Original Article

Clinical Spectrum and Outcomes of Non-lupus Crescentic Glomerulonephritis : An Experience from Eastern India

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Aims : To evaluate the clinical profile, histomorphology and clinical outcome of patients with Crescentic Glomerulonephritis (except Lupus) treated with pulse intravenous Cyclophosphamide using European Vasculitis Study Group (EUVAS) protocol.

Materials and Methods : Prospective observational single center study over a period of one and half year. Relevant clinical, laboratory and histological data were recorded. End points of study: death, completion of 6 month of follow up or end stage renal disease, whichever is earlier.

Results : Total 1023 renal biopsies were performed during the study period.4.40% (n=45) had Crescentic Glomerulonephritis (CrGN) of which 3.42%(n=35) were non-Lupus and 0.98%(n=10) were Lupus Nephritis. Amongst the non-Lupus 91% (n=32) were pauci-immune& rest were Anti-GBM (AGBM) & IgA Nephropathy (IgAN). 68.75% (n=22) were ANCA positive and 10(31.25%) were ANCA negative. 54.55% (n=12) c-ANCA positive and 45.45% (n=10) were p-ANCA positive. Average age was in 21 to 60 years with Male: Female ratio was 1:2.2. Maximum crescents were in Anti-GBM (93%) followed by ANCA group (65%). At presentation 80% (n=28) were oligoanuric & 82.86% (n=29) patients required dialysis. 68.57% (n=24) patients responded to EUVAS regimen while 31.42% (n=11) did not respond. 20% (n=7) remained dialysis (HD) dependent and 37.14% (n=13) non-HD Dependent. ANCA positive responded better to EUVAS protocol than ANCA negative and worst outcome noted in AGBM and IgAN.

Conclusion : Non Lupus CrGN treated by EUVAS protocol has an initial response rate of 66%. No histological or clinical parameter was significantly associated with response to therapy. Sepsis was the most common cause of death.

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Key words **: Crescentic, Glomerulonephritis, Lupus.**

Rapidly Progressive Glomerulonephritis (RPGN) is a severe form of Nephritic Syndrome characterized by the rapid loss of renal function, accompanied by proteinuria, glomerular hematuria and often, oliguria[1,2]. Histologically, RPGN is usually associated with Crescentic Glomerulonephritis (CrGN) defined as presence of crescents in >50% of glomeruli on renal biopsy. In this study we have focused on non-Lupus CrGN. Prior to 1970s the outcomes for most of CrGN cases were dismal. Subsequently, cyclophosphamide and steroids have dramatically improved the remission rates[3]. Early diagnosis and treatment can significantly alter the course of the disease and may prevent irreversible loss of renal function. European Vasculitis Study Group (EUVAS) has provided a robust evidence for pulse cyclophosphamide therapy (EUVAS CYCLOPS protocol) and have led to consensus guidelines ie, European League Against Rheumatism (EULAR) recommendations for treatment of Antineutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (AAV) which is the most common non-Lupus CrGN[1,3] The evidence for pulse cyclophosphamide in other form of non-Lupus CrGN is less well established. The prevalence, serotype frequencies and clinico-pathologic phenotypes in AAV are influenced by racial/ethnic and geographic factors[4]. Despite the effectiveness of pulse cyclophosphamide therapy, the adverse effects of cyclophosphamide, particularly infections are a serious concern. These in turn may be affected by the socio-economic status and may vary across different populations. We planned this

Editor's Comment :

- Acute Renal Failure is a Medical Emergency and evaluation and management should be started at earliest possibility to prevent Renal death.
- There should be high degree of suspicion of Rapidly Progressive Renal Failure(RPGN) to all patients requiring dialysis when the disease duration less than 3 months.
- Renal Biopsy should be offered and to be done to all RPGN cases to see what is actually going on inside the Kidneys for better Renal survivability.

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study with the aim of evaluating the clinical profile, histomorphology and outcome of Crescentic Glomerulonephritis (except that due to Lupus) treated with European Vasculitis Study Group (EUVAS) intravenous cyclophosphamide protocol in patients presenting to our tertiary care institute.

Materials and Methods

This is a prospective observational single centre study conducted at Institute of Postgraduate Medical Education & Research (IPGME&R), Kolkata, one of the largest tertiary care centers of Eastern India from January 2012 to December 2013. Patients of any age group diagnosed with Crescentic Glomerulonephritis (histologically) due to any etiology other than Lupus were included in the study. Informed and written consent of patient and that of the legal guardians in case of minors of the patient was taken before enrollment. Patients who refused or could not be given EULAR protocol, those who were not willing to participate and those who refused renal biopsy were excluded from the study.

Clinical, laboratory data and details of renal biopsy findings were recorded. Patients will be evaluated at presentation regarding: Clinical data including age, sex, skin or throat infection, blood pressure, systemic manifestations such as skin rash, arthritis, serositis, edema, manifestations of uremia, oliguria, gross hematuria and history of medications.

As a protocol laboratory parameters including urinalysis, serum creatinine, urea, sodium, potassium calcium, phosphorus, uric acid, complete blood count, plasma proteins, albumin, cholesterol, Anti-Streptolysin O (ASO), Anti-Nuclear Antibody (ANA), complement 3 (C3), anti-double stranded Nuclear Antibody (anti ds-DNA) and 24 hour urinary protein excretion. Anti-Neutrophil Cytoplasmic Antibody (ANCA) by ELISA and immunofluorescence and anti-Glomerular Basement Membrane (anti-GBM) were done for all the patients presenting as RPGN. Renal biopsy was considered for all RPGN patients. Only those who satisfied the inclusion criteria were included in the study. Subsequent investigations including Renal Function Test (RFT), complete hemogram, urine analysis and other investigations as and when needed were done at each follow up visit weekly after discharge for one month, then twice a month for 3 months and monthly thereafter. Renal biopsy was done in strict surgical aseptic procedure with real time Ultrasonography (USG) guided method after obtaining written informed consent. The protocol for renal biopsy procedure and assessment has been described in supplementary data and supplementary Table 1 respectively. The protocol of treatment, modifications as per renal function, age and leucopenia (as mentioned in supplementary Table 2) and follow up is specified in supplementary data. The definition used for RPGN, CrGN, treatment responses and relapse have been given in supplementary data. The patients were followed up till attainment of end stage renal failure (requiring renal replacement therapy for 3 months), death or last follow-up at December, 2013, whichever was earlier.

Results are presented as means with standard Deviation (SD) for normally distributed data, or medians with percentiles for non-normally distributions. Nominally distributed continuous variables were compared using t-test. Categorical variables are compared using chi-square tests. All statistical tests will be two-sided with a P-value of <0.05 taken to indicate statistical significance. Independent variables affecting outcome have been analyzed using multivariate analysis.

Results

A total of 1023 patients underwent renal biopsy during the study period. Among these 92(8.99%) patients had histological diagnosis of Glomerulonephritis with Crescents and 45 (4.40%) had Crescentic Glomerulonephritis (CrGN). Of these 45, 22.22% had lupus CrGN and 77.78% had non-lupus CrGN. The ratio of males: females for non-Lupus CrGN was 1:2.1. 91% of non Lupus CrGN were Pauci-Immune CrGN (PICrGN) while Antiglomerular basement membrane antibody disease (Anti-GBM) and Immunoglobulin A Nephropathy (IgAN) comprised 6% and 3% of all non-Lupus CrGN. One patient with Anti-GBM disease also had pANCA positivity. This patient

Table 1 — *Age-wise distribution and baseline laboratory features of different types of non lupus Crescentic Glomerulonephritis*

Age	Pauci-immune CrGN*	Anti-GBM CrGN*	IgAN#
Age groups :			
All (N=35)	91%	6%	3%
Age 1 to 20 years (N=6)	83%	0%	17%
Age 21 to 60 years (N=26)	92%	8%	0%
Age 61 to 100 years (N=3)	100%	0%	0%
Average age in years	38.41±14.834	33.50±4.95	17
Male: female	1:2.2	1:1	
Average Serum Creatinine (mg/dL)	5.08±3.664	12.94±2.475	8.62
Average Proteinuria (g/24 hours)	2.84±1.614	0.98±0.489	1.35

*CrGN : Crescentic Glomerulonephritis,
IgAN : Immunoglobulin A Nephropathy

Table 2 — *Clinical profile of different non lupus Crescentic glomerulonephritis*

Characteristic	AGBM	ANCA+	ANCA-	IgAN	P
Male	1(%)	7(%)	3(%)	0(%)	0.852
Female	1(%)	15(%)	7(%)	1(%)	
Age (in years)	33.5±4.95	36.05±14.624	43.6±14.676	17±0	0.263
Duration of symptoms (in weeks)	3.5±0.707	4.14±1.49	3.9±1.792	8±0.0	0.106
Oliguria	2 (100%)	17(77%)	8(80%)	1(100%)	0.837
Gross Hematuria	0	1(5%)	0	0	0.895
Fever	1 (50%)	17(77%)	6(60%)	1(100%)	0.602
Seizures, Encephalopathy	2 (100%)	2(9%)	0	0	0.001
Rash	0	5(23%)	1(10%)	0	0.691
Arthralgias	1 (50%)	2(9%)	1(10%)	0	0.361
Hypertension	0	4(18%)	2(20%)	0	0.874
Creatinine (mg/dl)	12.94 ± 2.475	4.507 ± 2.534	6.324 ± 5.550	8.62	0.263
Nephrotic range Proteinuria(no.)	0 ± 0	0.23 ± 0.249	0.29 ± 0.296	0 ± 0	0.429

has been included in Anti-GBM group for discussion henceforth. The age wise distribution of non lupus CrGN and the baseline laboratory parameters in each of the biopsy diagnoses has been shown in Table 1. Among pauci-immune group 68.75% were ANCA positive and 31.25% were ANCA negative. The clinical characteristics of patients with non lupus CrGN has been shown in Table 2. The average delay in diagnosis was 3.5±0.70 weeks in AGBM group, 4.14±1.49 weeks in ANCA positive group and 3.90±1.792 weeks in ANCA negative group and 8 weeks in IgAN. Organ systems involvement in various types of non Lupus CrGN has been shown in Table 3. The histological findings in the various non Lupus CrGN has been shown in Table 4. Table 9 shows the proportionate distribution of cellular, fibrocellular and fibrous crescents in PICrGN patients at diagnosis.

In 82.86% (n=29) patients required dialysis at presentation. 74.29% (n=26) were treated plasmapheresis. The therapeutic response to the IV Cyclophosphamide protocol has been shown in Table 5. Complete or partial remission has been clubbed together as total response. The patients who did not achieve either form of remission have been considered as resistant. 68.57% patients in our study responded to EULAR regimen but about 1/3rd of patients did not respond to therapy. The average follows up was 8±1.25 months. 42.86% of patients died during therapy and 57.14% survived with the therapy during follow-up period.

The outcomes in the form of dialysis dependence (HD Dep), no dialysis dependence (non-HD) and death has been shown in Fig 1. We analysed the association of various clinical and biopsy parameters with response/resistance in non lupus CrGN as shown in Table 6 but none were found to be statistically significant. The cumulative clinical response and outcomes at the end of follow up are shown in Table 7.

Only 37.14% of patient maintained remission either partial or complete and about 60% of patients entered into ESRD eventually on follow up. 50% of the patients who maintained remission had chronic kidney disease. At the end of follow up 42.86% patients died. Most patients who did not respond died within three months of diagnosis and rest of non responders were dialysis dependent till last follow up. ANCA positivity or negativity status did not differ significantly on

Table 3 — *Organ systems involvement in various types of non lupus CrGN*

Organ System Involvement	Number of Patients	% of Patients	AGBM	ANCA+	ANCA-	IgAN
Total Number of Patient	35		2	22	10	1
Renal	35	100%	100%	100%	100%	100%
Pulmonary	12	34.3%	2(100%)	5(22.7%)	4(40%)	1(100%)
Upper Respiratory Tract	4	11.42%	1(50%)	1(4.5%)	2(20%)	0
Musculoskeletal	4	11.4%	1(50%)	2(9.1%)	1(10%)	0
Neurologic	4	11.4%	2(100%)	2(9.1%)	0	0
Gastrointestinal	2	5.7%	0	1(4.5%)	0	1(100%)
Cutaneous	6	17.1%	0	5(22.7%)	1(10%)	0
Ocular	1	2.8%	0	1(4.5%)	0	0
Fever	25	71.4%	2(100%)	17(77.3%)	5(50%)	1(100%)
Otic	22	62.8%	1(50%)	14(63.6%)	6(60%)	1(100%)

Table 4 — *Histological findings in different categories of non lupus Crescentic Glomerulonephritis*

	AGBM	ANCA+	ANCA-	IgAN	P
No of glomeruli in the biopsy	22.5 ± 10.61	19.55 ± 9.16	18.7 ± 9.09	14 ± 0	0.888
Globally sclerosed glomeruli	1 ± 1.41	2 ± 3.42	4.5 ± 5.74	6 ± 0	0.351
% Glomeruli with crescents	93.33 ± 9.43	65.05 ± 34.57	63.53 ± 48.17	100 ± 0	0.620
% Glomeruli with BM thickening	0(0)	0(0)	2(20%)	0(0)	0.151
% Glomeruli with mesangial cellularity	0(0)	6(27%)	3(30%)	0(0)	0.762
% Glomeruli with mesangial matrix expansion	0(0)	3(14%)	2(20%)	0(0)	0.856
% Interstitial fibrosis/ tubular atrophy	0	7.5±14.45	5.0±8.81	10±0	0.835
Presence of ATN	0(0)	3(14%)	1(10%)	0(0)	0.916
Presence of vasculopathy	0(0)	5(23%)	4(40%)	1(100%)	0.230

Table 5 — *Response of different types of non lupus Crescentic Glomerulonephritis using EULAR protocol*

	Patients Treated	Total response	Resistant
AGBM	2	0 (%)	2 (100%)
ACNA+	22	16 (72.73%)	6 (27.27%)
ANCA-	10	7 (70%)	3 (30%)
IgAN	1	1 (100%)	0 (0%)
Total	35	24 (68.57%)	11 (31.43%)

Table 6 — *Association of various parameters with response to treatment*

	Responders	Resistant	P
Age in years	39.62 ± 17.24	38.29 ± 15.71	0.867
Female gender	10(76.9%)	5(71.4%)	0.787
Serum Creatinine at presentation	4.13±3.013	6.51±4.326	0.091
Globally sclerosed (GS) glomeruli	11.53 ± 15.69	28.24 ± 31.09	0.123
Percent of glomeruli with crescents	59.79 ± 38.65	54.68 ± 38.86	0.782
Glomerular infiltrate	7(53.8%)	3(42.9%)	0.639
Mesangial cellularity	3(23.1%)	1(14.3%)	0.639
Mesangial matrix expansion	3(23.1%)	1(14.3%)	0.639
Interstitial fibrosis/ tubular atrophy	1(7.7%)	2(28.6%)	0.212
Acute tubular necrosis	1(7.7%)	2(28.6%)	0.212
Vasculopathy	4(30.8%)	1(14.3%)	0.417

Table 7 — *Cumulative Outcomes in non lupus Crescentic Glomerulonephritis at the end of follow up*

	Patients Treated N	Remission (at 6 months)	Relapse (cumulative, at the end of 6 months)	ESRD (defined at 3 months)	Death (cumulative, at the end of 6 months)
AGBM	2	0	0	2(100%)	2(100%)
ANCA+	22	10(45.46%)	0	12(54.56%)	8(36.36%)
ANCA-	10	3(30%)	1(10%)	6(60%)	4(40%)
IgAN	1	0	0	1()	1(100%)
Total	35	13(37.14%)	1(2.86%)	21(60%)	15(42.86%)
P value		0.450	0.462	0.450	0.220

cumulative outcomes though numerically cANCA responded slightly better. Cause of death in different types of non lupus CrGN have been shown in Table 8. Sepsis was the most common cause of death. All the patients in AGBM and IgAN group died shortly before completion of therapeutic course. Table 9 shows comparison of clinical and laboratory parameters at baseline and at end of cyclophosphamide induction therapy in the PICrGN groups. There is significant improvement in clinical parameters like urine output, renal function tests and markers of inflammation. Fig 2 shows renal survival in non lupus crescentic glomerulonephritis patients.

Table 8 — *Cause of death in different types of non lupus Crescentic Glomerulonephritis*

	AGBM	IgAN	ANCA +	ANCA -	Total
Septicemia	2 (100%)	1 (100%)	4 (50%)	1 (25%)	8(53.33%)
Cardiac	0	0	3 (37.5%)	1 (25%)	4(26.67%)
Others	0	0	1 (12.5%)	2 (50%)	3(20%)
Total	2	1	8	4	15

Discussion

The reported incidence of CrGN has been variable, ranging from 2 to 10% in studies from Europe, America as well as from Asia[5-8]. Studies from other parts of India have reported an incidence of 2 to 5%[9-12]. Previous study from our Institute showed incidence of 7.5%[13]. We found a similar incidence of CrGN. Though the previous study from our institute found male: female ratio of 1:1.3, in this study we found female predominance with ratio 1:2.1 despite excluding Lupus CrGN. Some other studies have also reported a female pre-ponderance[5,6]. The proportion of lupus and non-lupus CrGN was about 20% and 80% respectively, comparable to that other Indian studies ie, 20 to 30% and 80 to 70% respectively[5,6,8].

Some studies from our country have not found a significant number of ANCA negative pauci immune GN contributing to PICrGN[5,6], however, we found serologically, only about 60% had ANCA positivity and rest were negative for both cANCA and pANCA, similar to some other larger series/studies[14-16]. These group of patients have been found to have negative ANCA serology despite repeated testing.

The mean age of patients in our study in PICrGN group was lesser in our study compared to that reported from other countries[10,17-19]. A study reported ANCA negative PICrGN patients to be significantly younger than ANCA positive patients[20]. Other studies from India also found PICrGN in younger

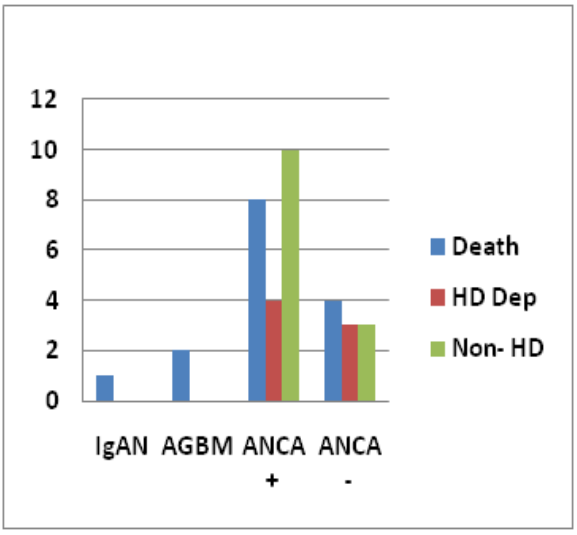

Fig 1 — Patient outcomes (death, HD Dep= hemodialysis dependent, Non-HD= not dialysis dependent) at the end of induction in IgAN (Immunoglobulin A nephropathy), AGBM (Anti glomerular basement membrane disease), ANCA + (positive) and ANCA - (negative) patients

Table 9 — *Clinical and laboratory changes in pauci-immune Crescentic Glomerulonephritis before and after induction therapy using EUVAS regimen*

Clinical	p-ANCA positive			c-ANCA positive			ANCA negative		
	Before	After	p	Before	After	P	Before	After	P
Urine volume (ml)	1067±539.75	1195±1223.94	0.709	1237.5±511.74	991.67±1145.11	0.452	855±520.39	730±1060.45	0.695
Creatinine at biopsy (mg/dl)	4.04±1.87	1.74±1.87	0.017	4.9±2.71	1.54±2.02	0.002	6.32±5.55	2.25±2.78	0.105
Urea at biopsy (mg/dl)	105.2±50.92	44.3±38.31	0.012	115.58±59.38	36.25±45.5	0.004	118.6±68.69	53±64.84	0.105
CRP (mg/l)	24.7±7.62	13.1±5.13	0.010	21.58±4.58	15.25±7.76	0.019	25.2±5.69	17±7.36	0.049
ESR (mm/1 h)	67.3±13.33	38±16.26	0.002	76.75±18.6	48.17±21.12	0.002	83.11±15.41	43.2±13.76	<0.001
24 h urinary Protein excretion(g)	3.12±1.34	0.28±0.27	<0.001	2.87±1.55	0.18±0.23	<0.001	2.54±2.01	0.29±0.3	0.006

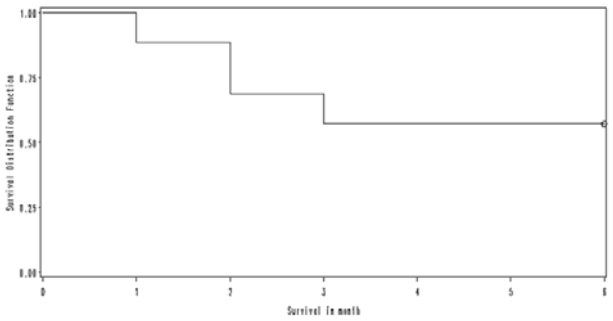

Fig 2 — Renal survival in non lupus Crescentic Glomerulonephritis patients on cyclophosphamide therapy

patients similar to our study 5[21]. Whether these findings are related to role of ethnicity in the pathogenesis of ANCA remains speculative.

Serum creatinine at presentation was highest in Anti GBM followed by IgAN and PICrGN in that order. This is consistent with natural history of Anti-GBM disease as it is often aggressive presenting with severe renal dysfunction compared to PICrGN[1]. The most common clinical presentation was oliguria. Fever was common constitutional symptom. Hypertension was observed in about 20% of patients. Pulmonary involvement was seen in 1/3rd of patients and upper respiratory tract involvement was seen in approximately 17% of all patients. Respiratory involvement was seen in both ANCA positive and ANCA negative patients. Central Nervous System (CNS) involvement was found in both patients with Anti-GBM disease and in 9% of ANCA positive patients. CNS involvement is uncommon but has been reported earlier in Anti-GBM disease[22-24]. The pathogenesis of this phenomenon is unclear. Of the PICrGN patients, ocular, nervous system and gastrointestinal involvement was only seen in ANCA positive and not in ANCA negative group. One patient with Anti-GBM disease with pANCA positivity had otic and nasal involvement. Some studies have reported lesser extra-renal involvement in ANCA negative patients[16,25] while others have noted significant extra renal involvement in ANCA negative patients as well[26]. Whether this is partly due to false negative/low titres of ANCA antibody due to inaccuracies of ANCA testing[27] or if truly it is reflective of ANCA negativity being a part of the spectrum of small vessel pauci immune vasculitidies continuum is difficult to establish definitively.

Histologically, percentage of crescents were higher in Anti-GBM patients than in PICrGN patients. This is consistent with previously published literature[28]. There was only 1 patient with IgA CrGN (100% of IgAN) hence the % of crescents in Anti-GBM disease as compared to the other groups was not statistically significant. Other reported biopsy parameters were similar across all groups.

About 66% patients achieved some form of remission (complete and partial) on therapy. The total response rates in ANCA vasculitis patients treated with pulse cyclophosphamide in previous studies was about 80%[29,30]. However, these trials were not exclusively done in severe (crescentic) ANCA vasculitis. The trials done in severe ANCA vasculitis found a total response rate of about 60%[31]. A trial that compared rituximab versus cyclophosphamide in severe AAV found improvement in Glomerular Filtration Rate (GFR) of about 20ml/min/1.73 m^2 . Thus, despite a significant rate of response most patients with severe ANCA vasculitis continued to have GFR less than 60ml/min/ 1.73 m^2. We also found at the end of follow up 60% had ESRD and about 15% had remission but had chronic kidney disease. Rituximab, the newer agent used in induction has been also found non inferior to cyclo-phosphamide[28]. Hence, the therapy for ANCA vasculitis though has improved immensely, it is far from satisfactory. None of the clinical and histological parameters (glomerular, tubulo-interstitial or vascular) included in our study were significantly associated with response to treatment. Some studies have found histological parameters to be predictive of

outcomes[32,33]. Our study was confined to CrGN alone which itself is severe form of injury; this could have been the reason why we did not find significant association of histology with outcomes.

Most patients who were resistant to therapy died during the study. Amongst the patients who did respond to therapy about 16% died and only 37% of patients maintained remission and stable kidney function. Sepsis was the most common cause of death followed by cardiac causes. One of the reasons for high incidence of sepsis was that most patients presented with dialysis requiring renal failure and needed non tunnelled dialysis catheter insertion which has high risk of catheter related bloodstream infection. The socio-economic background and nutrition status of patients may also have impact on susceptibility to infections. Measures to prevent infection ie, antibiotic prophylaxis, monitoring for leukopenia, counselling regarding measures to maintain personal hygiene meticulously, consideration of switching to tunnelled venous dialysis catheter from non tunnelled catheter in that requiring dialysis for prolonged duration may be improve outcome. At baseline none of the patients had overt cardiac involvement. The terminal event was cardiac in some patients. Whether this was due to vasculitis perse or secondary to other complications could not be definitively ascertained. Other Indian studies have also reported a less than satisfactory outcome in PICrGN[14,34]. Limitations of study are relatively small sample size and shorter follow up.

Conclusion

Non lupus CrGN treated by EUVAS protocol has an initial response rate of 66%. But the number of patients who survived and had sustained remission was about 37%. No histological or clinical parameter was significantly associated with response to therapy. There is significant morbidity and mortality associated with resistance to cyclophosphamide therapy as well as its adverse effects in those responsive to cyclophosphamide. Sepsis was the most common cause of death. Measures to prevent infection may improve outcomes in non-Lupus Crescentic Glomerulonephritis.

Limitation : Limitations that the study was carried out in a single referral tertiary Hospital

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