

# Long term outcome of Immunoglobulin M (IgM) Nephropathy of Children in National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, Bangladesh

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## Abstract

**Background:** Immunoglobulin M nephropathy (IgMN) is a new clinico-immunopathologic entity which present mainly as idiopathic nephrotic syndrome in both children and adults. The clinical manifestation of IgMN are highly variable presenting with isolated haematuria or asymptomatic proteinuria. About 6 to 23 percent of IgMN patient developed end stage kidney disease. Usually treated with immunosuppressive agents (cyclosporine/tacrolimus) along with corticosteroid has response rates up to 50%. In our institute last few years we have observed a surprisingly rise of IgM nephropathy in children.

**Objective:** To see the response of IgMN children treated with tacrolimus or mycophenolate mofetil(MMF) and long term follow up to observe their outcome.

**Methodology:** This was a prospective observational study done in the Department of Paediatric Nephrology, National Institute of Kidney Diseases & Urology, Dhaka, starting from January/2014 to December/2017. The study population consists of 86 IgMN children, age ranges from 2 to 12 years. The study was approved by institutional ethical review committee and informed written consent was taken from every parents. Twenty seven patients(Group-I) were selected purposively and treated with MMF and 59 patients (Group-II) treated with tacrolimus for 2 years. Patients were followed up three monthly onward in a prescribed form including adverse effect of drugs. Clinical outcome data like remission, active disease, active disease with renal impairment and dependency on renal replacement therapy(RRT) were documented for statistical analysis.

**Results:** Of 86 IgMN children most of them were older than >8-12 years in both groups and the highest percentage were clinically diagnosed as frequently relapsing nephrotic syndrome. In Group I 43.48% children remain on remission, 13.04% have active disease, 30.43% are active disease with impaired renal function and 4.35% went into RRT. In Group II 55.56% children remain on remission, 12.96% have active disease, 16.67% are active disease with impaired renal function and 5.56% dependent on RRT.

**Conclusion:** From above observations, the overall prognosis of IgMN children is not good. The clinical course and disease outcome did not differ significantly between two groups treated with mycophenolate mofetil and tacrolimus.

**Key words:** Childhood nephrotic syndrome, IgM nephropathy, mycophenolate mofetil, tacrolimus.

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## Introduction:

Immunoglobulin M nephropathy (IgMN) is recently described and still a controversial clinico-immunopathologic entity which present mainly as idiopathic nephrotic syndrome in both children and adults<sup>1</sup>. Although, it is widely believed that this lesion was described for the first time in 1978 by two independent research groups led by Cohen<sup>2</sup> and Bhasin<sup>3</sup> in patients presenting with heavy proteinuria, the deposits of predominant IgM in glomeruli, in fact, were first described in renal biopsies in 1974 by Putte et al<sup>4</sup> in patients presenting with persistent or recurrent

haematuria. Soon after the formal recognition of the disease as a distinct entity in 1978, many series were reported throughout the world. The incidence of IgM nephropathy varies in different studies from 2% to 18.5%<sup>3,5,6</sup>. The pathogenesis of IgMN remains unclear, some have suggested abnormal T-cell function or a depressed immune-aggregate clearance by mesangial cells<sup>7,8</sup>. In support of these theories, many studies have found elevated serum IgM or IgM immune-complex concentrations in patients with IgM nephropathy<sup>9,10</sup>. The clinical manifestations of IgMN are highly variable, present with isolated haematuria or asymptomatic proteinuria<sup>11,12</sup>. The natural history and prognosis of IgMN depends on its presentation and morphology of renal tissue. Important complications of IgMN is the transition of mesangial proliferative glomerulonephritis to progressive kidney disease on repeat biopsies<sup>13</sup>. The rate of end stage renal disease development in many reported studies varied from 6 to 23 percent<sup>12,14,15</sup>. Corticosteroid constitutes the backbone of treatment in minimal change disease or primary focal segmental glomerulosclerosis<sup>16</sup>. Immunosuppressive agents like oral calcineurin inhibitors(cyclosporine/ tacrolimus) has been used in a number of studies with response rates of up to 50%<sup>12</sup>. Recurrent disease after transplantation has been successfully treated with anti-CD antibodies(rituximab), in combination with plasma exchange and immunoglobulins<sup>17</sup>. Last few years from 2009 in our institute, on kidney biopsy series IgM nephropathy were surprisingly increased and 2014, 2015, 2016 & 2017 it was more than one-third of total biopsy. We reviewed articles about IgM Nephropathy to organize the management of IgM Nephropathy, but no such consensus have been found. Then we decided to treat IgMN in children with mycophenolate mofetil(MMF) or tacrolimus along with steroid and long term follow up was given to observe their response.

#### Methodology:

This prospective study was done in the department of Paediatric Nephrology, National Institute of Kidney Diseases & Urology, Sher-e-Bangla Nagar, Dhaka, from January/2014 to December/2017. All relevant information including family history, previous treatment of nephrotic syndrome prior to biopsy, number of relapses or steroid response were documented in

record form. The study was approved by the institutional ethical review committee. Informed written consent was taken from every patient/parents after explaining the treatment protocol. The study population consists of 86 IgMN children, proven by renal biopsy (immunofluorescence study), age ranges from 2-12 years.

IgM nephropathy in children with systemic diseases and age less than 2 years or more than 12 years were excluded as there was no separate adolescent ward. The patients were selected purposively for 27 who were treated with MMF at a dose of 20-30 mg/ kg (600mg/m<sup>2</sup>) in two divided doses for 2 years(Group-I) and 59 were treated with tacrolimus at a dose of 0.1 to 0.2mg/kg (Group- II) for twenty four months introduced during in-patient or immediately after discharged. Children of both groups were treated with prednisolone as Kidney Diseases Improving Global Outcome(KDIGO) guidelines and tapered up to threshold level. Angiotensin converting enzyme inhibitor(ACEi) also added as anti-proteinuric effect at a dose of 5-6mg/m<sup>2</sup>, calcium and vitamin D along with MMF or tacrolimus. Patients were followed up three monthly onward for 7 years starting from the initiation of treatment. Each follow up was documented in a structured form including weight, height, anaemia, proteinuria, blood pressure and following investigations were done: complete blood count, serum creatinine, random blood sugar, trough level of tacrolimus, urine routine examination and yearly USG of KUB. Any untoward effect of drugs was also documented in each follow up visit. Clinical outcome data like remission, hypertension, active disease with normal renal function, active disease with renal impairment and dependency on renal replacement therapy (RRT) were documented for statistical analysis. Data analysis was done by using SPSS by applying appropriate statistical formula such as unpaired t test, Chi squared test between two groups. The level of statistical significance was set up at a p value of <0.05.

#### Observation and results

The study enrolled 86 children suffering from IgM nephropathy. Among them 55 were male and 31 were female and M:F=1.7:1. The number of patients were more in age range of eight to 12 years in both group (table-I). The mean age was higher in Group II than in Group I which is statically significant (p<0.001).

Table I

*Demography of IgM nephropathy children(n=86).*

Sex	Group I	Group II	Ratio
Male	19	36	M:F=1.7:1
Female	08	23	
Total	27	59	
Age (Years)	n(%)	n(%)	P value
2-5	2(7.41)	4(6.78)	
>5-8	7(25.93)	14(23.73)	
>8-12	18(66.67)	41(69.49)	
Mean±SD	5.0±4.2	7.8±4.1	P=0.006

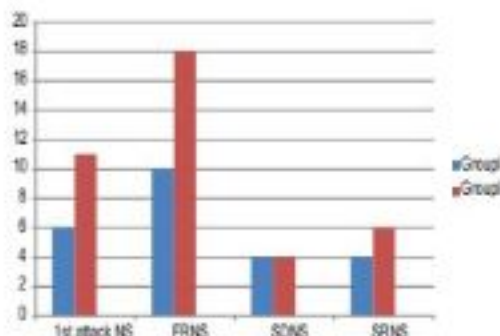
In this study, Kidney biopsy showed the maximum percentage of IgM nephropathy (table-II).

**Table-II**

*Kidney biopsy during the study period from 2014 to 2017.*

Year	Nephritic syndrome	Total biopsy	IgM nephropathy(%)
2014	126	58	17(29.31)
2015	236	53	26(49.06)
2016	229	51	17(33.33)
2017	216	47	26(55.32)
Total	807	209	81(38.76)

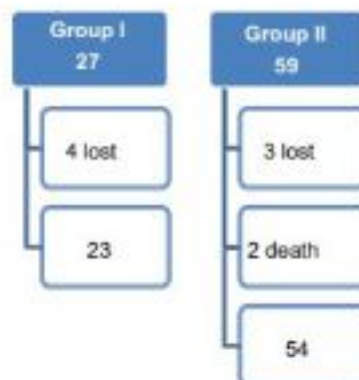
In this study, most of our children had been suffering from frequently relapsing nephrotic syndrome(FRNS) prior to kidney biopsy, the second group was the initial episode of nephrotic syndrome (Fig-1).



**Fig-1: Clinical diagnosis of IgM nephropathy children(n=86)**

In our study, we followed up the IgMN children three monthly but 4 children from Group I and 3 children from Group II has been lost their schedule and 2 were died at home due to septicemia from Group II. So up to the last we did follow up of total 77 IgMN children..

**Patient flow chart**



Re-biopsy were done in only 9 IgM nephropathy children due to unsatisfactory response during the follow up period, all were from Group II and most of them were focal segmental glomerulosclerosis (table-III).

**Table III**

*Re-biopsy findings (n=09).*

Findings	Number(%)
Focal segmental glomerulosclerosis (FSGS)	06(66.67)
Focal segmental proliferative GN	02(22.22)
IgA nephropathy	01(11.11)

In this study, mean follow up period was 4.52 years and 3.55 years in Group I and Group II respectively (table-IV). Complete remission were observed 43.48% and 55.56% in Group I and Group II IgMN children respectively and that of total 51.95% (table-IV). Active disease and deterioration of renal function observed more in Group I (30.43%) than in Group II (16.67%) and that of total 20.78%. About 6 percent(5.19%) IgMN children developed ESRD who have gone through renal replacement therapy (table-IV)

**Table IV**  
Outcome results (n=77).

	Group I(n=23)	Group II (n=54)	Total	p-value
Duration of follow up, years	4.52(0.85-7.14)	3.55(0.17-6.67)		0.091
Outcome, n(%)				
Remission	10(43.48)	30(55.56)	40(51.95)	0.082
Hypertension	2(8.70)	5(9.26)	7(9.09)	0.750
Active disease, normal kidney function	3(13.04)	7(12.96)	10(12.99)	0.331
Active disease, impaired kidney function	7(30.43)	9(16.67)	16(20.78)	0.360
Renal replacement therapy	1(4.35)	3(5.56)	4(5.19)	0.608

### Discussion

The present study included only paediatric age group ranging from two to twelve years with a median age of 7.8 years. But Myllymaki et al. had a wide range of age distribution, with the adult patients being more in number than children.<sup>11</sup> In our study age range (>8-12 years) were highest in both groups (table-I). Some studies of IgMN have reported a male predominance<sup>1,3,10,19</sup> whereas others have reported a larger female population.<sup>2,6,8,18,21</sup> A higher number of males than females were observed in our study and male female ratio was 1.7:1 (table-I). On kidney biopsy series from 2014 to 2017, IgMN occupied the greater portion and it was more than one third (38.76%) of total kidney biopsy (table-II).

The steroid response rates in patients with IgMN varies considerably between the studies, with a mean percentage of steroid resistance of 28%.<sup>13,15,21</sup> In the current study, 12% IgMN children were steroid resistant nephrotic syndrome and 14% were steroid dependent which is considerably lower than reported previously. Clinical diagnosis prior to biopsy frequently relapsing nephrotic syndrome had occupied the maximum (fig-1). In a recent report by Kari et al. of the morphological pattern of steroid-resistant nephrotic syndrome in 36 children living in Saudi Arabia, IgMN was the second most common cause of steroid-resistant nephrotic syndrome, constituting 28% of the cases.<sup>20</sup>

In this study, 86 IgMN children were treated with MMF or CNI (tacrolimus) along with low dose prednisone and had been taken follow up for 7 years. In the other studies, where IgM nephropathy children had been treated with a combination of steroid and calcineurin inhibitors (cyclosporine/tacrolimus) with excellent result.<sup>22,23,24</sup> Zeis et al. studied 64 children with IgMN

and reported that 30% progressed to FSGS.<sup>12</sup> In a study done by Mokhtar, four out of 36 cases (11%) had histological evidence of FSGS on biopsy<sup>13</sup>. In our study re-biopsy were done due to poor response and/or relapse in 9 IgMN children and 66.67% were found FSGS (table-III).

In this study, mean follow up period was 4.52 years and 3.55 years in Group I and Group II respectively (table-IV). In a study by Myllymaki et al. mean post biopsy follow-up was 8 years.<sup>11</sup> Complete remission were observed 43.48% and 55.56% IgMN children in Group I and Group II respectively but not statistically significant and that of total 51.95% (table-IV). Active disease and deterioration of renal function were developed more in Group I (30.43%) than Group II (16.67%). Total 16 IgMN children (20.78%) out of 77, developed CKD seven years after histological diagnosis and treatment. End stage kidney disease (ESKD) developed in four children (5.19%) who have gone through renal replacement therapy (table-IV), but other studies the reported incidence of ESKD in patients with IgMN ranges from six to 23%.<sup>10,12,15</sup> Another study done by Myllymaki et al. who studied 110 patients with IgMN, adults and children, reported that 23% had progressed to ESKD.<sup>11</sup>

### Conclusion:

From above observation, the overall prognosis of IgM nephropathy in children is not remarkable. This longitudinal follow up draws a conclusion that the better response were achieved after the treatment with tacrolimus than mycophenolate mofetil, but not statistically significant.

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