Consensus guidelines for the treatment of Nephrotic Syndrome in Children of Pakistan

Endorsed by Pakistan Pediatric Association- Nephrology Group

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Introduction

Childhood Nephrotic Syndrome is one of the most common kidney diseases encountered in children. Our country; Pakistan; is the 6th most populous country of the world with more than 200 million people out of which 31% are children between the ages of 0 – 14.[1]

The exact etiology of this disease is still unknown. However, in children vast majority gets better with immune suppression. The recommended protocol of treatment for different varieties of Nephrotic Syndrome has been revised based on current evidence.

As Pakistan has few qualified pediatric nephrologists, these children are usually treated by family physicians, pediatricians and also adult nephrologists. Each treating physician follows different protocols and in many cases children are either inadequately treated or receive over treatment. This results in increased morbidity and in many cases long term complications.

The Pakistan Pediatric Association Nephrology Group has felt the need to standardize the protocols for treatment of this disease based on current evidence all over the country so that this potentially treatable condition can be addressed uniformly.

A consensus group was formed between the Pediatric Nephrology Departments of the Sindh Institute of Urology and Transplantation (SIUT) and the National Institute of Child Health (NICH) who met regularly and discussed all the current practices and personal experiences in light of recent evidence.

A document was compiled and circulated electronically amongst all the members of the group and objections to these protocols were invited. After reaching consensus amongst the group these guidelines were compiled in a publication form and circulated across the country using the platform of Pakistan Pediatric Association and the Pakistan Society of Nephrology.

It must be emphasized that these guidelines are based on current scientific evidence and they are still evolving. The most notable development in practice in last 5 years is in the duration of steroids that should be given for the first episode and subsequent relapses. It has been noted that there is no statistically significant difference in the number of relapses between cohorts who receive a shorter duration of treatment (2 to 3 months) as compared to a prolonged duration (6 months).

Since these results have not been incorporated in most of the Textbooks of Pediatrics, we believe that this document will help all the practicing physicians to review the literature and adapt to the current recommendations.

We have compiled these guidelines with the best intentions for our children and have tried to incorporate all the common varieties of this disease and its associated complications. It is by no means complete and final. All physicians are advised to use their personal judgment in individual cases and we beg to communicate with us if there are any differences in opinion or experience.

Nephrotic Syndrome (NS)

Diagnosis of NS:

Nephrotic Syndrome is characterized by:

a. Progressively increasing edema
b. Hypoalbuminemia (< 2.5 mg /dl)
c. Proteinuria (> 50mg/kg/day or Pr: Cr > 2 mg/mg or ≥ 3+ on urine dipstick)
d. Hypercholesterolemia (> 200 mg /dl)

In exceptional cases due to heavy proteinuria, the quantity of proteinuria measured at the time of presentation could be lower, however if the other 3 features are present the diagnosis can be made.
In almost one third of cases there is microscopic hematuria and hypertension at the time of initial presentation. In such cases history of progressively increasing edema and high serum cholesterol is most helpful to exclude the diagnosis of Acute Nephritic Syndrome.[2]

Classification based on the age of onset:

- Congenital NS (< 3months)
- Infantile NS (4months to 1 year)
- Childhood NS (1 to 12 years)
- Adolescent NS (13 to 18 years)

Classification based on the response to steroids:

Based on the response to treatment with steroids, NS can be classified into:

- Steroid Sensitive Nephrotic Syndrome (SSNS)
- Steroid Resistant Nephrotic Syndrome (SRNS)

SSNS can be further classified based on the frequency of relapses over 6 to 12 months period into:

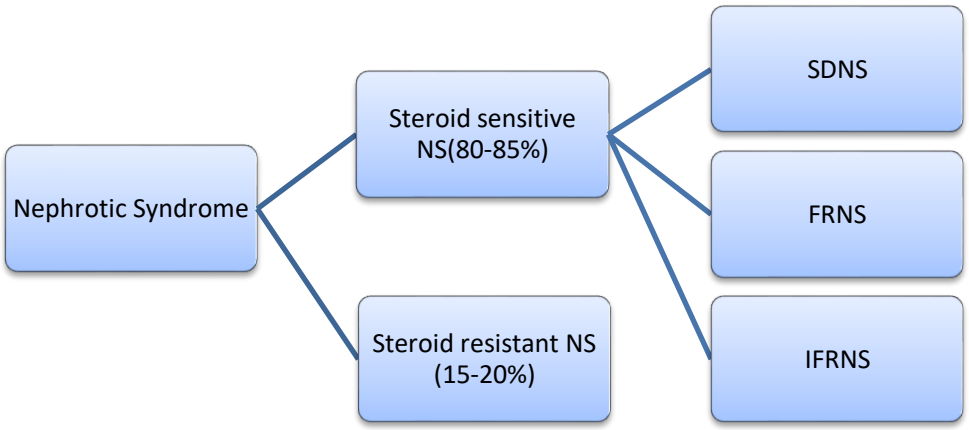
- Steroid Dependent Nephrotic Syndrome (SDNS)
- Frequently Relapsing Nephrotic Syndrome (FRNS) and
- Infrequently Relapsing Nephrotic Syndrome (IFRNS)

Definitions:

- SSNS: Complete remission of edema and proteinuria within 6 weeks of full dose (2mg/kg/day) of prednisolone.
    - SDNS: Two consecutive relapses on tapering steroids or within 2 weeks of stopping steroids
    - FRNS: Two relapses in first 6 months of response to steroids or 4 relapses in any 12 months during the course of treatment.
    - IFRNS: Less than 4 relapses in a year.

- SRNS: Persistent proteinuria and edema after 4 weeks of treatment with daily dose of 2mg/kg/day. In cases where there is decrease in the quantity of proteinuria and edema from the baseline after 4 weeks, the treatment can be prolonged up to 6 weeks. [3]

Figure 1: Classification of Nephrotic Syndrome (NS)



Treatment of first Episode:

Children presenting with nephrotic syndrome for the first time after 3 months of age to 12 years of age should be treated initially with steroids.

Choice of Steroids:

Prednisolone has remained a reference drug. In Pakistan, it is available as 5 mg tablets and 15mg/5ml suspension. We recommend use of plain (non-enteric coated) tablets as it is cheaper and has better absorption. The risk of gastro-intestinal bleeding due to steroids in ambulatory patients is 0.13% therefore; use of enteric coated prednisolone may not confer any additional benefit.[4]

Use of Antacids with Steroids:

It is customary to prescribe antacids with steroids. Aluminum containing antacids are known to decrease the absorption of steroids and H_2 receptor blockers like ranitidine should be prescribed at a dose of 2 to 4 mg/kg /day to a maximum of 150 mg/day. It must also be kept in mind that ranitidine may give false positive result for protein on "Multistic".[5] Proton pump inhibitors can be prescribed at 1mg/kg/day as once daily dose. Some authorities recommend using antacids only on as needed basis. In these consensus guidelines we have left the decision on the discretion of treating physician.

Dose of Steroids:

Dose of steroids should be calculated as mg/kg. If the dry weight is known the dose should be calculated using it however if it is not known then the recommended practice is to use the current weight and adjust the dose once remission is achieved.

Calculations based on body surface area have been found to give a higher cumulative dose of steroids and no additional benefit in terms of relapse rate.[6]

It is recommended to give the medications as a once daily dose instead of divided doses after breakfast because it results in lesser adrenal suppression, lesser side effects of steroids and better compliance.[7]

Treatment duration and Follow up:

We recommend treatment of first episode of NS with prednisolone for 12 weeks. The dosage should be 2mg/kg/day (maximum dose 60mg/day) taken once daily for 4 weeks regardless of when remission was achieved followed by 1.5 mg/kg (maximum dose 40mg/day) given on every other day (EOD) for 8 weeks. At the end of 12 weeks steroids should be stopped without tapering. A total of 3 follow up visits are advised at 2, 4 and 12 weeks.

First Follow up: In setups where urine dipsticks are available documentation of negative proteinuria on 3 consecutive days is ideal and the first follow up should be done once remission is achieved. However in many places provision of dipsticks for the parents may not be possible. In such cases we recommend that the first follow up should be done after 2 weeks since the median time to respond to full dose of steroids is 11 days (10 – 15 days).[8] In such cases only a urine dipstick done in the office is sufficient to document absence of proteinuria. Trace proteinuria on dipstick (<300 mg/dl) should be considered as remission.

Other methods to check proteinuria; like boiling urine; is cumbersome and a source of anxiety for the parents and the child. We therefore do not recommend checking urine for proteinuria by any other method.

Re-enforcement of counseling about the need for compliance, anticipated side effects and balanced diet should be done on this visit. Even if proteinuria and edema persists after 2 weeks next follow up is advised again after 2 weeks.

Second Follow up: On second follow up at 4 weeks from start of steroids, if the proteinuria and edema persist child should be labeled as primary SRNS and further treatment is advised as per protocol mentioned in the section of SRNS.

If the child is in remission, the dose should be reduced to 1.5mg/kg every other day (EOD) for next 8 weeks. It should be then stopped without tapering to complete a total duration of 12 weeks.

In rare cases of late responders, when proteinuria and edema has decreased but not completely resolved after 4 weeks then trial of full dose for 2 more weeks has been seen to induce remission. In such cases if there is proteinuria more than trace even after 6 weeks, they should be then treated as SRNS.

In cases when a delayed response is seen after 6 weeks, the dose should be decreased to 1.5mg/kg EOD for another 6 weeks and then steroids are stopped.

Third Follow up:

Third follow up during first episode should be done at 12 weeks and if there is remission, steroid treatment should be stopped and parents should be advised to return if there is relapse.

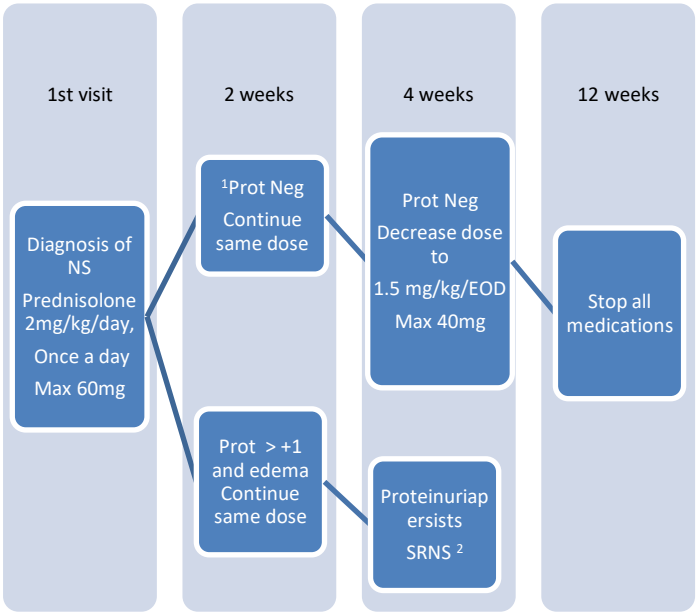
Subsequent Follow ups:

It is suggested to document sustained remission with urine dipstick at 3 months, 6 months and then annually for 5 years. If no relapses are documented in 5 years, no further specific follow ups are required.

Justifications for the recommended duration:

The optimal duration of treatment for the first episode of NS is still being debated. Multiple evidence based guidelines and meta-analysis had shown a superior outcome with prolonged duration of treatment up to 6 months. [9, 10, 11] Recently conducted well designed trials have proven that the difference in the number of relapses with shorter duration of steroids compared to longer duration is not statistically significant. [12, 13, 14, 15] However, for shorter duration there is still no comparative recent trial between 8 weeks versus 12 weeks. APN trials conducted in 1980s have demonstrated a superior outcome with 12 weeks duration when compared to standard 8 weeks therapy. [16] There are other trials that have compared cumulative dosages and have proven that lower cumulative dose has less long term side effects and equal relapse rate. After discussion among our group, in these guidelines we have suggested use of lower cumulative dose with 12 weeks therapy.

Fig 2: Algorithm of treatment for first episode of NS



Relapse with Upper respiratory infection (URI)

Children suffering from SSNS are known to have multiple relapses. A relapse is confirmed when the child has proteinuria and edema. Most of these relapses are associated with a preceding viral infection. [17, 18, 19, 20]

If the child is already receiving alternate day treatment with steroids and develops URI with relapse of proteinuria then the same dose is increased to daily dosage for one week and if remission is achieved the dose should be brought back to the baseline. This one week therapy is additional to the total recommended duration of treatment for children who were already receiving treatment.

If the child is already off medications, prednisolone 0.5mg/kg/day for one week is recommended. At the end of one week if proteinuria has remitted then all medications should be stopped. In cases where the proteinuria does not remit after one week of daily treatment, they should be treated as relapse.

Children who are on steroid sparing agents like Levamisole, Cyclophosphamide, CNIs and others can also be treated with the same protocol if they have acute viral infections although there is no controlled trial to evaluate its efficacy.

Treatment of Relapse

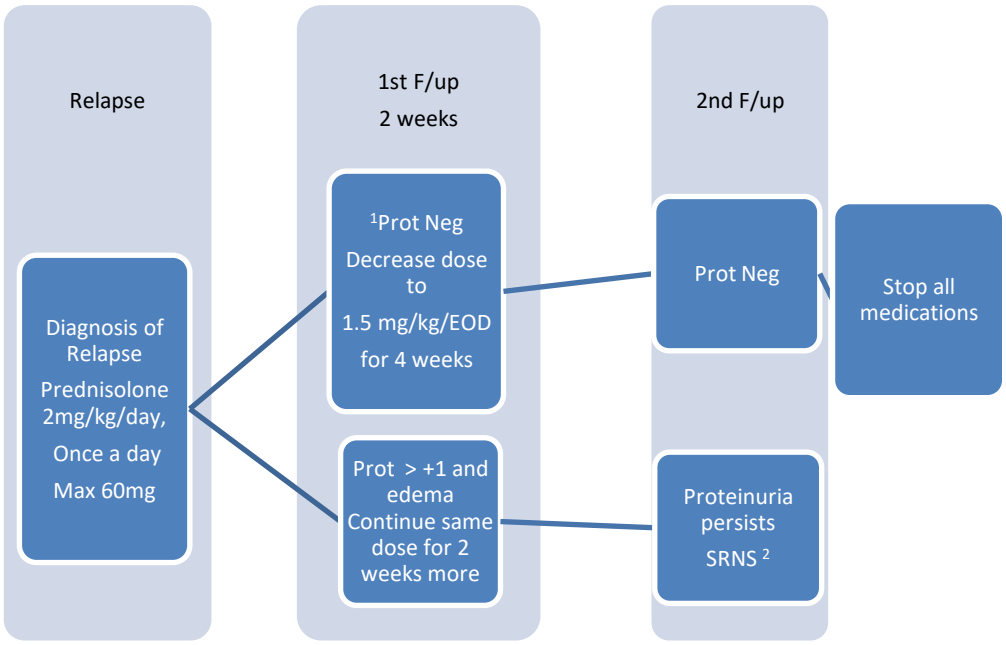
Children who develop proteinuria and edema in absence of a viral infection or those who do not respond to one week treatment of low dose daily steroids should be started on full dose Prednisolone (2mg/kg/day) once daily.

In setups where provision of dipsticks is available the follow up should be done once proteinuria is documented negative or trace on 3 consecutive days. However, in cases where checking daily urine dipstick is not possible our group recommends that for relapse also, like in the first episode, the first follow up should be done at 2 weeks of starting treatment.

Once the child is in remission the dose should be decreased to 1.5 mg/kg/ EOD for another 4 weeks and then the treatment is stopped without tapering.[21]

In case of persistent proteinuria and edema for 4 weeks the child should be labeled as "Late non-responders" and further treatment should be done as described in the section on SRNS.

Figure 3: Algorithm of treatment of Relapse of Nephrotic Syndrome



Treatment of Adolescent NS

First episode of NS after 12 years of age is labeled as Adolescent NS. It has been shown that the morphology of kidney lesions in this age group is different with higher incidence of membranous nephropathy.[22] More children in adolescent age groups are noted to have SRNS and Membranous Nephropathy.

We recommend performing a kidney biopsy before starting treatment along with serologic markers for Hepatitis B and C, anti- nuclear anti body (ANA), anti- double stranded DNA antibody (anti-dsDNA) and serum complements (C3 and C4).[23]

If the biopsy shows membranous or mesangiocapillary pattern than the treatment protocol is similar to adult protocol and is described in the later sections. If however the morphologic lesions are similar to the commonly seen lesions in INS of childhood like MCD, FSGS, IgMN or MesPGN then we recommend same protocol of treatment as of children of younger age group.

Treatment of Steroid Dependent Nephrotic Syndrome (SDNS)

Children who have had 2 consecutive relapses while tapering steroids or within 2 weeks of stopping treatment with steroids should be diagnosed as SDNS and treated with a steroid sparing agent.

The first choice of alternate medication in SDNS should be Cyclophosphamide (CyP) as it has shortest duration of treatment with best results as compared to all other agents.[24], [25]

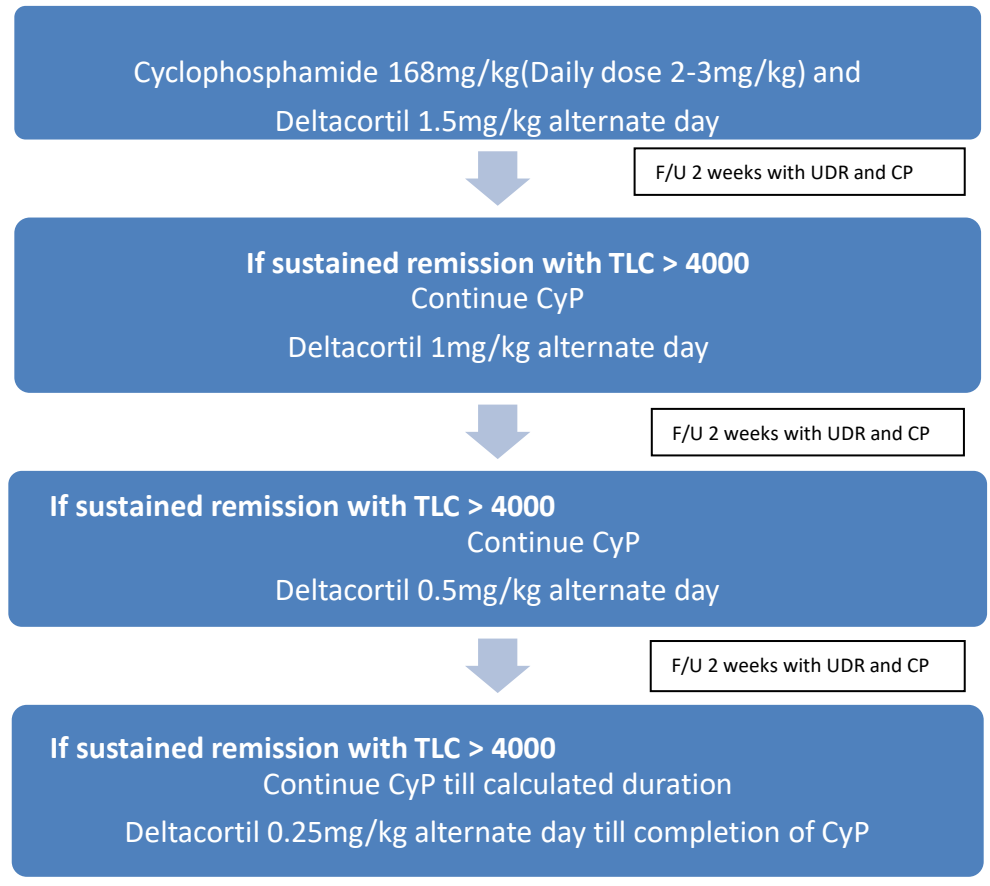
The recommended cumulative dose is 168mg/kg and the daily dose should be between 2 to 3 mg/kg. Sample calculation is shown in Table. Based on these calculations the total duration of treatment with CyP should be between 56 to 84 days (8 -12 weeks).

Before starting treatment with CyP, complete remission should be achieved by giving 2 weeks of prednisolone 2mg/kg/day as a single morning dose. It should be remembered that CyP is not so effective in SRNS so only children who have achieved remission with steroids should be offered this therapy. Bone marrow suppression is the most common side effect so total leukocyte count (TLC) should be monitored every 2 weeks for the duration of treatment. If the TLC is less than 4000, CyP should be held for 1 to 2 weeks till TLC improves. It should be then restarted with same dose to complete the cumulative dose.

Prednisolone 1.5 mg /kg/EOD (Max 40mg/day) should be given along with CyP for the first 2 weeks and then reduced by 0.5mg/kg/EOD every 2 weeks to reach a minimum dose of 0.25mg/kg/EOD till the treatment is complete. All the medications can be stopped at once when the planned duration is complete.

Children who relapse after completing the course of Cyclophosphamide should have a kidney biopsy and treatment with Cyclosporine should be offered. The protocol for Cyclosporine treatment is described under the section of SRNS.

Figure 4: Algorithm for treatment of Steroid Dependent Nephrotic Syndrome



Treatment of FRNS

Children who have frequent relapses (2 relapses in initial 6 months or 4 relapses in any 12 months) are at risk of receiving high dose of steroids over a long period of time. There is strong evidence that these children benefit from a course of Levamisole. [26,27,28]

Levamisole not only has antihelminthic activity but also works as an immunomodulator. It is marketed in Pakistan as Ketress in 40 mg tablets and 40mg/5ml suspension. The recommended dose is 2-2.5mg /kg day as a single dose given on alternate days with a maximum dose of 160mg/day. Although there are studies that have shown a better result of Levamisole with daily dosages, however after discussion among our group the consensus based on personal experiences, we recommend Levamisole to be given on alternate days.

It should be started only after complete remission has been achieved with full dose of steroids. At the beginning 1.5mg/kg/EOD (Max 40mg/day)prednisolone should be given for initial 4 weeks. It should be then tapered by 0.5mg/kg every 2 weeks to reach a dose of 0.25mg/kg/EOD over next 8 weeks. Steroids can be stopped after one year of treatment while levamisole is continued in same dose.

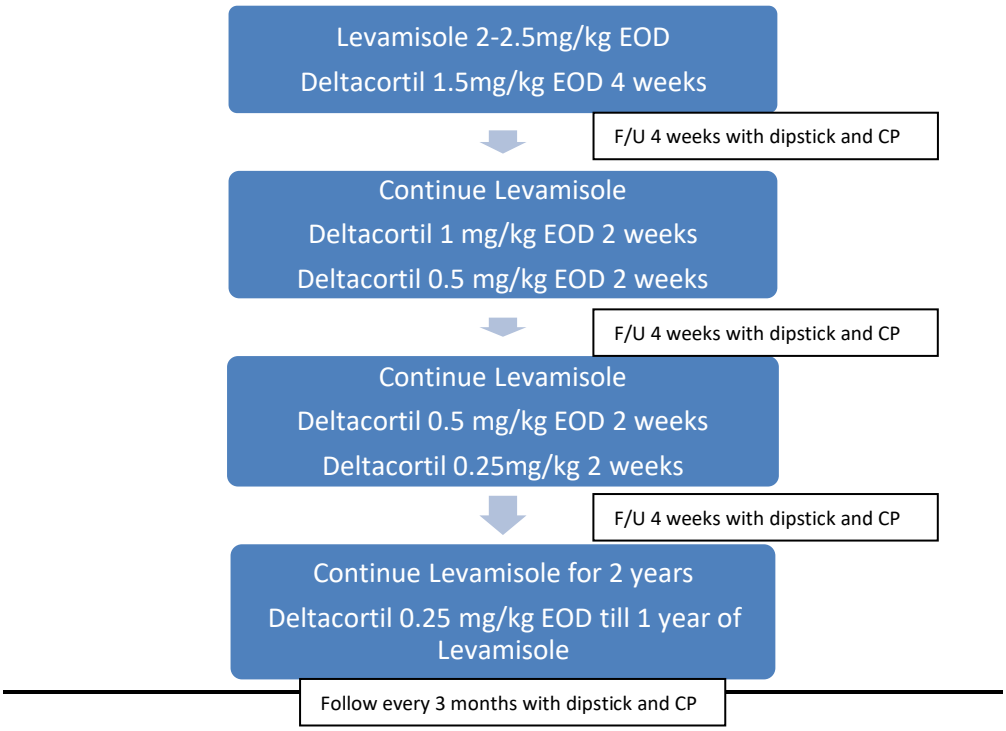
Although Levamisole has a good safety profile but rarely neutropenia and ANCA associated vasculitis have been reported. There are also few reported cases of increased transaminases. We recommend monthly follow ups for first 3 months with a Complete Blood Count, LFTs and urine dipstick and if the child is tolerating the treatment well then they can be followed every 3 months till one year of treatment is completed.

In case if there is a relapse while taking levamisole and low dose steroid then it should be treated with full dose of steroids for 2 weeks followed by 1.5mg/kg/EOD for 4 weeks. Steroids should then be brought to the same dose as it was before the relapse. Children who relapse during the second year with no steroids should be treated as per relapse protocol with 2mg/kg/day for 2 weeks and then 1.5mg/kg/EOD for 4 weeks and then stop steroids.

In children who have had 2 relapses while on levamisole within a period of 6 months, levamisole should be stopped. These children should then be treated with Cyclophosphamide as per protocol of SDNS.

If no relapses are seen with Levamisole for 2 years and at least one year without steroids, it can be discontinued.

Figure 5: Algorithm of treatment for FRNS



Steroid Resistant Nephrotic Syndrome (Primary and Late non-responders)

Children who do not go into remission after 4 weeks of full dose steroids therapy or those who have partial response after 6 weeks should be treated as SRNS. These patients can have a primary steroid resistance or may have been sensitive to steroids in the past but develop resistance with subsequent relapses (Late non-responders).

SRNS carries the worst long term prognosis in terms of renal survival among all other categories of childhood NS. A thorough workup at the time of diagnosis and a regular long term follow up must be maintained for all these children.

They should have a baseline work up to rule out secondary etiologies like hepatitis B and C and also screening with serum complement levels to rule out an underlying nephritic etiology.

Kidney biopsy should be performed as soon as the diagnosis is established and before alternate treatment is started.

The available facilities, resources and expertise to deal with this entity may vary in different hospital setups. In these guidelines, we could not come to a consensus treatment that can be followed in every center. **We recommend that the treating physician should use their best judgment in choosing the immune suppression protocol for their patients with SRNS**. Following is our impression about the recommended treatment options with their references.

Pulse Methylprednisolone:

It has been hypothesized that children who fail to respond after 4 weeks of full dose of steroids, have a lower density of glucocorticoid receptors on their peripheral mononuclear cells.[29] Mendoza et al had introduced a protocol of treatment of steroid resistant FSGS with very high doses of IV methylprednisolone for over 18 months and the same group even showed a 5 year follow up of such patients with significantly lower complications.[30,31] The French society has also recommended giving 3 pulses of IV methylprednisolone if the child does not respond to 4 weeks of full dose.[32]

The results from Mendoza protocol have not been replicated in other studies and as a group we all agreed that steroids can be very toxic for children especially in long term. Even 3 consecutive pulse doses have never achieved remission in our personal experiences and we do not recommend 10 to 15 folds higher dose of steroids to be given to children who have not responded to an already high dose for 4 weeks.

Calcineurin Inhibitors:

If the eGFR is more than 90ml/min/1.73m^2 and histopathology shows Minimal change disease or its variants, Focal segmental glomerulosclerosis and IgM nephropathy then Calcineurin inhibitors (CNI) like Cyclosporine (CyA) or Tacrolimus (Tac) should be initiated.[33]

CyA should be started at a dose of 5mg/kg/day in two equal divided doses along with 1mg/kg/EOD dose of steroids. It is available in capsules of 25mg, 50mg and 100mg and in liquid formulation containing 100mg/ml.

The first follow up is recommended after 6 weeks of starting CyA and if complete remission is achieved then steroids can be tapered by 0.25 mg/kg/EOD every 2 weeks till it is stopped over 8 weeks. All patients receiving CyA should have serum creatinine and serum albumin checked 3 to 4 times a year.

Children who still have proteinuria after 6 weeks should continue the same dose of CyA and steroids for another 6 weeks. If no response is seen after 3 months of therapy, CyA trough levels should be checked where available and dose should be adjusted to achieve a trough level of 120 – 150 ng/ml.

Those who respond to CyA with sustained remission after 6 months should receive a tapering dose with 0.5mg/kg/day lower dose every 2 months till a minimum dose of 1mg/kg/day of CyA is reached. Once they maintain remission on minimum dose for 6 months and have completed 2 years of total therapy then treatment can be stopped.

Patients who relapse on tapering dose of CyA should be brought back to the effective dose with concomitant steroids at 1 mg/kg/EOD on which remission was sustained. Steroids can again be tapered once remission is achieved.

One commonly used alternate treatment to CyA in patients with preserved GFR is Tacrolimus. It is also a preferred treatment for those children who develop cosmetic side effects of CyA. In Pakistan it is available in capsule in strength of 0.5mg, 1mg and 5mg. Some pharmacists can constitute a suspension of required strength for younger children. It is started at a dose of 0.1 to 0.15mg/kg/day in two equally divided doses along with Prednisolone 1mg/kg/EOD. Due to the higher cost of Tacrolimus, some centers use it only for patients who do not respond to CyA with adequate levels after 6 months. Tacrolimus like CyA can then be stopped after 2 years of treatment. In cases of no response, Tacrolimus trough levels should be checked and dosage should be adjusted to achieve trough levels of 6 to 8 ng/ml.

Many children who are treated with CNIs do not get into complete remission in terms of proteinuria after 6 months of adequate dose. If the proteinuria has decreased significantly from the baseline, serum albumin is more than 2.5mg/dl and eGFR is more than 90ml/min/1.73m2, then they are considered as partial responders. In such cases, steroids should be tapered off and CNI dose should also be slowly tapered to a minimum effective dose. This treatment is then continued for indefinite period.

Patients whose eGFR decreases below 60ml/min/1.73m^2 during treatment should be evaluated thoroughly for any acute illness and if the renal functions recover to the baseline CNI can be restarted with close monitoring.

Mycophenolate Mofetil:

Mycophenolate Mofetil (MMF) as monotherapy or in combination with CNI has also been seen as effective treatment of SRNS in several studies. The recommended dose of MMF in recent literature is still evolving. It is recommended that the dose should be titrated according to the levels of MPA. The trough level should be higher than 3mcg/ml with MPA-AUC more than 45 mcg-hr/ml. To achieve these levels a much higher dose of MMF is required as compared to the dose that is used in post-transplant patients. [34, 35] These levels are usually achieved by a dose of 1200mg/m^2. If a positive response is seen with Tacrolimus or MMF within 3 months, steroids can be tapered off followed by slow taper of Tacrolimus to achieve sustained remission with minimum dose for 6 months.

Cyclophosphamide:

Although the use of Cyclophosphamide is mostly beneficial in SDNS and FRNS with Levamisole failure, however, it has been shown to induce remission in few patients with SRNS in small scale controlled trials. [36, 37]

It may have side effects related to bone marrow suppression, alopecia and gonadal toxicity and others. Careful monitoring and selection of patients is required before treating children with SRNS with this drug.

ACEI / ARBs:

Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) are known to decrease the filtration pressure in the glomeruli and in turn reduce the proteinuria. This anti-proteinuric effect of these medications can be used to treat nephrotic syndrome. Since all Steroid Sensitive varieties respond well to steroids therefore, the use of ACEI and ARBs is mostly reserved for SRNS who develop decreased GFR and cannot continue CNIs or those who do not respond to them.[38] Moreover, use of salts like Enalapril is preferred because of once to twice daily dosing as compared to Captopril which requires three times a day dosing for better compliance and sustained levels.

Due to the reduction in filtration pressure the serum creatinine may rise reversibly and up to 30% from baseline is usually acceptable. Moreover chronic use is associated with chronic cough, anemia hyperkalemia and hypotension, so judicious use with close monitoring is recommended.

Rituximab:

The use of Rituximab in SRNS has not been as successful to achieve remission as it is reported with steroid dependent and frequently relapsing NS and that too with a high relapse rate as soon as the effect of the drug wears off. However, since there are no set international guidelines for the treatment, it should be tailored according to the availability of resources and expertise of the treating center.

Statins:

Hyperlipidemia is an essential feature of Nephrotic Syndrome. In children with steroid sensitive variety it improves as soon as proteinuria resolves. However, in SRNS with partial response to CNI, hypercholesterolemia is commonly seen. Treatment with statins in

these children has been shown to increase the effect of Cyclosporin. [39] We recommend that children with partial response to CNIs should get their lipid profile checked and statins may help improve the response.

Figure 6: Algorithm for treatment of SRNS

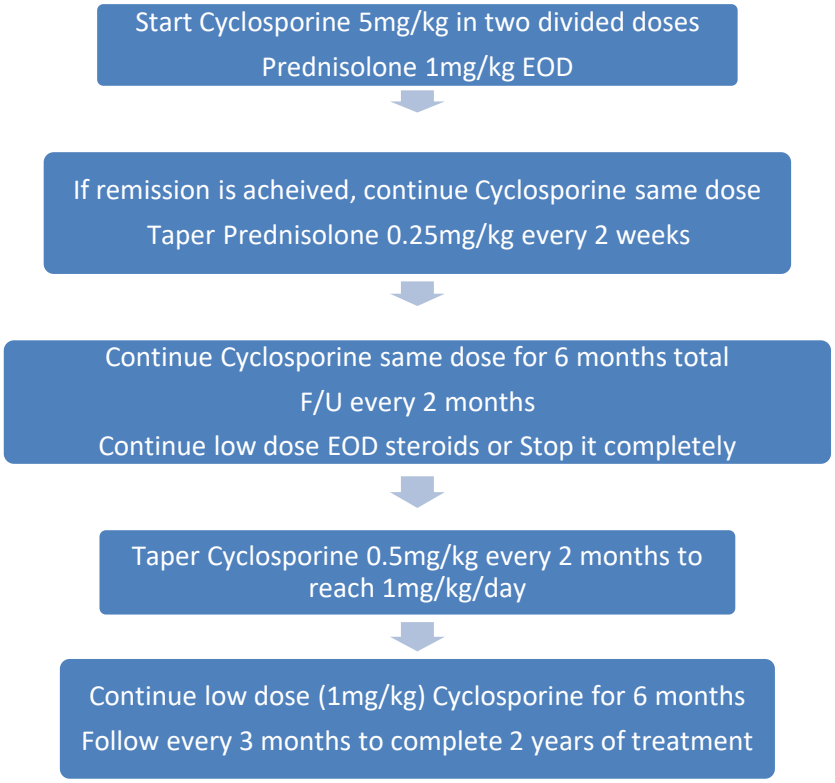
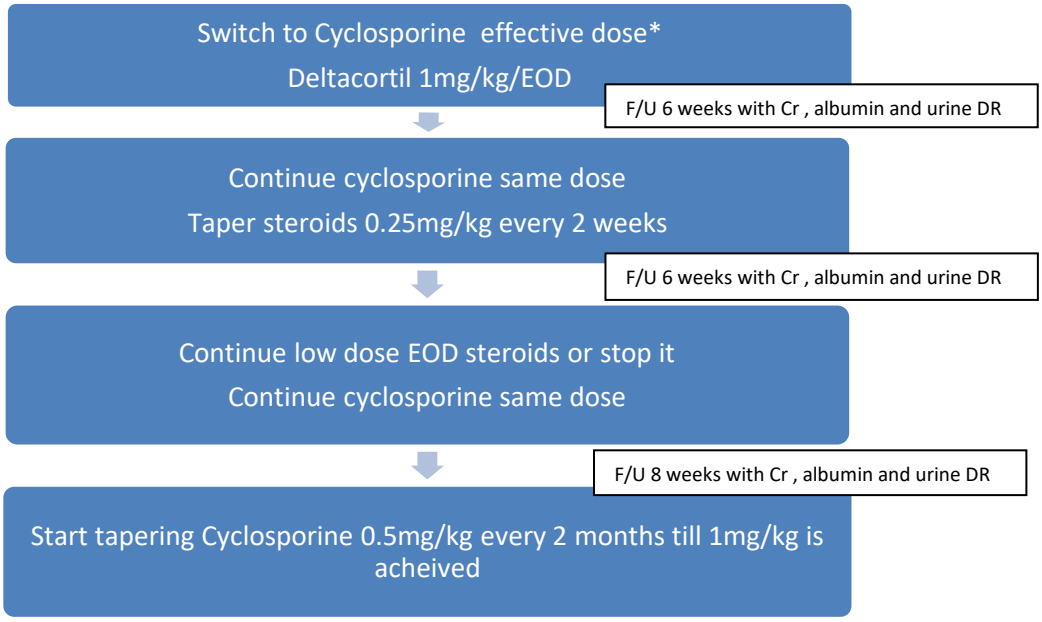


Figure 7: Algorithm for treatment of Relapse on cycl



***Effective dose:** Dose of cyclosporine on which patient achieved remission

Figure 8: Algorithm for treatment of SRNS with Tacrolimus:

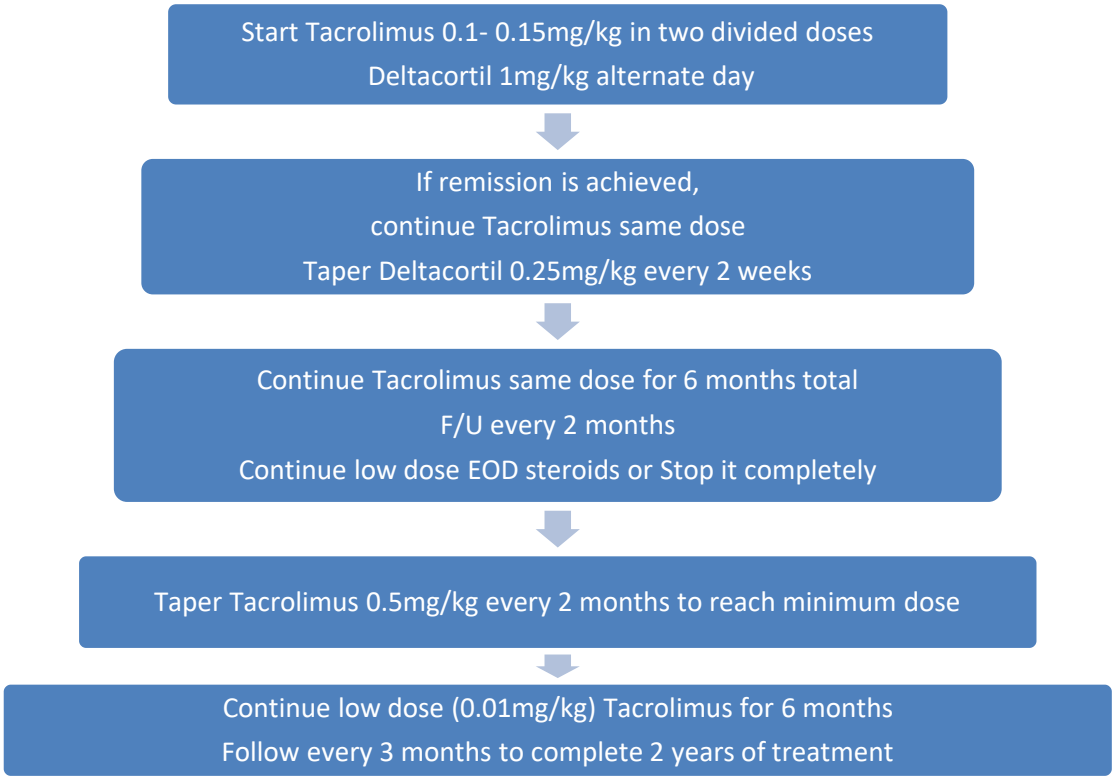
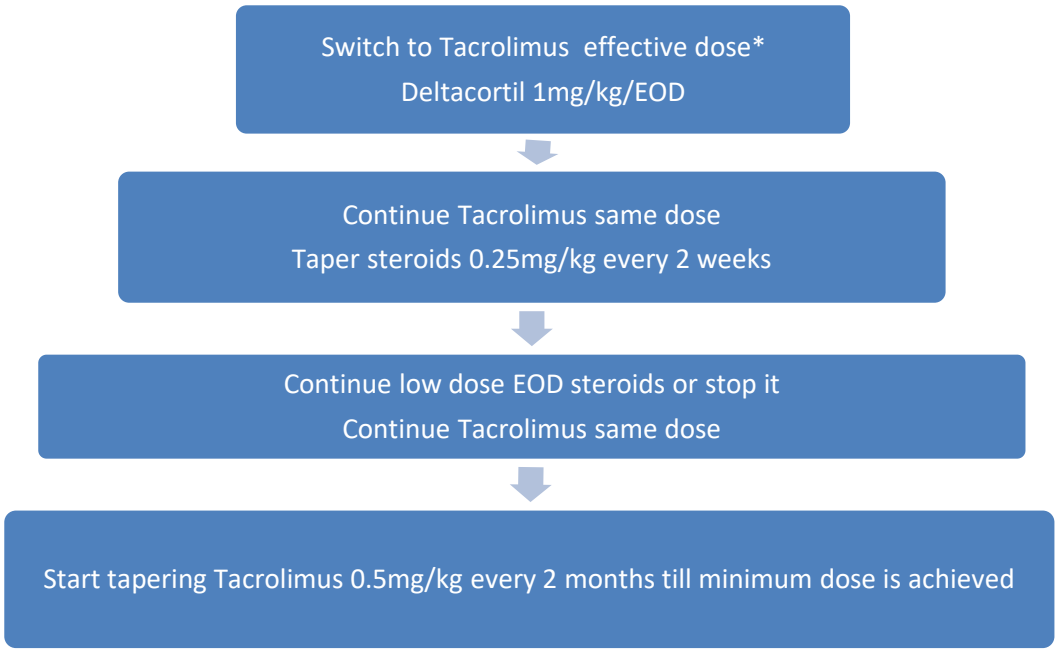


Figure 9: Algorithm for treatment of Relapse on Tacrolimus



Idiopathic Membranous Nephropathy

Membranous Nephropathy (MN) in children below 12 years of age is relatively uncommon and was seen in 8% of children who had undergone kidney biopsy for Nephrotic Syndrome at a single center in Pakistan.[40] It is more common in adolescent age group.[41]

Once all secondary etiologies are ruled out, Anti phospholipase A2 receptor (PLA_2R) antibody, should be checked where available. Lower levels of PLA_2R antibody is associated with better prognosis.[42]

For all children with MN it is recommended that the urinary protein losses should be quantified using either 24 hours collection or spot urinary protein creatinine ratio as a baseline.

Based on the degree of proteinuria, blood pressure, renal functions and PLA_2R antibody levels (where available) on presentation, risk stratification should be done. Those children who have proteinuria of less than 4gms/day, with controlled blood pressure, normal renal functions and lower PLA_2R antibody levels can be categorized as low risk group and should be treated with ACEI or ARBs without any immune suppression indefinitely till complete remission is achieved.

Children who can be categorized as high risk include

a. persistent proteinuria of more than 8gm/day after 3 months or more than 4 gm/day after 6 months of anti-proteinuric medications
b. high blood pressure even after maximum dosage of ACEI and ARBs after 3 months
c. eGFR of less than 90 ml/min on presentation or drop in eGFR of more than 20% during the course of treatment within 3 months
d. where testing is available, high titres of PLA_2R antibody.

The high risk group should be treated with immunesuppression. The choice of immune suppression protocols include steroids, Cyclophosphamide, plasma exchange, Calcineurin inhibitors and Rituximab.[43], [4445]

Since the availability and expertise with different immune suppression varies in different setups, the choice is left at the discretion of the treating physician.

Mesangiocapillary Glomerulonephritis (MCGN) / Membranoproliferative Glomerulonephritis (MPGN)

Fortunately, the incidence of idiopathic MCGN/MPGN is low. Children with these lesions may present as either Nephrotic Syndrome or with acute deterioration of renal functions.[46]

In cases of MPGN/MCGN when the clinical presentation is of rapidly progressive glomerulonephritis (RPGN), the treatment protocol includes pulse treatment with high doses of steroids however, with NS, the evidence to suggest the benefit of corticosteroids and other immunosuppressive agents is of low quality.[47]

It is generally treated with Angiotensin converting enzyme inhibitors (ACEI) and/or Angiotensin receptor blockers (ARB) as mainstay of treatment. Other general measures in the treatment of Nephrotic Syndrome like control of edema, hypertension, nutrition and vaccination should be advised as detailed in a later section.

Congenital Nephrotic Syndrome

Nephrotic syndrome appearing within 3 months of birth is labeled as congenital NS. In majority of these cases there is an evidence of genetic mutations and in some cases it may be a part of a syndrome with other associated congenital abnormalities.[48] . Please see Table 1 for these associations.

Approach to a child with CNS:

If the Nephrotic Syndrome is diagnosed within 3 months of life the baseline investigations should include antibody profile to rule out congenital TORCHS (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex and Syphilis) infections and HIV exposure in utero.

Due to heavy protein losses these children are at a very high risk of acquiring thyroglobulin deficiency which may have serious neurologic consequences during infancy. We recommend to start thyroxine replacement while thyroid profile is awaited and tailor the

dose according to TSH levels. In children with normal TSH levels but heavy proteinuria we usually continue low dose thyroxine with close monitoring of thyroid profile.

To reduce proteinuria it is recommended to treat with Enalapril (0.2 to 0.6 mg/kg/day). Diuretics can be used for severe edema either as IV infusion or as daily oral dose, however it should be borne in mind that chronic use of loop diuretics may result in electrolyte abnormalities and diuretic resistance.

This entity carries poor prognosis specially in developing countries where renal replacement therapy for small children is not widely available. In developed countries early initiation of peritoneal dialysis and nutritional build up through percutaneous endoscopic gastrostomy (PEG) tube followed by cadaveric kidney transplantation has been used successfully to treat these children.

It is imperative to counsel parents regarding the prognosis and risk of recurrence in future pregnancies.

Table 2: Common associated genetic abnormalities of Congenital Nephrotic Syndrome

Genetic	Syndromes	Unknown	Infections
• **NPHS 1 mutation (Finnish type)** • **NPHS 2 mutation (AR FSGS)** • **WT 1 mutation (DMS)** • **Laminin β 2 mutation**	• Denys Drash (WT1 mutation with DMS) • Pierson and Galloway-Mowat Syndrome (Neurologic abnormalities with CNS) • Nail Patella Syndrome (LMX 1 B mutation with dystrophic nails and Patella) • Schimke immune-osseous dysplasia (SMARCAL1 mutation and FSGS) • Cockayne Syndrome • Jeune's Syndrome	MCD FSGS Non dysmorphic DMS	Congenital Syphilis Congenital CMV Congenital toxoplasmosis

AR = Autosomal Recessive FSGS = Focal Segmental Sclerosis, DMS = Diffuse Mesangial Sclerosis, MCD = Minimal Change Disease, CMV= Cytomegalovirus

Nutrition in Nephrotic Syndrome:

The role of certain food products as a cause of Nephrotic Syndrome or its relapse is still in evolution. It is a firm belief of many people that the root cause of all the systemic diseases is through the gut. There has been limited research on this topic. The 7th edition of *Pediatric Nephrology* textbook by Avner et al has dedicated a whole chapter on this subject. There has been small scale experimental studies in which just avoidance of milk proteins and gluten containing diet has cured nephrotic syndrome in a small number of children.[49] However, there are no international guidelines on this subject.

It has been observed in our practice with the Pakistani population that some parents consider rice, salt, oil, beef, spices and other food products to be so harmful that the food for a child with Nephrotic Syndrome is cooked separately with no salt or oil and strict restrictions are enforced.

In absence of any known food allergies, there is no scientific evidence for the beneficial role of these restrictions. On the contrary, such strict restrictions may result in nutritional deficiencies. Children on steroids may experience increased appetite and in such case it results in distress and unnecessary anxiety for the parents and children.

Our group recommends restricting fluids according to the urine output and avoiding added salt till edema is present. A little more than recommended daily allowance of protein is also suggested. Otherwise hygienic and balanced diet should be advised.

Treatment of Edema in Nephrotic Syndrome:

The most worrying aspect of nephrotic syndrome for parents is edema. In most cases with mild to moderate edema, only fluid and added salt restriction is best to avoid electrolyte and volume related issues. Diuretics are indicated only if significant edema is present which is causing discomfort in walking and lying down. Oral Furosemide at 1-3mg/kg daily for 3 to 5 days is usually advised. Other class of diuretics like thiazide and potassium sparing drugs can be added if there is no response to loop diuretics. In diuretic resistant edema intravenous albumin (1gm/kg) is advised along with judicious dose of furosemide (2-3mg/kg). Since intravenous albumin has a short half life and is costly so it should be used judiciously. It is better to avoid albumin infusion in compromised renal function due to risk of

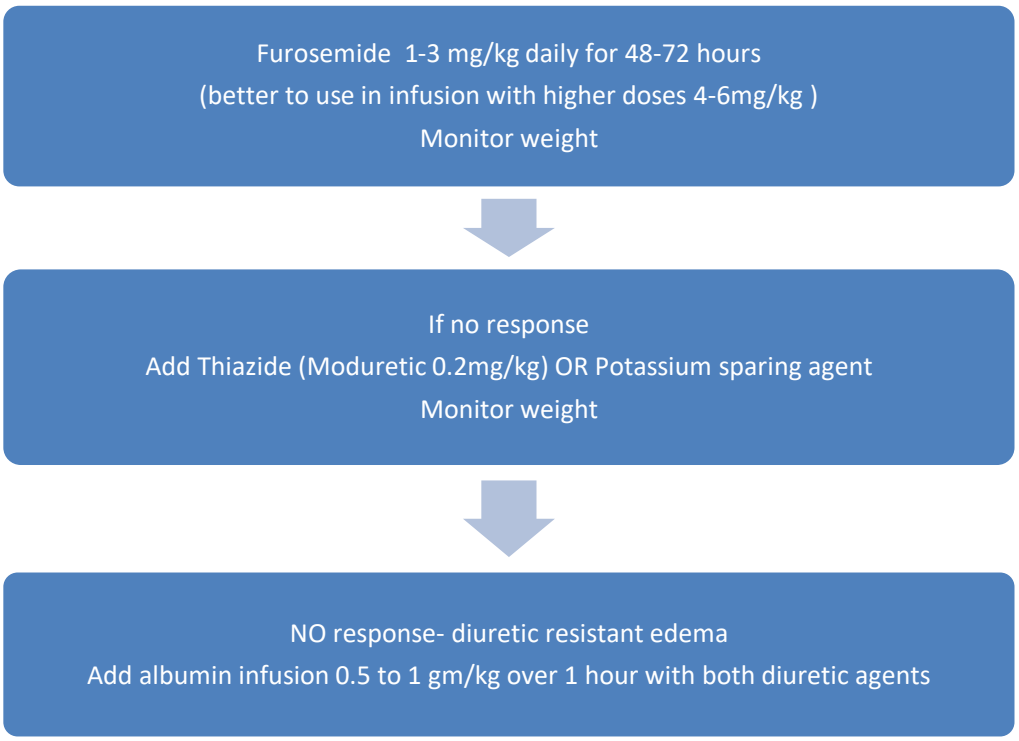
pulmonary edema.[50] In such cases of deranged renal functions and severe anasarca with respiratory distress, acute peritoneal dialysis or simply drainage of ascitic fluid has been done to relieve the respiratory distress.

The dosages of diuretics are given in table 3

Table 3: Dosages of different diuretics

Drug	Dose
Furosemide (IV or Oral)	1-3mg/kg/day
Furosemide (IV infusion)	4-6mg/kg diluted in 100ml over 4 hours
Hydrochlorthiazide(HCT) **Moduretic 5 mg/50 mg (amiloride and HCT)**	1-3mg/kg/day
Furosemide 40 mg and Amiloride 5mg	Dosage can be adjusted for individual drug and can be given as a single tablet in select cases
Metolazone	0.2mg/kg/day
Albumin 20% infusion	0.5-1gm/kg over 1 hour with diuretics

Figure 10: Algorithm for treatment of severe edema with diuretics



Infectious complications of nephrotic syndrome:

- Spontaneous Bacterial Peritonitis (SBP)
- Varicella
- Fungal infections

Spontaneous Bacterial Peritonitis (SBP)

SBP affects 1.7 – 3.7 % children with nephrotic syndrome.[51] Most common organism involved is Streptococcus Pneumoniae. Other bacteria involved can be Staphylococci, Escherichia Coli and Haemophilus Infleunzae.[52]

Usually child presents with fever, vomiting, abdominal pain and distension. Clinical examination reveals abdominal tenderness and ascites. Required blood workup includes complete blood count, CRP and blood culture. Diagnostic paracentesis should be avoided in these cases because it may leak ascitic fluid from the puncture site resulting in cellulitis. The diagnostic yield of this test is also not superior to blood cultures and in most cases does not provide any high yield diagnostic information. First dose of antibiotics (Ceftriaxone 70mg/kg/day) should be given immediately. Total duration of antibiotics is tailored according to clinical response, blood culture and sensitivity report. A total of 5 to 7 days of antibiotics is usually enough to treat mild to moderate infection. In cases of severe infection with evidence of septic shock or a beta lactam resistant pneumococcus addition of Vancomycin may be considered. Due to the increasing prevalence of multidrug resistant bacteria in Pakistan, judicious use of broad spectrum antibiotics must be ensured.

Cellulitis

Children with nephrotic syndrome are at risk of soft tissue infections. During acute disease they lose globulins and other regulatory proteins of the immune system. Moreover, they are receiving high dosages of immune suppressant medications, which make them prone to severe infections. Simple and localized cellulitis in these children may rapidly progress into necrotizing fasciitis. Prompt evaluation and treatment of soft tissue infections in these children is strongly recommended.

A thorough clinical examination is essential to document warmth, site, extent, color, tenderness, collection and bullae formation. Complete blood count, C- reactive protein, blood culture and tissue/pus culture (If obtained after incision and drainage of collection or debridement) should be sent and empirical broad spectrum antibiotics are started. Choice of definitive antibiotic and duration of therapy depends on clinical response and culture report.

Varicella infection:

Varicella infection (Chicken pox) and Zoster (Shingles) may be a serious disease in immune suppressed patients. Diagnosis is clinical based on presence of crops of vesicular lesions in different stages of healing all over the body. Same infection localized to a sensory dermatome is called zoster and represents reactivation of previous infection.

In children with nephrotic syndrome due to their compromised immune status such viral infections can disseminate rapidly. Immunosuppresion should be stopped or reduced and acyclovir (80mg/kg/day divided every 6 hours for 5 days) should be started. Renal functions are monitored and child should be kept adequately hydrated.[53] In non immune child with accidental exposure to varicella patient, post exposure prophylaxis with VZIG within 96 hours is recommended or acyclovir orally (40mg/kg/day divided 4 doses for 7 days) can be given.[54] (4)

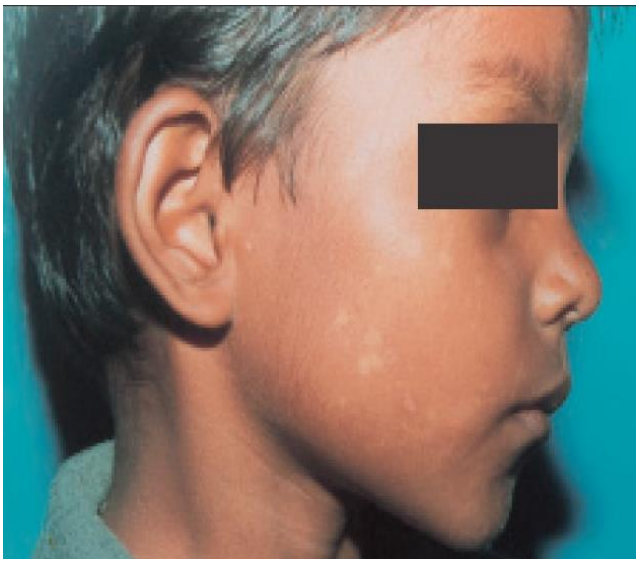
Fungal infections:

Immunosuppresion in nephrotic syndrome can lead to various fungal infections, most commonly observed are tinea versicular, tinea corporis, oral, perianal and esophageal candidiasis.

Tinea Versicular:

It presents as whitish spots and most of the time wrongly labeled as sign of calcium deficiency. It is treated withlocal application of terbinafine, miconazole and clotrimazole.

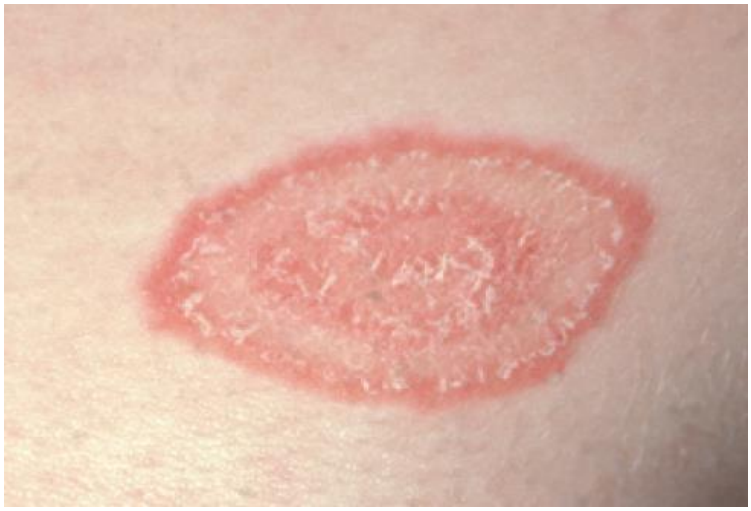
Figure 11: Tinea Versicolor



Tinea Corporis:

Most commonly presents with annular patch or plaque, raised scaling border and central clearing. It is usually treated with topical miconazole, clotrimazole and terbinafine.[55]

Figure12: Lesion of Tinea corporis



Oral, esophageal and perianal candidiasis :

Oral or esophageal candidiasis (Commonly known as oral thrush) is caused by candida species. In mild to moderate involvement local application of miconazole, nystatin and clotrimazole is enough. If no response is seen or involvement is severe at presentation specially when dysphagia is present then systemic Fluconazole is recommended. [56]

Vaccination:

For children who have missed their scheduled vaccination program according to the Extended Program of Immunization (EPI), catch up immunization is advised.

Non- EPI vaccines like varicella and influenza should be given as these viral infections may cause relapse and significant morbidity in non-immunized children with Nephrotic Syndrome.

All the vaccinations should ideally be administered during the remission phase when they are off immune suppression. Children during the acute phase of illness or while on immune suppressive medications should not receive live vaccines like Varicella, measles, mumps, rubella, rotavirus and oral polio. All other inactivated or killed vaccines are considered safe in immune compromised patients. [57]

Due to the high incidence of communicable diseases in Pakistan we recommend that live vaccines should be deferred until:

- Prednisolone dose is less than 2mg/kg/day or total dose is less than 20mg /day for children who weigh more than 10 kg.
- At least 3 months after stopping cyclophosphamide, CNI and MMF
- All live vaccines should be avoided in CNS.

Alternate Steroids and their equivalent dosages:

In most cases the steroid of choice is plain prednisolone tablets. Enteric coated forms can be used, however the bioavailability may decrease and there is additional cost with no significant benefit. Other steroids like hydrocortisone, dexamethasone and deflazacort have been used in small trials with no significant benefit and hence not recommended.

If a child for any reason cannot swallow medications during acute illness then a nasogastric or oral tube can be used to administer Prednisolone. In rare cases Intravenous formulations can be given with following conversions.

Table 4: Corticosteroid conversion estimates

Glucocorticoid	Equivalent dose	Biological half-life (hours)
Prednisolone	5mg	18-36
Hydrocortisone	20mg	8-12
Methylprednisolone	5mg	18-36
Dexamethasone	0.75mg	36-54

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