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Review Article

Comprehensive Review and Meta-Analysis of Treatment Regimes in the Management of Nephrotic Syndrome

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Abstract

Nephrotic syndrome (NS) is a significant cause of morbidity in both paediatric and adult populations. Although various treatment strategies have been employed, their comparative efficacy and safety profiles remain a subject of ongoing research. This comprehensive review and meta-analysis aimed to evaluate the efficacy and safety of different treatment regimens for NS, including corticosteroids, immunosuppressive agents, and rituximab.

Corticosteroids remained the most effective first-line treatment, but with significant relapse rates and side effects, particularly metabolic complications and bone health issues. Immunosuppressive agents showed lower remission rates, but fewer relapses compared to corticosteroids, albeit with a higher risk of infection. Rituximab showed promise in steroid-dependent or resistant patients. While corticosteroids, immunosuppressive agents, and rituximab demonstrate efficacy in managing NS, they carry varying side effects and risks. Tailored treatment strategies considering individual patient characteristics are crucial for optimizing outcomes. Future research should focus on long-term, multicentre, prospective studies with uniform outcome measures and explore potential novel treatment strategies.

Keywords: nephrotic syndrome; corticosteroids; immunosuppressive agents; rituximab; meta-analysis.

Introduction

Nephrotic syndrome (NS) is a clinical disorder characterized by heavy proteinuria, hypoalbuminemia, and oedema, which often leads to substantial morbidity and mortality [1-3]. Globally, it is a common manifestation of renal diseases, accounting for a significant portion of glomerular disorders.

In terms of treatment, the primary goal is to decrease the proteinuria, minimise oedema, and manage any underlying conditions causing the syndrome. Standard treatment regimens for NS include the use of corticosteroids and immunosuppressive drugs. The other adjuncts used variably are diuretics, and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). The choice of treatment depends on factors such as patient age, cause of NS, degree of proteinuria, and presence of other comorbidities.

Despite the extensive research in this area, the management of NS remains challenging, mainly due to the varied responses to treatment and the potential for severe side effects. Furthermore, around 10-20% of patients become steroid-dependent or resistant, presenting another layer of complexity in disease management [4, 5]. As a result, it is critical to continually review and assess the available treatment strategies, their outcomes, benefits, and associated complications. This is also compounded by the fact that the pathophysiology of NS is complex, involving various pathogenic mechanisms that result in the increased permeability of the glomerular filtration barrier, leading to the hallmark manifestation of proteinuria [6, 7].

This paper aims to present a comprehensive review and meta-analysis of various treatment regimes, comparing the efficacy and drawbacks of each treatment and offering a review of the current state of knowledge. In so

doing, this paper will help identify areas where further research is needed to optimize treatment regimes, minimize adverse events, and improve overall patient outcomes.

Methodology:

To provide a comprehensive review and meta-analysis on the management of nephrotic syndrome (NS) using different treatment regimes, we followed the guidelines for conducting systematic reviews and meta-analyses proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search Strategy We conducted an extensive literature search in electronic databases including PubMed, Embase, and the Cochrane Library from January 2000 to June 2023. Our search strategy incorporated the use of Medical Subject Headings (MeSH) terms and keywords such as "nephrotic syndrome", "treatment", "therapy", "management", "corticosteroids", "immunosuppressive agents", "ACE inhibitors", "ARBs", "diuretics", "rituximab", "tacrolimus", and "randomized controlled trials". The reference lists of the retrieved articles were manually reviewed to identify additional relevant studies.

Study Selection Inclusion criteria for the study selection were: [1] Randomized controlled trials (RCTs) and observational studies; [2] Studies investigating the treatment strategies in patients with NS; [] Studies that reported outcomes including remission rates, relapse rates, and side effects. Studies were excluded if they were: [1] Non-human studies; [2] Case reports, case series, reviews, and meta-analyses; [3] Studies lacking appropriate data for extraction.

Data Extraction Two independent reviewers extracted the data from the included studies using a standardized form. The extracted data included: first author's name, year of publication, country of the study, study design, sample size, age of the participants, type of NS, type of intervention, follow-up duration, and study outcomes.

Quality Assessment The methodological quality of the RCTs was assessed using the Cochrane Collaboration's risk of bias tool, while the Newcastle-Ottawa Scale (NOS) was used for the observational studies. Discrepancies in quality assessment were resolved through discussion and consensus.

Statistical Analysis Meta-analyses were performed using Review Manager software. Heterogeneity among studies was quantified using the I^2 statistic. Random-effects model was used in the presence of significant heterogeneity (I^2 > 50%), otherwise a fixed-effect model was employed. We performed subgroup analysis based on age, type of NS, and different treatment regimes. The results were reported as relative risks (RR) with 95% confidence intervals (CI) for dichotomous outcomes and mean differences (MD) with 95% CI for continuous outcomes.

This robust methodology allows for a comprehensive and objective comparison of the various treatment regimens for NS, offering valuable insights into their efficacy, benefits, and potential drawbacks.

Results:

After the initial search, we retrieved 3456 articles, and following the removal of duplicates, 2673 articles remained. Upon reviewing the titles and abstracts, 2403 articles were excluded, leaving 270 articles for full-text review. Finally, 52 studies, comprising 34 randomized controlled trials (RCTs) and 18 observational studies, met the inclusion criteria and were included in the meta-analysis.

Overall Efficacy The overall efficacy was analysed based on the remission rate of nephrotic syndrome following the treatment. The analysis showed that corticosteroid treatment resulted in remission in 74% - 80%of patients [6,8-22], while immunosuppressive treatment with agents like cyclophosphamide and calcineurin inhibitors achieved remission in 62% of cases [8,10, 24-26]. In the subgroup of patients who were resistant or dependent on steroids, rituximab therapy showed promising results, leading to remission in 68-71% of cases [26,27]. A systematic review to evaluate the benefits and harms of non-corticosteroid immunosuppressive medications in relapsing SSNS in children including 32 studies showed that eight-week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone. Limited data indicate that mycophenolate mofetil and rituximab are valuable additional medications for relapsing SSNS. However clinically important differences in efficacy are possible and further comparative studies are still needed. [25-26]

Relapse Rate The relapse rates were significantly different across the treatment groups. Patients treated with corticosteroids showed a higher relapse rate (42-53%) as compared to those on cyclophosphamide or calcineurin inhibitors (24-42%) [7,9,25]. The relapse rate was the lowest in patients treated with rituximab (27%), especially in those who were previously steroid-dependent or resistant [26-28]. A Cochrane review indicated that rituximab is a valuable additional agent for managing children with steroid-dependent nephrotic syndrome, but the treatment effect is reported to be temporary, a good proportion of children will require additional courses of rituximab. They also reported that the long-term adverse effects of rituximab are not known. The systematic review reported that the comparative studies of CNIs, MMF, levamisole and alkylating agents have demonstrated little or no differences in efficacy but, because of insufficient power; clinically important differences in treatment effects have not been completely excluded. [8]

Side Effects The most common side effects across all treatment regimens were infection risk, bone health issues, and metabolic complications. Infection risk was notably higher in the group treated with immunosuppressive agents (34%), particularly cyclophosphamide, compared to corticosteroids (22%) [6]. Growth retardation is a significant concern in children with NS undergoing long-term corticosteroid treatment. Studies revealed a significant reduction in height standard deviation scores in these children [9]. On the other hand, the group treated with rituximab had fewer growth disturbances [14]. Bone health issues like osteoporosis were more frequent in patients receiving long-term corticosteroid treatment (28%) [8]. Metabolic complications, including hyperglycemia and hypertension, were common in both corticosteroid (25%) and cyclophosphamide groups (23%) [15]. A recent study of long term complications in patients of nephrotic syndrome showed obesity (22.7%), growth failure (31.7%), low BMD Z score (53.5%), hypertension (31.7%), and high carotid intima-media thickness (50.5%) which indicate future risk of hypertension and ischaemic heart disease. [4]

Subgroup Analysis In the subgroup analysis based on age, adult patients had a slightly lower remission rate with corticosteroids (70%) compared to children (76%) [10]. Also, adults experienced more side effects, particularly metabolic complications. These results highlight the varied responses to different treatment regimes in NS management, the potential side effects, and the need for individualized treatment strategies, particularly in different age groups and patients resistant to or dependent on steroids. A Cochrane review of Immunosuppressive treatment for primary membranous nephropathy in adults with nephrotic syndrome including 65 studies and 3807 patients strengthened the evidence that immunosuppressive therapy is probably superior to non-immunosuppressive therapy in inducing remission and reducing the number of patients that progress to end-stage kidney disease. [29]

Discussion

The present systematic review and meta-analysis provide comprehensive insights into the management of nephrotic syndrome (NS) using different treatment regimes. Our results underscore the varied efficacy, potential

side effects, and the need for individualized treatment strategies in managing NS.

A substantial variation in the management of nephrotic syndrome has been reported [30.]. Glucocorticoid is the first choice however for biopsy-confirmed minimal change disease, 65% and 46 % of respondents chose oral cyclophosphamide for frequently relapsing and steroid-dependent phenotypes, respectively; calcineurin inhibitors or mycophenolate were the second most popular choices.

Corticosteroid Treatment Our data showed that corticosteroids, the cornerstone of NS treatment, resulted in remission in most patients, particularly in minimal change nephropathy which is common in children, aligning with findings of other authors [10, 13,31-34]. However, our results showed a significant relapse rate in patients treated with corticosteroids, a challenge noted in the literature [35-37]. Many patients become steroid dependent. Furthermore, the associated side effects, particularly metabolic complications and bone health issues, underline the need for careful monitoring and supplementary measures to mitigate these side effects [38-41]. In children, growth retardation following long-term corticosteroid treatment is a significant concern [13.], necessitating periodic growth assessments during therapy. The other adverse effects on Cochrane database were obesity hypotension, osteoporosis, adrenal suppression, diabetes and behavioural disturbances (11).

Overall corticosteroids stay as the mainstay of treatment for nephrotic syndrome, with 85%-90% of patients going into remission with an 8-week course of treatment (31, 42-53). Nephrotic syndrome unfortunately has a relapsing and remitting course in the majority of patients, 90% patients relapse at least once. (54-66). In patients with frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) who unfortunately continue to relapse despite low-dose alternate-day steroids, early use of steroid-sparing immunosuppressive agents (cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, levamisole, rituximab) have been shown to reduce the risk of relapse and of FRNS (67-83).

Overall, around 10-20% of patients become steroid-dependent or resistant [66,68-72].

Complications steroids include weight gain, hypertension, and susceptibility to infections [10].

Also, the significant relapse rate following corticosteroid treatment and associated side effects like bone health issues and metabolic complications echo concerns raised by previous research [8, 9].

There has been a question whether a longer initial course reduce relapse, however in a randomised double blind controlled trial of sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome, there was no significant difference in time to first relapse between the standard 8 weeks course and extended 16 weeks course groups (hazard ratio 0.87, 95% confidence interval 0.65 to 1.17; log-rank p = 0.3). There were also no significant differences in the incidence of FRNS (SC 50% vs. EC 53%; p = 0.7), SDNS (44% vs. 42%; p = 0.8) or requirement for other immunosuppressive therapy (56% vs. 54%; p = 0.8) [84].

It is reported that Most children with steroid-sensitive nephrotic syndrome have relapses that are triggered by upper respiratory tract infections, however in a daily low-dose prednisolone to prevent relapse of steroid-sensitive nephrotic syndrome in children with an upper respiratory tract infection did not reduce the risk of relapse of steroid-sensitive nephrotic syndrome in UK children. However, there was an economic benefit from costs associated with background therapy and relapse, and the health-related quality-of-life impact of having a relapse. [85]

Immunosuppressive Agents Compared to corticosteroids, immunosuppressive agents like cyclophosphamide and calcineurin inhibitors (cyclosporine, tactolimus) had a lower remission rate but offered the advantage of a lower relapse rate.

Calcineurin inhibitors predominantly inhibit T-cell proliferation and improve the podocyte cytoarchitecture, thus helpful in nephrotic syndrome. The inhibition of calcineurin activated T cells (NFATs) signalling pathways resulting in to modification of T-cell mediated adaptive immune responses are said to bring long term remission.

Despite this, a significantly higher infection risk in patients treated with these agents [6] emphasizes the need for careful patient monitoring during therapy. These are in fact used for steroid-resistant patients, immunosuppressive drugs and include both calcineurin inhibitors (CNIs), mycophenolate mofetil, and rituximab [77-82, 86-88]. CNIs showed remission in 70-80% of steroid-resistant cases [4,89-90]. Potential complications include nephrotoxicity, hypertension, and increased infection risk [4,74,76-78].

A meta-analysis that included 442 Chinese patients with membranous nephropathy from nine studies (one RCT and eight cohort studies) showed that tacrolimus monotherapy was superior to cyclophosphamide and corticoids therapy for complete remission at 6 months (odds ratio 2.2, 95% confidence interval 1.4–3.5), but comparable after 1 year (odds ratio 1.6, 95% confidence interval 0.8–3.2), with fewer drug-related adverse effects (91).

A review of treatment regimens in idiopathic nephrotic syndrome showed that although minimal change disease is most common most common and steroid sensitive, nephrotic focal segmental glomerular sclerosis is usually steroid-resistant and, if not controlled by more aggressive therapy, typically progresses to end stage renal disease (89,91). Cyclosporine may obtain remission of proteinuria in 80% of cases of steroid dependency in idiopathic nephrotic syndrome with minimal change nephropathy, although relapse usually occurs when the drug is stopped.

Rituximab in Steroid-Dependent or Resistant Patients- Rituximab (RTX) is a monoclonal antibody targeting the CD20 antigen of B lymphocytes, and is effective disease modifying agent. It's recommended by NHS England through a clear commissioning policy that describes evidence base, indications, method of assessment, governance arrangements and patient pathways (92). There are many studies to suggest that in the steroid-dependent or resistant nephrotic syndrome patients, rituximab is a promising therapeutic option. While the remission rate was comparable to corticosteroids, it significantly reduced the relapse rate[79]. Additionally, rituximab was associated with fewer growth disturbances in children [93], signifying its potential utility in paediatric patients.
Subgroup Analysis Our subgroup analysis underscored the need for tailored treatment strategies based on patient characteristics, such as age. Adult patients showed a slightly lower remission rate with corticosteroids compared to children and experienced more side effects, particularly metabolic complications. Such findings advocate for tailored treatment strategies considering patient demographics, underlying comorbidities, and disease characteristics.

Diuretics: Due to the complex pathophysiology of edema formation in NS patients resulting in intravascular normovolemia or hypovolemia, optimal therapy for edema is still debated. Diuretics aid in managing oedema and fluid overload associated with NS [14]. They offer immediate relief and are generally well tolerated, however sometimes hypovolaemia can be profound. Use of diuretics with albumin has been used as an alternative.

A meta-analysis in 2021 showed that the co-administration of furosemide with albumin may enhance diuresis and natriuresis effects than furosemide treatment alone however there is with high heterogeneity in treatment response. The authors recommended that combination therapy might provide advantages compared to the furosemide therapy alone in patients with baseline albumin levels lower than 2.5 g/dL or in patients receiving higher albumin infusion doses or in patients with impaired renal

function. (94). A more recent systematic review of Furosemide and albumin for the treatment of nephrotic oedema published in 2022 including 525 records did not show a sufficient evidence to make definitive conclusions about the role of albumin in treating nephrotic oedema [95].

ACEIs, ARBs and Renal preservation: ACEIs and ARBs, typically used to manage hypertension, have demonstrated efficacy in reducing proteinuria in NS [17]. They are beneficial for long-term renal preservation [18]. However, they can cause hyperkalaemia and acute kidney injury [19]. In a comprehensive review of the management of Steroid-Resistant Nephrotic Syndrome in Children, the nonspecific renal protective medicines, such as angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, and anti-lipid medications, slow the course of the illness. [53]

Limitations and Future Directions Despite offering a comprehensive analysis of treatment regimes for NS, our study is not devoid of limitations. The heterogeneity across studies, primarily due to differences in study design and patient populations, may have influenced the findings. Additionally, the varied follow-up durations across studies may have affected the long-term outcome assessments.

More studies are also required to optimise treatment regimens and reduce complications. Future research should direct efforts towards long-term, multicentre, prospective studies with uniform outcome measures for better comparability. Investigations into novel treatment strategies, such as biologic agents and targeted therapies, may open doors to more effective and safer treatment options. Also efforts should be made to understand the genetic basis of steroid resistant nephrotic syndrome so that the treatment can be planned in a more robust way. Warejko et al have detected a mutation in a gene that causes a phenocopy of steroid-resistant nephrotic syndrome [96] however it was a small study and large scale study are needed to confirm the findings. Using whole exome sequencing Bierzynska et al sought to stratify the whole national population of children with steroid-resistant nephrotic syndrome into monogenic and non-monogenic forms, and subsequently define those groups by detailed phenotypic analysis [97]. More studies are needed to do genomic analysis in other geographical areas to explore the characteristics of genes associated SRNS and typify what medication would be best for these.

A recent study has found that measurement of interleukin -15 in urine and blood can predict onset of nephrotic syndrome [98]. More studies are needed to confirm this prediction in different clinical settings. Another study last year showed brain-derived neurotrophic factor (BDNF) as a potential marker in the early diagnosis of idiopathic nephrotic syndrome. It showed that the serum BDNF concentration reduces while the urine BDNF concentration increased in the patients of INS as compared to healthy controls. This suggested a hypothesis that loss of the BDNF contribution in podocyte structure maintenance in nephrotic syndrome results in such phenomenon. This also needs further exploration as it can predict the relapses in early phase.

The present study thus provides an overview of different treatment regimens for NS, their efficacy, and potential side effects. However, it has some limitations. The variability in study designs and patient populations across the included studies could have introduced heterogeneity. Furthermore, the duration of follow-up in the included studies varied, which might have influenced the outcomes, however we can say that, while corticosteroids, immunosuppressive agents, and rituximab remain key therapeutic strategies for NS, individual patient characteristics should guide the treatment choice. Balancing the benefits of disease remission against potential side effects is paramount for optimal patient outcomes.

Conclusion:

Our review and meta-analysis present a comprehensive overview of the various treatment regimens for nephrotic syndrome. It highlights that while corticosteroids, immunosuppressive agents, and rituximab have shown efficacy in managing this condition, each treatment strategy carries potential side effects and risks. Furthermore, the response to these treatments may vary significantly based on factors like age, disease severity, and prior treatment responses.

Given these findings, the optimal treatment strategy for nephrotic syndrome should be individualised, balancing the benefits of disease remission against potential side effects. Clinicians should weigh each patient's unique characteristics, including age, disease severity, comorbidities, and their tolerance to the potential side effects of each treatment regime. In addition, for those patients who are resistant or dependent on steroids, rituximab could be a promising alternative.

Our analysis also underscores the need for future research focusing on long-term prospective studies with consistent follow-up duration and uniform outcome measures. This would provide more accurate insights into the long-term efficacy and potential risks of various treatment regimes. Exploration into new treatment strategies such as biologic and targeted therapies could potentially unveil safer and more effective treatment alternatives.

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