **Results:** The treatment with chlorambucil led to complete remission, defined by the resolution of edema and disappearance of

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***Corresponding Author**

Aamir Jalal Al-Mosawi,

Advisor Doctor and Expert Trainer, Baghdad Medical City and Iraqi Ministry of Health Baghdad, Iraq,

Email: almosawiaj@yahoo.com

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significant proteinuria. Follow-up was lost after eight weeks of treatment. The choice of chlorambucil was influenced by its availability and ease of administration in the clinical context. **Conclusion:** This archival report supports a pragmatic, context-sensitive approach to managing childhood steroid resistant nephrotic syndrome without immediate renal biopsy in selected cases. The observed clinical response to chlorambucil and the evidence of histologic variability in idiopathic nephrotic syndrome underscore the importance of individualized decision-making. While modern practices emphasize biopsy-guided therapy, revisiting historical strategies may offer valuable insights, especially in settings with limited resources.

Keywords: Steroid-Resistant Nephrotic Syndrome, Minimal Change Disease, Focal Segmental Glomerulosclerosis, Chlorambucil, Renal Biopsy, Pediatric Nephrology, Historical Perspective.

INTRODUCTION

Childhood nephrotic syndrome is characterized by generalized edema caused by hypoalbuminemia secondary to heavy proteinuria. Most cases are primary, and descriptions date back to the 15th century. In 1484, Cornelus Roelans likely reported the first case, describing generalized swelling in a child. In 1722, Theodore Zwinger provided a clearer clinical description, noting oliguria and suggesting tubular obstruction. In 1827, Richard Bright linked edema and proteinuria to kidney disease. John Bostock later demonstrated the relationship between proteinuria and hypoalbuminemia. In 1846, George Johnson emphasized the heterogeneity of Bright's disease and suggested systemic involvement. In 1905, Friedrich von Müller introduced the term "nephrosis" to describe non-inflammatory renal disease. This concept was further refined in 1914 by Franz Volhard and Theodor Fahr, who distinguished non-inflammatory nephrosis from inflammatory nephritis, shaping the modern understanding of nephrotic syndrome [1-3].

Childhood nephrotic syndrome is predominantly steroid-responsive but often marked by frequent relapses and steroid dependence. Since the 1950s, corticosteroids and synthetic adrenocorticotropic hormone (ACTH) analogs have been central to management. Henry Lewis Barnett and colleagues first explored ACTH and cortisone therapy in 1950. Gavin Arneil and Wilson reported effective cortisone use in 1952, with further clinical outcomes in 1953 demonstrating induction of diuresis. By 1954, Lauson et al. showed ACTH improved glomerular permeability, and Arneil later reported prednisolone use in 1956.

In 1968, John Stewart Cameron established that minimal change disease, the most common histopathological type responds consistently to corticosteroids within eight weeks [1,2].

During the 1970s, cytotoxic agents such as chlorambucil and cyclophosphamide were introduced for difficult or steroid-toxic cases.

In 1980, Tanphaichitr et al. proposed T-cell dysfunction in minimal change disease and demonstrated successful use of levamisole as an immunostimulant, achieving remission without significant side effects. Subsequent studies, including those by Patrick Niaudet in 1984, confirmed levamisole's role in reducing relapses and steroid requirements, though with variable response rates. The British Association for Pediatric Nephrology further validated levamisole in 1991 as an effective steroid-sparing therapy for maintaining remission. Concerns about cyclosporine-induced nephrotoxicity, highlighted by Capodicasa (1986) and Brodehl (1991), increased interest in safer alternatives. By 1998, Briggs introduced mycophenolate mofetil as a promising steroid-sparing agent for resistant cases, particularly in minimal change disease [2,4].

Table-1 summarizes the evolution of treatment of childhood nephrotic syndrome. Figure-1 shows the evolution of therapeutic strategies in nephrotic syndrome.

Table 1. Evolution of Treatment of Childhood Nephrotic Syndrome [4]

Year	Researcher(s)	Treatment / Drug	Key Findings / Contribution
1950	Henry Lewis Barnett and team	ACTH, Cortisone	First exploration of ACTH and cortisone therapy in nephrotic syndrome
1952–1953	Gavin Arneil & Wilson	Cortisone	Effective use; induced diuresis; outcomes reported in 16 patients
1954	Lauson et al.	ACTH	Improved glomerular permeability in childhood nephrotic syndrome
1956	Gavin Arneil	Prednisolone	First reported use for treating nephrotic syndrome

1968	John Stewart Cameron	Corticosteroids	Minimal change disease identified as steroid-responsive within 8 weeks
1970s	Multiple researchers	Chlorambucil, Cyclophosphamide	Introduced for difficult cases with steroid toxicity
1980	Tanphaichitr et al.	Levamisole	Suggested T-cell dysfunction; achieved remission in 7 children without side effects
1984	Patrick Niaudet	Levamisole	Reduced steroid dependence; effective in some frequently relapsing cases; mild hematologic side effects
1986	Capodicasa et al.	Cyclosporine	Reported potential nephrotoxicity
1991	Brodehl	Cyclosporine	Reinforced concerns about nephrotoxicity
1991	British Association for Pediatric Nephrology	Levamisole	Proven effective in maintaining steroid-free remission vs. placebo
1998	Briggs	Mycophenolate mofetil	Proposed as steroid-sparing alternative to cyclosporine

This aim of this paper is to highlight a pragmatic approach to the initial management of young children with idiopathic steroid-resistant nephrotic syndrome without immediate renal biopsy. The approach was based on the high likelihood of minimal change disease in early childhood and on evidence suggesting histopathologic variability and transition between, focal segmental glomerulosclerosis, and diffuse mesangial proliferation. A representative case treated successfully with chlorambucil is presented. This paper revisits this strategy in the context of historical practice and provides expert commentary on its potential relevance in selected modern clinical settings.

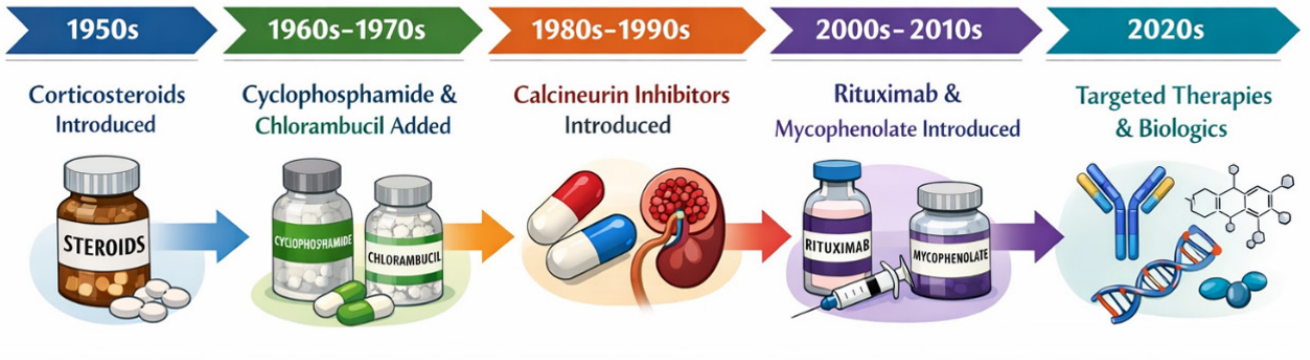

Figure 1. The evolution of therapeutic strategies in nephrotic syndrome.

PATIENTS AND METHODS

An archival case seen before 2003 is described. A male child was referred at the age of 20 months with secondary steroid-resistant idiopathic nephrotic syndrome, without significant hematuria, hypertension, or renal impairment.

The initial episode of nephrotic syndrome occurred at one year of age and responded completely to corticosteroid therapy within three weeks. A second episode developed at 18 months of age. The patient received daily oral prednisolone for eight weeks but developed persistent generalized edema, ascites, scrotal edema, and heavy proteinuria (4+ by dipstick), along with features of steroid toxicity.

RESULTS

Prednisolone was shifted to an alternate-day regimen, and chlorambucil was initiated at a dose of 0.2 mg/kg/day. Complete remission defined by resolution of edema and disappearance of significant proteinuria was achieved after five weeks of therapy.

Prednisolone was shifted to an alternate-day regimen, and chlorambucil was initiated at a dose of 0.2 mg/kg/day. Complete remission—defined by resolution of edema and disappearance of significant proteinuria—was achieved after five weeks of therapy.

No infectious trigger for steroid resistance was identified. Follow-up was lost after completion of eight weeks of chlorambucil therapy. The choice of chlorambucil was influenced by its availability and ease of administration in the given clinical setting.

DISCUSSION

The management of childhood idiopathic nephrotic syndrome, particularly steroid-resistant forms, has traditionally relied on renal biopsy to guide therapy. However, in children under six years of age without significant hematuria, hypertension, anemia, or impaired renal function, the probability of minimal change disease has been reported to approach 90–95%.

Historical evidence has also demonstrated that renal histopathology in idiopathic nephrotic syndrome is not static. Sequential biopsies have revealed transitions among minimal change disease, focal segmental glomerulosclerosis, and diffuse mesangial proliferation, raising questions about the necessity and timing of biopsy in all cases.

Histopathologic Variability in idiopathic nephrotic syndrome

Several studies have documented dynamic changes in renal histology:

In 1971, Renée Habib with Marie-Claire Gubler [5] and Claude Kleinknecht [3] described the spectrum of lesions in childhood nephrotic syndrome and noted that focal segmental glomerulosclerosis lesions may be missed on initial biopsy, suggesting that some patients initially diagnosed with minimal change disease may later be found to have focal segmental glomerulosclerosis; these cases are frequently associated with steroid resistance.

In 1985, Tejani reported that focal segmental glomerulosclerosis lesions had developed in 60% of 48 patients with steroid resistant minimal change disease, in association with aggravation of symptoms [6].

Waldherr et al. (1978) and Joh et al. (1998) suggested that focal segmental glomerulosclerosis may evolve from minimal change disease or mesangial proliferative patterns in some patients [7,8].

Conversely, some patients with diffuse mesangial proliferation, with or without focal sclerosis on initial biopsy, may lose mesangial hypercellularity over time and show minimal change disease or focal segmental glomerulosclerosis on repeat biopsy (Southwest Pediatric Nephrology Study Group) [9].

Furthermore, typical features of focal segmental glomerulosclerosis may be missed if the renal biopsy is too superficial, as lesions are more likely to be present in the juxtamedullary region.

In addition, because of the focal nature of the disease, biopsy samples may underestimate its extent. Taken together, these observations support the concept that, particularly in children, minimal change disease, diffuse mesangial proliferation, and focal segmental glomerulosclerosis represent a spectrum of idiopathic nephrotic syndrome, which may occur sequentially or in combination in the same patient [4,5,9].

Figure-2 shows the histopathologic variability in idiopathic nephrotic syndrome.

These findings highlight the limitations of renal biopsy and should be considered when interpreting histologic results in clinical decision-making, particularly in cases of steroid-resistant nephrotic syndrome.

In our patient, treatment with available therapeutic options was initiated successfully prior to performing a biopsy, illustrating one practical approach in selected clinical circumstances.

Chlorambucil, an alkylating agent was introduced in 1955 for the treatment of malignant lymphoma by David Goitein. 1n 1956, Aguirre described the results of treating several childhood malignancies with chlorambucil. The use of chlorambucil in the treatment of the nephrotic syndrome was reported as early as 1966 [4].

In 1973, Warren E. Grupe reported the use of chlorambucil in combination with prednisone in the treatment of 23 children with steroid-dependent nephrotic syndrome. Many of the patients had evidence of steroid toxicity. Growth retardation was present in about 50% of the patients.

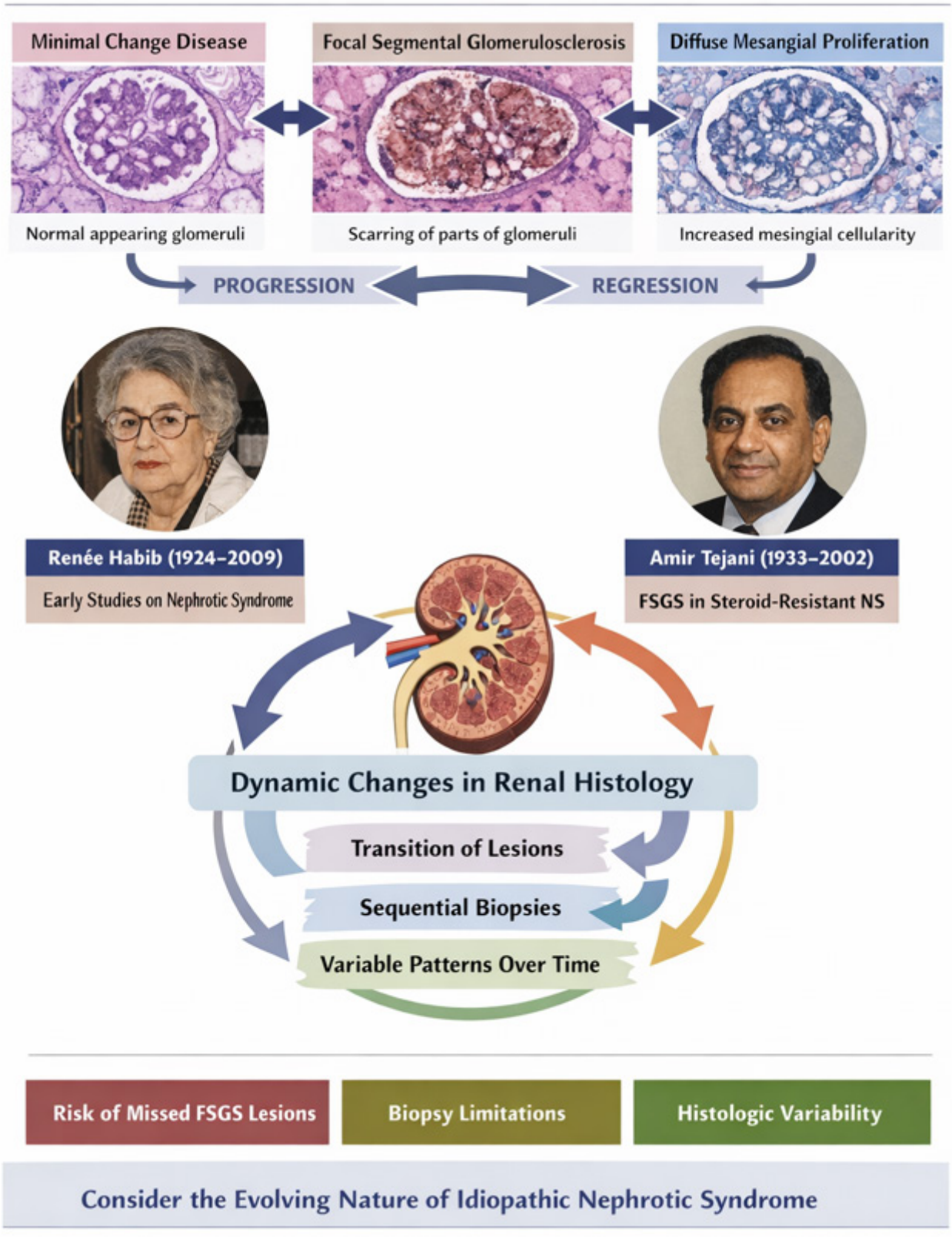

Figure 2. Histopathologic Variability in idiopathic nephrotic syndrome.

The patients were treated with chlorambucil for 2 to 12 weeks until leukopenia was induced. All patients experienced complete remissions lasting up to 4-12 years. Subsequent relapses requiring further prednisone therapy have been seen in only 13% with a follow-up of 7 months to 5 years (average 26.6 months). Complications were considered to be minimal and no mortality was reported.

The author concluded that chlorambucil, when used as an adjunctive treatment with prednisone, can provide effective treatment in initially steroid responsive nephrotic children who develop frequent relapses or become steroid dependent [10].

During the same year, Jeffrey S. Penso and his research group in the United States published a commentary on the work of Dr. Grupe, emphasizing that chlorambucil should be used in carefully selected pediatric patients with nephrotic syndrome because of its potential effects on testicular and ovarian function [4].

In 1976, Dr. Grupe and his colleagues reported a controlled study which included twenty-one children with either steroid-dependent or frequently relapsing nephrotic syndrome. The patients were treated with chlorambucil plus prednisone or prednisone alone. Patients treated with prednisone alone (The controls) continued to relapse at the same rate. All control patients experienced a recurrence of proteinuria by seven months.

Patients treated with chlorambucil plus prednisone for 6-12 weeks remained in complete remission, without needing further treatment during 12 to 34 months. The authors emphasized that immediate side effects commonly seen with cyclophosphamide were not observed with chlorambucil.

Comparison with previous studies suggested that remission induced by chlorambucil is more stable than that with cyclophosphamide.

The authors concluded that chlorambucil is valuable in the treatment of frequently relapsing nephrotic syndrome [11].

In1978, Hobart Jorge Baluarte and colleagues reported a controlled study which included children with frequently relapsing nephrotic syndrome who were receiving prednisone (60 mg/square meter on alternate days). Ten patients were treated chlorambucil (0.2 mg/kg daily) for 56 to 60 days, and eleven patients were treated chlorambucil in increasing doses (0.2 to 0.63 mg/kg daily) for 42 to 77 days.

Two patients in each group subsequently relapsed. Three treated with increasing dose of chlorambucil developed infections.

The authors concluded that a stable dosage (0.2 mg/kg daily) treatment is as effective as an increasing chlorambucil dose treatment in achieving long-term remission in frequently relapsing nephrotic syndrome [12].

During the same year, Guesry and colleagues reported a study which included twenty-one prepubertal and pubertal boys treated with oral chlorambucil for nephrotic syndrome before or during puberty. 9 patients developed testicular hypotrophy, 13 patients had considerable elevation of FSH, 17 patients had azoospermia, two patients had severe oligospermia, and repeated sperm counts showed no improvement. Therefore, the authors concluded that chlorambucil should be used with great caution, even in children.

Fiere et al. (1978) and Zimonyi and colleagues (1979) reported the occurrence of acute myeloid leukemia following treatment of nephrotic syndrome treated with chlorambucil [4].

Wiggelinkhuizen and colleagues (1979) reported a study which included thirteen children who had initially steroid responsive nephrotic syndrome but experienced frequent relapses. Treatment with chlorambucil was associated with remission for an average of 31 months. No side-effects were reported. The authors recommended that a dose of 0.2 mg/kg daily for eight weeks should not be exceeded [13].

The studies from the 1970s consistently demonstrate that chlorambucil is an effective steroid-sparing agent in children with steroid-dependent or frequently relapsing nephrotic syndrome. When used in combination with prednisone, it achieved high rates of sustained remission, often lasting months to years, and was shown in controlled studies to be superior to prednisone alone in maintaining remission. However, these benefits are tempered by important safety concerns. While short-term toxicity appeared relatively low in several studies, significant long-term adverse effects were increasingly recognized. These included gonadal toxicity (e.g., azoospermia, testicular atrophy, and hormonal disturbances), increased susceptibility to infections at higher doses, and rare but serious risks of malignancy such as acute myeloid leukemia.

Table-2 summarizes the 1970s studies reported the use of chlorambucil during the 1970s.

Overall, chlorambucil was regarded as a potent and effective therapeutic option during this period, particularly for difficult cases, but its use required careful patient selection, dose limitation, and awareness of potentially serious long-term complications.

In 1992, Besbas et al. from Turkey reported the treatment of 40 children with steroid- and cyclophosphamide-resistant nephrotic syndrome with chlorambucil. Total remission was achieved in eight children (20%), while partial remission was achieved in 5 children (12.5%) [14].

In 2010, Jameela A Kari and Manal Halawani from Saudi Arabia emphasized the difficulty in attaining remission in childhood steroid-resistant nephrotic syndrome. They reported that of 7 children who had steroid-resistant nephrotic syndrome treated with oral chlorambucil, only two (28.5%) achieved remission. Treatment was not associated with side effects [15].

Table 2. Studies on Chlorambucil in Nephrotic Syndrome (1970s) [4]

Author (Year)	Study Design / Population & Treatment Regimen	Outcomes & Adverse Effects	Conclusions
Grupe WE (1973)	23 children with steroid-dependent nephrotic syndrome treated with chlorambucil + prednisone for 2–12 weeks (until leukopenia)	100% complete remission lasting 4-12 years; relapse in 13%; minimal complications; no mortality	Effective adjunct in steroid-dependent/ frequently relapsing cases
Penso et al. (1973)	Commentary on chlorambucil use in pediatric nephrotic syndrome	Concerns about gonadal toxicity (testicular/ovarian function)	Recommended cautious use in selected patients
Grupe et al. (1976)	Controlled study (21 children); chlorambucil + prednisone (6–12 weeks) vs. prednisone alone	Sustained remission (12–34 months) in treatment group; all controls relapsed by 7 months; no cyclophosphamide-like side effects	Chlorambucil effective; remission more stable than cyclophosphamide
Baluarte et al. (1978)	Controlled study; fixed dose (0.2 mg/kg/day) vs. increasing dose (0.2–0.63 mg/kg/day) in frequently relapsing children	Similar efficacy; 2 relapses per group; infections in 3 patients (higher-dose group)	Fixed low dose as effective as escalating dose
Guesry et al. (1978)	21 prepubertal and pubertal boys treated with oral chlorambucil	Testicular hypotrophy (9), ↑FSH (13), azoospermia (17), oligospermia (2)	Significant gonadal toxicity; use with great caution
Fiere et al. (1978)	Case report of chlorambucil use	Development of acute myeloid leukemia	Raised concern about leukemogenesis
Wiggelinkhuizen et al. (1979)	13 children with frequently relapsing nephrotic syndrome treated with chlorambucil (0.2 mg/kg/day for ~8 weeks)	Remission for average 31 months; no side effects reported	Effective; dose should not exceed 0.2 mg/kg/day for 8 weeks
Zimonyi et al. (1979)	Case report of chlorambucil use	Development of acute myeloid leukemia	Confirmed risk of malignancy

Expert Opinion

This archival approach reflects a rational, experience-based strategy developed in an era when access to renal biopsy and advanced immunosuppressive agents was limited. Several points merit consideration:

1. Biopsy Avoidance in Selected Cases

In carefully selected young children with typical features of idiopathic disease, delaying biopsy may be reasonable, particularly when clinical indicators strongly favor minimal change disease and when biopsy resources are limited.

2. Histologic Plasticity

The documented transition between minimal change disease, focal segmental glomerulosclerosis, and diffuse mesangial proliferation, supports the concept that early biopsy findings may not definitively predict long-term disease behavior.

3. Therapeutic Role of Chlorambucil

Chlorambucil demonstrated efficacy in inducing remission in this case.

Historically, some clinicians considered it a viable alternative to cyclophosphamide or calcineurin inhibitors, particularly where concerns existed regarding toxicity, monitoring requirements, or availability.

4. Safety Considerations

While alkylating agents, including chlorambucil, carry risks such as bone marrow suppression and potential long-term malignancy, these risks must be weighed against those associated with other immunosuppressive therapies, especially in constrained healthcare settings. It is generally recommended that chlorambucil dose should not exceed 0.2 mg/kg daily for eight weeks.

5. Contemporary Relevance

Modern guidelines generally recommend renal biopsy in steroid resistant nephrotic syndrome. However, this archival experience remains relevant in:

- Resource-limited environments
- Situations where biopsy is not feasible
- Carefully selected patients with classical clinical features

CONCLUSION

This archival report supports a pragmatic approach to the management of childhood SRNS without immediate renal biopsy in selected cases. The observed clinical response to chlorambucil and the evidence of histologic variability in INS highlight the need for individualized, context-sensitive decision-making.

While current standards emphasize biopsy-guided therapy, revisiting such historical approaches may provide valuable insights, particularly for clinicians practicing in settings with limited resources.

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The author has the copyrights of all the sketches (Figures) included in this paper.

CONFLICT OF INTEREST

None.

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