

# **Diethylcarbamazine (DEC) in Relapse cases of Nephrotic Syndrome in Filarial Endemic Region: A case Series**

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## **Author Contribution**

This work was carried out in collaboration among all authors. Author JG designed the study and author TV wrote the first draft of the manuscript. Authors DP and AP managed the literature searches. All authors read and approved the final manuscript.

## **Abbreviations**

UTI: urinary tract infection; DEC: diethyl carbamazine citrate; T temperature; AG abdominal girth; URTI upper respiratory tract infection; DOAday of admission; CP crystalline penicillin

## Abstract

**INTRODUCTION-** Incidence of nephrotic syndrome (NS) and filariasis both is high in China, Japan & India. Studies have shown association of filariasis in NS. In coastal belt of Gujarat, Filariasis occurs as the mosquito responsible is still prevalent. Therefore, filariasis association may be causing persistence of edema in NS relapse cases. After a 7<sup>th</sup> relapse patient was treated successfully with diethyl carbamazine citrate (DEC), we decided to study, the effect of DEC on weight loss and urine protein, in relapse patients of NS.

**MATERIAL METHOD-** In relapse patients of NS, DEC was given by oral route in dose of 72 mg/kg/cycle for 7 days. Weight record and urine protein was measured daily. Steroid as Tab prednisolone was administered at 2 mg/k/d.

**RESULTS-** The 1<sup>st</sup> case was a steroid dependent nephrotic syndrome with the 7<sup>th</sup> relapse; he had been on prednisolone and Levamisol for 3 years. DEC was started on day 3 of admission and response was seen on the 5<sup>th</sup> day. Urinary protein became nil on day 10, and patient has been relapse free for 1 year. In each of the other 4 cases with 1<sup>st</sup>, 2<sup>nd</sup>, 2<sup>nd</sup> and 4<sup>th</sup> relapse respectively, response of DEC was seen within 2 days. Thus, after starting DEC weight and urine protein reduced within 2 days in 5 relapse cases. Filaria was not detected in blood film of any patient and Elisa tests done in 2 were negative.

**CONCLUSION-** Further randomized studies with controls and better filarial detection methods are required for DEC to be considered as an add-on drug in relapse cases of NS in, Filarial endemic regions, as it is faster acting, effective, similar to Levamisol and safe.

## Keywords

Nephrotic syndrome; Diethylcarbamazine DEC; Filariasis; Levamisole; Relapse; steroid sensitive;

## Introduction

Nephrotic syndrome is characterized by heavy (nephrotic range) proteinuria at >3.5 gm/24hr or a urine protein creatinine ratio >2, hypoalbuminemia (< 2.5 g/dl), hyperlipidaemia (cholesterol >200 mg/dl), and edema.[1]

Prednisolone suppresses autoimmunity in nephrotic syndrome & so induces remission early. But long term use of prednisolone can cause steroid toxicity [2]

Diethyl carbamazine citrate (DEC) is an anti-parasitic agent used in the treatment of lymphatic filariasis, tropical pulmonary eosinophilia, and loiasis & acts by inhibiting arachidonic acid metabolism. DEC alters organelle membrane of Mf (microfilariae) and affects muscular activity of Mf. Side effects of DEC due to release of antigens from dying filariae are fever, skin rash, and swollen tender glands in neck, visual disturbance, nausea, dizziness and itching.[3]

Levamisole as immunomodulator for nephrotic syndrome is more effective in filarial endemic countries and beneficial effect of levamisole are reported only from south east asia countries.[4] As we see glomerular pathology occurs because of parasitic infections, instead of using levamisole, we can use a more specific antifilarial agent, DEC, which has lower side effects.

## Method

Here we are discuss the effect of DEC in minimal change nephrotic syndrome patients who had responded to steroids and who presented again with relapse. DEC is not a 1<sup>st</sup> line treatment of nephrotic syndrome here, we were using it when such patients came with relapse.

**Protocol:** In these five cases of relapse of nephrotic syndrome, each patient was treated as follows: Tab Prednisolone 2mg/kg/day till remission, and then switch over to alternate day therapy. Immuno-modulators are continued or added as required. DEC (Hetrazan<sup>®</sup> Wyeth) was started in all patients by oral route in the dose of 72mg/kg/cycle total dose over a period of 7 days (Table 1). After admission, weight was recorded and urine protein was measured daily (Figure 3-7). Investigations are mentioned in Table 2. As per university guideline participant consent has been collected and preserved by the authors.

## Results - Course during treatment and Outcome

In the index case A, with 7<sup>th</sup> relapse, foci of infection was urinary tract infection (UTI) so treatment for UTI was started. Till 4<sup>th</sup> day no recovery was seen so considering relapse and no any recovery seen even after starting antibiotics so started DEC on 3<sup>rd</sup> day of admission (DOA). Edema started to reduce on 5<sup>th</sup> DOA and slowly it disappeared on 8<sup>th</sup> DOA, urinary protein became clear on 9<sup>th</sup> DOA (figure 3).

In the 2<sup>nd</sup> case (B) with the 4<sup>th</sup> relapse, foci of infection was chronic tonsillitis so considering bacterial infection we started antibiotics but there was no response so DEC was started on 4<sup>th</sup> DOA and after that edema gradually started to reduce on 6<sup>th</sup> day. (figure 4).

The 3<sup>rd</sup> case (C) was seen during the 2<sup>nd</sup> relapse. The foci of infection was UTI and treatment for UTI started. Even after 7 days, no signs of recovery was seen so we commenced DEC on the 7<sup>th</sup> DOA and after that edema reduced on 9<sup>th</sup> DOA and Urinary Protein became clear on 10<sup>th</sup> DOA (figure 5).

In the 4<sup>th</sup> case (D) with 2<sup>nd</sup> relapse, foci of infection was due to tonsillitis and antibiotic was started. Even after 6 days on antibiotics no change in edema and proteinuria was seen so DEC was started on 6<sup>th</sup> DOA and

after that edema started to resolve slowly from the 7<sup>th</sup> DOA and Urinary Protein became clear on 9<sup>th</sup> DOA (figure 6).

The foci of infection in the 5<sup>th</sup> case (E), was pharyngitis and symptomatic and specific treatment was started. But no response till 6<sup>th</sup> day so DEC started on 6<sup>nd</sup> DOA and after that edema started to reduce on 9<sup>th</sup> DOA & Urinary Protein became clear on 4<sup>th</sup> DOA (figure 7).

Filaria was not detected in midnight thick blood film of any patient. Elisa test done in 2 patients was negative. Thus it was seen that from case one to subsequent four cases, all responded rapidly following introduction of DEC, within a week; which otherwise may take a longer time. This reduced the duration of therapy including steroids. No adverse events were detected by using DEC.

Table 1: Case Details

History	Examination	Treatment
<b>A.4 Y/F:</b> Eyelid and pedal swelling - 7 day abdominal distension - 3 days, decreased urine output - 2 days UTI (Ecoli +ve) 7 <sup>th</sup> relapse, steroid sensitive	T Normal Eyelids swelling Pedal edema (pitting), transverse umbilicus AG-64cm BP-94/68mmHg	Inj. ciprofloxacin(7day) Tab. levamisole (4day) Tab. Prednisolone (20mg) (8day) DEC for 7days Tab zinc for 12days
<b>B. 2 Y/M:</b> Swelling of eyelid - 3days cough and cold - 2days Tonsilitis 4 <sup>th</sup> relapse, steroid dependent	T-Normal AG-64cm, BP-96/70 mmHg Throat-congested, Tonsil enlarged Eyelids swelling Pedal edema +(pitting)	Inj. Amoxiclav for 5 days Tab. Prednisolone for 6days DEC for 7days
<b>C.5.5 Y/M:</b> fever 4day, Eyelid swelling 4 day, Swelling over abdomen 2 days, UTI (urine pus cells) 2 <sup>nd</sup> relapse, steroid sensitive	T-Normal AG-64cm BP-96/70 mmHg Pedal edema + transverse umbilicus	Inj. ciprofloxacin (10 d) Tab. Prednisolone (10 d) Tab. amoxicillin (1day) DEC for 7days Tab zinc for11days
<b>D.6 Y/F:</b> eyelid swelling- 2 days Pedal swelling- 2 days Cough- 2 days, Tonsilitis 2 <sup>nd</sup> relapse, steroid sensitive	T-Normal AG-60cm, BP- 100/70 mmHg Throat congested, Tonsil enlarged Eyelid swelling Pedal edema (pitting)	Inj. amoxiclav for 4 days Tab. prednisolone for 4 days DEC for 7 days
<b>E.6 Y/M:</b> eyelid swelling - 3 days, swelling over abdomen - 3 days Pharyngitis 1 <sup>st</sup> relapse, steroid sensitive	T-Normal AG-62cm, BP-98/66 mmHg Throat-congested PA-visible veins, edema over abdomen, liver+2cm	Inj. CP for 5 days Inj. amoxyclav for 4 days Tab. prednisolone for 9 days DEC for 7days

T temperature, AG abdominal girth, CP crystalline penicillin, DEC diethyl carbamazine citrate, UTI urinary tract infection; *Doses*- Inj. ciprofloxacin- 10mg/kg/d; Tab. Levamisole- 2mg/kg/d, 3d in a week for 6 week; Tab. Prednisolone- 2mg/kg/d; DEC- 72mg/kg/cycle; Tab zinc- 20mg/d; Inj. CP- 50,000 IU/kg/dose; **Amoxiclav**- amoxicillin +clavulanic 30mg/kg 8 hourly.

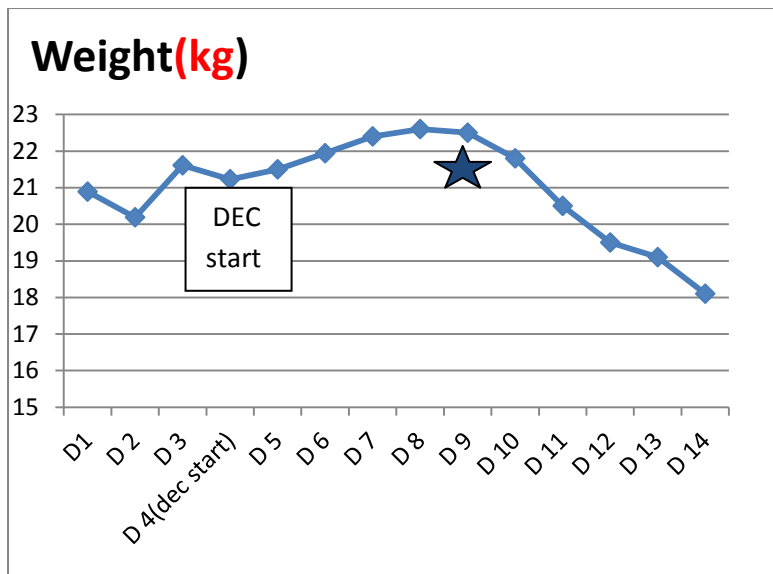
Table 2: Investigations on admission

Investigations	Case 1	Case 2	Case 3	Case 4	Case 5
Total Protein (g/dl)	3.9	4	4.02	3.92	3.2
S. Albumin (g/dl)	1.42	1.5	1.42	1.63	2.1
S. Globulin (g/dl)	2.48	2.5	2.60	2.29	2.8
A/ G ratio	0.57	2.5	0.55	0.71	0.75
S. Cholesterol (mg/dl)	525	385	467	321	320
24hr Urine Protein (mg/24hr)	>2000	670	452	395	410
Urine Protein Creatinine ratio (mg/mg)	7.9	9.19	12.85	12.5	8
Weight (kg) Maximum/ on discharge	21.9/ 18.1	20/ 18.8	21.3/ 19.3	20.2/ 18.2	20.6/ 18.2

S serum; A/G serum albumin/ globulin ratio

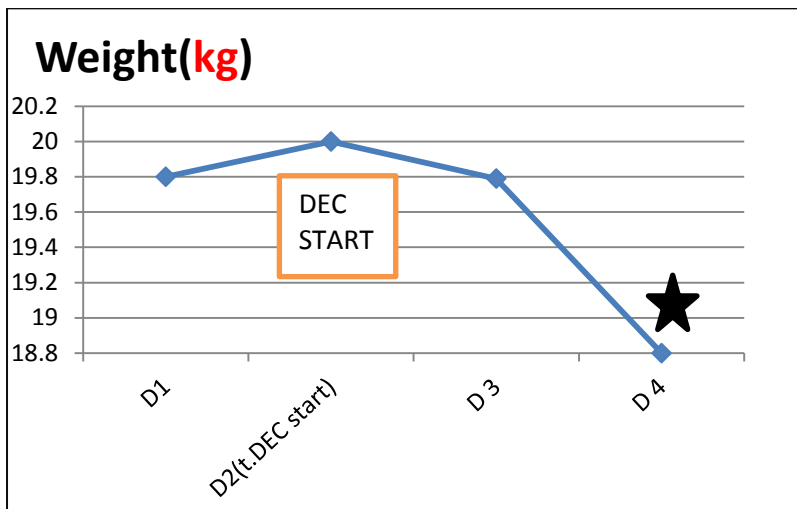
Normal values: T. protein 6-8g/dl; S. Albumin 3.5-5g/dl; S.Globulin-0.5-3g/dl; A/G ratio-0.8-2.0; S. cholesterol <200mg/dl; 24hr urine protein 30-150 mg/24hr; Urine protein creatinine ratio <0.2mg/mg

Figure 3: Case A-4yr female- 7<sup>th</sup> Relapse



★ ----Shows urine Urinary Protein becomes nil

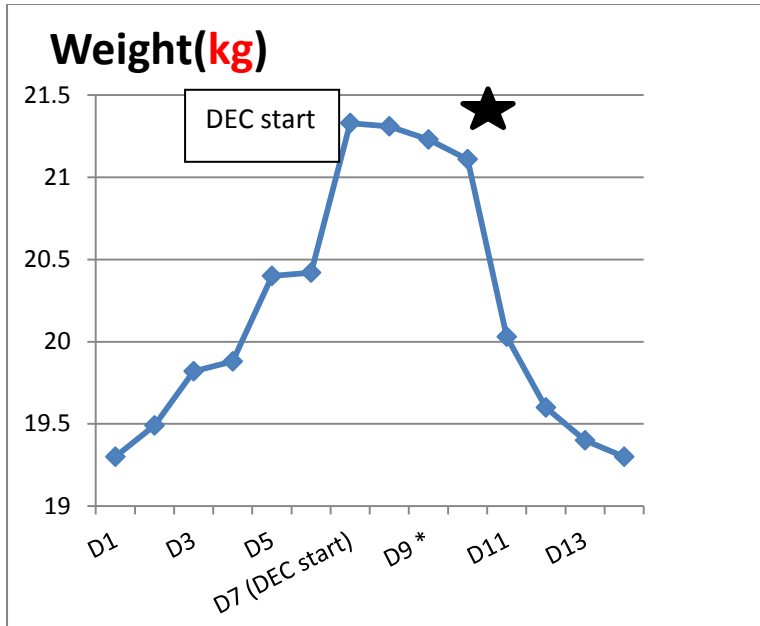
Figure 4: Case B 2yr male 4<sup>th</sup> Relapse



★----Shows urine Urinary Protein becomes nil

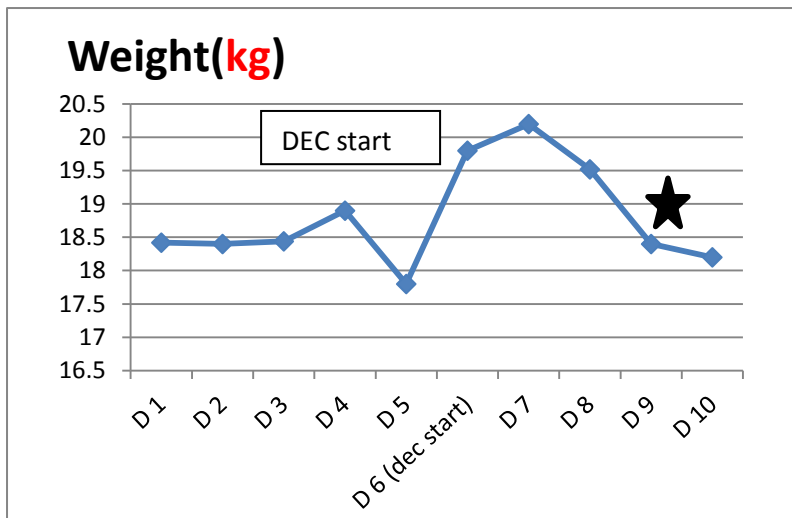


Figure 5: Case C. 5.5yr male -2<sup>nd</sup> relapse



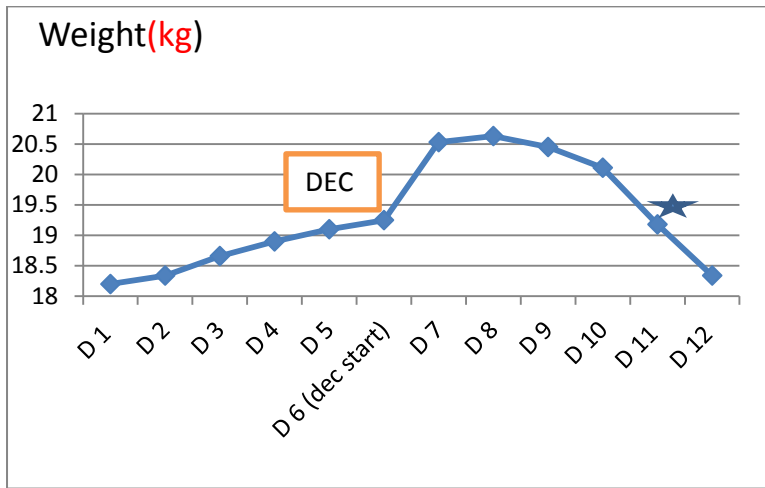
★----Shows urine Urinary Protein becomes nil

Figure 6: Case D -6yr Female – 2<sup>nd</sup> relapse



★ ----Shows urine Urinary Protein becomes nil

Figure 7: Case E .6yr Male -1<sup>st</sup> Relapse



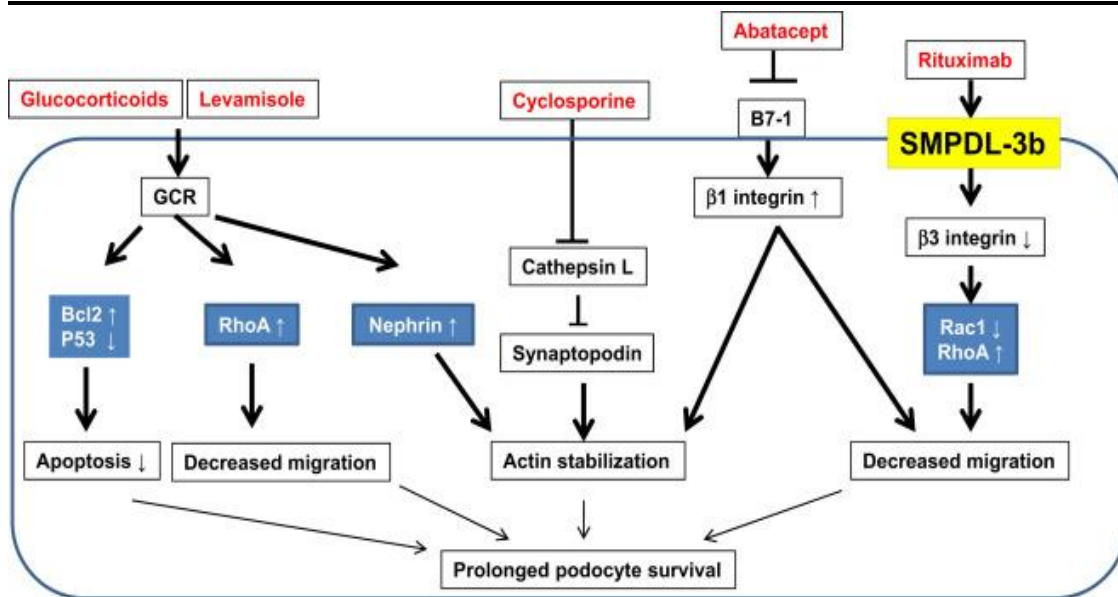
★ - Shows urine Urinary Protein becomes nil

**Discussion:**

It is a denovo study in nephrotic syndrome patients. Initially reports were done to find out any foci of infection and as per report symptomatic management was done. Still in all these cases edema and heavy range proteinuria, did not disappear so considering connection of nephrotic syndrome with filariasis we started DEC. After starting DEC as effect occur initially weight loss starts slowly and urine heat coagulation becomes clear day by day.

In 1966, a new drug levamisole was discovered [5] and due to its immunemodulator property [6], its use had been increased in frequent relapsers, steroid resistant & steroid dependant nephrotic syndrome. But its side effects like leucopenia, rash, seziures limit its use in nephrotic syndrome [7]. Levamisole attenuates podocyte apoptosis and increase in RhoA (ras homolog family member A) activity and decrease in degradation of synaptopodin protein; and so prolonging podocyte survival[8].

**Figure 1** Mechanism of action of Drugs used in Nephrotic Syndrome (Figure reproduced from ‘Nonimmunologic targets of immunosuppressive agents in podocytes’ by Yoo TH [8])



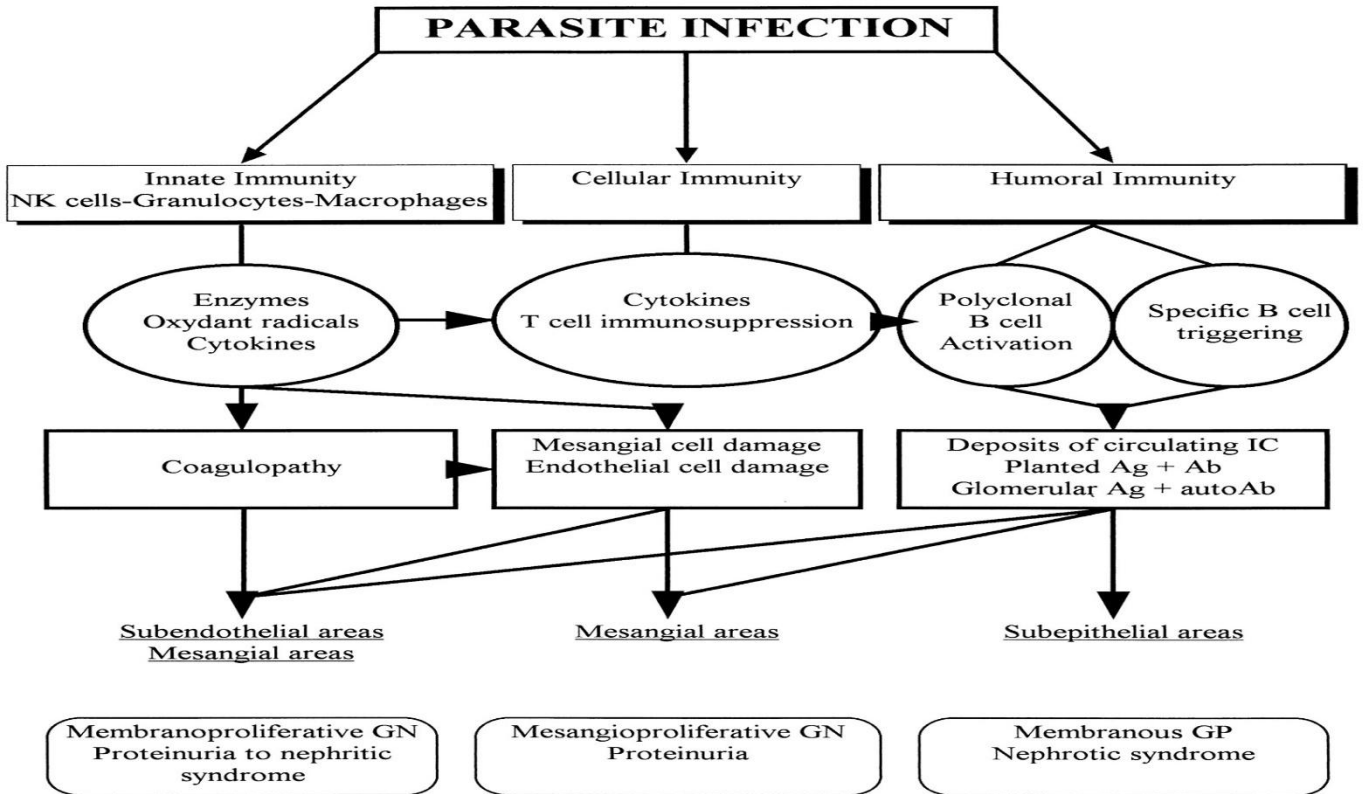
GCR=Glucocorticoid receptor ; Bcl2=B cell lymphoma 2; p53= tumor protein 53; b7-1=membrane protein;  
 RhoA=ras homolog family member A; SMPD-3B=Sphingomyelin phosphodiesterase acid like 3B;  
 Rac1=Rac family small GTPase 1

Incidence of nephrotic syndrome was quite high in China, Japan, India and many Asian countries in 1950s[9] and incidence of lymphatic filariasis was also quite high in those countries.[10] There is a clear association of filariasis and nephrotic syndrome.[11] In the Coastal belt of Gujarat, filariasis still occurs as the mosquito responsible for it, therefore filariasis association causing persistence of edema in nephrotic syndrome is possible. However, this (Bhavnagar) being an endemic coastal belt for filariasis and presentation with edema, so we decided to introduce DEC, an anti-filarial drug.

After filarial infection of human body the generated toxins affect several compartments of the immune system. And play a role in fighting parasitic infections & in the pathogenesis of associated glomerulopathies. During infection, released inflammatory mediators directly damage the different glomerular cell types & participate in the activation of specific subsets of T and B cells, resulting in different levels of antigen, antibody & immune complexes. Depending on the site of the immune-complex deposition and on the type of primary damaged glomerular cells, different glomerular lesions develop.[12]

DEC works well in filariasis and other parasitic infections and due to serious side effects of levamisole & due to possible association of filariasis with nephrotic syndrome, it can be used in nephrotic syndrome as it is cost effective and safety is better than levamisole.

**Figure 2** Effect of Parasitic Infection (Figure reproduced from 'The nephrotic syndrome associated with filariasis' study done by Yap HK[11])



NK cell=Natural killer cell; GN=glomerulonephritis; Ag=antigen; Ab=Antibody; GP-glomerulopathy

## Conclusion

As per above case reports, after Starting DEC, weight and urine protein started to reduce within 2 days in the first difficult case and subsequent 4 more cases of NS relapse in filarial endemic belt at Bhavnagar.

Mechanism could be that DEC works well in filariasis and has also effects on immune system similar to Levamisole that is used as immunomodulator. However, both also act as an anti-filarial agent.

It is cost-effective and safe. *However, DEC need to be studied in further randomized controlled study with efforts to detect filarial antigen* for it to be considered in relapse cases of NS in Filarial endemic regions.

### *What is already known?*

Levamisole is used for steroid dependant nephrotic syndrome. It is also a wormicidal drug acting on filarial worms. Filaria has been linked with minimal change nephrotic syndrome and filarial antigen has been observed in kidney biopsy. Diethylcarbamazine (DEC) is the drug of choice for Filarial infection.

### *What this Case Series adds?*

The effect of DEC (when added to Prednisolone) in relapse cases of nephrotic syndrome in filarial endemic region appears to reduce edema and proteinuria within 3-4 days of administration. **DEC need to be studied in further trials** with control, for relapse cases of NS.

### *Limitations*

This is a *denovo case series* and it is a proof of concept case series. A study with control and filarial confirmation is recommended.

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