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Original Research Article

# Spectrum of infection in children with steroid responsive nephrotic syndrome

**Dr. Payal Mittal[1], Dr. D. K. Bhagwani[2], Dr. Pranav Gupta[3], Dr. Abhishek Singh[4]**
[1]Senior Resident, Department Pediatrics, F H Medical College, NH-2, Tundla
[2]Senior Specialist, Department Pediatrics, Hindu Rao Hospital, Delhi
[3]Senior Resident, Department Pediatrics, Hindu Rao Hospital, Delhi
[4]Assistant Professor, Department of Community Medicine, SHKM Govt. Medical College, Haryana

***Corresponding author**
Dr. Abhishek Singh
Email: mail2aks1@yahoo.co.in

**Abstract:** Infection in patients with nephrotic syndrome has been described as hallmark of idiopathic nephrotic syndrome. The aim of present article is to study the clinical profile of infections in children with steroid responsive nephrotic syndrome and correlation of serum albumin and serum cholesterol level with episodes of infection in children with steroid responsive nephrotic syndrome. The predictive value of C-reactive protein in cases of suspected infection in children with nephrotic syndrome was also taken into consideration. This cohort study comprised of minimum of 62 children from November 2008 to October 2010 with steroid responsive Nephrotic syndrome presenting with symptoms of infections to Hindu Rao Hospital Emergency/ward/Nephrology clinic and follow up of children attending the nephrology clinic at monthly interval. Among steroid responsive nephrotic syndrome children we found most common infection was upper respiratory tract infection (65.1%) followed by acute diarrhoea 23.15%, Urinary tract infection 2.34%, pneumonia 1.67%, tuberculosis 1.34%, septicaemia + peritonitis1.34% , chronic suppurative otitis media 1%, miscellaneous 4.36 %. On evaluation of biochemical parameter of nephrotic syndrome our study revealed total protein, albumin were significantly ($p<0.05$) lower and cholesterol was significantly higher on comparing infection with no infection during relapse. CRP was positive during pneumonia, septicaemia, peritonitis. Infections are more common in frequent relapse and steroid dependent nephrotic syndrome children. CRP is useful as a marker during invasive bacterial infection.
**Keywords:** Albumin, Infections, Nephrotic syndrome, Steroids

## INTRODUCTION

Nephrotic Syndrome is an important chronic disease in children. About 80% children with idiopathic nephrotic syndrome show remission of proteinuria following treatment with corticosteroid and are classified as steroid sensitive [1]. Infections remain an important complication of children with nephrotic syndrome especially in the developing countries as India. Besides being the commonest cause of mortality, infections result in significant morbidity and may also be responsible for a poor response to steroid therapy or induce relapse in a child who has already attained remission. There have been several studies of infections in nephrotic syndrome predominantly from developed countries and most of hospitalized children. Since the majority of children with nephrotic syndrome are managed on an outpatient basis, these studies do not cover the entire spectrum of infection [2].

Infection in patients with nephrotic syndrome has been described as hallmark of idiopathic nephrotic syndrome [3]. The mortality rate from infection is high: an estimated 1.5% children with nephrotic syndrome died from overwhelming infection during follow up [4]. In the past many children with nephrotic syndrome died from infection and particularly from peritonitis due to Pneumococci [5].

With the advent of antibiotic therapy and steroid therapy in the last 50 years, much progress has been achieved, with dramatic reduction in the mortality [6]. Despite the improvement in the mortality rates in INS following the introduction of steroid therapy and other immunotherapy, it is still necessary to keep in mind that these agents can also predispose patients to infectious process [6, 7]. Even so, the use of these drugs serves to

maintain the patients free from recurrences and to control proteinuria for prolonged periods [7].

## MATERIALS AND METHODS

This is a prospective cohort study, done in department of pediatrics Hindu Rao hospital from November 2008 to October 2010. Total 62 children with steroid responsive nephrotic syndrome between 1-12 year of age were enrolled for this study. Study population was divided in 4 groups as first episode, infrequent relapse, frequent relapse and steroid dependent. Children with congenital renal disease, steroid resistant nephrotic syndrome, Children less than one year and more than 12 year, children on other immunosuppressive (Cyclophosphamide, cyclosporine, tacrolimus etc.), statin and albumin were excluded from study. This study is broadly divided in 4 parts i.e.

1. Diagnosis of nephrotic syndrome (hypoalbuminemia (serum albumin less than 2.5gm/dl), hyperlipidemia (serum cholesterol more than 200mg/dl) and edema. Nephrotic range proteinuria is present if early morning urine protein is 3+ or 4+ (on dipstick or boiling test).And Identification of group: First episode, Infrequent Relapse, Frequent Relapser (Two or more relapse in initial six months or more than three relapses in any twelve months.), Steroid Dependent (Two consecutive relapses when on alternate day steroid or within 14 day of its discontinuation.)
2. Clinical profile of children (symptoms with which they presented).
3. Investigation for infections complete blood count, renal function test, total serum protein, serum albumin, total cholesterol, urine routine and culture, fluids (pleural, peritoneal, cerebrospinal fluid) gram stain, cytology, biochemistry, culture. Urine culture in all patient with first episode, relapse and with symptom of UTI frequency, dysuria, fever, hematuria. Ultrasound in all patients of UTI. CRP was done as semi quantitative (>6-positive)
4. Treatment of nephrotic syndrome and infection.

## RESULTS

Study group comprise of 62 children (male 41, female 21) who had total 298 infections during study period. Mean age at onset of nephrotic syndrome was 3.5 yr with maximum number of patient's age of onset ranging between 1-5 year. Children are distributed according to their response to steroid as 1st episode (14) Infrequent relapser (27) Frequent relapser (4) SDNS (17). There are 2 deaths in our study; mortality is due to infection (septicemia).

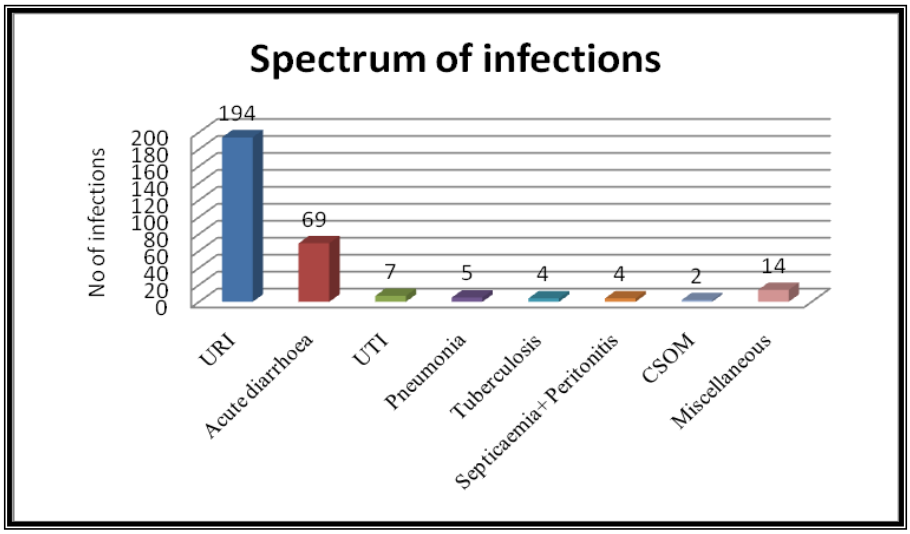


**Fig 1A: Spectrum of infections in 62 children with steroid responsive nephrotic syndrome**

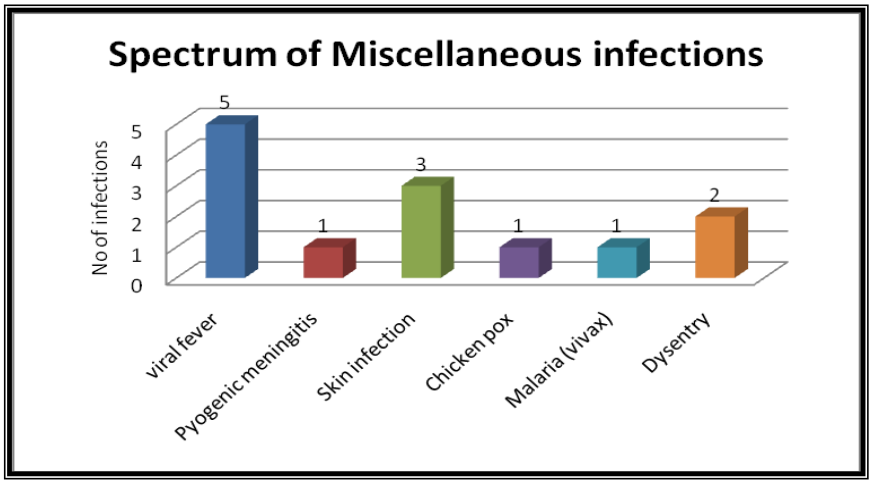


**Fig 1B: Spectrum miscellaneous of infections in 62 children with steroid responsive nephrotic syndrome**

Upper respiratory tract infection was the most common infection found and was the commonest infection causing relapse (65.1%). The other major infection was acute diarrhoea. Other infections like Urinary tract infection, pneumonia, tuberculosis, septicaemia, peritonitis, chronic suppurative otitis media , miscellaneous (miscellaneous infection include viral fever, pyogenic meningitis, skin infection, chicken pox, malaria, dysentery) were collected to less than 5% of presentation. Incidence of infection is more in frequent relapser and steroid dependent nephrotic syndrome children (p=0.04).There were 2 death due to septicaemia. In this study we found no significant difference in blood urea and serum creatinine with infection and no infection group Children who presented with infection with relapse had significantly lower serum albumin ($p<0.05$) and significantly higher cholesterol ($p<0.05$). On comparing individual infection with no infection our study revealed albumin was statistically significantly lower ($p<0.05$) with tuberculosis but highly significantly lower($p<0.01$) with urinary tract infection, pneumonia and septicaemia +peritonitis while total protein was significantly lower with upper respiratory tract infection and miscellaneous infection(viral fever, pyogenic meningitis, skin infection, malaria and dysentery) and highly significantly lower with pneumonia and septicaemia peritonitis. Cholesterol was significantly higher in urinary tract infection and highly significantly higher during tuberculosis, septicaemia +peritonitis and miscellaneous infection. Albumin was less than 1.5 gm/dl during pneumonia, septicaemia and peritonitis

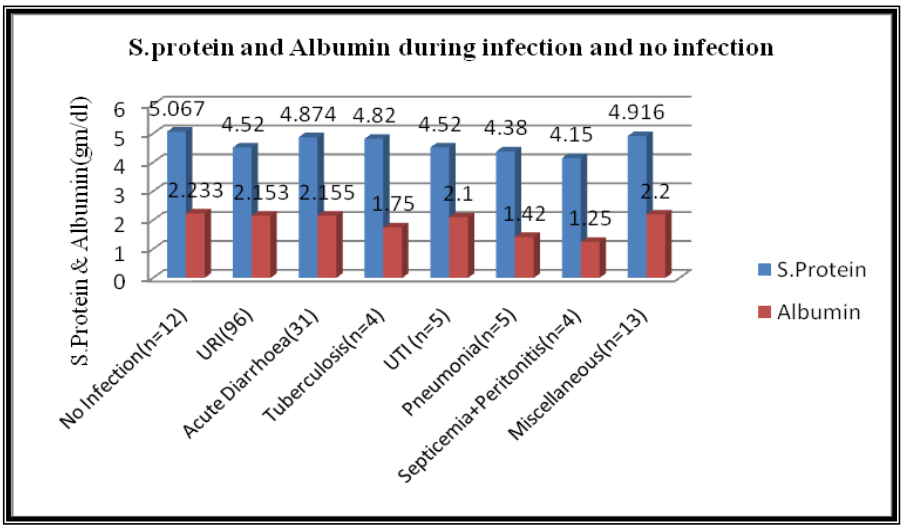


**Fig 2: Serum protein and albumin in different infection during relapse in children with steroid responsive nephrotic syndrome**

Total 7 number of urinary tract infection was found with male to female ratio of 3:4. All UTI were due to gram negative organism 6 E.Coli and only 1 klebsiella. C-reactive protein was positive only in 11 infections (pneumonia, septicemia, and peritonitis, 1 episode of CSOM and 1 episode of UTI).

**DISCUSSION**

Nephrotic syndrome represents an immunocompromised state, predisposing to various infections. The study design of this study was to identify spectrum of infections, correlation of albumin and cholesterol with infection. In our study we found upper respiratory tract infections being most common infection as similarly reported by Alwadhi *et al.;* [8] (Delhi) and Moorani *et al.;* [9] (Pakistan). The association of respiratory viral infections with onset of an episode of nephrotic syndrome or with exacerbations and relapses is known, but the exact relationship between the two events is difficult to define because viral URI are common in childhood and often ignored. Thus it is difficult to state with certainty whether an episode of URI has led to an episode of nephrotic syndrome or the two events are independent of each other.

Nevertheless, a prospective study conducted in Children's Hospital Ottawa over two winter seasons, among 32 children with nephrotic syndrome reported that 71% of exacerbations (defined as an increase in proteinuria from negative or trace to 3+ for >7 days) and 69% of relapses were temporally associated with URI (within the preceding 5–10 days) [10]. We also found density of infections were more in steroid dependent nephrotic syndrome and frequent relapser which is similar to Emilia *et al.;* [11] and Gulati *et al.;* [2]. This may be due to the long term immunosuppressive therapy to steroid dependent and frequent relapser children or disease per se. In this study 3 children had septicaemia of which 2 died and one patient who survived was on ventilator for 7 days. 1 patient was lost to follow up.

In our study we found 7 urine culture positive cases of which 6 were positive for E. coli and 1 positive for Klebsiella. In this study all isolated organisms were gram negative similar to other studies. E. coli is the most common organism isolated from urine culture similar to Gulati *et al.;* [2] and Senguttuvan *et al.;* [12]. We also found urinary tract infection during remission this is similar to McVicar *et al.;* [13] who found UTI`s have no role in the incidence of relapses in nephrotic syndrome. It is interesting that Gram negative organisms were responsible for most infections, including urinary tract infection and chronic suppurative otitis media which is similar to Gulati *et al.;* [2]. Sterile cultures in pneumonia, septicaemia and peritonitis might be due to administration of antibiotics prior to admission.

On evaluation of biochemical parameter of nephrotic syndrome our study revealed total protein, albumin were significantly ($p<0.05$) lower and cholesterol was significantly higher on comparing infection with no infection during relapse. And on comparing individual infection with no infection our study revealed albumin was statistically significantly lower ($p<0.05$) with tuberculosis but highly significantly lower($p<0.01$) with urinary tract infection, pneumonia and septicaemia +peritonitis while total protein was significantly lower with upper respiratory tract infection and miscellaneous infection(viral fever, pyogenic meningitis, skin infection, malaria and dysentry) and highly significantly lower with pneumonia and septicaemia+peritonitis.

Albumin was less than 1.5 gm/dl during pneumonia, septicaemia and peritonitis similar to Hingorani *et al.;* [14] they found during peritonitis serum albumin level less than or equal to 1.5 gm/dl at initial presentation were estimated to have a 9.8 fold increased in the odds of developing peritonitis than those with an initial albumin greater than 1.5gm/dl.
Cholesterol was significantly higher in urinary tract infection and highly significantly higher during tuberculosis, septicaemia +peritonitis and miscellaneous infection. These suggest that defects in humoral as well as cell-mediated immunity may predispose children to such infections. The serum albumin levels have been found to correlate well with serum properdin B levels. It is however quite possible that infections increased protein catabolism and the lower serum albumin was due to infections per se2.

In this study we have also studied C-reactive protein as a guide to bacterial infection to start antibiotic therapy and effect on activity of C-reactive protein with nephrotic syndrome. There was no effect on C-reactive protein activity with nephrotic syndrome similar to J Eskola *et al.;*. In our study among 298 infections CRP was positive during 11 infections only. It was positive in all 5 episodes of pneumonia, 3 episodes of septicaemia, 1 episode each of peritonitis, CSOM (chronic suppurative otitis media) and UTI. This result is similar to Eskola *et al.;* [15]. CRP does discriminate the invasive bacterial disease from other

infections. It was not affected by nephrotic activity per se. With present study CRP was positive during relapse as nephrotic state does not affect CRP. As CRP was positive in 1 case of urinary tract infection (probably indicator of upper urinary tract infection) and negative in 6 culture positive cases (probably lower urinary tract infection) which is similar to Hellerstein *et al.;* [16]. Hence CRP is useful in differentiating upper and lower urinary tract infection.

## CONCLUSION

To conclude infections are more common in frequent relapser and steroid dependent nephrotic syndrome children. Total protein, albumin was lower and cholesterol was higher during infection as compared to no infection. CRP is useful in differentiating invasive from invasive infection.

## CONSENT

Written informed consent was obtained from all the patients for publication of this case series.

## ETHICAL CONSIDERATIONS

This study has been approved by an ethical Committee of Hindu Rao Hospital. Also patient's parents will be asked for their informed consent, giving full details, for inclusion in this study.

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