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Study of major infections observed in children suffering from nephrotic syndrome from Bihar region

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Abstract
Infections remain an important cause for morbidity and mortality in children with nephrotic syndrome. Pneumococcal infections are the most common invasive bacterial infections in these children. Infections can lead to repeated relapses, poor response to steroid therapy and prolonged hospitalization. Hence the present study was planned to evaluate the major infections in the children's suffered from the Nephrotic Syndrome in the Bihar region.
The present study was planned in the Upgraded Department of Paediatrics in Patna Medical College Patna from Feb 2018 July 2018.Total 50 children's diagnosed with the nephrotic syndrome were enrolled in the present study. The enrolled children's with the Nephrotic syndrome were evaluated for the major infections. Major infections were defined as infections affecting deep organs and tissues which warrant hospitalization.
The complications of the nephrotic syndrome can be divided into two categories, disease-associated and treatment-related. Hence it is important to start with early identification and appropriate treatment for acute complications. From the present study and the reported literature it can be concluded that major infections remain an important complication of nephrotic syndrome in children, especially during relapses. Drug resistant organisms should be considered while treating these infections in children with nephrotic syndrome. Counselling the parents is very important for the prompt management of these children.

Keywords: nephrotic syndrome, children's, infections, drug resistant

Introduction
Nephrotic syndrome is a common kidney disease characterized by heavy loss of protein in urine, low blood protein levels, high cholesterol levels and swelling. This disease can occur at any age but is seen more frequently in children compared to adults. Nephrotic syndrome is characterized by its cycle of response to treatment, manifested by gradual tapering and discontinuation of medication, treatment free period of remission and frequent relapses causing swelling. As the cycle of recovery and recurrence repeats for a long period (years), this disease is a matter of worry for both the child and the family.
The kidney works as a sieve (filter) in our body that removes waste products and extra water from blood and passes them out via the urine. The size of the holes of these filters is so small so that in normal circumstances proteins that are large in size do not pass into the urine. In nephrotic syndrome the holes of these filters become large, so protein leaks into the urine. Because of the loss of protein in urine, the level of protein in the blood falls. Reduction of protein level in blood causes swelling (the medical term for the swelling seen in these patients is edema). The severity of edema varies depending on the amount of protein lost in the urine and reduction in protein level of blood. The kidney function (i.e., the ability to filter waste products or the glomerular filtration rate), per se, is normal in most patients with nephrotic syndrome.
In over 90% of children the cause of nephrotic syndrome (called primary or idiopathic nephrotic syndrome) is not known. Primary Nephrotic Syndrome is caused by four pathological types: minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy and membranoproliferative glomerulonephritis (MPGN). Primary nephrotic syndrome is a "diagnosis of exclusion", i.e. they are diagnosed only after secondary causes have been excluded. In less than 10 % of cases, nephrotic syndrome may be secondary to different conditions such as infection, drug exposure, malignancy, hereditary disorders or systemic diseases such as diabetes, systemic lupus erythematosus and amyloidosis.
The most common cause of nephrotic syndrome in children is minimal change disease (MCD). This disease occurs in 90 percent of cases of idiopathic nephrotic syndrome in young children (under age six) and in 65% of cases in older children.
In a typical child with minimal change disease, blood pressure is normal, red blood cells are absent in urine and the values of serum creatinine and complement 3 (C3) are normal. Of all the causes of nephrotic syndrome, minimal change disease is the least stubborn, as over 90% of the patients respond well to steroid therapy [1].
Along with obtaining a complete medical history, a series of biochemical tests are required in order to arrive at an accurate diagnosis that verifies the presence of the illness. In addition, imaging of the kidneys (for structure and presence of two kidneys) is sometimes carried out, and/or a biopsy of the kidneys. The first test will be a urinalysis to test for high levels of proteins, [2]. As a healthy subject excretes an insignificant amount of protein in their urine. The test will involve a 24-hour bedside urinary total protein estimation. The urine sample is tested for proteinuria (>3.5 g per 1.73 m2 per 24 hours). It is also examined for urinary casts,

which are more a feature of active nephritis. Next a blood screen, comprehensive metabolic panel (CMP) will look for hypoalbuminemia: albumin levels of ≤2.5 g/dL (normal=3.5-5 g/dL). Then a Creatinine Clearance CCr test will evaluate renal function particularly the glomerular filtration capacity [3]. Creatinine formation is a result of the breakdown of muscular tissue, it is transported in the blood and eliminated in urine. Measuring the concentration of organic compounds in both liquids evaluates the capacity of the glomeruli to filter blood. Electrolytes and urea levels may also be analysed at the same time as creatinine (EUC test) in order to evaluate renal function. A lipid profile will also be carried out as high levels of cholesterol (hypercholesterolemia), specifically elevated LDL, usually with concomitantly elevated VLDL, is indicative of nephrotic syndrome.

A kidney biopsy may also be used as a more specific and invasive test method. A study of a sample's anatomical pathology may then allow the identification of the type of glomerulonephritis involved. However, this procedure is usually reserved for adults as the majority of children suffer from minimum change disease that has a remission rate of 95% with corticosteroids. A biopsy is usually only indicated for children that are corticosteroid resistant as the majority suffer from focal and segmental glomerulosclerosis [4]. Further investigations are indicated if the cause is not clear including analysis of auto-immune markers (ANA, ASOT, C3, cryoglobulins, serum electrophoresis), or ultrasound of the whole abdomen.

The prognosis for nephrotic syndrome under treatment is generally good although this depends on the underlying cause, the age of the patient and their response to treatment. It is usually good in children, because minimal change disease responds very well to steroids and does not cause chronic renal failure. Any relapses that occur become less frequent over time; the opposite occurs with mesangiocapillary glomerulonephritis, in which the kidney fails within three years of the disease developing, making dialysis necessary and subsequent kidney transplant. In addition children under the age of 5 generally have a poorer prognosis than prepubescents, as do adults older than 30 years of age as they have a greater risk of kidney failure [5]. Other causes such as focal segmental glomerulosclerosis frequently lead to end stage renal disease. Factors associated with a poorer prognosis in these cases include level of proteinuria, blood pressure control and kidney function (GFR). Without treatment nephrotic syndrome has a very bad prognosis especially rapidly progressing glomerulonephritis, which leads to acute kidney failure after a few months.

Infections remain an important cause for morbidity and mortality in children with nephrotic syndrome. Pneumococcal infections are the most common invasive bacterial infections in these children. Infections can lead to repeated relapses, poor response to steroid therapy and prolonged hospitalization. Hence the present study was planned to evaluate the major infections in the children's suffered from the Nephrotic Syndrome in the Bihar region.

Methodology

The present study was planned in the Upgraded Department of Paediatrics in Patna Medical College Patna, from Feb 2018 to July 2018.Total 50 children's diagnosed with the nephrotic syndrome were enrolled in the present study. The enrolled children's with the Nephrotic syndrome were evaluated for the major infections. Major infections were defined as infections affecting deep organs and tissues which warrant hospitalization.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

- **Inclusion Criteria:** Children's of age 1 to 12 years, Diagnosed with the Nephrotic syndrome.
- **Exclusion Criteria:** Children with congenital nephrotic syndrome

All children fulfilling the inclusion criteria were subjected to a thorough clinical examination. Data including age, gender, clinical features, laboratory parameters and type of infection, were computed.

Results & Discussion

The data from the 50 patients were collected and presented as below. The data were gathered and discussed with the already reported literature.

Patients with relapses, especially frequent relapses have a higher risk of developing serious infections, and prolonged steroid therapy significantly contributes to this. Present study showed more major infections in relapses than initial episode nephrotic syndrome. Pneumonia was the commonest infection in our study. UTI was the second most common infection in our study which correlate with studies from other parts of India and other developing countries.

Table 1: Clinical Profile of the children's

Parameters	**No. of Cases**
Male	32
Female	18
Mean age in year	2 – 8 years
Clinical Profile	**No. of Cases**
Fever	41
Abdominal pain, vomiting or diarrhea	26
Specific urinary symptoms	9
Cough and/or tachypnea	24
Shock	3
Hypertension	5
Leucocytosis	22
Neutrophilia	18
Thrombocytosis	23
Thrombocytopenia	2

Table 2: Major infections Observed

Major infections	**Total Cases**	**Initial episode Cases**	**Relapses Cases**
Pneumonia	21	6	15
Urinary tract infections	13	3	10
Septicemia	8	3	5
SBP	4	0	4
Cellulitis	2	2	0
Perinephric abscess	1	1	0
Pulmonary tuberculosis	1	1	0
Total infections	50	16	34

Table 3: Pathogens isolated

Pathogens isolated	Total	Multi Drug Resistant
E. coli	7	7
Methicillin Resistant Staphylococcus Aureus	4	0
Klebsiella	3	2
Coagulase Negative Staphylococcus	2	0
Proteus	1	0
Pneumococci	2	0
Overall bacteria	19	9

Antibiotics played an important role in treating the infections that arose from nephrotic syndrome, and the mortality rate reduced drastically from two-third to 35% [6]. It is important to point out that prior to availability of steroids multiple desperate treatments were tried. A study from Boston noted the various treatments that were attempted from 1926 to 1948 for nephrotic syndrome. Dietary modification and low salt diet were probably the most effective treatments at that time. There were some weak mercurial diuretics with little if any action. Other drastic measures, such as the induction of measles and vaccinia, were instituted. Many of the children inoculated had some form of post-infection diuresis and decrease in proteinuria (11 out of 14), only to recur. Other supportive measure included blood transfusions, antibiotic therapy, treatment with thyroid extract, decapsulation of the kidney, testosterone, multiple vitamins, horse antiserum, and parathyroid hormone.

The causes of nephrotic syndrome in the neonate and infant can be divided broadly into acquired or hereditary etiologies. Acquired cases may be due to a variety of infectious, toxic, and immunologic etiologies and tests to rule out syphilis, toxoplasmosis, hepatitis B, cytomegalovirus, or rubella infections constitute part of the initial work-up (Eddy & Symons 2003) [7]. Although the genetic underpinnings of nephrotic syndrome have long been appreciated, it has only been over the past decade that studies of monogenic forms of nephrotic syndrome have been fruitful and have since helped decipher the pathophysiologic mechanisms of the glomerular filtration process.

The nomenclature for glomerulonephritis associated with infections has become confusing. In a recent study, Glassock *et al*. [8]. proposed a nomenclature for glomerulonephritis associated with infections, which were classified into two, post-infectious glomerulonephritis (PIGN) and Infection-related glomerulonephritis (IRGN). Some patient exhibited some clinical findings, such as fever, weight gain and leg edema, simultaneously, and there was no latent period. Such a clinical course suggested that our patient had IRGN, which was directly related to the infection itself, but without any evidence of an ongoing infection. Another possibility must be considered, i.e., that the causative agent could directly damage the kidney tissue, followed by immunocomplex-type glomerulonephritis, as suggested in parvovirus B19 IRGN [9]. Increased mitosis is usually interpreted as a repair process of tissue injury.

Glomerulonephritis associated with infection is commonly triggered by streptococci, although many other organisms, including bacterial, viral, parasitic, rickettsial and fungal infections, can also cause the condition [10-11].

Acute glomerulonephritis associated with several viral infections, such as B19, hepatitis A virus, measles, yellow fever and Epstein-Barr virus, was reported [10-11]. In such cases, extrarenal specific symptoms associated with viruses (such as rash, liver injuries, lymph adenopathy, and arthralgia) were present. Patients with NS are at increased risk for infections. Although the incidence of infections in NS has decreased in advanced countries, they are still a major problem in developing countries.

Sepsis remains one of the main causes of death in children with NS [12]. Children treated with cytotoxic drugs have a higher clinical infection rate than those treated only with prednisolone [13]. In children with NS, Streptococcus pneumoniae is known to be the most important organism in primary peritonitis. However, other organisms such as β-hemolytic streptococci, Haemophilus and Gram-negative bacteria are also frequently found [14-15]. Cellulitis is also the result of β-hemolytic streptococci or a variety of Gram-negative bacteria.

Several immunological factors such as low serum immunoglobulin G concentrations, factor B and factor I in the alternative pathway components, transferrin, depressed T-cell function, and physiological factors such as fluid collection in cavities and dilution of local humoral defenses by edema may play a major role in the susceptibility of nephrotic patients to infection8).

Conclusion

The complications of the nephrotic syndrome can be divided into two categories, disease-associated and treatment-related. Hence it is important to start with early identification and appropriate treatment for acute complications. From the present study and the reported literature it can be concluded that major infections remain an important complication of nephrotic syndrome in children, especially during relapses. Drug resistant organisms should be considered while treating these infections in children with nephrotic syndrome. Counselling the parents is very important for the prompt management of these children.

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