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(A Journal of continuing education in kidney diseases)

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Renal Association Journal appears twice in a year and it publishes original articles, review articles, clinical communications, recent advances in renal diseases and letters to the editors. The editors reserve the right to select from submitted manuscripts and the right of stylistic changes or abridgements. The manuscripts may not be offered elsewhere for printing and publication; following acceptance, the publisher acquires all copywright.

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III. **BOOKS**

Grindley MF: Manual of histologic and special staining Nephrologic, Elammarion, Paris, 1965.

ABBREVIATIONS

Angstrom	A
body surface area	BSA
body weight	body wt.
centimeter	cm
celius	C
complement components	C1,C2,C3
Correlation coefficient	r
creatinine clearance	Ccr.
curie (s)	Ci
Equivalents	Eq
Fahrenheit	F

Glomerular fitration rate	GFR
gram (s)	g
Grams per cent	g/100mi
half-time	tf1/2
hour (s)	hr
inch	inch
International Unit (s)	IU
Intramuscular	im.
intraperioneal	i.p.
intravenous	i.v.
inulin clearance	Cln
Kilogram (s)	Kg
liter (s)	L
meter (s) or milli	m
microns (s) or micro	µ
milligram (s) per cent	mg/100ml
minute (s)	min
molar	M
mole (s)	mole (s)
Molecular weight	molwt
nanogram (s) (millimicrogram)	ng
nanoliter (s) (millimicroliter)	nl
normal (concentration)	N
not significant	NS
optical density	OD
osmole (s)	Osm
probability	P
second (s)	sec
standard deviation	SD
standard error	SE
standard error of the mean	SEM
ultraviolet	UV
unit (s)	U
volt	V

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To

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Review Article

Management of Lupus Nephritis - An Update

M Nizam Uddin Chowdhury

Summary:

Renal involvement is common in systemic lupus erythematosus (SLE). According to ARA criteria renal involvement is defined as proteinuria ++/ 0.5 gm/day /active sediment (RBC cast or cellular cast). Management of lupus nephritis depends on the severity and histological class of lupus nephritis. Aggressive antihypertensive therapy to maintain blood pressure less than 130/80 mmHg, antiproteinuria therapy with angiotensin converting enzyme inhibitors (ACEIs) often in combination with angiotensin receptor blockers (ARBs), aggressive lipid lowering with statins etc are common in all classes. Proliferative lupus nephritis require aggressive therapy with various combinations of immuno suppressive agents. End stage renal disease due to lupus nephritis require renal replacement therapy in the form of dialysis or renal transplantation. Overall graft function rates at 5 or 10 years in patients with lupus nephritis are similar to patients with other diseases.

(Bang. Renal J. 2008; 27(2): 33-41)

Renal involvement is common in idiopathic systemic lupus erythematosus (SLE). An abnormal urinalysis with or without an elevated plasma creatinine concentration is present in a large proportion of patients at the time of diagnosis, and may eventually develop in more than 75 percent of cases. The most frequently observed abnormality is proteinuria[1].

Classification — A new classification system of lupus nephritis developed by a group of renal pathologists, nephrologists, and rheumatologists was formulated and published in 2004[2-4] . This system, compared with the modified WHO 1982 system, appears to be associated with increased reproducibility[4,5].

Minimal mesangial lupus nephritis (class I)

Mesangial proliferative lupus nephritis (class II)

Focal proliferative nephritis (Class-III)

Diffuse proliferative nephriti s(class-IV)

Membranous lupus nephritis(class-V)

Advanced sclerosing lupus nephritis (class VI)

Approach to diagnosis :

SLE is diagnosed on the basis of ARA criteria. Discussion of extrarenal manifestation of SLE is beyond the scope of this paper. Following investigations are done as routine and specific test for SLE.

Routine investigations: Urine for routine and microscopic examination, complete blood count with E.S.R.,X-ray chest P/A view, urea, creatinine, serum electrolytes, blood glucose.

Specific investigations: ANA, Anti dsDNA, if urine shows proteinuria and/or active sediment urinary total protein followed by renal biopsy if required, if patients has history of unusual venous /arterial thrombosis or fetal loss antiphospholipid antibody is done. In patients with anti dsDNA negative anti Sm antibody may be helpful.

According to ARA criteria renal involvement is defined as proteinuria ++/0.5gm/day/active sediment(RBC cast or Cellular cast). Most patients with LN require renal biopsy[6,7]

Treatment of lupus nephritis*:*General management:[8] Aggressive antihypertensive and antiproteinuric therapy with an angiotensin converting enzyme (ACE) inhibitor, often in combination with an angiotensin II receptor blocker (ARB). The goal blood pressure is less than 130/ 80 mmHg and goal protein excretion is less than 500 to 1000 mg per day. Aggressive lipid lowering with statin therapy. The goal serum LDL cholesterol is less than 80 to 100 mg/dL (2.1 to 2.6 micromol/L).

Immunosuppressive therapy: Aggressive immuno-suppressive therapy is primarily indicated in the following patients with LN who are at high risk for progressive renal failure: Ï% Those with diffuse (class IV) or severe focal (class III) proliferative glomerulonephritis, whether primary or by transformation from another type of LN. Ï% Those with severe or progressive membranous lupus (class V), defined as having marked nephrotic syndrome or a rising serum creatinine, or membranous in association with class III or class IV disease (eg, mixed membranous and proliferative disease). Immunosuppressive therapy for proliferative LN consists of induction and maintenance phases.

Induction therapy involves the administration of agents to achieve remission of immunologic disease. Complete

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remission was defined as serum creatinine <130 percent of the lowest level during treatment, proteinuria <1 g/day, and urinalysis with <10 red blood cells per high power field and no cellular casts, for at least six months off immunosuppressive therapy (other than low dose prednisone and hydroxycholorquine). Partial remission or stabilization was defined as stable serum creatinine at <150 percent of the lowest level during treatment for at least six months off therapy, regardless of level of proteinuria or findings on urinalysis.However, the NIH criteria defined complete and partial responses largely based upon the serum creatinine, whereas we believe the goal in treating active lupus is to achieve inactive disease, which may still leave residual proteinuria and renal insufficiency.[9,10]

Once remission is achieved.

Maintenance therapy is given for a prolonged period to help prevent relapse. Maintenance therapy is also aimed at preventing nonimmunologic progression of the renal disease.

Immunosuppressive Therapy Ffr Different Class:

Mesangial Disease - Both class I or II mesangial lupus are generally associated with an excellent renal prognosis. They require no specific therapy for renal involvement unless there is progression to more severe glomerular involvement, and are then treated accordingly.

Membranous Lupus -Corticosteroids in combination with a number of agents, such as cyclophosphamide, chlorambucil, cyclosporine, mycophenolate mofetil, azathioprine and tacrolimus have been tried, but controlled clinical trials evaluating different regimens are limited. Examples of studies comparing different treatment regimens in patients with membranous lupus nephritis include:

In a preliminary National Institutes of Health (NIH) study, 41 patients were randomly assigned to alternate day prednisone alone, or in combination with pulse cyclophosphamide every other month, or cyclosporine (d"5 mg/kg per day), for one year[11] . Compared with the prednisone alone group at one year, the groups treated with either cyclophosphamide or cyclosporine had higher remission rates (46 versus 13 percent) and lower rates of persistent nephrotic syndrome (19 versus 60 percent). There was a trend to more relapses with cyclosporine compared to cyclophosphamide.

The Ponticelli group retrospectively analyzed the effects of corticosteroids alone (eight patients), and methylprednisolone and chlorambucil alternated every other month for six months (11 patients)[12] . Compared to combination therapy, those receiving corticosteroids alone had a higher rate of renal flares (88 versus 10 percent) and a lower rate of complete or partial remissions (38 versus 90 percent) at a mean follow-up of 114 months (versus 83 months for combination therapy). These benefits must be confirmed in a prospective controlled trial of a larger number of patients to properly assess the role of chlorambucil in this setting.

In an uncontrolled study of 38 Chinese patients with pure membranous lupus (58 percent with nephrotic-range proteinuria) treated with prednisone plus azathioprine, complete and partial remission at one year was achieved in 67 and 22 percent, respectively[13] . Among those who underwent remission, low-dose prednisone plus azathioprine was continued indefinitely; at a mean follow-up of 90 months, relapse had occurred in six patients (19 percent).

In a randomized controlled trial of 140 patients with lupus nephritis, 27 of whom had membranous lupus, oral mycophenolate mofetil was compared with intravenous cyclophosphamide[14]. Although this study was not powered for such a subgroup analysis, complete and partial remission were attained by 7 of 14 patients treated with mycophenolate, and 4 of 13 treated with cyclophosphamide[14,15].

In an uncontrolled study, 13 patients with a mean urine protein-to-creatinine ratio of 5 were treated with prednisone (mean dose of 31 mg/day), mycophenolate mofetil (mean dose of 1173 mg/day), and aggressive renoprotective therapy (goal sitting systolic blood pressure of 120 mmHg or less with an ACE inhibitor and/or angiotensin II receptor blocker (ARB) and a statin if the LDL-cholesterol was above 100 mg/dL [2.6 mmol/L])[16] . At a mean follow-up of 16 months, a complete remission (urine protein-to-creatinine ratio <0.5) was observed in nine patients (70 percent), while the urine protein-to-creatinine ratio was less than 0.8 in two other patients (15 percent). Favorable results of treatment with MMF and ACE inhibitor or ARB were reported in another series of 10 patients treated with MMF for a mean of 19 months[17].

Recommendations[18]

All patients should be treated with the general *antihypertensive, antiproteinuric, and lipid-lowering* measures.

The optimal therapy of patients with membranous lupus is uncertain as data are limited, but treatment should be based upon severity of disease:Patients with asymptomatic

non-nephrotic proteinuria are often not given immunosuppressive therapy. Consideration may be given in selected patients, such as those with mild extrarenal symptoms, to a two to four month trial of prednisone alone.Patients with nephrotic syndrome are often treated for four to six months with cyclosporine (3 to 5 mg/kg per day) plus low-dose prednisone (5 to 10 mg/day). Patients with marked nephrotic syndrome or a rising serum creatinine are typically treated with the same regimen as that used for diffuse proliferative glomerulonephritis. Similarly, patients with class III and V disease or class IV and V disease (eg, mixed membranous nephropathy and proliferative disease) are treated in the same way as those with proliferative disease alone.

Diffuse or severe focal proliferative or severe membranous lupus nephritis

Is Immunosuppressive drug required ?

National Institutes of Health (NIH) performed follow-up study of avoiding kidney failure with cytotoxic therapy compared to corticosteroids alone at 10 to 12 years among survivors[19]. 90 percent with cyclophosphamide, 60 percent with azathioprine, 20 percent with prednisone alone.Results with azathioprine were better than those with prednisone alone during the first 10 years of follow-up, but not during longer follow-up, and are clearly inferior to cyclophosphamide [19-24] .

Choice of immunosuppressive drugs:

NIH trial in 82 patients with mostly class IV LN (mean baseline serum creatinine of approximately 1.1 mg/dL [100 µmol/L]) compared three regimens: one year of monthly pulse methylprednisolone (1 g/m2); pulse intravenous cyclophosphamide (0.5 to 1.0 g/m2 monthly for six months and then quarterly for at least two years); and combination therapy methylprednisolone plus cyclophosphamide)[25] . All patients also received oral prednisone as in the earlier NIH study described above. At a median follow-up of five years, remission occurred in 85, 62 and 29 percent of the 65 non-censored patients treated with combination therapy, cyclophosphamide alone, and methylprednisolone alone, respectively. Renal remission considering censored patients as failures occurred in 61, 48, and 26 percent, respectively. Relapse occurred in 0, 7, and 36 percent of the patients treated with combination therapy, cyclophosphamide alone, and methylprednisolone alone, respectively. However, cyclophosphamide therapy was associated with a higher incidence of adverse events. Osteonecrosis occurred almost as frequently as with methylprednisolone alone, infections and amenorrhea were more frequent, and the three deaths were in the cyclophosphamide group.

A randomized trial by the Dutch Working Group[24] on SLE included 87 patients with mostly class IV LN (mean serum creatinine 1.2 mg/dL [112 µmol/L], and protein excretion 4 g/day) . The patients were assigned to pulse cyclophosphamide (750 mg/m2 monthly for six months, then every three months for seven doses) or to azathioprine (2 mg/kg per day for two years) plus pulse methylprednisolone (1000 mg intravenously for three days, repeated at two and six weeks); all patients were treated with prednisone . After the initial two years, all patients were treated with azathioprine (2 mg/kg per day) and 10 mg/day of prednisone for two more years, then lower doses for an additional year. During the initial two years of therapy, there were no differences between the two groups in the rate of complete and partial remissions (90 percent). However, after a median follow-up of 5.7 years, a smaller proportion of patients in the cyclophosphamide group experienced relapses (4 versus 27 percent; relative risk 8.8, 95% CI 1.5-32). Although not statistically significant, fewer had doubling of serum creatinine (4 versus 16 percent), and deaths or end-stage renal disease (4 versus 11 percent).

In a multicenter trial, 140 patients (including over one-half black) with active LN were randomly assigned to mycophenolate mofetil (1 g twice daily) or intravenous cyclophosphamide (0.5 to 1 g/m2 monthly) for a total of 24 weeks of therapy [26] . All patients received oral prednisone. At 24 weeks,a greater proportion of patients in the mycophenolate group achieved complete remission (22 versus 6 percent), an effect that reached statistical significance at 24 weeks. The rate of partial remissions was similar (30 versus 25 percent). There were no significant differences between the treatment arms in the serum creatinine, urinary protein excretion, proportion with inactive urinary sediment, and importantly, in serologic markers of disease activity (C3, C4 and anti-dsDNA antibody levels). The mycophenolate and cyclophosphamide arms also had the same proportion of patients with worsening of some renal variables, and bacterial, fungal, and viral infections. However, severe infections (such as pneumonia, lung abscess, necrotizing fasciitis, gram-negative sepsis) and death (in two patients) only occurred with cyclophosphamide. After study end, the patients were followed for a mean of 36 months. Renal failure (seven versus four patients) and death (eight versus four patients) were nonsignificantly more common in the cyclophosphamide group. The frequency of relapses and their treatment were not reported.

Oral versus Intravenous cyclophoshamide

Oral nonpulse therapy may be an option if intravenous cyclophosphamide is not feasible [27,9,20,21,22] . This was illustrated in the following reports of Chinese patients with biopsy-proven diffuse proliferative glomerulonephritis[30,51]: In a study of 66 patients treated with oral cyclophosphamide (2.5 mg/kg per day) and prednisolone for six months, followed by treatment with azathioprine for up to 24 months and prednisolone for nearly 60 months, complete remission was attained in 82 percent after 15 months of treatment, and partial remission was achieved in an additional 12 percent. Overall, 72 percent remained free of disease at a median follow-up of 88 months, and none had reached end-stage renal disease. In a retrospective review of 212 patients, one-half received oral cyclophosphamide (1 to 2 mg/d for six to nine months, total dose 16 gm), while the others were administered intravenous cyclophosphamide (0.5 to 1 g/m2 monthly for six months, then quarterly for six doses, total dose 9 gm)[22]. There was a higher rate of complete remissions (69 versus 50 percent) in the oral therapy group. However, after adjusting for chronicity and severity of renal manifestations, the cumulative dose, but not route of administration, was associated with response to therapy. After a mean follow-up of 108 months, there was no significant difference in the risk for the composite outcome of doubling of serum creatine, dialysis, or death.

Cyclophosphamide regimens

Euro-Lupus Nephritis Trial[28] — To better assess the long-term effect of low-dose short-term cyclophosphamide, 90 patients with proliferative LN (two-thirds with class IV histology) were randomly assigned either to six pulses of fixed low dose (500 mg) intravenous cyclophosphamide given every two weeks (cumulative dose of 3.0 g) or to six monthly doses of intravenous cyclophosphamide and then two quarterly pulses (0.5 g/m2 initially, with subsequent doses increased or decreased based upon white blood cell count nadir) . All patients also received an initial pulse of intravenous methylprednisolone (3 daily pulses of 750 mg); this was followed by oral glucocorticoids (initial dose of 0.5 mg/kg per day of prednisolone for four weeks), which was subsequently tapered to low dose maintenance therapy. Two weeks after the last cyclophosphamide infusion in both arms, azathioprine (2 mg/kg per day) was started and continued to at least month 30. At follow-up at a median of 41 months, the following results were noted: The differences in rates of treatment failure (16 and 20 percent for low and high dose groups, respectively), renal remissions (71 and 54 percent), and renal flares (27 and 29 percent) were not statistically significant. Although not statistically significant, episodes of severe infection were more common among the high dose group. Extended follow-up at a median period of 73 months also revealed no difference in the two groups with respect to end-stage renal disease or doubling of the serum creatinine concentration [28] . With multivariate analysis, a good early response to therapy was predictive of better long-term outcomes. Thus, in this group of Europeans, a low dose cyclophosphamide induction regimen was as effective as a high dose regimen. However, the generalizability of these results is unclear, given that the study only enrolled Europeans without significant renal dysfunction (mean baseline serum creatinine 1.15 mg/dL [102 µmol/L]); further data are required before this regimen can be recommended.

Recommendations[18]

Initial pulse corticosteroids — In patients with severe active disease (acute renal failure or crescentic glomerulonephritis), therapy may also be initiated with intravenous pulse methylprednisolone (500 to 1000 mg daily for three days) to induce a rapid immunosuppressive effect. This one-time three day regimen substitutes for the one day regimen that is administered with pulse cyclophosphamide.

For initial induction therapy in severe LN, monthly intravenous pulse cyclophosphamide, a total of six monthly intravenous cyclophosphamide pulses for initial induction therapy with concurrent six monthly pulses of intravenous methylprednisolone given at a dose ranging from 500 to 1000 mg[29,30].

Intravenous cyclophosphamide dose of 0.75 g/m2 of body surface area given in a saline solution over 30 to 60 minutes.To diminish the risk of toxicity, the initial dose should be reduced to 0.5 g/m2 body surface area in patients who are obese or elderly (eg, age greater than 70 years) and in those with moderate to severe renal dysfunction (eg, if the estimated creatinine clearance is less than 40 mL/minute).

If the leukocyte nadir after the first administration of cyclophosphamide (usually 10 to 14 days post-infusion) is less than 4000/µL and/or the absolute neutrophil count is less than 1500/µL, the dose at the next infusion should be reduced by 0.25 g/m2 body surface area or even transiently withheld if the counts are very low. If, on the other hand, the total white cell nadir is greater than 4000/µL, the absolute neutrophil count is greater than 1500/µL, and the patient has not improved, the cyclophosphamide

dose at the next infusion may be increased by 0.25 g/m2 body surface area. The maximum dose is 1.0 g/m2 body surface area. Oral prednisone is also part of the regimen which begins with a dose of 1.0 mg/kg per day (maximum 60 mg/day) for six to eight weeks. This is tapered over a period of weeks to months in initial decrements of 5 to 10 mg/day per week and then much more slowly (as little as 1 mg/day per month at doses below 10 mg/day). The goal is to attain the minimum prednisone dose required for control of extrarenal symptoms.

Role of mycophenolate — Although only relatively short-term follow-up is available, some clinicians prefer to use mycophenolate mofetil plus corticosteroids as induction therapy, particularly in patients with relatively mild disease or in those who are concerned about the side effects associated with cyclophosphamide. In the two major mycophenolate versus cyclophosphamide trials cited above, the mean plasma creatinine at the initiation of therapy was 1.1 to 1.2 mg/dL (97 to 106 µmol/L). Mycophenolate therapy is started at a dose of 500 mg twice daily, which is increased by increments of 500 mg per week to a maximum dose of 2.0 to 3.0 g/day based upon clinical response and the ability to tolerate side effects.

Maintenance Immunosuppression

Up to one-half of patients with proliferative LN relapse following reduction or cessation of immunosuppression[31-34], with relapse rates ranging from 5 to 15 per 100 patient years (averaging about 8 per 100 patient years of follow-up)[33]. Once a patient has attained a remission, immunosuppression is continued to help maintain remission, prevent relapse, and decrease the risk of developing end-stage renal disease. There are limited data regarding the relative efficacy of the different maintenance regimens[35,36].

The first trial included 59 patients with severe LN who received induction therapy with intravenous pulse cyclophosphamide (four to seven monthly doses) plus prednisone (0.6 mg/kg per day for three months, then 0.3 mg/kg per day for three months) . Subsequently, patients continued low-dose oral prednisone (0.1 to 0.2 mg/kg per day), and were randomly assigned to one of the following: mycophenolate (500 to 3000 mg/day), azathioprine (1 to 3 mg/kg per day), or intravenous cyclophosphamide (0.5 to 1.0 g/m2 every three months). The median treatment duration was 24, 29, and 30 months for the cyclophosphamide, mycophenolate, and azathioprine groups, respectively. With respect to the primary end points, five patients died (four and one in the cyclophosphamide and mycophenolate groups, respectively), and five developed chronic renal failure (three in the cyclophosphamide group and one each in the azathioprine and mycophenolate groups). Based upon a Kaplan-Meier analysis at six years, the event-free survival rate for the composite end point (patient and renal survival) was significantly higher with mycophenolate and azathioprine (90 and 80 percent, respectively) compared to cyclophosphamide (45 percent). Seventeen patients (29 percent) had a renal relapse (eight, six, and three patients in the cyclophosphamide, azathioprine, and mycophenolate groups, respectively). The overall relapse-free rate was significantly higher with mycophenolate than cyclophosphamide. Compared with the other two groups, cyclophosphamide was associated with significantly more hospital days/patient-year, more infections, and a higher incidence of amenorrhea.

The second trial included 69 patients with class IV or severe class V LN who received induction therapy with intravenous methylprednisolone (0.5 to 1 g/day for three days) and oral prednisone (1 mg/kg per day for two weeks, tapered to 0.5 mg/kg per day) plus oral cyclophosphamide (2 mg/kg per day for three months) [37] . Subsequently, patients were randomly assigned to cyclosporine (mean dose 3 mg/kg per day, adjusted to maintain trough levels 75 to 200 ng/mL) or azathioprine (2 mg/kg per day, tapered to 1.5 mg/kg per day after one month if proteinuria <1 g/day). All patients continued prednisone (tapered to 0.2 mg/kg per day by six months, and to a mean dose of 8 mg/day by 12 months). Therapy was administered for two years.Nine patients withdrew from the study due to side effects during the second year, and an additional 12 were lost to follow-up, with a similar distribution between the two treatment groups. At four year follow-up, the following results were reported: lupus flares occurred with similar frequency in the cyclosporine (five renal, two extrarenal) and azathioprine (seven renal, one extrarenal) groups. Two (cyclosporine) and three (azathioprine) flares occurred during the two years of active therapy. There was no difference in the change in creatinine clearance in the two groups. Reduction in proteinuria from >2 g/day at baseline to <0.5 g/day in both groups, but achieved earlier in the cyclosporine group (6 versus 12 months). No patient died or reached end-stage renal failure.

Recommendations[18] - The available trials demonstrate that maintenance therapy with mycophenolate or azathioprine is safer and more effective than maintenance therapy with intravenous cyclophosphamide, with perhaps fewer relapses with mycophenolate. Maintenance therapy with

cyclosporine may be as effective as azathioprine, but is associated with long-term nephrotoxicity and is more expensive and more cumbersome to administer.

Upon completion of induction therapy (and achievement of remission), maintenance immunosuppressive therapy for at least 18 to 24 months, followed by a slow taper, based upon anecdotal experience that relapse rates are higher with shorter courses of maintenance therapy.To minimize overall toxicity, non-cyclophosphamide is preferred over cyclophosphamide as maintenance regimens once a stable remission has been attained with cyclophosphamide or mycophenolate.

Among those who receive intravenous six month pulse cyclophosphamide induction therapy, switch to a maintenance regimen with mycophenolate (1 to 2 g/day) or azathioprine (2 mg/kg per day to a maximum of 150 to 200 mg/day) is recommended. Maintenance therapy is started at least four weeks after the last dose of cyclophosphamide, and should not be started until the white blood cell count is >4000/μL and the absolute neutrophil count is >1500/μL.If mycophenolate mofetil was used for induction therapy, this agent is continued for maintenance therapy at a dose of 1 to 2 g/day. Some prefer mycophenolate because there are much more data on the efficacy of mycophenolate compared with azathioprine and the available evidence suggests that mycophenolate may be better for maintenance therapy than azathioprine. However, mycophenolate is contraindicated in pregnancy and is listed as a category D drug (positive evidence of risk) for use in pregnancy by the FDA. As a result, females of childbearing potential should have a negative pregnancy test within one week prior to beginning therapy. Two reliable forms of contraception should be used beginning four weeks prior to, during, and for six weeks after therapy.

Low-dose oral prednisone is continued after the switch to maintenance therapy. The goal is to attain the minimum prednisone dose required for control of extrarenal symptoms and avoid relapses, and will therefore vary among patients. In a comparative maintenance trial, the mean prednisone dose ranged from 0.05 to 0.20 mg/kg per day.

Disease Resistant To Induction Therapy

The approach to the infrequent patient who is resistant to induction therapy varies based upon the agent used for initial therapy and the severity of disease. Patients with persistent active disease who are treated with mycophenolate as first-line therapy are typically given a course of intravenous cyclophosphamide as described above.

Among patients who appear to be resistant to cyclophosphamide at six months, data are extremely limited. The two major alternatives are to switch to mycophenolate [38-40] or to continue intravenous pulse cyclophosphamide at three month intervals. Data on mycophenolate is limited to small case series.

Rituximab — Rituximab is an anti-CD 20 antibody that depletes B lymphocytes, used in the treatment of B cell lymphoma and in a variety of autoimmune disorders. Favorable results have been noted in small observational studies and case reports of LN resistant to conventional therapies[41-44] and as primary therapy . In the largest reported experience, 22 patients with class III or IV LN who had persistent disease activity despite continued immunosuppression were treated with rituximab (0.5 to 1 g on days 1 and 15) . Previous and concurrent therapy included corticosteroids in all patients, plus azathioprine, mycophenolate mofetil, methotrexate, and/or cyclophosphamide (11 patients).

Three months after the administration of rituximab, five had a complete response (normal serum creatinine, inactive urine sediment, and protein excretion <500 mg/day), and seven had a partial response (>40 percent improvement in renal parameters). The effect of rituximab in those patients initially treated with cyclophosphamide was not specifically noted.

Several trials are ongoing, including the LUNAR and EXPLORER studies. The LUNAR study, will evaluate the efficacy and safety of rituximab in combination with mycophenolate mofetil compared with mycophenolate plus placebo.

Alternative agents — Other modalities that have been evaluated include intravenous immune globulin[45,46], high-dose chemotherapy with stem cell transplantation (evaluated primarily in patients with cerebritis, myelitis, and/or vasculitis)[47], other chemotherapeutic agents, monoclonal antibody therapy, intravenous azathioprine, cyclosporine, leflunomide, immunoadsorption, pentoxifylline, complement inhibitors (such as anti-C5 antibody), and oligonucleotide therapy directed against anti-dsDNA antibodies [48] .

Relapsing Disease

Relapse is primarily defined as renewed clinical activity (among patients with initial remission), as manifested in the kidney by an active urine sediment that is often accompanied by increasing proteinuria and a rise in the

serum creatinine. The new finding of red cell and/or white cell casts is a particularly strong predictor of relapse[49].

Monitoring

Serial monitoring of the urinalysis, urine protein/creatinine ratio, serum creatinine, and serologic factors be performed every three to four months in stable patients to detect renal relapses. In some patients, a renal biopsy may be required to verify recurrent active LN rather than nonimmunologic progression of renal disease.

Patients who are noted to have an increase in anti-dsDNA titers or new hypocomplementemia should be monitored carefully (particularly over the ensuing three months) but should not be treated solely for changes in serologic activity.

Treatment

The treatment varies with severity and timing. Given the increased drug exposure, greater attention must be paid to potential toxicity.

Among patients with relatively mild relapses determined clinically, a trial of oral prednisone can be considered in patients who are no longer on maintenance. For those on maintenance therapy, one can increase the dose of prednisone as well as the maintenance drug, particularly if it has been tapered.

By comparison, reinstitution of the initial induction regimen is usually warranted in patients with moderate to severe relapse while no longer on immunosuppressive therapy. If cyclophosphamide is reinstituted, some investigators prefer to limit the total drug exposure by shortening the duration of the induction regimen to a maximum of four monthly pulses of intravenous cyclophosphamide.

End-stage renal disease due to lupus nephritis

A significant number of patients with lupus nephritis progress to end-stage renal disease, although the overall prognosis has improved. The development of renal failure is, in most patients, associated with gradual complete or partial resolution of the extrarenal and serologic manifestations of lupus[50-53]. In one study, for example, the percentage of patients with active clinical lupus fell from 55 percent at the onset of dialysis to 6.5 percent in the fifth year and, in a small number of cases, to zero percent in the tenth year . The incidence of serologic activity fell from 80 to 22 percent during this time span. Furthermore, those patients in whom the disease remains active generally have only mild to moderate symptoms . The mechanisms responsible for this often permanent remission of lupus are not well understood.

Dialysis — Patient survival with either hemodialysis or continuous ambulatory peritoneal dialysis appears to be similar to that in the general population of patients with end-stage renal disease[51,53]. There is, however, an increased risk of death during the first three months of dialysis, due primarily to sepsis and other complications of high-dose steroid therapy [28] . Among those undergoing peritoneal dialysis, an increased risk of peritonitis and non-catheter related infection may also be observed.

It has been recommended that patients with lupus be dialyzed for at least three to six months before renal transplantation is performed, particularly among those relatively rapid progression to renal failure . There are two potential advantages to this regimen: it may lead to a further reduction in lupus activity; and it gives patients with relatively acute renal failure time to recover sufficient renal function for dialysis to be discontinued.

Renal Transplantation[54-57] Most, but not all , studies have found that overall graft survival rates at 5 and 10 years in patients with lupus are similar to those in patients with other diseases. This was shown in a long-term study of 33 adults with lupus nephritis and 70 matched controls . At a mean follow-up of 90 months, both groups had similar actuarial 15 year patient (80 and 83 percent) and allograft survival (69 and 67 percent) rates.

Recurrent disease — Reviews of published reports have shown a rate of clinically recurrent renal disease in the transplant of 2.0 to 9.0 percent in patients with lupus, which is thought to reflect diminished immunologic activity . The incidence of recurrent symptoms of lupus was also low at 5.7 percent .

However, a higher rate was observed in a subsequent study of 54 patients with lupus, of whom 31 underwent renal biopsy because of worsening renal function and proteinuria ; among those with at least 3 months of follow-up, recurrent lupus nephritis was noted in 15, resulting in a recurrence rate of 30 percent. This higher incidence may be due to the increased use of allograft biopsies. One patient lost the allograft because of recurrent lupus at 10.5 years.

The measurement of serologic parameters, such as complement levels and titers of anti-double stranded DNA antibodies, may not be an accurate assessment of disease activity or help predict disease recurrence in the allograft . In one series of nine patients with recurrent lupus nephritis, for example, only three had serologic evidence

of active lupus and only one had extrarenal symptoms (arthritis) . The incidence of graft loss because of recurrent disease is extremely low, being less than two to four percent in most studies .

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Risk factors of Urinary Tract Infection (UTI) in Children with Nephrotic Syndrome

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Summary:

This study was carried out to determine the risk factors of UTI in nephrotic children. This was a case control study where patients were followed up prospectively. Patients were selected in a nonrandom purposive technique. Children of 1 to12 years of age presented with nephrotic syndrome over a period of one year were included.They were divided into Group I – UTI positive and Group II – UTI negative depending on urine culture (positivity >10^5 CFU/ml). A total of 101 children with male female ratio of 1.7:1, mean age 5.96±3.2 years were included and followed up for a variable period (3-15 months).Different clinical and laboratory parameters of both groups were recorded and compared. Group-I comprised of 45 and Group-II 56 children. UTI was present in 44.5% of study population and incidence was 24.7 per hundred nephrotic patient's follow up months. Important risk factors for UTI in nephrotic children were younger age group below 6 years (odds ratio-OR=6.98), uncircumcised boys(OR=61.36), low serum IgG(OR=6.63), low serum albumin(OR=3.78), low serum total protein(OR=3.86), neutrophilic leucocytosis (OR=2.8), high ESR(OR=6.15), high spot urine protein:creatinine ratio (OR=8.4), hypercholesterolemia (OR=2.6) and hypertriglyceridemia(OR=3.9). By logistic regresssion it was found that age, serum IgG, serum albumin, serum total protein, ESR together could predict the presence or absence of UTI in 81.2% of study subjects. The prediction is better in case of UTI positive children (87.5% vs 73.3%). Thus youner age,low serum protein as well as immunoglobulin and circuncission status are the srong predictors or risk factors in urinary tract infection for children with nephrotic syndrome .

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Introduction:

Urinary tract infection is a major cause of morbidity among children. The incidence of UTI in general population is 1% in boys and 3% in girls before the 11th year of life[1]. Urinary tract infections (UTI) are of special interest because of their association with vesicoureteric reflux and propensity for long term renal damage[2]. Incidence of UTI in nephrotic children has been shown as 13.2% [3]. Gulaty et al(1996) in their study showed that UTI is the most common infection in nephrotic syndrome children and associated with significantly lower serum albumin and higher serum cholesterol concentrations than the nephrotic syndrome children without infections[3]. It has been reported by Senguttuvan et al(2004) that UTI is the commonest (46%) infection in childhood nephrotics followed by peritonitis, acute respiratory tract infection and tuberculosis[4]. Infectious episodes in nephrotic patients are responsible for high morbidity and can also predispose to inadequate response to corticosteroid therapy and recurrences among patients in remission[5]. In nephrotic syndrome, the infectious episode results from a group of alterations that synergistically increase the patients' susceptibility to infections. These alterations are low serum level of immunoglobulins, particularly IgG, due to low production and to a lesser extent to increased catabolism and renal losses; defect in the opsonization of bacteria; and immunosuppressive therapy[5].

Symptoms like fever and other physical findings may be minimal in the presence of corticosteroid therapy. Therefore, a high index of suspicion, prompt evaluation and early initiation of antibiotic therapy are critical. Occult infections may manifest as a steroid non response or relapse in a child who has already attained remission[6].

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There are a number of studies in Bangladesh regarding incidence, etiology and antibiogram of urinary tract infection in childhood nephrotic syndrome. But the risk factors of UTI was not investigated in this group of children.The aim of this study was to identify clinical, laboratory and immunological risk factors as a predictors of UTI in children with nephrotic syndrome.

Methodology:

This study was carried out in the department of Pediatric nephrology, National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, Bangladesh. This was a case control study with follow ups.Subjects were selected in a nonrandom purposive technique. Nephrotic syndrome children 1 to12 years of age attending the department of Pediatric Nephrology, NIKDU, during the period of July2005 to June2006 for the treatment of initial attack, relapse were included. Nephrotic syndrome was diagnosed as per the International Study of Kidney Diseases Criteria (ISKDC) [7]. Subjects with congenital urinary tract anomalies, neurogenic bladder or with chronic illnesses like tuberculosis, hepatitis B & C positive were excluded.

Detail history was taken and clinical examination was done and recorded on a datasheet. Laboratory investigations including urine microscopy, urine culture & sensitivity, spot urine protein: creatinine ratio, complete blood count with perpheral blood film, serum albumin, serum total protein, lipid profile, complements C3, C4, and serum IgG level were done in all patients at the begining and after treatment of UTI.The patients were devided in Group I – UTI positive and Group II UTI negative depending on the report of urine culture (positivity $>10^5$ CFU/ml). Then different clinical and laboratory parameters of UTI positive nephrotic syndrome were compared with those of UTI negative nephrotic syndrome children. After correction of UTI with appropriate antibiotics,all children were treated with oral prednisolon according to ISKDC protocol[7]. The subjects were followed up over a period of 3 to 15 months (total nephrotic patient follow up months 356) and urine microscopy & culture and sensitivity (C/S) was done as needed. Statistical analysis was done by SPSS version 11.5. Independent t test, Chi-square test withYate's correction and Logistic regression were performed. Level of significance was taken as $p< 0.05$. Ethical clearence was approved by Institutional Ethical Review Committee, NIKDU.

Results :

A total of 101 children with male female ratio 1.7:1, mean age 5.96±3.2 years (range 1 to 12 years) were included in this study. Number of subjects in Group-I (UTI positive) was 45 and Group-II (UTI negative) was 56. UTI was present in 44.55 of cases and incidenceof UTI was is 24.7 per hundred nephrotic patient's follow up months from 356 patient month (Table -1).

Table-I

Incidence of UTI in nephrotic syndrome children.

Episode of UTI	Patient number	Total episodes of UTI	Follow up months	Incidence of UTI (per 100 nephrotic patient month)
1	22(48.9)	22		
2	10(22.2)	20		
3	7(15.6)	21	356	88x100÷356=24.7
4	5(11.1)	20		
5	1(2.2)	5		
Total	45 (100.0)	88		

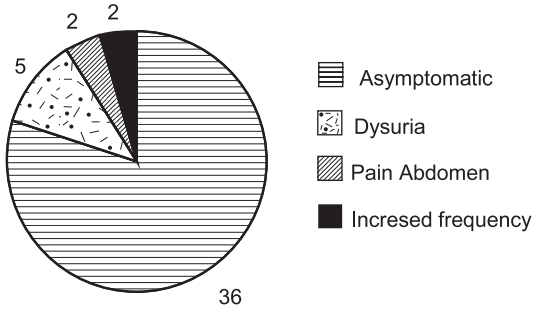

Fig.-1: *Clinical Presentation of UTI in Nephrotic Children*

Amongst 45 UTI positive nephrotic children majority (n=36) were asymptomatic, 5 had dysuria, 2 had abdominal pain and 2 had increased frequency of micturition and none had fever (Fig.-1). *Escherichia coli* was the commonest organism responsible for 63(72%) episodes of UTI in this study population, followed by *Pseudomonas sp.* 14(16%), *Proteus* 4(5%), and *Klebsiela* 3(3%). Seventy three percent (n=33) of UTI were resistant to majority of the antibiotics at sensitivity.

Table-II

Risk factors of UTI in Nephrotic Syndrome Children

Risk factors	Group-I (n=45)	Group-II (n=56)	Chi-square test (with Yate's correction)	P value & Odds Ratio(OR) With 95% Confidence Interval(CI)
Age				
<6 years	39	27	$\chi^2_{(1)}$ 16.291	p<0.001,OR 6.98
6 to12 years	6	29		(95%CI2.551to19.106)
Circumcision (males)				p<0.001, OR=61.36
Not done	27	11	$\chi^2_{(1)}$ 28.33	(CI 7.379 to 510.29)
Done	18	25		
Spot urine protein : creatinine ratio				
>4	42	35	$\chi^2_{(1)}$ 13.09	p<0.001
<4	3	21		OR = 8.4
TC of WBC/cumm				p<0.001,
>11000	31	13	$\chi^2_{(1)}$ 21.171	OR = 7.3
<11000	14	43		
Neutrophil(%)				p<0.05,
>60	32	26	$\chi^2_{(1)}$ 6.217	OR = 2.8
<60	13	30		
ESR in mm first hour				
>50	41	35	$\chi^2_{(1)}$ 10.966	p<0.001,
<50	4	21		OR=6.15
S.Albumin(g/dl)				
<1.5	24	13	$\chi^2_{(1)}$ 9.750	p<0.01
>1.5	21	43		OR=3.78
Serum total protein(g/dl)				p<0.01,
<4.0	16	7	$\chi^2_{(1)}$ 7.541	OR=3.86
>4.0	29	49		
Cholesterol(mg/dl)				p<0.02,
>400	32	27	$\chi^2_{(1)}$ 5.385	OR=2.6
<400	13	29		
Triglyceride(mg/d)				p<0.001,
>300	33	23	$\chi^2_{(1)}$ 10.51	OR=3.9
<300	12	33		
IgG (mg/dl)				
<700	37	23	$\chi^2_{(1)}$ 17.52	p<0.001,
700-1600	8	33		OR=6.63
C3 (mg/dl)				P=NS
<90	11	4	$\chi^2_{(1)}$ 5.906	
90-180	34	52		
C4(mg/dl)				P=NS
<10	2	0	$\chi^2_{(1)}$ 2.539	
Oct-40	43	56		

Table-III
Logistic Regression Table

Variable content in the model			-2 log Likelihood ratio	Nagelkerk R^2	Hosmer Lomeshow goodness of fit			Classification table The cut off value is 0.5	
	χ^2	Sig.			χ^2	df	P	Predicted correctly	
Age								Group-I	87.5%
Serum IgG									
S. Albumin	59.829	p<0.001	78.987	59.8%	6.33	8	0.61	Group-II	73.3%
S.TotalProtein									
ESR								Overall	81.2%

Chi-square test showed (Table-II) significant risk of UTI was associated in age below 6 years with OR=6.9, high spot urine protein:creatinine ratio above 4 with an OR= 8.4, leucocytosis above 11000/cumm with an OR=7.3, neutrophilia above 60% with an OR=2.8, serum albumin below 1.5 g/dl with an OR=3.78, serum total protein below 4g/dl with an OR= 3.86, IgG level below 700mg/dl with an OR= 6.63. Uncircumcised boys (27 vs 11) in this study found to have higher risk of UTI with an OR of 61.36.

By logistic regression (Table-III) it was found that the variables like age, serum IgG, serum albumin, serum total protein, ESR together could predict the presence or absence of UTI in 81.2%. But the prediction was better in case of UTI positive children (87.5% vs 73.3%).

Discussion

This study suggests that age below 6 years is an important risk factor for development of UTI in nephrotic children. This finding is consistent with Shenguttuvan et al (2004), where they found 62.7% infection in children below 6 years, and young children were 1.7 times more prone to develop infection when compared to nephrotics above 6 years[4]. In this study increased susceptibility to UTI in lower age group nephrotic children may be due to significant hypoalbuminemia, which may have a pathophysiological role in predisposing lower age group children to infection. Moreover, nephrotic syndrome in childhood is common between two to six years of ages, and they become more immunodeficient during active disease and more prone to bacterial infection[6].

In this study 44.5% of nephrotic children found UTI positive which is similar with the findings of previous studies 40.26%[3],46%[4],42.22%[8] . But other previous studies[1,8,9,10,11,12] suggested much lower incidence of UTI in nephrotic syndrome children which may be due to inclusion of only hospitalized children with complications, because majority of UTI in nephrotic patients do not require hospitalization and managed on an outpatient basis. In this series the UTI prevalence of 44.5% among nephrotic children is much higher than the prevalence of 1 to 3% reported in the general population[1]. The incidence of UTI in this study per hundred total nephrotic patients' months is 24.7.This indicates that UTI is very high in nephrotic child compared to general population.

Eighty percent of UTI were asymptomatic in this study. Steroid non response or relapse were their presenting features and UTI was diagnosed during screening of urine for infection as part of the study protocol. Asymptomatic UTI in nephrotic syndrome has also been found in different previous reports[3] .

Uncircumcised boys in this study found to have higher risk of UTI. This finding is consistent with previous study report[13] of general population where uncircumcised boys are 10 to 39 times more likely to have UTI than circumcised boys. Absence of circumcision may compromise the protection provided by a longer urethra in males[13].

From this study it is evident that age below 6 years, male child without circumcision, low serum IgG, low serum albumin, low serum total protein, high ESR, high spot urine protein:creatinine ratio, neutrophilic leucocytosis, hypercholesterolemia and hyper triglyceridemia are the important risk factors for development of UTI in nephrotic children. Hypercholesterolemia in infection positive patients has also been observed by Senguttuvan et al(2004)[4]. Significantly lower serum albumin and higher serum cholesterol in NS children with UTI has been reported by Gulati et al(1996)[3]. Hypercholesterolemia may

have a direct pathophysiologic role as it has been observed that hypercholesterolemic serum inhibits lymphocyte proliferation in response to specific and nonspecific antigen stimulation[14]. Gulati et al(1995) stated that nephrotic children who developed infectious complications had significantly lower total plasma protein and lower serum albumin level ($p<0.01$)[15]. They suggested that, this might cause defect in humoral as well as cell mediated immunity which predisposes to infection. Hypoalbuminemia and hypercholesterolemia have been found significantly higher in nephrotic syndrome with UTI in some other studies[3,7,8].

In this study a significant association of UTI have been found with low IgG level. Rubin et al(1975) also found lower levels of serum IgG, C3 and C4 in patients with peritonitis[16]. Patients with nephrotic syndrome have been found to have decreased serum immunoglobulin concentration and T cell dysfunction [9,16,17,18].

Conclusion:

It may be concluded that risk factors for UTI in nephrotic syndrome children are age less than 6 years; uncircumcised state in boys, low serum IgG, low serum albumin, and protein, higher proteinuria, and hypercholesterolemia and hypertriglyceridemia. Thus nephrotic syndrome children when present with relapse or non-response to therapy should be screened for UTI and treated promptly and properly. It was a hospital based short duration study with small sample size. For drawing definitive conclusion about risk factors of UTI in nephrotic syndrome a longterm cohort study with a large sample is needed.

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Original Articles

Immune Deposits in Glomerular Diseases and Their Clinical, Histopathological and Immunopathological Correlation

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Summary:

Glomerulonephritis (GN) is a common renal disease attributing to chronic renal failure (CRF). Early diagnosis and treatment of GN depends on urine and blood examination followed by light and immunofluorescent microscopic study of renal biopsy. Aim of this study was to demonstrate the frequency, pattern and site of deposition of immunoglobulin IgG, IgA, IgM and C_3 by direct immunofluorescence (DIF) microscopic technique in different types of GN and to correlate their association with clinical and histopathological findings. In this study, majority of the cases were in the 21-30 years age group (27.27%). Most frequent clinical presentation of glomerulonephritis was nephrotic syndrome (61.22%; n=98) and commonest type of glomerulonephritis was mesangioproliferative GN (40.81%). Among 98 cases studied, 49 cases (50%) were DIF positive. The most frequent type of depositions were C_3 in various combinations (98%) followed by IgG (67.35%) and IgA (40%). Most common site of immune deposit was mesangium followed by glomerular basement membrane. Granular deposition was the most frequent pattern of immune deposition. Immune-depositions were present in all cases of IgA nephropathy, membranous, diffuse proliferative and membranoproliferative GN. It can be concluded that glomerular immune deposit is present in about half of the glomerulonephritis and the frequency and type of deposition vary with the type of GN.

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Introduction:

Glomerulonephritis is a common renal disease leading to chronic renal failure in both developed and developing countries[1]. Renal biopsy remains the "gold standard" for the diagnosis of glomerular diseases. To evaluate kidney biopsy, complete clinical and laboratory information should be correlated with light, immunofluorescence and electron microscopic findings. Clinical presentations vary with different histopathologic patterns of GN. Focal as well as diffuse proliferative, crescentic and mesangial proliferative GN usually present with nephritic syndrome. Pathological correlation of nephritic syndrome is proliferative GN[2].The morphologic pattern affecting the glomerular basement membrane (GBM) and visceral epithelial cells are seen in membranous GN, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) which typically present with nephrotic range proteinuria[2]. Membranoproliferative GN is a hybrid lesion that presents a combination of nephritic-nephrotic features. Glomerular deposition diseases can trigger nephrotic type, nephritic type or combination of both and thus show marked clinical and morphologic overlap[2]. The site of the antibody deposition within the glomerulus is a critical determinant of clinico-pathologic presentation. Relatively anionic antigens are repelled by the GBM and trapped in the sub-endothelial and mesangial location causing proliferative GN[2]. Relatively cationic antigens tend to permeate GBM and deposits within sub-epithelial aspects of GBM and visceral epithelial cells causing nephrotic type response. Acute sub-endothelial deposits are responsible for leukocyte infiltration, vasoconstriction and thrombotic microangiopathy causing nephritic syndrome, but sub-epithelial and/or intramembranous immune-deposits usually cause nephrotic range proteinuria[2].

Direct immunofluorescence microscopic (DIF) study has resulted in a considerable expansion in the understanding of human glomerular diseases[3]. The DIF technique may correlate significantly with light microscopic diagnosis

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and clinical syndromes. Immune-deposits of IgG/IgA/C3 were found in higher frequency in patients of hematuria due to secondary cause and patients with immune-deposits of IgA/C_3 had recurring respiratory infection[4]. Since the treatment of glomerulonephritis is often determined by the histopathologic findings, any technique that identifies the particular lesion quickly, easily and definitely may be of clinical assistance. The combination of histologic technique with immunofluorescence technique is useful.

The aims of this study were to analyze renal biopsies to detect and correlate the findings of DIF with the various patterns of glomerulonephritis and clinical syndromes.

Material and Methods :

Renal tissue (needle biopsy) specimens were obtained from patients biopsied in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Dhaka Medical College Hospital (DMCH), Combined Military Hospital (CMH) and other referral hospitals of Dhaka city.

The light microscopic (LM) and DIF study were done in the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka and in the Histopathology Department of Armed Forces Institute of Pathology (AFIP), Dhaka during the period from January-December, 1999.

Clinically diagnosed cases of nephrotic syndrome, nephritic syndrome, asymptomatic hematuria or proteinuria of various age groups were biopsied and included in this study. Clinical information was recorded in a pre-designed proforma before doing histopathology and DIF study. Renal biopsies were performed by nephrologists. At least two specimens of 12-20 mm in length renal tissues, one in 10% formalin for histopathology (light microscopic study) and another one in isotonic saline for DIF study were taken. Cryostat machine (for frozen section), fluorescent microscope (NIKON; Labophot-2, model-661012, Japan), phosphate buffer saline (PBS) and commercially prepared fluorescein isothiocyanate (FITC) conjugated goat antihuman IgG, IgA, IgM, and C_3 reagent (Sanofi Diagnostics Pasteur, Inc. 1000 lake Hazeltine Drive, Chaska, USA, MN 55318. Cat-800-666-5111) were used for DIF study. Formalin-fixed processed tissue sections were stained by both haematoxylin-eosin (H & E) and periodic acid Schiff (PAS) stain for histopathologic study. GBM thickness was observed under light microscope with PAS stain.

Histopathology and DIF evaluations of the biopsied specimens were verified by two other competent histopatholgists.

Following were the criteria to define different terms and various patterns of GN.

Adequate for DIF study: Presence of at least one glomerulus under fluorescent microscope.

Adequate for light microscopic study: Presence of at least 5 glomeruli under light microscope[5].

Proliferation: More than 3 mesangial cells embedded in matrix of one segment.

Endothelial proliferation: More than 2 nuclei per capillary loops.

Leukocyte infiltration: More than 5 leukocytes per glomerulus[6].

Crescentic GN: When at least 50% of the glomeruli involved with crescents.

Minimal change disease (MCD) when no evidence of any change or presence of minimal mesangial proliferation of less than 50% of the glomeruli in a section[7].

Lesions are classified as *focal or diffuse proliferative* when they involved the minority (< 50%) or majority (>50%) of glomeruli respectively[2].

IgA nephropathy: Predominant mesangial deposition of IgA detected by immunofluorescence microscopy[8]. Clinical presentation and patterns of 15 cases of IgA nephropathy in this study were evaluated separately.

Focal segmental glomerulosclerosis (FSGS): Segmental (one or two lobules) sclerosis with hyalinosis involving portions of fewer than 50% of the glomeruli in a section.

Sclerosis: Defined as increase in amount of homogeneous non-fibrillar extracellular material of similar composition to GBM and mesangium.

Membranous GN (MGN): Diffuse thickening of GBM due to sub-epithelial deposits of immune complex without evidence of inflammation or cellular proliferation.

Membranoproliferative GN (MPGN): Diffuse thickening of GBM with predominant proliferation of mesangial cells and extension of matrix often with interposition in between the endothelial cells and GBM causing tram-track appearance under light microscope[2].

Mesangioproliferative GN: Diffuse increase in glomerular cellularity predominantly due to mesangial cells often with concomitant increase in mesangial matrix[9].

Fluorescein dye conjugated antihuman antibodies (IgG, IgA, IgM and C_3) were fixed with the tissue section by ten times diluted anti-sera. The fall of ultraviolet light into the stained tissue section emits light of higher wave length to be visible (apple green colour) under fluorescent microscope if there is any antigen in the tissue section. Here antibodies and complement lies within the tissue section (if any) act as antigen and artificially prepared antihuman antibodies and complement act as antibody.

Total number of glomeruli, GBM, mesangial, endothelial and epithelial cells; infiltration of inflammatory infiltrates, tubules, interstitium and blood vessels were observed under light microscope[6,7].

Type (IgG, IgA, IgM and C_3), pattern (granular or linear), site (GBM or mesangium) and intensity of deposition in the glomeruli were observed under fluorescent microscope. The intensity of FITC staining was graded subjectively from 0 to +3: 0 being negative and +3 maximum intensity (mild +1; moderate ++2; marked +++3)[6,7].

The clinical information were recorded. Histopathological diagnosis of formalin-fixed processed renal tissue were made based on H&E and PAS stain followed by saline-fixed tissue frozen section under -25 degree centigrade temperature. These findings were then correlated and evaluated.

Results:

Out of 120 renal biopsies, 10 cases were labeled as inadequate for histopathologic study and 12 cases showed no glomeruli and inadequate for DIF study. Clinical, histopathological and DIF study were done among remaining 98 cases. Among them 56 were male (57%) and 42 female (43%). The age ranged from 8-70 years. Among 98 cases, mesangioproliferative GN (40.81%) was the most frequent pattern of GN followed by focal segmental proliferative GN (20.41%), IgA nephropathy (15.31%), MCD (10.21%) and membranoproliferative GN (10.21%) among all age groups. The most frequent clinical presentations of glomerulonephritis in this study group was nephrotic syndrome (61.22%) followed by isolated haematuria (11.22%) and nephritic syndrome (11.22%) (Table-1). Among fifteen cases of IgA nephropathy, 60% had mesangioproliferative GN, 26.75% chronic GN (CGN), 6.7% membranoproliferative GN (MPGN) and 6.75% focal segmental proliferative GN in light microscopy. Most frequent presentation in IgA nephropathy was micro or macro haematuria (46.7%) followed by nephrotic syndrome (26.7%). Among sixty cases (61.22%; n=98) presented with nephrotic syndrome commonest pattern of was mesangioproliferative GN (25.51%), followed by focal segmental proliferative GN (11.22%), MCD (10.21%), MPGN (6.13%), membranous GN (4.08%), crescentic GN (2.04%) and lupus nephritis (2.04%). On the other hand, 40 cases of mesangioproliferative GN (40.81%; n=98) of this study clinically presented with nephrotic syndrome (25.51%), isolated haematuria (7.15%), nephritic syndrome (1.02%), advanced sclerosis (1.02), non-nephrotic proteinuria (5.10%) and RPGN (1.02%). Twenty (20.41%; n=98) cases of focal segmental proliferative GN presented with nephrotic syndrome (11.21%), haematuria (3.06%), nephritic syndrome (4.08%) and non-nephrotic proteinuria (2.04%) (Table-1).

All MCD, membranous GN and lupus nephritis, (25.51%; n=98), mesangioproliferative GN, (11.2%; n=98) focal segmental proliferative GN and (6.13%; n=98) membranoproliferative GN presented with nephrotic syndrome.

Among 98 cases, mesangioproliferative GN (1.02%), focal segmental proliferative GN (4.08%), membranoproliferative GN (3.06%), focal segmental glomerulosclerosis (2.04%) and diffuse proliferative GN (1.02%) presented with nephritic syndrome. Mesangioproliferative GN (7.15%), focal segmental proliferative GN (3.06%) and membranoproliferative GN (1.02%) presented with haematuria (Table-I).

DIF study was done in 98 cases of which 49 cases (50%) were positive and another 49 cases (50%) DIF negative (Table-II). The sites of immune deposition were predominantly in the mesangium in case of IgA nephropathy, mesangioproliferative GN, FSGS and focal segmental proliferative GN and in the GBM in case of membranous and membranoproliferative GN. DIF positivity was seen in all of IgA nephropathy, MGN, MPGN and diffuse proliferative GN and lupus nephritis of the present study but in mesangioproliferative, MCD and crescentic GN were 36.67, 18.18 and 33.33 percent respectively (Table-IV). All of the glomerular depositions were granular in pattern. The most frequent type of single immune-deposits in 49 cases were C3 (98%), followed by IgG (67.35%) and IgA (40%). The most frequent combination of deposits were IgG+C3 found in 18 cases (36.73%, n=49) followed by IgA+C3 in (20.41%) cases (Table-III). In IgA nephropathy, depositions were mesangial, granular and mostly IgA along with mild deposition of C3. Finally a comparative study of different patterns of DIF in the present study is compared with other studies shown in the table-IV.

Table-I

Clinical presentation and histopathologic pattern (in percentage) (n=98)

Clinical features	Pattern of Glomerulonephritis										
	Mesangio proliferative GN	Focal segmental GN	MCD	MPGN	MGN	Crescentic FSGS	GN	DPGN	CGN	Lupus nephritis	Total
Nephrotic	25.51	11.22	10.21	6.13	4.08	—	2.04	—	—	2.04	61.22
Isolated Hematuria	7.15	3.06	—	1.02	—	—	—	—	—	—	11.22
Nephritic	1.02	4.08	—	3.06	—	2.04	—	1.02	00	—	11.22
Advanced sclerosis	1.02	—	—	—	—	1.02	—	1.02	3.06	—	6.13
Non-nephrotic Proteinuria	5.10	2.04	—	—	—	—	—	—	—	—	07.15
RPGN	1.02	—	—	—	—	—	1.02	—	1.02	—	03.06
Total	40.81	20.41	10.21	10.21	4.08	3.06	3.06	2.04	4.08	2.04	100

Table-II

Histopathologic pattern and DIF findings in 98 study cases

Pattern of GN	Cases	DIF positive (%) (n=49)		DIF negative (%) (n=49)	
Mesangioproliferative GN	30	11	(36.67)	19	(63.33)
Focal segmental proliferative GN	18	03	(16.67)	15	(83.33)
IgA nephropathy	15	15	(100)	—	—
Minimal change disease	11	02	(18.18)	09	(81.82)
Membranoproliferative GN	08	08	(100)	—	—
Membranous GN	04	04	(100)	—	—
FSGS	03	—	—	03	(100)
Crescentic GN	03	01	(33.33)	02	(66.67)
Diffuse proliferative GN	02	02	(100)	—	—
Chronic glomerulonephritis	01	00	000	01	100
Lupus nephritis	02	02	100	—	—
Total	98 (100)	49		49	

Table-III

Distribution of immunoglobulin IgG, IgA, IgM and of 49 DIF positive cases in various pattern C3

Immunoglobulin and C3	No. of cases (n=49)	Percentage
IgG + C3	18	36.73
IgA + C3	10	20.41
IgG + IgM + C3	06	12.24
IgA + IgG + C3	05	10.20
IgG +IgA + IgM + C3	04	08.16
IgM + C3	03	6.12
IgA + IgM + C3	01	04.04
C3 only	01	04.04
IgM only	01	04.04
Total	49	100

Table-IV

Comparative study of DIF positive cases by different authors

Pattern of GN	DIF positive findings in percentage						
	Morel-Marogor, 1972	Larsen, 1978	Metha et al, 1983	Tabassum, 1988	Sharmin, 1994	Nabir, 1996	Present study
Mesangioproliferative	53.33	85	45	80	70	60	36.67
Focal proliferative	74.58	90.67	65	60	50	40	52.48
MCD	—	60	57.1	—	—	—	18.18
Membranous GN	100	100	100	100	100	100	100
MPGN	100	100	100	100	100	100	100
IgA nephropathy	100	100	100	100	100	100	100
Diffuse proliferative	83.88	77.7	100	100	100	100	100
CGN	—	—	—	—	50	00	—
Crescentic GN	76	65	33	100	100	—	33.33
FSGS	76.32	40	60	33.33	10	—	66.67
Lupus nephritis	100	100	100	100	100	100	100

Discussion:

Nephrotic syndrome is generally the most frequent clinical presentation of glomerulonephritis as shown by Cameron, 1980 (57.77%)[10]; Ziauddin et al, 1993 (56.6%)[11] and Rahman et al, 1984 (94%)[12]. This is mostly similar to our study (61.22%). There is a wide variation regarding the commonest pattern of glomerulonephritis.

Studies of Rahman et al, 1984, Ziauddin et al, 1993 and Nabir Uddin, 1996 showed that MCD, diffuse proliferative GN and focal segmental proliferative GN were the most frequent pattern of GN respectively[13]. But the study of Tabassum, 1998 and Sharmin, 1994 along with our study reveal mesangioproliferative GN is the most frequent pattern of GN[14, 15]. Diffuse proliferative GN is the commonest pattern of GN in western world [16, 17, 18]. In fact, mesangial cellularity of MCD is conbsidered as an intermediate step in the evolution of MCD to FSGS[19]. By light microscopy, evidence of segmental proliferations may be missed if the biopsy specimen contains insufficient number of glomeruli.

In this study, DIF was positive in 50% cases. Similar results were obtained by other two investigators of Bangladesh[14,15]. Our study also reveals predominantly generalized distribution of deposits either in the mesangium or GBM (93.88%) rather than focal (6-12%) which signifies generalized involvement of immune-deposits in glomerular diseases. More or less similar findings were reported by other authors [14, 15, 20, 21].

Conventionally, apparently normal glomeruli in light microscope and no deposition in DIF study are regarded as MCD. But our study reveals DIF positivity of 18.18% in MCD cases which was also observed by others.[4, 21]. Brenner and Rector in 2004 explained about DIF positivity due to differentiation between mild prominences of mesangial cells as observed in MCD and definite mesangial proliferation is subjective and highly susceptible to artifacts of sectioning and specimen preparation[5].

The most frequent type of single immune-deposits was IgG followed by C_3 and IgA in the study of Tabassum, 1998 and Nabir, 1996 which is dissimilar to our study (C_3 followed by IgG and IgA). The most frequent presentation (haematuria), pattern and combination of deposition (IgA+C3) in IgA nephropathy also showed very similar results reported by Sharmin, 1994 and Khan et al, 1990 [15, 23]. It was also observed that the type, site, pattern and intensity of immune-depositions greatly modify the clinical presentation and course of GN[2]. There is a variation in in reporting of DIF positivity by different authors (Table-IV).

Conclusion:

It is found in the present study that 50% of the glomerulonephritis had immune-deposition in the glomerulus. Though somewhat expensive; DIF was proved to be simple, rapid, sensitive and highly specific diagnostic

procedure. Common site of immune deposition was in the glomerular mesangium with a predominant granular pattern and combinations of C3 with other immunoglobulin were mostly seen. Although the site, type, pattern and intensity of immune-deposits was identified by fluorescent microscope but identification of the exact location of the site (sub-endothelial or sub-epithelial or intramembranous) of immune deposits, was not possible in the absence of electron microscopy.

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Case Report

Paroxysmal Nocturnal Haemoglobinuria - A Case Report

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Summary:

Paroxysmal nocturnal haemolysis (PNH), an uncommon accuired haemolytic disorder charectarized by chronic haemolytic anemia due to intravascular haemolysis, often associated with nocturnal haemoglobinuria, thrombotic events, serious infections and sometimes bone marrow failure. Diagnosis is usually suggested by the characteristic intermittent hemoglobinuria and the demonstration of haemosiderin in the urine. Diagnosis is confiremed by positive serologic tests like Hams test and Sucrose haemolysis tests. With the exception of bone marrow transplantation no definitive therapy is available and management is largely supportive.

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Introduction:

Paroxysmal nocturnal hemoglobinuria (PNH), an uncommon acquired hematologic disorder characterized by chronic hemolytic anaemia due to intravascular hemolysis, often associated with nocturnal hemoglobinuria, thrombotic events, serious infections and sometimes bone marrow failure.[1] The underlying cause is a somatic mutation of the phosphatidylinositol glycan (GPI) complementation class A (PIGA) gene, followed by a survival advantage of the PNH clone, which results in a deficiency of GPI anchored proteins on hemopoietic cells.[2] In particular the complement regulating proteins CD-55 and CD 59 are deficient. The defect involves both increased binding of C3b and increaded vulnerability to lysis by complement. Classically patients report episodic reddish brown urine (hemoglobinuria). In addition to anaemia, these patients are prone to thrombosis, especially mesenteric and hepatic vein thromboses.[1,2] As this is a stem cells disorder, PNH may progress either to aplastic anaemia, to myelodysplasia, or to acute myelogenous leukaemia.[1] PNH should be suspected in confusing cases of haemolytic anaemia or pancytopenia requiring multiple blood transfusions.

Case Summary:

A 28 years old man from Patuakhali presented with general weakness and fatigue for 3 years. He gives history of passing red colored urine that continues for several days followed by severe weakness and yellow coloration of his eyes and pain and discomfort in epigastrium. He improves spontaneously after 7 to 10 days. Similar episodes were happening at an interval of several months and he received 18 units of fresh blood transfusion in several years. He used to notice more red coloured urine after awakening from sleep. He does not give any history of frequency or dyuria, joint pain, skin rash or passage of stone. Apart from management by the general physicians he was evaluated by urologists of both home and abroad for passage of red urine that proved no abnormality in urinary tract.

On examination he looked very pale, no pedal oedema. Blood pressure 130/80 mmHg and yellowish sclera. Peripheral pulses were normal and there was no purpuric spot or bruises in skin and mucous membrane. Clinically liver and spleen were not palpable and other systemic examination revealed normal findings.

Investigations showed Hb 6.2gm/dl, ESR 60 mm in 1st hour, TC 9,000 polymorphs 48%, lymphocyte 42%, monocytes 06%, eosinophil 04% and platelet count 2,50,000 per c.mm. Reticulocyte counts was 16% serum bilirubin 2.8mg/dl, SGPT 35 U/L, blood urea 15 mg/dl, serum creatinine 1mg/dl. Urine routine examination albumin (+), RBC –occasional, pus cells -0-3/hpf. Urine culture showed no growth and urine AFB not found. Urine cytology for malignant cells was negative. X-ray chest and X-ray KUB normal. USG of KUB region normal and I.V.U was normal. Blood film and bone marrow study showed combined deficiency with features of myelodysplastic syndrome. Urinary

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hemoglobin 0.4 gm/dl and urinary hemosiderin present (+++). Hams Acid serum test was positive.

A diagnosis of paroxysmal nocturnal hemoglobinuria was made and he was treated conservatively with 4 units of fresh blood transfusion, vitamins and folic acid supplements. He improved uneventfully and was advised to have periodic follow up under hematologist care.

Discussion:

PNH usually appears first in adult life, most commonly in the third or fourth decade and affects both sexes equally[3]. It is not hereditary and is unrelated to race.[3] Our patient is young and developed the symptoms in his 3rd decade of life. The onset is insidious and hemoglobinuria is the cardinal clinical feature, usually present and the onset in 50 percent cases.[3] Our patient during each episode had hemoglobinuria from the onset and he used to pass brownish urine both during day and night usually after awakening from sleep. The cause of the nocturnal exacerbation of hemoglobinuria is poorly understood.

In addition to the sleep related patterns, most patients experience irregular but recurrent exacerbations of hemolysis and hemoglobinuria. Our patient was having episodic hemoglobinuria and severe anaemia for 3 years. Fortunately he did not develop any thrombotic complications. PNH is associated with striking predisposition to intravascular thromboses especially with in the venous circulation. Intra-abdominal veins, cerebral veins and superficial dermal veins are common sites of thrombosis[2,3]. Fatal thromboses usually involve the protal system or the brain[2]. Both acute and chronic renal insufficiency occurs in patients with PNH[2]. ARF is associated with hemoglobinuric crisis and may resolve without residual damage.

Blood picture shows anaemia of varying severity and reticulocyte are increased. Our patient had reticulocyte count of 16%. In active phase, hemoglobin is usually found in serum which appears pinkish thereby helps to differentiate from myoglobinuria. The serum bilirubin is moderately increased. The bone marrow is hypercellular during hemolytic phase of the disorder and in the aplastic phase, there is a reduction in all marrow elements.

Diagnosis is usually suggested by the characteristic intermittent hemoglobinuria and the demonstration of hemosiderin in the urine[3]. In our patient urine showed hemosiderin. The diagnosis is confirmed by positive serologic tests, Hams test (acidified serum lysis) and sucrose hemolysis test (sugar water).[3] These tests are sensitive and specific when properly performed but their accuracy is strongly operator dependent.[2] These complement- based assays are being replaced by newer techniques. Monoclonal antiboides to GPI anchored proteins (eg. anti CD55 and anti CD 59) are more reliable method of diagnosis[2,4]. By analyzing the expression of GPI – AP on hematopoietic cells using monoclonal antibodies and flow cytometery, the abnormal cells can be readily identified[2,4]. Recently Brodsky and colleagues developed a very sensitive assay for PNH by exploiting the properties of the bacterial toxin aerolysin that hinds to the GPI anchor. Using this method, as few as 0.004% GPI-AP cells could be identified[2,4].

With the exception of bone marrow transplantation no definitive therapy is available and management is largely supportive. Transfusion with concentrated red cells relieves anemia for a considerable time as the transfused cells have a normal lifespan in the patient. Androgenic steroid appears to be effective in cases with prominent marrow hypoplasia whereas prednisolone is most useful in patients with overt hemolysis[3]. Recently, Eculizumab, a humanized monoclonal antibody directed against the terminal complement proteins C5 has been shown to reduce hemolysis and greatly improve symptoms and quality of life for PNH patients[5].

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Abstract from Current Literature

(Bang. Renal J. 2008; 27(2): 44-48)

Chronic crusting, nasal carriage of Staphylococcus aureus and relapse rate in pulmonary Wegener's granulomatosis

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Wegener's granulomatosis is a systemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract and necrotizing crescentic glomerulonephritis. Nasal carriage of S. aureus is considered a risk factor for S. aureus infections. The aim was to examine possible risk factors for relapse including refractory nasal carriage of Staphylococcus aureus in patients with Wegener's granulomatosis. Swab cultures from anterior nares for S. aureus were taken in consecutive patients (n=28), with limited (n=15) and systemic forms (n=13) of biopsy-proven Wegener's granulomatosis. The occurrence of infection and relapses were identified according to defined criteria. Seventeen of the 28 patients (60%: 95% Cl, 41-76%) were found to be chronic nasal carriers of S. aureus (> or =80% of nasal cultures positive for S. aureus). A hazard regression analysis identified chronic nasal carriage of S. aureus as independent risk factor for relapse (HR-4.56; Cl 2.45-7.65) in patients with limited Wegener's granulomatosis. Chronic nasal carriage of S. aureus characterized patients with Wegener's granulomatosis, who are more prone to relapses.

J Physiol Pharmacol. 2008; 59 Suppl 6:825-31.

Use of mizoribine as a rescue drug for steroid-resistant pediatric IgA nephropathy.

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Recent clinical trials have shown a beneficial effect of mizoribine (Miz), an immunosuppressive drug, in the treatment of new-onset pediatric IgA nephropathy (IgAN). In this study, we evaluated the efficacy of Miz treatment in three children with established steroid-resistant IgAN. The patients had IgAN featuring persistent proteinuria and diffuse mesangial proliferation and had failed to respond to 2 years of treatment with prednisolone. Based upon the second biopsy results, patients were given methylprednisolone (mPSL) pulse therapy that induced a transient reduction in proteinuria, which was reversed when the mPSL dose was tapered. Miz therapy was then instigated in place of pulse mPSL. All three patients showed a substantial reduction in proteinuria and resolution of hematuria within 5 months. A follow-up biopsy in two of the patients showed a substantial reduction in the severity of glomerular lesions and a decrease in the number of activated macrophages. In conclusion, Miz therapy was found to be a safe and effective therapy in three cases of steroid-resistant pediatric IgAN. The ability of Miz to reduce the number of activated macrophages may be an important mechanism by which this drug ameliorated renal disease in these patients

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Role of systemic anticoagulation in patients undergoing vascular access surgery

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The role of per-operative systemic heparin to improve primary patency rate of vascular access surgery is controversial. The aim of this study was to assess the risk and benefit of systemic heparin during creation of vascular access for hemodialysis in patients with chronic renal failure. Patients undergoing creation of side to end radio-cephalic arteriovenous fistula over distal forearm for hemodialysis were prospectively randomized into two groups. First group received 5000 IU of intravenous heparin during surgery whereas second group did not receive any anticoagulation. Post-operative complications and outcome of surgery were compared between the two groups. Among 50 patients, 25 received heparin and 25 did not. Although there was no significant difference in operative times between these two groups ($p = 0.24$), early post-operative bleeding complication was more common in patients receiving heparin ($p < 0.01$). The primary 6-

week patency was 96.0% for patients receiving heparin and 92.0% for those not (p = 0.46). Thus per-operative systemic anticoagulation during vascular access surgery is associated with increased incidence of bleeding complication and offers no benefit in terms of primary patency

Nepal Med Coll J. 2008;10:222-4.

Spirometry parameters in patients undergoing hemodialysis with bicarbonate and acetate dialysates

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Introduction: End-stage renal disease causes impairment of all body organs including the heart and the lung. The main problems in the afflicted patients are pulmonary edema due to increased permeability of the capillaries, intravascular and interstitial volume overload, hypertension, and congestive heart failure. These changes cause altered physiologic and mechanical function of the lungs and subsequently increase in airway resistance. We aimed to study the impact of hemodialysis on spirometry parameters.

Materials And Methods: In a cross-sectional study performed on 41 patients on maintenance hemodialysis, spirometry was done before and after the dialysis session. The patients were on either acetate or bicarbonate hemodialysis with the same method, dialysis machine, and duration of dialysis. Alterations in spirometry parameters including forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, and maximal midexpiratory flow rate were determined and their relation with serum electrolytes, serum creatinine, blood urea nitrogen, and hemoglobin were analyzed.

Results: Twenty-nine patients undergoing dialysis with bicarbonate dialysate and 21 on dialysis with acetate were compared. Improvement in spirometry parameters was only significant in patients undergoing dialysis with bicarbonate dialysate. All spirometry parameters showed significant increases in the bicarbonate group except for the FEV1/FVC ratio. Furthermore, significant increase in these parameters was only prominent in the men. Postdialysis weight reduction and laboratory indexes had no significant correlation with improvement of spirometry parameters.

Conclusions: Dialysis with bicarbonate dialysate causes significant improvement in spirometry parameters in men on maintenance dialysis. This effect might be independent of the effect of removing the volume overload by dialysis

Iran J Kidney Dis. 2008;2:149-53.

Randomized study of darbepoetin alfa and recombinant human erythropoietin for treatment of renal anemia in chronic renal failure patients receiving peritoneal dialysis

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Background/Purpose: Darbepoetin alfa can be administered less frequently than recombinant human erythropoietin (r-HuEPO) for the treatment of anemia in chronic renal failure (CRF) patients. We aimed to confirm that darbepoetin alfa at a reduced dosing schedule can safely maintain a target hemoglobin level in CRF patients undergoing peritoneal dialysis.

Methods: Forty-five PD patients receiving r-HuEPO were randomized in a 1:1 ratio to continue r-HuEPO or to change to darbepoetin alfa (open-label). Patients were maintained within a target range of haemoglobin for 5.5 months by adjusting the dose and then the frequency of darbepoetin alfa and r-HuEPO over the initial 4 months. The evaluation period was the final 1.5 months. A total of 37 patients completed the study.

Results: During the evaluation period, the hemoglobin of the darbepoetin alfa group was higher than that in the baseline period (10.46 +/- 0.22 g/dL vs. 9.98 +/- 0.18 g/dL, $p < 0.05$). Hemoglobin remained similar in the r-HuEPO group. The average dose in the darbepoetin alfa group was 93.0 microg/month, while the average dose in the r-HuEPO group was 18,339.9 units/month. The dosing frequency was less in the darbepoetin alfa group (3.9 times/month vs. 9.2 times/month). We divided the darbepoetin alfa group into low-dose (< 70 microg/month) and high-dose (> or = 70 microg/month) subgroups. The body weight in the high-dose group was higher than that in the low-dose group (66 +/- 11 kg vs. 52 +/- 4.4 kg, $p < 0.01$).

Conclusion: Both darbepoetin alfa and r-HuEPO safely maintain hemoglobin levels within the target range in peritoneal dialysis patients

J Formos Med Assoc. 2008;107: 843-50.

Therapeutic effect of Tripterygium wilfordii on proteinuria associated with sirolimus in renal transplant recipients.

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Sirolimus (SRL) is a potent immunosuppressive drug used to prevent acute allograft rejection after renal transplantation. Nevertheless, the occurrence of proteinuria has recently been recognized among patients on SRL-based therapy. The aim of this study was to investigate the therapeutic effects of Tripterygium wilfordii Hook F. (T II) on proteinuria associated with SRL in renal transplant recipients. According to accepting T II, 36 recipients were divided into 2 groups: T II group (n = 21) and valsartan group (n = 15). The T II group was administered 1 mg/kg/d, and the valsartan group, 80 mg twice per day for 12 months. Efficiency was then evaluated. Complete remission: proteinuria decreased by >50%; partial remission: proteinuria decreased by 20% to 50%; ineffective: proteinuria decreased by <20%. Upon 12-month follow-up, the total effective rates in the T II group and the valsartan group were 95.2% and 86.7% ($P < .05$), respectively. Twenty of 21 patients with proteinuria in the T II group were negative at 3-month follow-up with disappearance of edema. There were some adverse events that had greater incidence rates in the valsartan group compared with the T II group, such as hyperkalemia (26.7% vs 4.8%). We concluded that the application of T II markedly reduced proteinuria associated with SRL in renal transplant patients

Transplant Proc. 2008; 40:3474-8.

Two-year observation of a randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplantation.

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Objective: To evaluate the safety and feasibility of steroid or mycophenolate mofetil (MMF) withdrawal from tacrolimus-based immunosuppressant regimen in renal allograft recipients.

Methods: A cohort of 45 patients following cadaveric renal allograft transplantation were randomly divided into 3 groups based on the regimen of combination of tacrolimus, steroid, and MMF: triple therapy group, steroid withdrawal group, and MMF withdrawal group. During 2 years, survival of patients and allografts, clinical acute rejection, adverse events, hepatic and renal allograft function, and blood lipids were monitored to evaluate the safety and feasibility of steroid or MMF withdrawal after renal transplantation.

Results: During two-year observation, steroid or MMF was successfully withdrawn from immunosuppressant regimen based on tacrolimus without any clinical acute rejection. Patient and graft survival rates were 100% and all the renal allografts kept excellent function. Some adverse events occurred and there were no significant differences among groups.

Conclusion: Withdrawal of steroid or MMF in low-immunological-risk renal allografts treated with tacrolimus-based immunosuppressant regimen can be achieved with no increased risk of acute rejection

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Sepsis-related acute kidney injury: a protective effect of drotrecogin alpha (activated) treatment?

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Erratum in: Acta Anaesthesiol Scand. 2009 Feb;53(2):275.. van Doorn, K J [corrected to Janssen van Doorn, K].

Background: Drotrecogin alpha activated (DrotAA) is licensed for treatment of patients with severe sepsis and organ failure. Among the latter, acute kidney injury (AKI), defined as the persistence of oligo-anuria following adequate resuscitation, is one of the most apprehended. We conducted a prospective, observational, and controlled study to test the hypothesis that DrotAA beneficially affected the evolution and outcome of AKI, complicating acute sepsis-induced cardiopulmonary failure.

Methods: Forty-six patients were studied. Thirty subjects received standard treatment for sepsis without DrotAA. In the remaining 16 patients, DrotAA was added as a continuous infusion of 24 microg/kg/h for 96 h.

Results: Mean age, causes of sepsis, and severity/organ failure scores were comparable between patients treated with or without DrotAA. Mortality at 28 days was high

and comparable between both treatment groups (56% vs. 69%, DrotAA vs. no DrotAA; P=0.5). When oligo-anuria was present at the start of the study, it persisted during treatment in all patients, with no significant difference between groups. Both treatment groups presented with baseline mean daily fractional excretion of sodium values >2% that remained high during the observation period, regardless of whether DrotAA was given or not. Kidney histology showed a preserved renal architecture with tubular necrosis in all specimens. Similar glomerular, tubulo-interstitial, and vascular alterations were present in both treatment groups.

Conclusion: In this small cohort of patients with severe sepsis who received adjuvant DrotAA treatment, no effect on urine output, tubular function, or mortality could be demonstrated.

Acta Anaesthesiol Scand. 2008; 52: 1259-64.

Tirofiban preserves platelet loss during continuous renal replacement therapy in a randomised prospective open-blinded pilot study.

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Introduction: Approximately one third of all patients with cardiogenic shock suffer from acute kidney injury. Percutaneous coronary intervention, intra-aortic balloon pump, and continuous renal replacement therapy (CRRT) require effective antiplatelet therapy and anticoagulation, resulting in a high risk for platelet loss and bleeding events. The reversible platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban was investigated to preserve platelet number and activation in a prospective open-blinded endpoint evaluation study.

Methods: Forty patients with cardiogenic shock and acute kidney injury requiring CRRT were randomly assigned to two groups receiving unfractioned heparin (UFH) (n = 20) or a combined anticoagulation with UFH and tirofiban (n = 20). The primary endpoint was platelet loss during CRRT. Secondary endpoints were urea reduction, haemofilter life span, bleeding events, and necessity for platelet transfusions.

Results: In UFH-treated patients, the percentage of platelet-monocyte aggregates significantly increased ($P < 0.001$) and consecutively platelet cell count significantly decreased ($P < 0.001$). In contrast, combined treatment with UFH and tirofiban significantly decreased platelet-monocyte aggregates and platelet numbers ($P < 0.001$).

Conclusions: This pilot study provides evidence that the use of tirofiban in addition to UFH prevents platelet loss and preserves platelet function in patients with cardiogenic shock and acute kidney injury requiring CRRT. The pathophysiological inhibition of platelet aggregation and platelet-monocyte interaction appears to be causally involved

Crit Care. 2008;12: R111. Epub 2008 Aug 29.

Opportunity: a randomized clinical trial of growth hormone on outcome in hemodialysis patients.

Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, El Nahas M, Feldt-Rasmussen B, Lange M, Mitch WE, Wanner C, Wiedemann J, Ikizler TA.

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Background: The mortality rate of maintenance hemodialysis (MHD) patients remains high. Measures of protein-energy wasting, including hypoalbuminemia, are strongly associated with their high mortality. Growth hormone (GH) may improve lean body mass (LBM) and serum albumin levels, and health-related quality of life (HRQoL), which are significantly and positively associated with survival in MHD patients. The OPPORTUNITY Trial will examine whether GH reduces mortality and morbidity and improves overall health in hypoalbuminemic MHD patients. HYPOTHESIS: The primary hypothesis is that daily recombinant human GH injections, compared with placebo, improve survival in hypoalbuminemic MHD patients. Secondary hypotheses are that GH improves morbidity and health, including number of hospitalized days, time to cardiovascular events, LBM, serum protein and inflammatory marker levels, exercise capacity, and HRQoL, and has a favorable safety profile.

Design/Measurements: This is a prospective, double-blind, multicenter, randomized clinical trial involving 2500

MHD patients, up to 50% with diabetes mellitus, from 22 countries. Patients are randomized in a 1:1 ratio to receive daily injections of GH (20 microg/kg per day) or placebo for 104 weeks. Key inclusion criteria include clinically stable and well-dialyzed (Kt/V > or =1.2) adult MHD patients with serum albumin <4.0 g/dl. Exclusion criteria include active malignancy, active proliferative or severe nonproliferative diabetic retinopathy, uncontrolled hypertension, chronic use of high-dose glucocorticoids, or immunosuppressive agents and pregnancy.

Conclusions: The Opportunity Trial is the first large-scale randomized clinical trial in adult MHD patients evaluating the response to GH of such clinical endpoints as mortality, morbidity, markers of body protein mass, inflammation, exercise capacity, and HRQoL.

Clin J Am Soc Nephrol. 2008;3: 1741-51.

Announcements

(Bang. Renal J. 2008; 27(2): 49)

ESRD: State of the Art and Charting the Challenges for the Future, Sheraton Boston Hotel, April 23–26, 2009

This international world class conference, a 20 year follow-up to the 1989 Dallas Morbidity and Mortality Conference, will review and examine progress achieved, the current knowledge of ESRD, medical and non-medical determinants of outcomes, with a goal of how to enhance future care. The program, developed by an international Steering Committee, with Drs. Theodore Steinman and Thomas Parker as Co-Chairs, will critically dissect factors that determine patient care—going beyond the usual quality measures. Internationally prominent keynote speakers will explore the role of government in ESRD care and the direction of health care in America. The provocative meeting is endorsed by the ASN, EDTA, ERA, ISN, NKF and RPA. Information on the program and registration is available on our website. Registration is limited. http://www.cme.hms.harvard.edu/courses/ESRD

40th Course on Advances in Nephrology, Dialysis and Transplantation, Milan Marriott Hotel, Milan, 5–8 December 2008

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14th International Vasculitis & ANCA Workshop Lund, Sweden and Copenhagen, Denmark, June 6–9, 2009

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John Feehally
ISN Secretary General
jf27@le.ac.uk

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