Is It Time to Switch to Low Dose Pulsed Methylprednisolone for Treatment of Flares in Systemic Lupus Erythematosus?

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Abstract
Background: Methylprednisolone (MP) therapy has gained popularity in clinical practise since its introduction in systemic lupus erythematous (SLE) treatment. Aim of the work: To compare between 'high dose' and 'low dose' pulsed MP in treatment of acute flares in SLE in terms of efficacy and adverse events. Patients and methods: The records of 473 SLE patients with an indication of pulse MP therapy were retrospectively analysed. Patients were divided into 2 groups where the 'high dose' group patients received 3-5 grams (gms) and the 'low dose' group patients received 1-1.5 gms. Both groups were compared in terms of efficacy assessed through percentage reduction of Systemic lupus eryhthematosus-2000 (SLEDAI-2K) score and cumulative doses of prednisolone; adverse events and mortality. Results: The study included 430 (92.4%) females and 43 (8.6%) males whose mean age was 28.13±8.2 years. The percentage decline in SLEDAI-2K 3 months after MP therapy was higher in the 'low dose' group (p=0.03) whereas percentage reduction of SLEDAI-2K was comparable in both groups 1 and 6 months after therapy (p=0.067, 0.184 respectively). Patients in the 'high dose' group received higher cumulative doses of oral prednisolone at 3 and 6 months following pulsed therapy (p<0.001). A higher incidence of adverse events, particularly infections (p<0.001) were recorded in the high dose group. Mortality over 6 months following treatment was comparable (p=0.09). Conclusion: Low dose pulsed MP therapy is equally efficacious to 'high dose' regimen yet with a lower incidence of adverse events.
Keywords: Systemic lupus erythematosus (SLE), Pulsed therapy, Methylprednisolone, High dose, Low dose

1. Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease characterized by a remitting-relapsing course with considerable morbidity and damage accrual [1]. Steroid use revolutionized management of SLE and significantly reduced mortality [2, 3]. Their use however is not without risks. The list of adverse events is a long one; infection perhaps is the most serious one with a high risk of mortality among SLE patients [4-6].

The use of pulsed methylprednisolone (MP) therapy in management of SLE flares became part of clinical practice especially in the setting of major organ affection and is included in a number of treatment recommendations [7-9]. Pulsed therapy has a number of advantages including higher efficacy, rapidity of action allowing for lower doses of oral prednisolone and faster tapering and hence lower cumulative doses of oral prednisolone with less damage accrual [10-13].

The basis of its use is its superior ability to mediate non-genomic actions through inactivation of phospholipase A2 enzyme and thus decreased production of arachidonic acid, changes in cellular membrane and interaction with membrane bound glucorticoid receptors (mGCR) with resultant inhibition of kinases and decreased lymphocytic activity. An additional advantage of pulsed therapy is its role in priming immune cells to genomic actions. The well-known adverse effects of steroids are mostly attributable to their genomic actions. Non-genomic pathway activation is associated with fewer side effects [10-13].

In spite of evidence of superiority to the standard 1mg/kg regimen, the use of pulsed therapy still carries a number of risks including infections, uncontrolled hypertension, poor glycemic control and risk of cardiovascular events [3,6,10,11]. Although pulsed therapy is in practice since the

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seventies the optimal dose is yet unknown and few small studies elaborated similar efficacy between low and high dose regimens with higher incidence of adverse events in the later [14-17].

2. Patients and methods

The records of 1000 SLE patients fulfilling the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for diagnosis of SLE [18] admitted to the Rheumatology department of Kasralainy Cairo University hospitals between 1996-2021 with an indication of pulsed MP therapy were collected and analysed. Patients were divided into 2 groups where the 'high dose' group patients received 3-5 grams (gms) and the 'low dose' group patients received 1-1.5 gms. Patients with incomplete data or follow up and patients receiving doses outside the mentioned ranges were excluded. Out of the 1000 patients' records analysed, 473 patients were eligible for inclusion in the current study.

Baseline demographic data including age, sex, disease duration, clinical characteristics, routine laboratory investigations including complete blood count (CBC), liver, renal function tests, urine analysis, 24 hour urinary protein and immunological investigations including Anti-nuclear antibodies (ANA), Anti-deoxyribonucleic antibody (Anti-DNA), serum complement factors C3 and C4, antiphospholipid antibodies (Anti-cardiolipin IgM, Anti-cardiolipin IgM, Anti-beta-2-glycoprotein antibody IgM, Anti-beta-2-glycoprotein IgG, Lupus anticoagulant) were recorded. Baseline assessment of disease activity using Systemic lupus eryhthematosus-2000 (SLEDAI-2K) score [19] and damage using Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) [20] were calculated. Data about indications of pulsed MP, cumulative dose of MP received and concomitant immunosupressives used 6 months following pulsed MP was obtained.

As a measure of efficacy follow up SLEDAI-2K at 1, 3 and 6 months following pulse MP were calculated. After comparison to baseline SLEDAI-2K percentage reduction in SLEDAI-2K was also calculated. The ability to use lower oral prednisolone doses and hence the cumulative steroid dose used 3 and 6 months after pulsed MP were considered another measure of efficacy.

Any adverse events that occurred following over 3 months following pulsed therapy were recorded. Infections were particularly analysed and divided into local and systemic infections. The site of infection, causative organism, results of culture and sensitivity done, the use of intravenous antibiotics and the need for hospitalization or surgical intervention were recorded. Factors that were significantly different between both groups and hence were possible cofounders for the occurrence of infection were also subjected to regression analysis. Data about mortalities that occurred within 6 months of pulsed therapy and whenever possible the cause of death were recorded.

As there was some dissimilarity between both groups a homogenous group of patients (143 patients) with proliferative glomerulonephritis (Class III, IV) nephritis who received high dose Cyclophosphamide (CYC) National Institute of Health (NIH) regimen were isolated and subjected to the same analysis as the whole cohort. The protocol of the study has been approved by the local ethics committee approval code MD-137-2019 and conforms to the provisions of the Medical Association of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Data were statistically described in terms of median and interquartile range, or frequencies (number of cases) and percentages when appropriate. Because the samples were large enough, comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided p values less than 0.05 was considered statistically significant. In order to identify the independent predictors of infections, all variables with $p<0.05$ in the univariate analysis were entered into a binary logistic regression model with sequential elimination of non-significant variables. Measures of association were expressed as odds ratios with a 95% confidence interval. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

3. Results

Baseline characteristics

The study included 430 (92.4%) females and 43 (8.6%) males whose mean age was 28.13±8.2 years. The 'high dose' group included 237 patients whereas the 'low dose' group included 236 patients. A comparison of demographic features, baseline clinical characteristics including disease activity assessed using SLEDAI-2K, medications used concomitantly with pulsed MP is demonstrated in Table 1. A group of 143 patients who had proliferative GN and received CYC-NIH regimen as induction treatment for nephritis was isolated and a comparison of those who received low dose MP (n=51) and high dose MP (n=92) regarding the aforementioned factors was done and is illustrated in Table 1.

Table 1: Baseline characteristics						
	Whole cohort (n=473)			Proliferative GN on high dose CYC (n=143)		
Variable Median (IQ range) or No (%)	Low dose n=236	High dose n=237	P	Low dose (n=51)	High dose (n=92)	P
Demographic data						
Female	218(92.4)	212(89.5)	0.27	45(88.2)	80(87)	0.83
Male	18(7.6)	25(10.5)		6(11.8)	12(13)	
Age	27(22:33)	27(23:32)	0.66	25(21:31)	26.5(23:31)	0.37
Age at onset	21(16:26)	21(18:26)	0.13	20(16:25)	22(19:26.5)	0.048*
Disease duration	5(2:9)	3(2:7)	0.08	5(1:7)	3(1:7)	0.42
Clinical characteristics						
Mucocutanous	227(96.2)	226(95.4)	0.55	51(100)	89(96.7)	0.55
Arthritis	143(60.6)	151(63.7)	0.48	34(66.7)	61(66.3)	0.97
Serositis	77(32.6)	75(31.6)	0.82	20(39.2)	30(32.6)	0.43
Nephritis	166(70.3)	188(79.3)	0.02*	-	-	-
Class I	2(1.4)	0(0)	-	-	-	-
Class II	30(21.1)	20(11.6)	0.02*	-	-	-
Class III/IV	94(66.2)	136(97)	0.008*	-	-	-
Class III	49(34.5)	62(36)	0.78	28(54.9)	35(38)	0.056
Class IV	45(31.7)	74(43)	0.04*	23(45.1)	57(62)	0.056
Class V	16(11.3)	16(9.3)	0.57	-	-	-
Neurological	36(15.3)	52(21.9)	0.06	5(9.8)	8(8.7)	1
Hematological	134(56.8)	108(45.6)	0.015*	23(45.1)	34(37)	0.38
Laboratory investigations						
Total leucocytic count	5.8(3.6:8.8)	6.3(4:9.5)	0.11	6.8(4.9:9)	6(4.1:9)	0.31
Absolute neutrophilic count	3.68(2.21:5.81)	3.65(2.2:5.74)	0.73	3.74(2.31:7)	3.89(2.43:6.16)	0.98
Absolute lymphocytic count	1.26(0.68:2.12)	1.39(0.8:2.43)	0.21	1.88(0.72:2.65)	1.44(0.84:2.7)	0.69
Serum creatinine	0.7(0.5:0.9)	0.8(0.6:1.2)	0.02*	0.8(0.5:0.9)	0.9(0.6:1.4)	0.018*
Serum albumin	3.3(2.8:3.8)	3(2.5:3.7)	0.01*	3(2.7:3.4)	3(2.4:3.5)	0.68
24 urinary protein	2(1.1:3)	2(1.4:3)	0.22	2(1.4:3.5)	2.4(1.7:3)	0.64
ANA	234(99.2)	236(100)	0.50	50(98)	92(100)	0.36
Anti-dsDNA	208(97.2)	221(98.7)	0.33	44(100)	89(98.9)	1
Complement consumption	140(79.1)	139(78.5)	0.90	27(81.8)	55(76.4)	0.53
Antiphospholipid antibodies	55(46.6)	59(55.1)	0.20	13(46.4)	28(66.7)	0.09
Baseline SLEDAI-2K	9(6:12)	10(8:12)	0.002*	10(8:14)	10(8:12)	0.74
Baseline SDI	0(0:0)	0(0:0)	0.75	0(0:0)	0(0:0)	0.46
Concomitant medications						
Cumulative oral prednisolone dose (3 months)	1.8(1.7:2.3)	2.3(1.8:2.7)	<0.001*	2.3(1.8:2.3)	2.7(2.3:2.7)	<0.001
Cumulative oral prednisolone dose (6 months)	3.2(2.7:1.1)	4.5(3.6:5.0)	<0.001*	3.6(3.2:4.1)	4.5(3.6:5.0)	<0.001*
Cyclophosphamide (NIH regimen)	85(36)	133(56.1)	<0.001*	-	-	-
Cyclophosphamide (Euro regimen)	13(5.5)	10(4.2)	0.52	-	-	-
Mycophenolate	40(16.9)	28(11.8)	0.11	-	-	-
Azathioprine	83(35.2)	55(23.2)	0.004*	-	-	-
Methotrexate	7(3)	1(0.4)	0.04*	-	-	-
Hydroxychloroquine	207(87.7)	222(93.7)	0.03*	46(90.2)	86(93.5)	0.74
Rituximab	8(3.4)	5(2.1)	0.40	-	-	-
Cyclosporin	2(0.8)	2(0.8)	1	-	-	-
Leflunamide	2(0.8)	0(0)	-	-	-	-

GN: Glomerulonephritis, CYC: Cyclophosphamide, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded deoxyribonucleic acid antibody, SLEDAI-2K: Systemic lupus eryhthematosus-2000 score, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. Bold values are significant at p<0.05

Regarding the indications of pulsed therapy patients; nephritis was the most common indication. The indications of pulsed therapy were compared between both groups (Table 2).

Efficacy

As the baseline characteristics of both groups were not similar the percentage reduction of SLEDAI-2K was used as a measure of efficacy. Although baseline SLEDAI-2K was significantly higher in the high dose group, the absolute SLEDAI-2K scores as well as percentage reductions of SLEDAI-2K were similar after 1 month and 6 months of treatment. The SLEDAI-2K score was significantly lower (p=0.003) and the percentage reduction (p=0.03) was

significantly higher in the 'low dose' group 3 months after pulsed MP (Figure 1a).

The ability to use a lower cumulative dose of oral prednisolone was considered another measure of efficacy. Patients who used high dose pulsed therapy however also received higher cumulative doses of MP 3 and 6 months following pulsed therapy (p<0.001 & , 0.001, respectively).

Table 2: Indications of pulsed methylprednisolone			
Indication No (%)	Low dose (n=236)	High dose (n=237)	P
Nephritis	123(52.1)	169(71.3)	<0.001*
Neuropsychiatric	14(5.9)	24(10.1)	0.13
Vasculitis	27(11.4)	15(6.3)	0.05
Mucocutanous	11(4.7)	1(0.4)	0.003*
Hematological	33(14)	18(7.6)	0.03*
Pulmonary	2(0.8)	0(0)	-
Serositis	12(5.1)	4(1.7)	0.04*
Arthritis	10(4.2)	1(0.4)	0.006*
Myositis	4(1.7)	5(2.1)	1
Bold values are significant at p<0.05			

Adverse events and mortality

All the reported adverse events were more frequently encountered higher in the 'high dose' group; difference was significantly higher in infection, elevated blood pressure, elevated blood pressure and osteonecrosis (p<0.001, <0.001, <0.001 & 0.036, respectively) (Table 3). Multivariate analysis identified cumulative dose of steroids at 3 months as the only independent predictor of infection (OR 1.001 95% CI 1-1.001). The remaining independent variables (Active nephritis, Baseline SLEDAI-2K, serum creatinine, serum albumin, CYC-NIH regimen use, HCQ use) did not show a significant independent effect. High dose pulsed therapy was the most important predictor of infection (OR 2.76 95% CI 1.8-4.25). Cumulative dose of steroids was also identified as a confouder although its effect was negligible (OR 1.001 95% CI 1-1.001). Details of nature of infections are available in supplementary data. There was no difference in incidence of mortality whether the cause of death was infection related or disease activity related (Table 3).

Patients with proliferative glomerulonephritis treated with cyclophosphamide (NIH-regimen)

Similar to the whole cohort, absolute value was lower and percentage reduction of SLEDAI-2K was higher in the 'low dose' group (Figure 1b). Cumulative dose of steroids at 3 and 6 months was higher in the 'high dose' group (<0.001 & <0.001, respectively) (Table 1). Both infections and elevated blood pressure were more frequently encountered in the 'high dose' group (p<0.001 & 0.024, respectively) (Table 3).

Table 3: Adverse events and mortality following pulsed therapy						
	Whole cohort			Proliferative GN on high dose CYC		
Adverse events*	Low dose (n=236)	High dose (n=237)	P	Low dose (n=51)	High dose (n=92)	P
Infection	70(29.7)	142(59.9)	<0.001*	15(29.4)	60(65.2)	<0.001*
Local	53(22.5)	97(40.9)	<0.001*	13(25.5)	41(44.6)	0.02*
Systemic	9(3.8)	31(13.1)	<0.001*	3(5.9)	10(10.9)	0.38
Sepsis/septic shock	8(3.4)	13(5.5)	0.27	0(0)	6(6.5)	-
Elevated blood pressure	8(3.4)	33(13.9)	<0.001*	1(2)	16(17.4)	0.006*
GIT complications	7(3)	12(5.1)	0.25	1(2)	2(2.2)	1
Elevated blood sugar	5(2.1)	24(10.1)	<0.001*	0(0)	6(6.5)	-
Osteonecrosis	5(2.1)	14(5.9)	0.04*	1(2)	5(5.4)	0.42
Psychosis	3(1.3)	5(2.1)	0.72	0(0)	0(0)	-
Myopathy	0(0)	1(0.4)	1	0(0)	0(0)	-
Venous thrombosis	0(0)	0(0)	-	0(0)	0(0)	-
Cardiovascular/ Cerebrovascular events	0(0)	0(0)	-	0(0)	0(0)	-
Mortality*	9(3.8)	18(7.5)	0.08	0(0)	6(6.5)	-
Infection related	1(0.4)	7(3)	0.07	0(0)	2(2.2)	-
Disease activity related	6(2.5)	6(2.5)	0.99	0(0)	2(2.2)	-
GN: Glomerulonephritis, CYC: Cyclophosphamide, GIT: Gastrointestinal tract *Adverse events occurred within 3 months and mortality occurred within 6 months of pulsed therapy. Bold values are significant at p<0.05						

4. Discussion

Since the introduction of pulsed MP therapy in SLE particularly nephritis, the regimen gained popularity in clinical practice. Physicians tend to prescribe higher doses of MP to sicker patients as noted in the current study. It is of note that MP Whether additional benefit is gained from such practice however was challenged by previous studies [14-17] and was the question the current study attempted to

answer.

Methylprednisolone's superior capacity to activate the non-genomic pathway is associated with fewer steroid related adverse effects. The pathway is active with doses of prednisolone equivalent greater than 100 mg/day. Higher dosages correlate with increased in vitro plasma concentrations. However, it is unknown if there is a certain dose at which the anti-inflammatory effects of the non-genomic route are saturated [10-13].

Back in 1987 a study including 21 patients compared a daily dose of 100 mg to 1000 mg MP for 3 days and found no significant difference between both groups; the study however didn't control for concomitant medications used [13]. Another retrospective study performed in 2002 including 55 patients didn't find a difference in terms of efficacy between 1-1.5 gms MP in comparison to 3-5 gms and reported a higher incidence of serious infections in the 'high dose' group [16]. Similar results were found in a retrospective study conducted in 2018 on patients with SLE and other autoimmune diseases who received doses of 1500 mg, 1500–3000 mg, and >3000 mg, with higher doses being associated with an increased risk of infections [17]. Clinical trials implementing low dose regimens (0.25-0.5 gm) for 2-3 consecutive days had favourable outcome with low incidence of complications particularly infections [21, 22].

The current study is retrospective; the dose of pulsed therapy was decided by the treating physician. Physicians were more likely to prescribe 'high dose' pulsed therapy to patients with more active disease and patients with nephritis particularly proliferative type. This explains the difference in patients' characteristics where patients in the 'high dose' group had significantly higher serum creatinine, lower serum albumin and were more frequently prescribed CYC-NIH regimen as induction therapy.

In order to overcome this setback we calculated percentage reduction of SLEDAI-2K as a measure of efficacy and subjected to analysis a relatively homogenous proliferative GN who used CYC NIH regimen for induction therapy. There was no evidence of superior efficacy in the 'high dose' group when percentage reduction of SLEDAI-2K was considered. On the contrary patients in the 'low dose' group had a better response 3 months following pulsed MP.

As reduction of prednisolone oral doses was decided upon the treating physician based on judgement of disease activity a faster steroid tapering regimen was considered another measure of efficacy; a target that couldn't be reached in the 'high dose' group. It is noteworthy that, in a previous study, a higher initial prednisolone dose given to SLE patients after diagnosis was linked to a higher cumulative dose over the ensuing 11 months [23].

On the other hand, the 'high dose' group experienced side effects more frequently, particularly infections. Infections in SLE are affected by a complex interplay of factors including disease activity, steroids and immunosuppressive drugs and are one of the most common causes of mortality. Numerous studies have linked pulsed therapy to an increased risk of infections [24-27]. A challenge faced when analysing the risk of infection in patients receiving pulsed therapy is that their disease and hence the immunosuppressive medications they receive tend to be more aggressive [25, 26] an issue we faced in our cohort as well.

Teh and colleques identified pulsed steroid was identified as a predictor of infection related mortality in univariate analysis, a relationship that was lost in multivariate analysis [25]. Noel et al. identified oral prednisolone dose, pulse MP both use and dose as well as immunosuppressive use as predictors in univariate analysis. In the multivariate analysis only pulse MP use and immunosuppressive use continued to be predictors [26]. Both oral prednisolone >15mg and the use of pulse MP were identified by Pimentel-Quiroz and colleagues as predictors; the risk magnitude, however, was higher with oral steroids than with pulsed therapy [27].

In the current study initial SLEDAI-2K, serum creatinine, serum albumin, CYC-NIH use and cumulative oral prednisolone were significantly higher in the 'high dose' group whereas HCQ use was significantly lower. These factors were identified as risk factors of infection in previous cohorts including Egyptian ones [16, 25, 27-31] and hence were studied as possible confounders. Cumulative dose of steroids was identified as a confounder although its effect was negligible (OR 1.001 95% CI 1-1.001). High dose pulsed therapy on the other hand had was the most important predictor of infection (OR 2.76 95% CI 1.8-4.25). Incidence of infections continued to be higher in the relatively homogenous subgroup of patients with proliferative GN.

Other adverse events experienced by our patients following pulsed therapy were uncontrolled hypertension and hyperglycemia; both adverse events were reproduced in other studies [31, 32]. Higher incidence of nephritis particularly proliferative GN in the 'high dose' group could have contributed to the higher incidence of uncontrolled hypertension. The significant difference however was replicated in the subgroup of patients with proliferative nephritis. Around 4% of our patients experienced osteonecrosis; incidence was lower than other studies as follow up period was shorter. Some studies revealed an association of osteonecrosis with pulse therapy [33, 34], others couldn't find such an association [35]. The peak initial oral GC dose and the high cumulative GC doses in the first months of treatment were also identified as risk factors [11, 35]. The use of 'high dose' pulsed therapy contributes both to peak initial dose and higher cumulative steroid doses.

The lower toxicity associated with activation of non-genomic pathway encouraged authors to recommend the use of pulsed MP not only for severe manifestations of SLE but also to moderate flares and

mild flares if recurrent or not responding to initial treatment [10, 36]. When it comes to steroid dosing however the concept of "less is more" [37] should be expanded to include pulsed MP as well.

The retrospective nature and hence the lack of homogeneity between patients in the 'high dose' and 'low dose' groups is the main limitation of the current study. The study however to the best of our knowledge is the largest of its type and adds to the body of evidence supporting the use of lower doses of pulsed therapy which had comparable efficacy to higher doses with a lower incidence of adverse events.

5. Statements and Declarations

Conflict of interest: none

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Authors Contributions

All authors contributed to the study's conception and design. Material preparation was done by Lobna A. Maged, Marwa Magdy, Geilan A. Mahmoud. Data collection was done by Marwa Magdy. Data analysis was done by Lobna A. Maged, Marwa Magdy, Geilan A. Mahmoud. The first draft of the manuscript was written by Lobna A. Maged, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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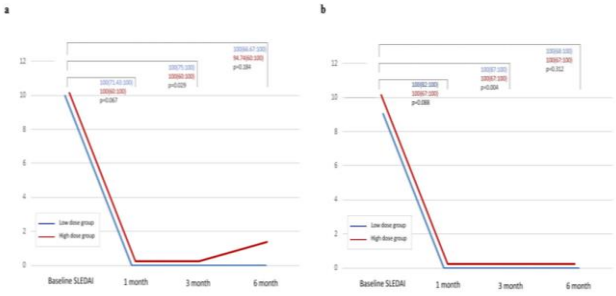
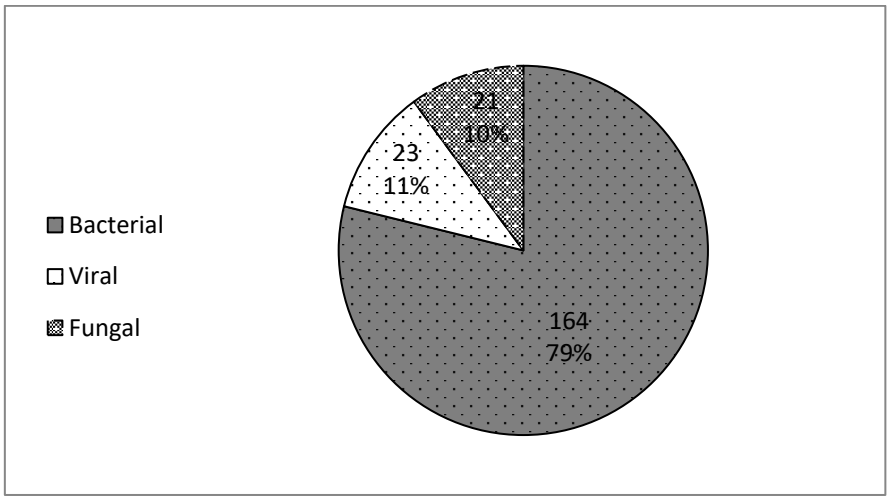


Fig 1 Changes in SLEDAI-2K over 6 months in (a) the whole cohort (b) patients with proliferative glomerulonephritis receiving Cyclophospamide NIH regimen. The y-axis represents the median SLEDAI-2K. The percentage reduction of the SLEDAI-2K is illustrated above the graph (Results are expressed as median (IQ range)) The percentage decline in SLEDAI-2K 3 months after MP therapy was higher in the 'low dose' group (p=0.03) whereas percentage reduction of SLEDAI-2K was comparable in both groups 1 and 6 months after therapy (p=0.067, 0.184 respectively) in the whole cohort. The percentage decline in SLEDAI-2K 3 months after MP therapy was higher in the 'low dose' group (p=0.004) whereas percentage reduction of SLEDAI-2K was comparable in both groups 1 and 6 months after therapy (p=0.088, 0.3 respectively) in the proliferative nephritis group



Supplementary Figure 1: Causative organisms of infection. The majority of infections were caused by bacteria 164(79%). Viral organisms were recorded in 23 (11%) patients and finally fungal organisms were recorded in 21(10%) patients

Supplementary Table 1: Sites of infection in the whole cohort	
Site of infection	No(%) (n=212)
Urinary tract	74(34.9)
Chest	38(17.9)
Wound infections	27(12.7)
Subcutaneous Abscess	25(11.8)
Mucus membrane	24(11.3)
ENT	14(6.6)
Vaginal	1(0.5)
Ocular	2(0.9)
GIT	5(2.4)
CNS	1(0.5)
Infective endocarditis	1(0.5)
ENT: Ear nose throat; GIT: Gastrointestinal, CNS: Central nervous system	

Supplementary Table 2: Microorganisms identified as cause of infection	
Microorganism	No (%)(n=99)
Escherichia coli	32(31.7)
Staphylococcus aureus	17(16.8)
Multi-drug resistant bacteria	4(4)
Pseudomonas	4(4)
Gram –ve cocci	3(3)
Proteus valgaris	1(1)
Klebseilla	6(5.9)
Hepes zoster	19(18.8)
Candida	12(11.9)