DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN IMMUNOBULLOUS DISEASES

Dissertation Submitted In
Fulfillment of University Regulation For

MD DEGREE IN
DERMATOLOGY, VENEREOLOGY AND LEPROLOGY
(BRANCH XII A)

THE TAMILNADU
DR. M. G. R. MEDICAL UNIVERSITY
CHENNAI

MARCH 2007

CERTIFICATE

Certified that this dissertation entitled **"DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN IMMUNOBULLOUS DISEASES"**is a bonafide work done by **DR. N. SINDHU**, Post graduate student of Department of Dermatology and Leprology and Institute of Venereology, Madras Medical College, Chennai- 3, during the academic year 2004 – 2007. This work has not previously formed the basis for the award of any degree or diploma.

Prof. Dr. B. PARVEEN, M.D., D.D.,
Professor and Head,
Department of Dermatology and Leprology,
Madras Medical College,
Chennai- 3

Prof. Dr .KALAVATHI PONNIRAIVAN, B. Sc., M.D.,
The DEAN, Madras Medical College,
Chennai- 3

SPECIAL ACKNOWLEDGMENT

My sincere thanks to

Prof. Dr .KALAVATHI PONNIRAIVAN, B. Sc., M.D.,

The DEAN, Madras Medical College for allowing me to do this Dissertation and utilize the institutional facilities.

DECLARATION

I, **DR. N. SINDHU**, solemnly declare that the Dissertation titled **DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN IMMUNOBULLOUS DISEASES** is a bonafide work done by me during 2004 – 2007 under the guidance and supervision of **Prof. Dr. P. PARVEEN M.D.,D.D.,** Professor and Head of the Department of Dermatology, Madras Medical College, Chennai.

The Dissertation is submitted to The Tamilnadu Dr. M. G. R Medical University towards partial fulfillment of requirement for the award of

M.D Degree in Dermatology Venereology and Leprology (Branch XII A)

Place:

Date:

DR. N. SINDHU.

ACKNOWLEDGEMENT

I am gratefully indebted to **Prof. Dr. B. Parveen M.D.,D.D.,** Professor and Head of Department of Dermatology for her invaluable guidance, motivation and help though out the study. I would like to express my sincere and heartfelt gratitude to **Prof. Dr. V.S. Dorairaj, M.D.,D.V.,** Director In charge, Institute of Venereology. I wish to thank Dr. N. Gomathy M.D., D.D., former Professor, Department of Dermatology and

Dr. N. Usman M.D., D.V., Ph.D., former Director, Institute of Venereology for their constant support and motivation.

I am very grateful to Dr. S. Jayakumar M.D., D.D., Additional Professor, Department of Dermatology for his invaluable guidance and help. I sincerely thank Dr. C. Janaki M.D., D.D., Reader of Dermatology (Mycology) for her priceless support.

I xpress my earnest gratefulness to Dr. D. Prabavathy M.D., D.D., Professor and Head of Department of Occupational Dermatology and Contact Dermatitis for her constant motivation and guidance. I thank

Dr. V. Somasundaram M.D., D.D., Additional Professor, Department of Occupational Dermatology and Contact Dermatitis for his benevolent help and support.

I express my sincere gratitude to Dr. K. Rathinavelu M.D.,D.D., Professor of Leprosy and Dr. R. Arunadevi M.D.,D.D., Lecturer/Registrar, Department of Dermatology for their support.

I incline to thank Dr. R. Priyavathani M.D., D.D., D.N.B.,

Dr. V. Anandan M.D.,(Derm), D.Ch., D.N.B.,(Paed) and Dr. K. Tharini M.D., Dr. M. Vijayanand M.D.,D.D., Assistant Professors, Department of Dermatology for their kind support and encouragement.

I thank Dr. A. Hameedullah M.D., D.D., Dr. S. Kumaravelu M.D., D.D., Dr. J. Manjula M.D., D.N.B., (Derm) and Dr. Aftab Jameela Wahab M.D.,D.D., for their support and help.

My sincere thanks to Dr. S. Mohan M.D, D.V. former Registrar, Dr. K. Venkateswaran M.D., D.V., Dr. P. Elangovan M.D., D.V., Dr. S. Thilagavathy M.D., D.V., Dr. V. Thirunavukkarasu M.D., D.V., Dr. D. Ramachandra Reddy M.D., D.V., Dr. P. Mohan M.D., D.V., Dr. S. Arunkumar M.D.,D.V., and Dr. S. Kalaivani M.D.,D.V., Assistant Professors, Institute of Venereology for their help and suggestions.

I am also thankful to Dr. K. Manoharan M.D., D.D., and Dr. V. Sampath M.D., D.D., for their continuing guidance and support.

I duly acknowledge the paramedical staff and my colleagues for their help and favours.

Last but not least I am profoundly grateful to all patients for their cooperation and participation in the study.

CONTENTS

INTRODUCTION

Pemphigus Vulgaris is a chronic autoimmune blistering disease of skin and mucous membrane. Prior to the advent of corticosteroids, the majority of patients with Pemphigus Vulgaris died from overwhelming sepsis. After introduction of systemic steroids, survival has improved dramatically. However mortality and morbidity is still very high due to steroid related side effects. Adjuvants like Azathioprine, Methotrexate and Cyclophosphamide were added to the treatment of Pemphigus Vulgaris to reduce the high morbidity associated with long term use of oral steroids.

Pulse therapy refers to the administration of a drug intermittently to accelerate the therapeutic efficacy. Pulse therapy using a combination of Corticosteroids and Cyclophosphamide is reported to reduce the mortality and morbidity of Pemphigus Vulgaris. This was introduced by Pasricha et al and by Kanwar.

PULSE THERAPY

Pulse therapy means administration of a drug or drugs intermittently to accelerate the therapeutic efficacy and reduce the possibility of adverse effects related to the daily dosage schedule. In case of pulse steroid therapy, large (supra pharmacological) doses are used to accelerate the therapeutic efficacy without much side effects.

The first reported use of pulse administration of corticosteroids is attributed to Kountz and Cohn[1] who used it successfully to prevent renal graft rejection. Subsequently, pulse doses of corticosteroids were used for several other diseases such as Lupus nephritis[2], Rheumatoid arthritis[3] and Pyoderma gangrenosum[4], but usually to deal with emergency situations only and not as a preferred method of treatment. Methyl prednisolone was the commonest drug used, in a dose of 1gm per dose commonly for 3-5 days as an infusion. Dexamethasone Cyclophosphamide Pulse therapy for pemphigus was first introduced by Pasricha at AIIMS, New Delhi in 1986[5].

THE STANDARD REGIMEN:

In its present form[6], it consists of giving 100 mg of dexamethasone dissolved in 500ml of 5% glucose as a slow intravenous drip over 2 hours repeated on 3 consecutive days. On the second day, the patient is also given

500mg of Inj. Cyclophosphamide in 500ml of 5% Dextrose. This constitutes one DCP. Such DCPs are repeated at exactly 28 day intervals counted from the first day of the pulse. In between the DCPs the patient receives only 50 mg of Cyclophosphamide orally per day. The DCP regimen is administered in four phases.

During the first few months (PHASE 1) the patient may continue develop recurrences of clinical lesions in between the DCPs. This phase is continued till the patient attains complete remission. Remission is defined as complete healing of the existing lesions and absence of new lesions.

During PHASE 2, the patient remains completely alright clinically but receives 9 more DCPs at exactly 28 day cycles along with 50mg Cyclophosphamide orally.

During PHASE 3, the DCPs are stopped and the patient receives only 50mg Cyclophosphamide orally per day for the next 9 months. After this, the treatment for pemphigus completely withdrawn and the patient is followed up for the next 10 years to look for a relapse if any (PHASE 4).

During the early days of DCP, 6 DCPs were given during phase 2 and the duration of phase 3 was 12 months.

OBJECTIVES OF DCP THERAPY:

1) To achieve a faster response and greater efficacy.

2) To reduce the need for long-term use of systemic steroids.

3) To achieve a steroid sparing effect.

CORTICOSTEROIDS:

Corticosteroids was first introduced in dermatology by Marion Sulzberger.

Pharmacological considerations:

They are - Anti-inflammatory

- Immunosuppressive

- Antiproliferative and

- Vaso constrictive.

Biology

The major naturally occurring Glucocorticoid is Cortisol. It is synthesized from cholesterol by the adrenal cortex. Normally less than 5% of the circulating Cortisol is unbound; this free cortisol is the active therapeutic molecule.

The remainder is inactive because it is bound to Cortisol Binding Globulin (CBG, also called Transcortin.) 95% or to albumin 5%. The daily secretion of cortisol ranges between 10 and 20mg with a diurnal peak at 8 A.M [7].

Cortisol has a plasma half-life of 90 minutes. Primarily the liver metabolizes it, although it exerts its hormonal effects on virtually every tissue in the body. The metabolites are excreted by the liver and the Kidney.

Mode of action:

1) Glucocorticoids act by binding to the intracellular Glucocorticoid receptor leading to dimer formation and subsequent binding to specific DNA regulatory sequences known as GLUCOCORTICOID RESPONSE ELEMENTS (GREs). This interaction leads to upregulation or down regulation of specific genes that encode for proteins, such as many cytokines and adhesion molecules.

2) Glucocorticoids can modulate transcription in a hormone dependent manner, not through direct binding to GREs, but through interference with the activity of other transcription factors such as AP-1, NF-κB, Immunophilin and CREB. These factors are involved in the inducible regulation of many genes, several of which relate to the immune cell function and production of inflammatory mediators[8]. In the case of NF-κB, Glucocorticoids can also block nuclear translocation and DNA binding of NF-κB through induction of IκB alpha protein and cytoplasmic trapping of NF-κB[9].

3)There are also post transcriptional effects of Glucocorticoids which include effects on RNA translation, protein synthesis and secretion. End result of all these many effects is that Glucocorticoids inhibit the access of inflammatory cells to tissue, interfere with function of fibroblasts and endothelial calls and suppress production and effects of humoral factors.

4) Glucocorticoids increase the synthesis of other important molecules such as Annexins 1 and 2. Annexins reduce the Phospholipase activity which reduces the release of arachidonic acid from membrane phospholipids[10,11] limiting the formation of Prostaglandins and Leucotrienes[12,13].

5) Glucocorticoids profoundly affect the replication and movements of cells. They induce monocytopenia, eosinopenia and lymphocytopenia and have a greater effect on T cells than on B cells[14].

6) Glucocorticoids affect cell activation, proliferation and differentiation. They modulate the levels of mediators of inflammation and immune reaction as seen with the inhibition of IL-1, IL- 2, IL- 6 and TNF synthesis[15,16].

7) They suppress monocyte and lymphocyte function more than polymorphonuclear leukocyte functions.

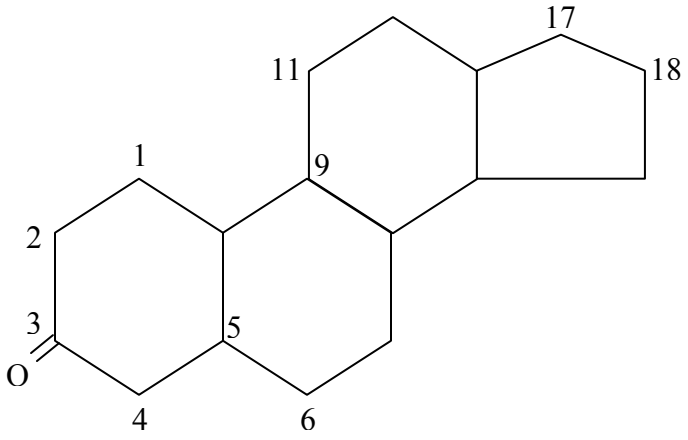
In Pulse therapy : Glucocorticoids exerts additional effects in addition to the above:

1)Glucocorticoids exert their effects by non genomic mechanism such as membrane bound receptors or physicochemical interaction with cellular membranes.

2) They also cause apoptosis of inflammatory cells, especially peripheral blood CD4+ T- Lymphocytes.

PHARMACOLOGY:

Basic steroid structure:



Classification of steroids according to duration of action

	Duration of action (hours)	**Plasma half-life (hours)**
Short acting:		
Hydrocortisone	8-12	90
Cortisone	8-12	30
Intermediate acting:		
Prednisone	24-36	60
Prednisolone	24-36	200
Methyl Prednisolone	24-36	180
Triamcinolone	24-36	300

Long acting:

Dexamethasone	36-54	200

PHARMACOKINETICS OF CORTICOSTEROID PULSE:

Conventionally, methyl prednisolone has been the agent used in corticosteroid pulse therapy. However, in India various workers have used dexamethasone with significant success. This is particularly due to the easy affordability and accessibility of the drug to the patients. The pharmacokinetics is complex. There is a rapid peak with a subsequent serum half life of 3 hours. A very large proportion of IV bolus rapidly enters the gut, manifests in part by the development of metallic taste in the mouth, and this reenters the venous space via the splanchnic circulation causing a secondary peak in the serum level. Cortisol levels do drop initially but reverts to normal levels within 24-48 hours after infusions[17]. After prolonged use of IV pulse doses of steroids in children, morning and evening levels of serum Cortisol and ACTH were estimated to be normal after 3 months to 5 years of weekly boluses[18]. Studies on bone metaboism have showed decreased absorbtion of calcium from the gut and its renal excretion, increased parathyroid hormone and 1,25dihydroxycholecalciferol, and decreased bone resorption and formation immediately after single boluses[19], but no net change except for a slight decrease

in hydroxyproline excretion after 3 boluses given on alternate days[20]. This was confirmed by a study of deoxypyridinoline excretion as a measure of bone collagen degradation.

Very high levels of corticosteroids obtained by pulse therapy exert additional effects that are not just a result of more number of drug molecules multiplying the same.

IMMUNOLOGICAL ALTERATION AND ANTI INFLAMMATORY ACTIVITY OF PULSE STEROID: There is an acute drop in the circulating T and B-cells 5 hours after infusion of pulse steroid which reverts to normal within 24 hours. However Leu-3a subsets of T-helper cells reach normal levels by 48 hours[21].

There is no significant rise in the uric acid excretion. Perhaps these doses of Corticosteroids do not kill a significant proportion of cells; rather it causes transient redistribution between the circulation and lymphoid organs. Normal immune responses do not appear to be affected by large pulses. Fan et al[22] found no change in the circulating immunoglobulin, primary or secondary antibody responses or delayed hypersensitivity skin reactions. Delayed hypersensitivity reactions to antigens to which the children had been exposed earlier and primary response to pneumcococcal vaccine.

Pulse Corticosteroids is used mostly to ameliorate the systemic inflammatory response syndrome, which is thought to result from activation of the complement system by bubble oxygenating pumps. It has been seen that those who receive pulse steroids have low circulating levels of complement activation fragments and pro-inflammatory cytokines IL-1, IL-6, IL-8, and TNF-ά and higher levels of anti-inflammatory IL-4 and IL-10 .

CYCLOPHOSPHAMIDE

An alkylating agent was first synthesized as a derivate of nitrogen mustard. It is used as an immunosuppressant in the treatment of various autoimmune disorders.

Pharmacokinetics:

Oral Bioavailability is 74%. Peak Plasma levels occur at 1 hour. It is widely distributed throughout the body including cerebrospinal fluid. The half life of the drug ranges from 2-10 hours. It is decreased in children and increased in cirrhosis. The drug is only 13% protein bound but its metabolites are approximately 50% protein bound in plasma.

Cyclophosphamide is primarily metabolized by the liver. It is a PRODRUG which gets activated in the liver by conversion through cytochrome P450 to 4-hydroxy cyclophosphamide. Its immunosuppressive properties are

due to the metabolite Chloracetaldehyde produced after side chain oxidation of Cyclophosphamide[23].

Hepatic metabolism is the principal route of elimination of Cyclophosphamide. Seventy percent of the drug is excreted in the urine as inactive compounds. Because the clearance of the active metabolites occurs by spontaneous degradation rather than renal excretion, renal failure does not influence toxicity directly. There is no need for dosage adjustment in the presence of either renal or hepatic failure[24].

MODE OF ACTION[25]:

Cyclophosphamide is an alkylating agent. It has the ability to form strong electrophiles that form covalent linkages to electron rich groups of DNA. The active metabolite is phosphoramide mustard, which undergoes cyclization to the reactive aziridium intermediate, which in turn alkalizes the DNA. The result is irreparable damage to the DNA and subsequent apoptosis of the cell.

Cyclophosphamide although highly toxic to the rapidly dividing cells is different from several other cytotoxic agents in that it is toxic to the cells in all phases of the cell cycle[26].

Cyclophosphamide is referred to as CELL CYCLE specific rather than a phase specific antineoplastic agent. It is the cell cycle specific characteristic of

Cyclophosphamide that is responsible for its cytotoxic effect on immune cells. It depresses B cell function more than T cell function. Suppressor T cells appear to be more affected than helper T cells.

ADVERSE EFFECTS:

Hematological toxicity:

Manifests as myelosuppression, which is the primary, dose limiting side effect. Thrombocytopenia occurs less frequently.

Leukocyte count nadir occurs 8-12 days after therapy is initiated.

Gonodal damage:

Azospermia and premature ovarian failure is a well defined side effect of Cyclophosphamide. The characteristic finding in male gonadal toxicity is testicular germ cell depletion, whereas in females it causes disappearance of primordial ovarian follicles.

Urological damage:

Cyclophosphamide causes increased frequency, dysuria, urgency, microscopic haematuria, hemorrhagic cystitis, fibrosis of bladder, and bladder necrosis.

One of the metabolic products, ACROLEIN is thought to be the cause of hemorrhagic cystitis. MESNA binds and inactivates acrolein, allowing for elimination of inactivated compounds in urine. Ensuring both adequate hydration and administration of mesna during treatment has been reported to decrease markedly the incidence of bladder complications.

Carcinogenesis:

Cyclophosphamide is linked to squamous cell carcinoma of bladder, urinary tract, and carcinoma of the renal pelvis and ureter.

INDICATIONS AND CONTRAINDICATIONS OF DCP THERAPY IN IMMUNOBULLOUS DISEASE[27]:

Since the pulse regimen virtually cures every pemphigus patient for the rest of his life and there are almost no side effects, all Pemphigus patients deserve to be treated with this regimen irrespective of whether they are having severe or mild disease. Even those patients who are in clinical remission but have to take maintenance doses of corticosteroids or immunosuppressive drugs can be made to give up maintenance doses by administering them a course of DCP regimen.

1) DCP therapy can be given to patients of all ages but the doses have to be reduced to half for children below the age of 12 years

2) It can also be given to patients with Diabetes mellitus, Hypertension,

Hyperacidity, Osteoporosis, Tuberculosis etc., but each patient must receive additional appropriate treatment for the concomitant disease whenever necessary.

3) Diabetic patients need to be given 10 units of soluble Insulin for every 500ml bottle of 5% glucose dissolved in the same drip in addition to the routine treatment for diabetes.

4) In Hypertensive patients, BP must be monitored regularly and the treatment for hypertension adjusted if necessary.

5) Patients having hyperacidity can continue to take antacids or H2 blockers as required

6) Even those having active tuberculosis can continue the pulse therapy along with the anti tubercular treatment.

7) Viral warts and molluscum contagiosum can also be treated concomitantly along with the pulse therapy.

8) If a patient has severely infected lesions or there is a serious infection elsewhere, the start of the pulse therapy can be delayed for a week or two till the infection has been brought under control.

9) Similarly patients having herpes simplex, herpes zoster or even chicken pox can be given concomitant treatment with acyclovir and the pulse therapy can be

continued except under exceptional circumstances when the viral infection is very severe.

The absolute contra indications are

1) Pregnancy

2) Lactation

3) Severe cardiac or respiratory compromise

In a pregnant lady, the pulse therapy is only to be postponed till the patient has delivered the baby and stopped feeding the child. Till that time the patient is to be maintained on a regular dose of corticosteroid just sufficient to keep the disease under control.

Patients who are unmarried or those who have not yet completed their family and want to have more children, have to be given dexamethasone pulses and not DCPs. Cyclophosphamide in the pulses has to be avoided because it can lead to amenorrhea or azospermia in a significant proportion of patients. The low dose daily Cyclophosphamide can be continued.

MODIFICATIONS TO STANDARD DCP REGIMEN[28]:

a) All hospitalized patients were treated for intercurrent infections and given conventional steroid therapy to control the activity of Pemphigus. The first pulse was initiated when the secondary infection was fully controlled and existing lesions were reduced in number.

b) When Cyclophosphamide 500mg was added to the drip on the second day of DCP, it was followed by an additional 5% dextrose of 500ml, to prevent the urinary complications of Cyclophosphamide.

c) As part of the protocol, the following supportive drugs were given to all patients: oral calcium 500 mg daily, during the first three phases, and

Inj. Vitamin D 3lakh units once a month during the first two phases.

d) Patients with oral lesions were encouraged to clean the oral cavity with regular brushing of the teeth. They were advised to massage a topical corticosteroid gel on the oral ulcers 3-4 times a day especially after meals and given ketoconazole 200mg per day orally and 500mg Ciprofloxacin or Cefadroxil twice daily. This change leads to the healing of oral lesions with in 2-3 months.

e) Earlier patients received only monthly pulses of corticosteroids, but with the observation many patients developed some degree of recurrence of lesions between the pulses in the early stages of therapy, daily corticosteroids were added in the first few months[29].

f) Patients with extensive active disease were also given interval pulses of dexamethasone[29]

FACTORS CONTRIBUTING TO THE SUCCESS OF DCP THERAPY[30]:

1) **The choice of the drug**: Conventionally methyl prednisolone was the drug most commonly used in corticosteroid pulse therapy. The choice of dexamethasone made the treatment more affordable and accessible to the patients 1000 mg of methyl prednisolone is equivalent to 138 mg of dexamethasone. However a dose of 1000mg of methyl prednisolone is as arbitrary as 100mg of dexamethasone and in the absence of evidence that 136mg of dexamethasone is more effective, nearly all centers continue to use 100mg boluses.

2) In the early days, DCP was administered in the ICU under continues cardiac monitoring. It is now given as a routine infusion often in a day care or a OPD setting.

3) The treatment has evolved in response to the observations of the results of the treatment in patients who were receiving this form of therapy.

a)Initially only dexamethasone pulses were used. Cyclophosphamide boluses were added because relapses were frequent with dexamethasone alone.

b) Insistence on the 28-day cycles for pulses is based on the observation that relapses are commoner in those who took pulses irregularly.

c) Current recommendation of administering 9 pulses during phase 2 was arrived at by observing that relapse rate was commoner in patients receiving 6 pulses during phase 2.

ADVANTAGES OF DCP:

1) Better control of the disease to the point of presumptive cure.
2) Near absence of steroid side effects.
   a) Studies[31] show that there is almost no risk of developing Diabetes, Hypertension, Peptic ulceration, Osteoporosis, striae, acne, hirsuitism, unless the patient was receiving or had received daily doses of steroids.
   b) Does not lead to an increase in body weight unless the patient was receiving daily Corticosteroids and if the patient had already developed cushingoid obesity due to previous treatment, the body weight and appearance wound actually return to normal during the pulse therapy.
   c) Studies[31] have found no significant effect of pulse therapy on bone mineral density or metabolism.
   d) The HPA axis was found to rapidly return to normal after pulse therapy than after daily doses of steroids.

3) Reduced length of stay in the hospital.

ADVERSE EFFECTS OF DCP THERAPY:

The adverse effects of pulse therapy can be due to the constituents of the pulse or due to the pulse itself and are subdivided as follows:

DUE TO CORTICOSTEROID[32]:

1) Viral, bacteria and fungal infections
2) Hyperacidity
3) Diabetes mellitus
4) Hypertension
5) Demineralization of bone / Avascular necrosis
6) Spontaneous rupture of the Achilles tendon[33]

DUE TO CYCLOPHOSPHAMIDE:

1) Leucopenia
2) Thrombocytopenia
3) Diffuse loss of hair
4) Diffuse Hyper-pigmentation of skin and hyperpigmented bands in nails
5) Hemorrhagic cystitis
6) Gonadal Damage
7) Carcinogenesis

DUE TO PULSE[34]:

1) Hiccups[35]

2) Facial flushing[36]

3 Weakness

4)Metallictaste

5)Muscle and bone pain

6)Generalisedswelling

7) Diarrhoea

8) GI bleeding

9) Headache

10) Loss of taste

11) Menstrual irregularities

12) Hair Loss

13) Sleep Disturbances

14) Palpitation

15) Hypotension

16)Arrhythmias

17)Congestive cardiac failure

18) Pulmonary oedema

19)Ischemic Heart Disease

20)Sudden Death

21) Acute Psychosis

22) Seizure

23)Anaphylaxis

Flushing: The high dose of Glucocorticoids produces vasodilation that is reflected as flushing over areas like face, palms and soles[37].

Palpitations: Glucocorticoids exert a positive inotropic effect over the heart and increase epinephrine synthesis[38].

Weakness: Hypothalamic Pituitary Adrenal axis suppression[39] produced by dexamethasone therapy at the level of pituitary persists for about 7-10 days[40],

and may result in reduced production of all hormones including ACTH. Such hormonal dysregulation might be responsible for the malaise.

Menstrual irregularities: Gonadotropin dysregulation because of pituitary suppression may be causing the menstrual irregularities.

Psychosis: Corticosteroids influence the physiology of the central nervous system in various ways. Glucocorticoid receptors are present at sites like cerebellum, hypothalamus and dentate gyrus, and most importantly the hippocampus[41]- an important channel receiving the sensory inputs controlling the behaviour. Suprapharmacological dose of the glucocorticoids, particularly dexamethasone has a special affinity for type 2 receptors that potentiate the damage to hippocampal cells produced by kainic acid[42], thereby suppressing the hippocampal excitability and producing various behavioural alterations.

Bad taste/ Diarrhea: Coincides with the pulses and responds to a 7 day course of Ciprofloxacin for 2-3 consecutive days. All the side effects related to corticosteroids were reported to be much less in cases of pulse therapy. Pituitary adrenal axis is suppressed in about half of the patients on pulse therapy. However, it reverts to normal in a few days and clinically the patients remain normal during the treatment and subsequent follow up.

Hair loss: Could be due to either drug induced or stress related tetogen effluvium. Dexamethasone influences the hormonal physiology of the hair follicle by inhibiting dihydro-testosterone whereas Cyclophosphamide has a direct cytotoxic effect on the hair follicle.

Head ache : May be due to cerebral vasodilatation.

Sleep disturbance: Glucocorticoids activate the CNS and decrease REM sleep[43].

Polyurea: This is due to the involvement of Atrial Naturetic Factor. Glucocorticoids increase the rate of transpcription of ANF in mRNA in cardiocytes[44], stimulate ANF secretion[45] and upregulate ANF receptors on endotheial cells.

Acute Cardiovascular complications:

These are among the serious adverse effects. They are very rare and typically occurred in patients with underlying kidney or heart disease. Electrolyte shifts and rapid rate of infusion were believed to underlie atleast some of the events.

ECG abnormalities can resolve with potassium infusion despite normal serum levels which suggests that electrolyte shifts may precipitate some of the

adverse effects[47]. Continuous cardiac monitoring is warranted only in patients with underlying kidney or heart disease and daily and post infusion electrolyte monitoring is indicated in these patients.

A slow rate of infusion, usually over 2-3 hours is recommended ,because a faster rate has been associated with a greater risk of arrhythmias, hypotension and electrolyte shifts.

Infections: The risk of increased pyogenic infections on the skin and candidiasis in the mouth persisted only as long as the patients had ulcers on the skin and oral cavity and therefore vigorous treatment with systemic antibiotics and antifungal agents during this period was helpful.

Viral or dermatophyte infections should be treated on their own merit without interrupting pulse therapy regimen.

All the side effects related to corticosteroids were reported to be much less in cases of pulse therapy. Pituitary adrenal axis is suppressed in about half of the patients on pulse therapy. However, it reverts to normal in a few days and clinically the patients remain normal during the treatment and subsequent follow up.

Monitoring of patients on Pulse therapy:

Before each pulse: Complete blood count, urine analysis, electrocardiogram, blood sugar, Renal Function Tests, Liver Function Tests, Serum Electrolytes.

After each pulse: Urine analysis, Serum electrolytes.

Chest x ray has to be done after every 6 pulses.

INDICATIONS FOR DCP PULSE THERAPY:

Although pulse therapy has been advocated for various cutaneous and systemic diseases, it can be categorized under 3 headings:

1) **Established dermatological indications**: Diseases where the therapy has been extensively used and there are a good number of studies regarding their efficacy.
2) **Dermatological diseases with limited experience**: Conditions where there are a few anecdotal reports of the efficacy of pulse therapy.
3) **Systemic disorders**

ESTABLISHED DERMATOLOGICAL INDICATIONS:

1) Pemphigus vulgaris[47-53]
2) Bullous pemphigoid[53]
3) Localized scleroderma[54]
4) Pyoderma gangrenosum[55-56]
5) Reiter's disease

DERMATOLOGICAL DISEASES WITH LIMITED EXPERIENCE:

1) Extensive alopecia areata/ alopecia universalis[57-58]
2) Extensive lichen planus[59]
3) Prurigo nodularis[60]
4) Generalized morphoea
5) DLE[61]
6) Extensive vitiligo
7) Allergic vasculitis
8) Disseminated porokeratosis[62]
9) Dariers disease
10) Hailey Hailey disease
11) Multiple Keloids
12) Post burn contractures
13) Sarcoidosis
14) Multicentric reticulohistiocytosis[63]
15) Peyronies disease
16) Urticarial vasculitis[64]
17) TEN[65]
18) SJS

SYSTEMIC DISORDERS

1)Systemic sclerosis[66-67]

2)SLE/renal lupus/lupus meningitis[68]

3)Rheumatoid arthritis

4)Graves disease with ophthalmopathy[69]

5)Kawasaki disease[70]

6)IgA nephropathy[71]

7)Moderate to severe ulcerative colitis[72]

OTHER PULSE THERAPIES FOR PEMPHIGUS

1**) Dexamethasone Azathioprine Pulse (DAP):**

Here cyclophosphamide is replaced with 50mg of Azathioprine daily during the first 3 phases. No bolus dose of Azathioprine is given during the pulse. This regimen is a viable option for patients who are unmarried or have not completed their family.

2) Dexamethasone Methotrexate Pulse (DMP):

Here Cyclophosphamide is replaced by 7.5mg of Methotrexate (three doses of Methotrexate 2.5mg at 12hourly intervals) weekly given orally during the first 3 phases of pulse therapy.

There are no reports of abnormal children fathered by men receiving Methotrexate therapy although the sperm motility may be abnormal during

treatment. Methotrexate has no apparent effect on the outcome of pregnancies occurring after it is discontinued.

DMP regimen can also be considered for patients who have not completed their family.

4) Pulse Glucocorticoid therapy:

Methyl prednisolone and dexamethasone are the glucocorticoids most frequently administered in the pulse regimen.

Doses of each pulse are usually 10-20mg/kg body weight for methyl prednisolone and 2-5mg/kg body weight for dexamethasone. Pulses are usually given daily for 3-5 days.

6) Cyclophosphamide pulse therapy:

Cyclophosphamide 500mg was dissolved in 25ml of distilled water which was added to 500mg of 5% dextrose and given slowly intravenous for 60 minutes.

It was followed by 500ml of normal saline. Similar pulses were repeated monthly for 12 months and 2 monthly for further 6 pulses.

Indications for cyclophosphamide pulse:

1) Resistance to control with prednisolone
2) Weight gain.
3) Psychosis
4) Aseptic necrosis of bone

5) Severe hypertension
6) Uncontrolled Diabetes

PEMPHIGUS

The term ‘Pemphigus’ refers to a group of autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intraepidermal blisters due to acantholysis (ie. separation of epidermal cells from each other) and immunopathologically by *in vivo* bound and circulating IgG antibodies directed against the cell surface of the Keratinocytes

Pemphigus is derived from the Greek word, Pemphix, meaning blister or bubble.

TYPES OF PEMPHIGUS

Pemphigus Vulgaris

Variant : Pemphigus Vegetans

Pemphigus foliaceus

Variant : Pemphigus herpetiformis

Variant : Pemphigus erythematosus

Induced Pemphigus

Intercellular IgA Dermatosis

Paraneoplastic Pemphigus

PEMPHIGUS VULGARIS

Affects all races and both sexes. It is a disease of middle age but patients are younger at presentation in India than in western countries[73]

INCIDENCE AND PREVALANCE :

Pemphigus Vulgaris accounts for approximately 70% of all cases of Pemphigus.

It is the most common autoimmune blistering disease in eastern countries, such as India, Malaysia, China, Middle east[74].

The Jewish race, especially Ashkenazi Jews, have an increased susceptibility to Pemphigus Vulgaris[75]. Pemphigus is less common in the west.

GENETICS :

Predisposition is linked to genetic factors. Certain major histocompatibility complex (MHC) class II genotypes, in particular alleles of HLA – DRBI*04 and DRBI*14 subtypes are common in patients with Pemphigus vulgaris[76]. These alleles produce amino acid substitutions in HLA – DRB1 peptide binding sites, which may influence antigen presentation and recognition by T-cells. Susceptibility may also be determined by genes encoding immunoglobulins.

ENVIRONMENTAL FACTORS :

Viral DNA (herpes simplex, Ebstein-Barr Virus, Human Herpes Viruses 6 and 8) has been detected in some skin biopsies from Pemphigus patients[77].

Pemphigus has coexisted with HIV infection[78].

Dietery agents implicated in the causation of pemphigus vulgaris are Allium group (onion,garlic), shallots,tannins (certain fruits), radish,phenols (artificial sweetners,preservatives,colouring agents),mustard (thiocynates)

PATHOGENESIS :

Autoantibodies against the surface of Keratinocytes occur in Pemphigus.

PEMPHIGUS VULGARIS ANTIGEN :

Also known as Desmoglein 3, is a desmosomal cadherin involved in mediating intercellular adhesion in the epidermis. The antibody binds to an extracellular domain on the amino terminal region of desmoglein 3 where it may have a direct effect on the function of desmosomal cadherins[79].

Desmoglein 3 is found in desmosomes. It is detected primarily in the lower epidermis, and is expressed more strongly in buccal mucosa and scalp skin than in the skin from the trunk.

Anti desmoglein 1 antibodies are more common in Indian patients.

Pemphigus Vulgaris sera may also contain auto-antibodies to desmocollins and antibodies to cholinergic receptors.

ANTIBODIES :

Patients with active disease have antibodies both IgG1 and IgG4 subclasses,but IgG4 are pathogenic[80]. Autoantibody production is Tcell

dependent ; auto reactive Th 1 and Th 2 cells specific for desmoglein 3 occurs in Pemphigus Vulgaris. Antigen-antibody complexes are found on desmosomes in early pemphigus lesions.

COMPLEMENT AND IMFLAMMATORY MEDIATORS:

Acantholysis can occur without complement but complement enhances pathogenicity. Pemphigus antibody fixes components of the complement to the surface of epidermal cells[81]. Antibody binding may activate complement with the release of inflammatory mediators and recruitment of activated T cells. Complement activation in Pemphigus is increased by interleukin-1α, Tumour necrosis factor - α.

PROTEASES :

Several Proteases are involved in the pathogenesis of Pemphigus Vulgaris of which the important is Plasminogen Activator, which converts Plasminogen to plasmin. Plasmin amplifies epidermal damage.

CLINICAL FEATURES :

Patients present with oral lesions, in 50-70% cases of Pemphigus Vulgaris. They may precede cutaneous lesions or be the only manifestation of the disease[82]. Intact bullae are rare in the mouth. More commonly patients present

with buccal or palatal erosions. Other mucous surfaces involved include conjunctiva, nasal, pharynx, larynx[83], esophagus, urethra, vulva, and cervix.

Cutaneous lesions are vesicles and bullae on apparently normal skin. They may be localized or generalized. Sites commonly involved are scalp, face, axillae, groins and pressure points. Bullae are initially tense and clear, but become flaccid and turbid in two or three days. Itching may be present.

Nikolsky's sign: This sign which is elicited by applying lateral pressure with the thumb or finger pad on skin over a bony prominence ,results in a shearing pressure that dislodge upper layers of epidermis from lower epidermis.[84] It can be elicited over the normal looking skin of a Pemphigus patient either close to the existing lesions (**Marginal Nikolsky sign**) or over normal looking skin at a distant site(**Direct Nikolsky sign**)

Bulla spreading sign or Lutz sign: Slow unidirectional pressure applied by a finger to the bulla cause peripheral extension of bulla beyond the marked margin

Asboe Hansen sign is a variation of bulla spreading sign it applies to a smaller, intact, tense bulla where the pressure is applied to the center of the blister.

The blisters rupture easily to leave behind painful areas of oozing and denuded skin that continue to extend showing little tendency to heal. A

characteristic offensive odour may emanate from them. They often become crusted. The erosions may be assosciated with pain.

Lesions in skin folds readily form vegetating granulations. Nail dystrophies, acute paronychia and subungual haematomas have been observed

A grading system for pemphigus was devised by Fleischi[85] based on the no of bulla/erosions.

LABORATORY FINDINGS :

1) **TZANCK SMEAR :** The base of the blister is gently scraped with a blunt scalpel the material obtained spread thinly on a glass slide

Tzanck cell is a large rounded cell, with hyperchromatic nucleus, a perinuclear halo and peripheral condensation of cytoplasm.

2) SKIN BIOPSY – HISTOPATHOLOGY

The earliest change consists of intercellular oedema with loss of intercellular attachments in the basal layer. Suprabasal epidermal cells separate from the basal cells to form clefts and blisters.

Basal cells remain attached to the basement membrane but separate from one another forming ‘Row of Tombstone’ appearance.

Blister cavity contains acantholytic cells. Blistering is preceded by eosinophilic spongiosis in some cases. The superficial dermis has a mixed superficial dermal inflammatory infiltrate which includes some eosinophils. [86]

1. IMMUNOPATHOLOGY

Direct Immunoflourescence :

IgG deposited on the surface of the Keratinocytes throught out the epidermis in and around the lesions. IgG1 and IgG4 are the most common subclasses. Complement components (C3), IgM and IgA are present less frequently than 1gG.

Indirect Immunoflourescence:

Shows circulating IgG antibodies directed against the cell surface of the keratinocytes in 90% of the cases. The best single substrate for the demonstration of these antibodies is the monkey esophagus.

2. IMMUNO ELECTRON MICROSCOPY :

Deposits of IgG and C3 are localized to the cell membrane.

3. ELISA

Detects antidesmoglein3 antibodies in 95% and antidesmoglein 1 antibodies in 50% of the cases.

TREATMENT :

Topical :

1. Saline / Potassium permanganate soaks
2. Topical antiseptics
3. Topical Steroids

Oral lesions : Good oral hygiene

Topical or intra lesional steroids

Topical ciclosporin mouth wash.

Systemic :

1. Systemic Steroids
   Prednisolone 1 – 1.5 mg / kg / day
2. Immunosuppresive agents
   Azathioprine 2.5 mg / kg / day
   Cyclophosphamide 1-3 mg / kg / day
   Cyclosporin 5 mg / kg / day
   Methotrexate 10 – 17.5 mg / week
3. Dexamethasone Cyclophosphamide Pulse therapy
4. Dexamethasone / Methyl Prednisolone Pulse therapy
5. Nicotinamide and Tetracycline
6. Oral / Intramuscular gold
7. Mycophenolate mofetil
8. Plasmapheresis
9. Intravenous Immunoglobulin

BULLOUS PEMPHIGOID

Definition : It is an acquired autoimmune blistering disease of the elderly characterized histologically by subepidermal bulla and immunopathologically by

deposition of antibodies and complement along the epidermal basement membrane zone.

AETIOLOGY :

Age : Affliction of the elderly

Sex : More common in males

Genetics : HLA DQ7 may be associated with Bullous Pemphigoid (only in males)

PATHOGENESIS :

The disease is characterized by IgG auto antibodies to hemidesmosome associated proteins within the adhesion complex. The auto antibodies have been shown to be pathogenic and complement to be necessary for blister formation[87].

ANTIGENS :

The two major antigens are BP 230 and BP 180, which are associated with hemidesmosomes[88].

BP 230, also known as BP AG 1 is intracellular and localized to the dense plaque. It resides on the short arm of chromosome 6.

BP 180, also known as BP AG 2 and collagen XVII is a transmembrane molecule with collagenous domains and a long extracellular portion[89]. The gene is situated on chromosome 10.

ANTIBODIES :

Anti BMZ antibodies are found in the IgG (Predominantly IgG1 and 1gG4) and occasionally IgA types.

COMPLEMENT :

The deposition of auto antibodies binds C3 along the dermoepidermal junction. C5a fragments are thought to stimulate the recruitment of neutrophils to the site of inflammation[90]

Autoantibodies bind to BP antigens and activate complement. Complement components set off an inflammatory cascade attracting leukocytes, degranulating mast cells and releasing inflammatory mediators. The activated inflammatory cells release lysosomal enzymes and proteases, cleaving the target antigens and disrupting the hemidesmosomes, resulting in blister formation.

Clinical Features :

Commonly starts with itching and a non specific rash. The rash may be either urticaria like or occasionally eczematous. Sometimes a figurate erythema may precede blister formation.

Blisters may arise on erythematosus and on normal skin and may be associated with edema. The blisters are tense. They appear mainly on the flexural aspects of the limbs and on the central abdomen. Their contents are usually clear serous exudates although occasionally this is blood stained. The blisters are tense and may remain intact for several days. Erythema may persist at the sites of previous blisters for many weeks or months. Milia may be profuse during the healing phase.

Mucosal lesions occur less frequently and is usually confined to mouth
Clinical variants :

Localised :

a) Pretibial localization
b) Localised Vulvar Pemphigoid[91]
c) Dyshidrosiform Pemphigoid

Generalised :

a) Vesicular

b) Vegetating

c) Childhood

d) Pemphigoid nodularis

e) Lichen Planus pemphigoides

f) Induced BP

INVESTIGATIONS :

1. Peripheral blood eosinophilia
2. Elevated serum IgE
3. Tzanck smear: Tzanck cell is not seen. A number of eosinophils are present.
4. Histopathology

Blister is subepidermal. The blister may contain numerous eosinophils and neutrophils. Biopsies of blisters from erythematous areas show a dermal (a cell rich patern)inflammatory infiltrate containing many eosinophils and neutrophils with lymphocytes and histiocytes. Cell poor pattern is observed when blisters develop on relatively normal skin. There is usually a scant perivascular lymphocytic inflammation with few eosinophils, some scattered through out dermis and some near the epidermis. Eosinophilic spongiosis may be seen.

4. IMMUNOPATHOLOGY

Direct Immunoflourescence

Best performed on perilesional biopsies. Biopsy will show either IgG and C3 (or C3 alone along the Basement membrane zone); deposition of IgA and IgM may also occur.

Indirect immunoflourescence :

Can be performed on blood, blister fluid or urine. About 75% have a circulating IgG auto antibody to the basement membrane zone.

5. IMMUNOBLOTTING :

Majority of patients have circulating auto antibodies that react with BP 180 and BP 230 antigens

6 . ELISA

Detects circulating auto antibodies to BP 180

Treatment

1. Topical / Intra lesional steroids
2. Systemic Steroids
3. Immunosuppresants

   Azathioprine 1-2.5mg / kg/ day

   Cyclophosphamide 1-3mg / kg / day

   Low dose methotrexate 5 - 10 mg / week

   Cyclosporine 5 mg / kg / day
4. Dexamethasone Cyclophosphamide Pulse therapy
5. Dapsone

6. Tetracycline and Nicotinamide
7. Plasmapheresis
8. IV Immunoglobulin

AIM OF THE STUDY

To study the compliance and complications of Dexamethasone Cyclophosphamide Pulse therapy in the management of Immunobullous diseases.

METHODS AND MATERIALS

This study was done at Government General Hospital, Chennai, during the period September 2004 – September 2006. This study included patients with Immunobullous diseases (Pemphigus Vulgaris and Bullous Pemphigoid) who were selected based on selection and exclusion criteria.

SELECTION CRITERIA

1. Patients with moderate to severe disease.
2. Patients whose disease activity was not controlled with systemic steroids and (or) immunosuppresives.
3. Patients who had completed their family
4. Patients who were willing to get admitted for the monthly cycles.

EXCLUSION CRITERIA

1. Patients with uncontrolled Diabetes Mellitus and Hypertension
2. Patients with H/o Myocardial infarction or compromised cardiac status.
3. Patients with hepatic (or) renal impairment
4. Patients with active Tuberculosis
5. Elderly > 60 years.

Details of History and Physical examination were recorded. Diagnosis was based on

a) Clinical features

b) Tzanck smear

c) Skin Biopsy

Informed consent was obtained from all the patients. Weight was measured at the time of enrollment and during subsequent admissions. A Grading based on the Fleischi criteria[85] was done at the time of first admission.

According to this criteria, the disease is considered

Severe - When the no. of bullae / erosions exceeds 40.

Moderate - When the no. of bullae / erosions is between 20 – 40

Mild - When the no. is less than 20.

The number of bullae or erosions were proportional to the percentage of the body surface area involved.

Laboratory evaluation done at the time of enrollment were

1) Complete haemogram

Hb, TC, DC, ESR , Platelet count

2) Blood Sugar

3) Blood Urea, Serum creatinine

4) Serum electrolytes

5) Liver function tests

6) Urine routine

7) Motion occult blood

8) Scraping for Candida (if the patients had oral lesions).

9) Pus culture and sensitivity

10) Urine culture and sensitivity

11) Blood grouping and typing

12) Chest X ray

13) Mantoux test

14) ECG, Cardiac evaluation

15) VDRL

16) ELISA for HIV

Ophthalmology and ENT opinion was obtained if necessary.

DCP was started only after controlling the infection with systemic antibiotics. If scraping was positive, patients were treated with systemic antifungals (Flucanazole 150mg orally biweekly for one week)

The regimen is given in four phases:

PHASE 1:

Dexamethasone (100mg dissolved in 500ml of 5% Dextrose) was given by slow intravenous infusion over 2 hours on 3 consecutive days along with Cyclophosphamide infusion 500mg on day 2. This constitutes one Pulse. These Pulses are repeated every 4 weeks. Between these pulses, patients were given 50mg cyclophosphamide once a day. This phase was continued till the patient attained remission.

Remission is defined as:

a) Disappearance of existing lesions.

b) Absence of fresh lesions

PHASE 2:

Four weekly pulses of Inj. Dexamethasone and Inj. Cyclophosphamide continued along with daily oral Cyclophosphamide for 6 months.

PHASE 3:

Four weekly pulses of Inj. Dexamethasone and Inj. Cyclophosphamide to be stopped and patient to receive only 50mg Cyclophosphamide orally daily for 1 year.

PHASE 4:

All the medications are stopped and the patients are followed up.

In this study, Phase 2 was given for 6 months (as followed in the old regime) to increase patient compliance.

Patients were admitted during each pulse. Complete haemogram, Blood sugar, Renal Function tests, Liver function tests, urine routine, serum electrolytes and ECG were repeated before every pulse. Regular monitoring of pulse and blood pressure were done during were done during the administration of the pulse. After the completion of each pulse, serum electrolytes and urine for RBCs was done. Chest x ray was repeated after every 6 pulses. The patients were followed for any adverse effects and relapse.

In this study, patients were given intermittent steroids depending on the severity of the disease. It was tapered according to the clinical response. Vitamin D injection was given after every 3 pulses and oral calcium was supplemented during the first two phases.

The patients were followed for any adverse effects and relapse.

OBSERVATIONS:

Twenty One patients with Pemphigus Vulgaris / Bullous Pemphigoid were enrolled for this study.

AGE / SEX DISTRIBUTION :

AGE (YRS.)	MALE	FEMALE
21 – 30	1	6
31 – 40	0	6
41 – 50	1	4
51 – 60	3	0

Majority of the patients were females (77%). Out of the 21 patients, 5 were males and 16 were females.

Among males, there was 1 each in the age group 21 – 30 yrs and 41 – 50 yrs, and 3 in the age group 51 – 60 yrs.

Out of the 16 females, 6 each were in the age group 21- 30 yrs and 31 – 40 yrs. 4 females were of the age group 51 – 60 yrs.

There was no male in the age group 31 – 40 yrs and no female in the age group 51 – 60 yrs.

CLINICAL TYPE :

	Male	**Female**
Pemphigus Vulgaris	1	14
Bullous Pemphigoid	4	2

15 patients out of the 21 patients had Pemphigus Vulgaris and the remaining 6 had Bullous Pemphigoid. Among patients with PV, 14 were females and only one was male. There were 4 males and 2 females among patients with Bullous Pemphigoid

AGE AND DISEASE DISTRIBUTION:

AGE (years)	**Pemphigus Vulgaris**	**Bullous Pemphigoid**
21-30	7	0
31-40	5	1
41-50	2	2
51-60	0	3

Majority of the patients (46.7%) with Pemphigus Vulgaris enrolled for the study belong to the age group 21–30 years. 5 patients with Pemphigus Vulgaris belonged to the age group 31–40 years and 2 patients belonged to the age group 41 – 50 years.

50 % of patients with Bullous Pemphigoid belonged to the age group 51-60 years, 1 patient belonged to the age group 31-40 years and 2 patients belonged to the age group 41-50 years.

GRADING OF SEVERITY

	PV	**BP**
Mild	0	0
Moderate	6	2
Severe	9	4

Severity of the disease was graded according to the Fleischi Criteria[85]. In this study, only patients with moderate and severe disease were enrolled. Out of 15 patients with Pemphigus Vulgaris, 6 had moderate disease while 9 had severe disease.

4 Patients with Bullous Pemphigoid had severe disease while 2 had moderate disease.

Duration of Disease Before Starting DCP.

DURATION (months)	MALE	FEMALE
0 – 6	2	3
7 – 12	2	5
13 – 18	0	5
19 – 24	1	2
25 – 30	0	1

The duration of the disease ranged from less than 6 months to 2 ½ yrs.

There were 2 males with disease duration ranging from 0 – 6 months and 7 – 12 months. 1 male had disease duration ranging between 19 – 24 months. Among the females, 3 had disease duration less than 6 months. With disease duration 7 – 12 months & 13 – 18 months, there was 5 females each ; 2 females with duration 19 – 24 months and 1 with duration 25 – 30 months.

DURATION OF INTERMITTENT STERIODS :

Out of the 21 patients, 19 patients received intermittent steroids. 2 patients with moderate Bullous Pemphigoid did not receive intermittent steroids.

Intermittent Steroids (Months)	PV	BP
0	0	2
1 – 3	10	4
4 – 6	4	0
7 – 9	1	0

10 patients with Pemphigus Vulgaris and 4 patients with Bullous Pemphigoid received intermittent steroids ranging from 1 – 3 months, 4 patients with Pemphigus Vulgaris received steroids for 4 – 6 months and 1 patient received it for 8 months. The last patient still has not attained complete remission.

RELATION OF DISEASE DURATION TO NUMBER OF PULSES:

DISEASE DURATION (months)	NUMBER OF PULSES
0-6	**4.2**
7-12	**5.1**
13-18	**5.5**
19-24	7
25-30	**7**

Patients with disease duration of less than 6 months attained remission faster,in 4.2 pulses. Those with disease duration 7-12 months needed 5.1 pulses, those with 13-19 months attain remission in 5.5 pulses. Patients with disease duration of more than 18 months took 7 pulses to attain remission

PHASE DISTRIBUTION:

PHASE	**PV**	**BP**
I	2	0
II	7	3
III	6	3

None of the patients have entered phase IV.

Out of the 15 patients with Pemphigus Vulgaris, 2 patients are in Phase I, 7 patients in Phase II, and 6 patients in phase III.

Among the Bullous Pemphigus patients, 3 patients each, are in Phase II and Phase III.

One patient with Pemphigus Vulgaris was lost to follow up during phase II.

PATTERNS OF REMISSION :

I : Moderate disease. May or may not require intermittent steroids. Attains remission faster $\leq$ 6 Pulses.

II : Moderate disease. Always requires intermittent steroids. Takes > 6 Pulses to attain remission

III : Severe disease. Requires intermittent steroids. Takes less than 6 Pulses to attain remission

IV : Severe disease. Requires intermittent steroids. Takes more than 6 Pulses to attain remission

2 patients have not attained complete remission.

Pattern of Remission	**No. of Patients**
I	6
II	1
III	8
IV	4

COMPLICATIONS :

IMMEDIATE

Immediate	No. of Patient	%
Palpitations	2	9.4
Diarrhoea	2	9.4
Hiccups	1	4.7
Psychosis	1	4.7

IMMEDIATE :

1. Palpitations : was noted in 2 patients. One of the patient had Mitral valve prolapse.

2. Diarrhoea : 2 patients developed diarrhea. Diarrhoea occurred within 2 hrs after starting the pulse.

3. Hiccups : Only one patient developed hiccups which started immediately on administering the pulse.

Psychosis : 1 patient who was emotionally stable before the pulse developed irrelevant talk on starting the pulse

DELAYED :

	No. of Patients	%	Appearance Average Pulses
Menstrual irregularities	4	26.6(F)	3.6
Weakness	5	23.5	2.5
Rise in Fasting Blood Sugar	3	13.1	6.5
Arthralgia	3	13.1	5
Infections	3	13.1	2.3
Hair loss	3	13.1	3.6
Headache	2	9.4	3
Taste loss	2	9.4	3.5
Weight gain	2	9.4	1.2
Avascular Necrosis	2	9.4	8.5
Increase in BP	2	9.4	3.5
Sleep disturbances	1	4.7	3
Striae	1	4.7	5
Blurring of vision	1	4.7	6

DELAYED :

1. Menstrual Irregularities :

2 patients developed amenorrhoea while other 2 developed decreased menstrual flow. These irregulauties were noted after an average of 3.6 pulses. This was the most common complication noted in this study.

2. Weakness :

This was one of the most common complication noted after administring pulse therapy. This was observed in 5 patients who developed it after an average of 2.5 pulses.

3. Rise in fasting Blood sugar

3 patients, including 1 known diabetic (who was on meal plan) had a rise in blood sugar level after an average of 6.5 pulses.

4. Arthralgia :

3 patients complained of vague pains and discomfort over the knee, ankle, hip joints after an average of 5 pulses. One patients also have severe back pain.

5. Infection :

3 patients developed infections after an average of 2.3 cycles.

6. Hair loss :

3 Patients noted reversible loss of hair after an average of 3.6 cycles.

7. Headache :

2 patients developed headache after an average of 3 cycles which was not related to any time of the day.

8. Loss of taste :

2 patients had partial loss of taste sensation after an average of 3.5 cycles.

9. Weight gain :

Weight gain (Significant) was noted in 2 patients. They had a weight gain of >10% of body weight.

10. Avascular Necrosis of head of femur:

2 patients developed avascular necrosis after an average of 8.5 pulses. One of the patient had completed phase II.

11. Rise in BP

2 patients developed significant rise in BP after an average of 3.5 pulses.

12. Sleep Disturbance :

1 patient developed difficulty in initiation of sleep, after 3 pulses.

13. Striae :

Only one patient developed striae after 5 pulses.

14. Blurring of vision :

1 Patient developed blurring of vision after 6 pulses.

DISCUSSION

The study included 21 patients with moderate to severe immunobullous disease (Pemphigus Vulgaris and Bullous Pemphigoid).

Majority (77%) enrolled for the study were females. Mean age group for Pemphigus was 32.06 years and for Bullous Pemhigoid was 49 years mean age for Pemphigus vulgaris and Bullous pemphigoid corresponds to that given in literature [73].

In the study done by Sachidanand et al[53], Pemphigus vulgaris, Pemphigus foliaceus, Bullous Pemphigoid, Dermatitis herpetiformis were included. This study only included patients with Pemphigus vulgaris and Bullous pemphigoid.

Intermittent steroids were given in between the pulses in the dose of 15-20mg to achieve a faster remission. Phase I was considered completed only when the patients did not require steroid supplementation and were free of the lesions between the pulses. In the study, it was given in 90.5% of the cases when compatred to the study by Lakshmi et al[28], where it was given in 45%. It was given for an average of 2.9 months.

Scalp and oral lesions were the last to respond and heal, in most of the patients as in the study by Lakshmi et al[28].

In the study, 19 patients (90.5%) attained complete remission. In the study by Sachidanand, 82%[53] attained complete remission. Among the 2 patients who attained compete remission, one patient has completed 9 pusles and the other patient has received only 3 pulses. The average pulses given to attain complete remission in this study was 5.4 pulses, as compared to the study by vikram et al[31] where the average was 6.5 pulses. In the study done by Sachidanand et al[53], 70% attained remission by the 3rd pulse, and in the study by Rao et al[28], it took an average of 8 pulses to attain complete remission.

Patterns of remission:

In the study, 4 patterns of remission were noted.

I. Moderate disease[85], may or may not require intermittent steroids, attained remission in less than 6 months.

II. Moderate disease, required intermittent steroids, attained remission in more than 6 pulses.

III. Severe disease[85], required intermittent steroids, attained remission in less than 6 pulses.

IV.Severe disease, required intermittent steroids, attained remission in more than 6 pulses.

This study was different from the patterns observed by Kanwar & Kaur[29] in that mild cases were not included and there was no cases of relapse.

PHASE:

The maximum number of patients are in Phase 2 (47.6%). None of the patients have reached Phase 4 due to the short duration of the study. The percentage of patients in Phase 1 is 9.5% and that in Phase 3 is 42.8%.

COMPLICATIONS:

Immediate: The immediate complications noted in our study were Palpitations 9.4%, Diarrhoea 9.4%, Hiccups 4.7%, Psychosis 4.7%. In the study by Bushan kumar and Rajesh Jain[34], the immediate complications were Palpitations 7.5%, Hiccups 6.1% and Psychiosis 3.6%.

Palpitations noted in the two patients subsided without any treatment. ECG taken immediately after the pulse showed only sinus tachycardia. Hiccups occurred at the rate of 5-6 per minute, which stopped completely within 24 hours. It was treated with Inj. Ondensetron. The patient who developed psychosis was given a short course of tricyclic antidepressants for 2 months. She did not develop psychosis during the subsequent pulses.

Delayed: The common delayed complications noted in our study were menstrual irregularities (26.6%), and weakness (23.5%).

These were the common complication noted by Bushan Kumar in this study[34].

Menstrual irregularities manifest as amenorrhoea or decrease in menstrual flow. Both the patients with amenorrhoea regained their menstrual flow spontaneously. Weakness, which manifested as lethargy, developed mainly in patients who were more than 40 years old. In three of the five patients, return to normalcy occured with the start of the phase 3.

Rise in fasting blood sugar occurred in 13.1% compared to 18% in the above study[34]. One of trhe patient was a diabeteic who was already on Inj. Insulin. With the increase in dosage of insulin levels, blood sugar levels returned to normal.

Arthralgia, which manifested as vague pains in the knee joint, ankle point, was noted in 13.1%, which was the same as that noted in the above study. Analgesics were given if the pain was severe.

Hairloss, was noted in 13.1%. The hair loss was diffuse which recovered partially during continuation of the pulses.

Infections noted in the study by Rao et al[28], were bacterial infections, viral (reactivation of herpes zoster), and fungal infections. In this study the infctions noted were vaginal candidaisis and urinary tract infction (one of the patient who developed infection was a diabetic). Rise in blood pressure was noted in 2

patients. They had normal blood pressure at the time of enrolment. This complication was noted in the study by Vikram et al[31]

Avascular necrosis of head of femur was noted in 9.4%. This complication was noted in the study by Rao et al[28]. The higher percentage of this complication in our study could be attributed to the longer duration of intermittent steroids in one patient, and to the history of trauma to the hip in another patient. Both the patients were in Phase II, when the complicatrion developed. They are maintened on analgesics and rest.

The other complications noted were infections (13.1%),Headache (9.4%), loss of taste sensation (9.4%), weight gain (9.4%), increase in blood pressure (9.4%), and striae (4.7%).

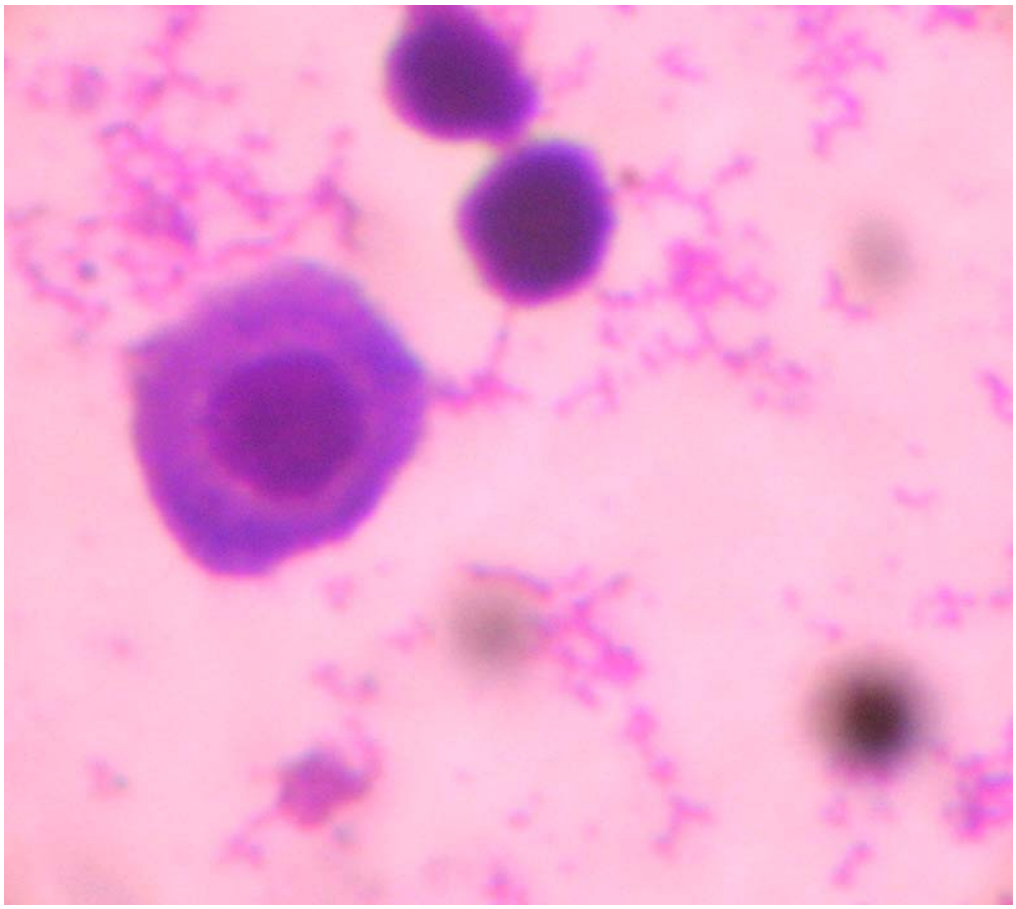
The head ache was diffuse and not related to any time of the day. It resolved within 2 or 3 days of the pulse. One patient had difficulty in initiation of sleep.

Weight gain was noted in 2 of the patients. Many of the patients developed weight gain during the period they received intermittent steroids, but after intermittent steroids were stopped, the weight returned to that at the time of enrollment.

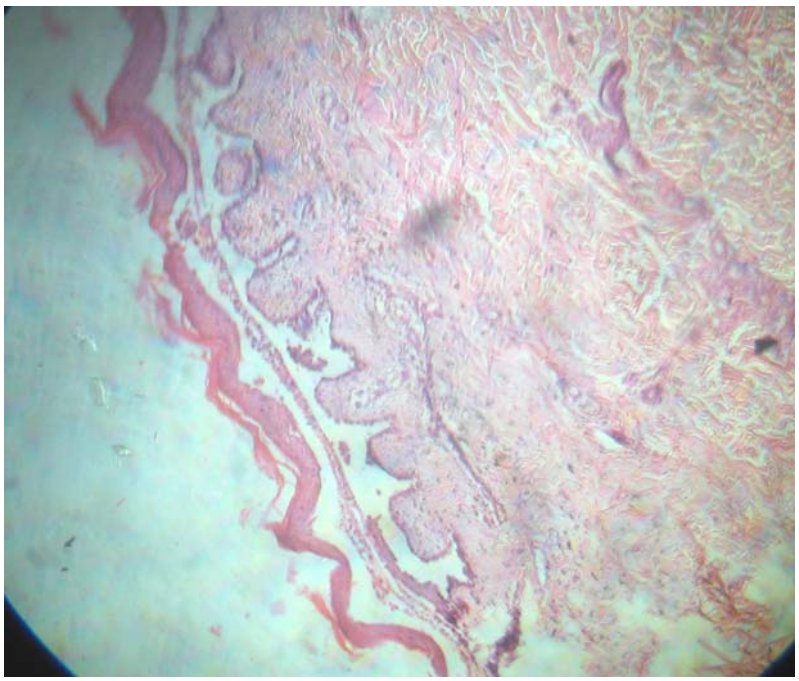
CONCLUSION

The results of the study indicate a high degree of positive outcome among patients diagnosed with immunobullous disease(Pemphigus vulgaris and Bullous Pemphigoid)

1) Clinical remission was achieved in 90.5% of the patients.
2) The time taken to attain complete remission was 5.7 pulses.
3) The response did not show much correlation with the severity of the disease.
4) There appeared to be correlation between the response and the duration of the disease at the initiation of therapy.
5) Patients with Bullous pemphigoid (irrespective of the severity and duration of disease) showed a faster response than Pemphigus vulgaris.
6) The common complications noted were menstrual irregularities and weakness. The other side effects noted in order of priority were arthragia, infections, rise in fasting blood sugar, palpitations, diarrhoea, head ache, taste loss, weight gain,avascular necrosis, increase in blood pressure, hiccups, psychosis, sleep disturbances, blurring of vision, stria. The serious complication noted was avascular necrosis of head of femur.
7) There was no cases of relapse or mortality associated with the therapy.

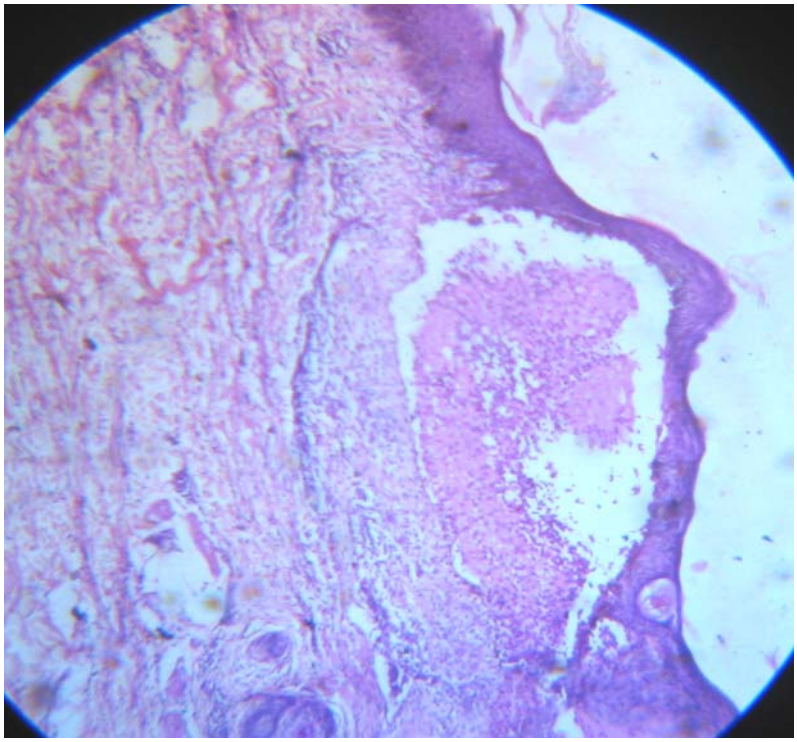


TZANCK CELL

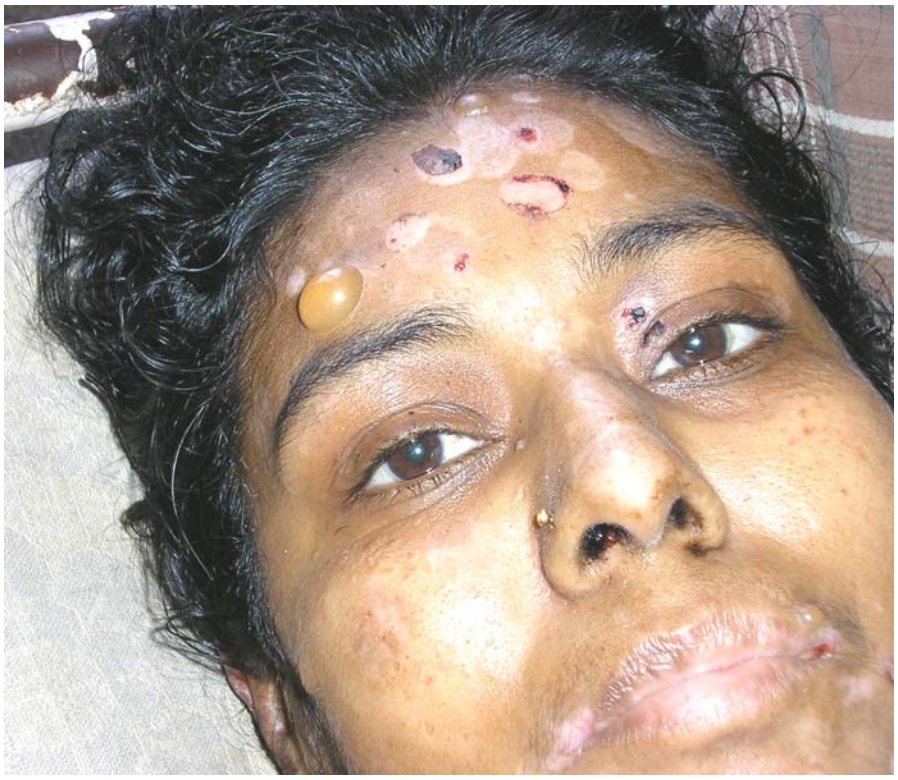


HP OF PEMPHIGUS VULGARIS SHOWING

SUPRABASAL BULLA

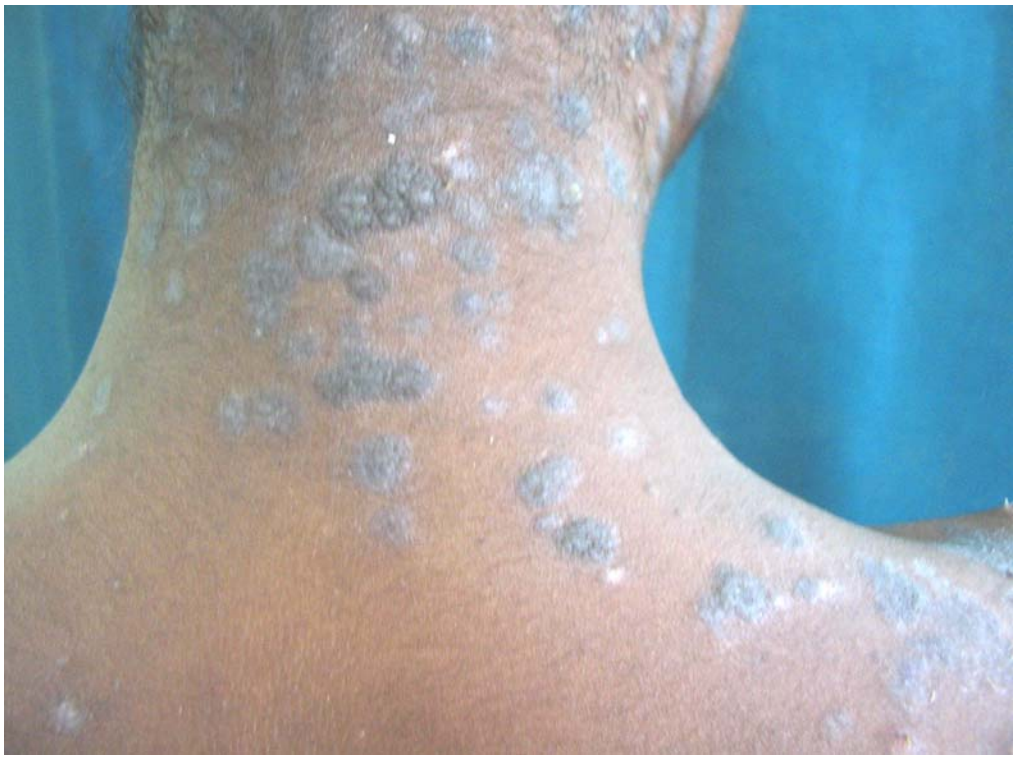


HP OF BULLOUS PEPHIGOID SHOWING SUB EPIDERMAL BULLA

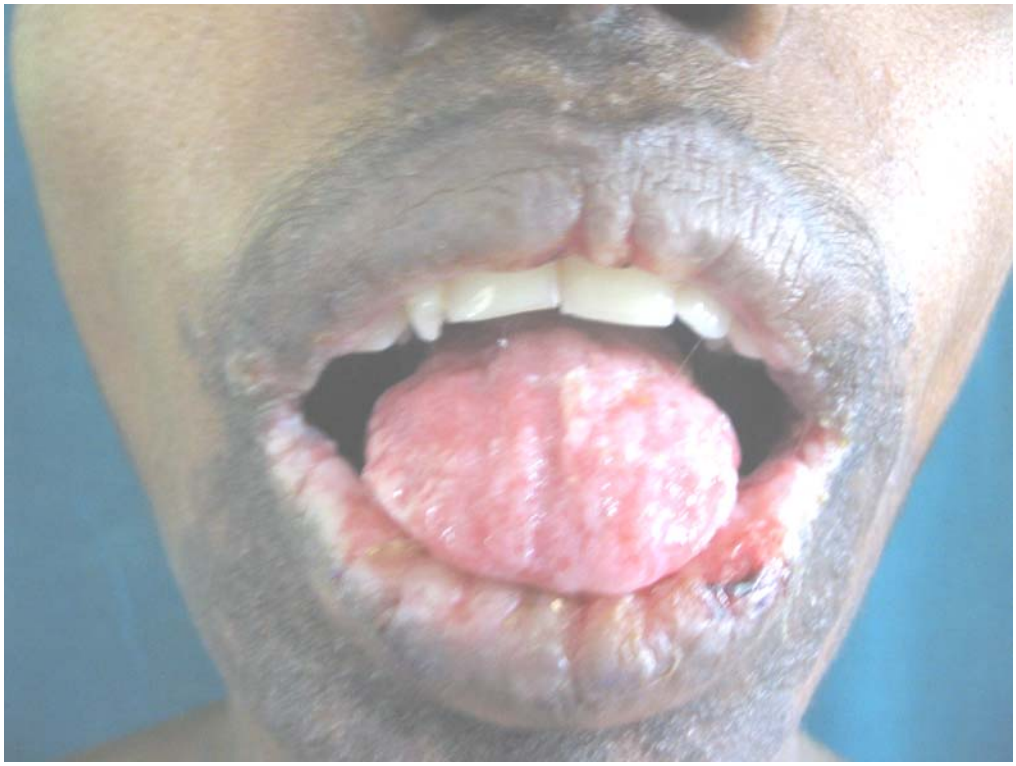


PATIENT WITH BULLOUS PEMPHIGOID BEFORE THERAPY

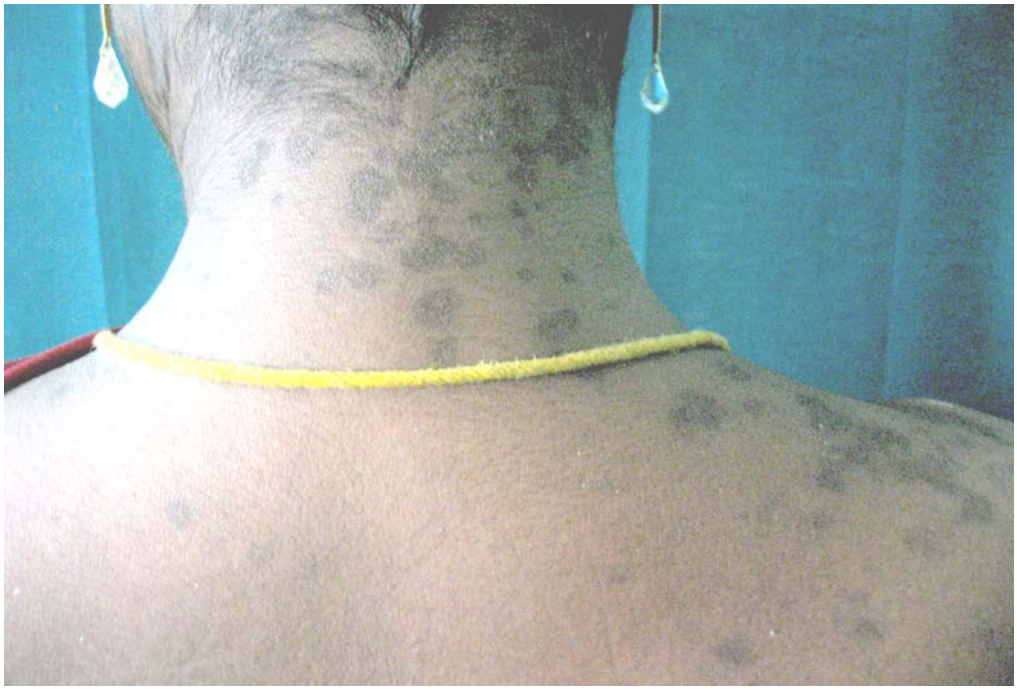
AFTER THERAPY



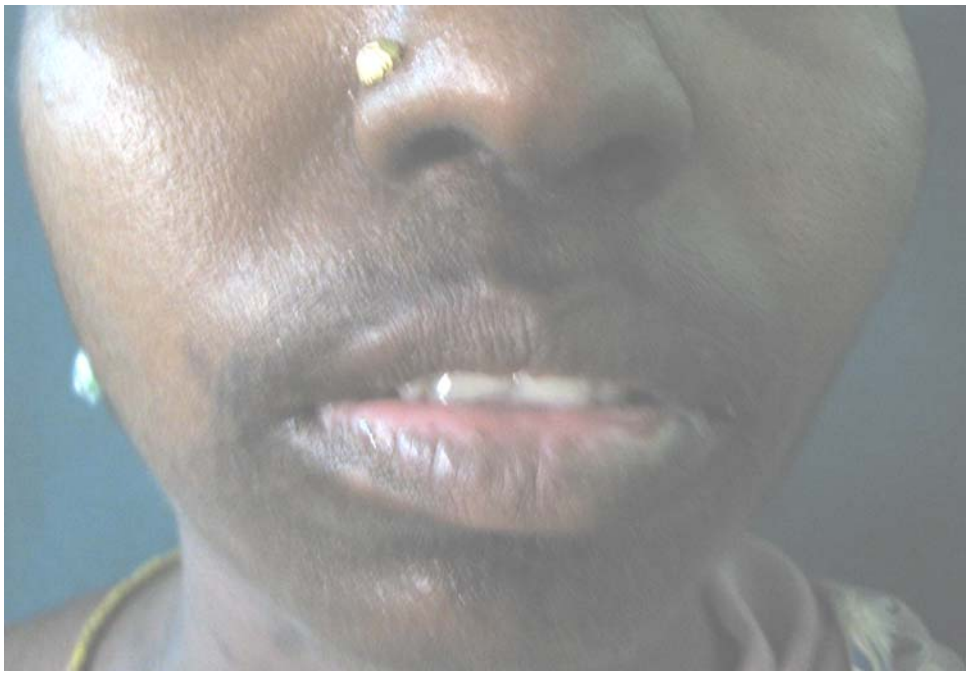
PATIENT WITH PEMPHIGUS VULGARIS BEFORE THERAPY

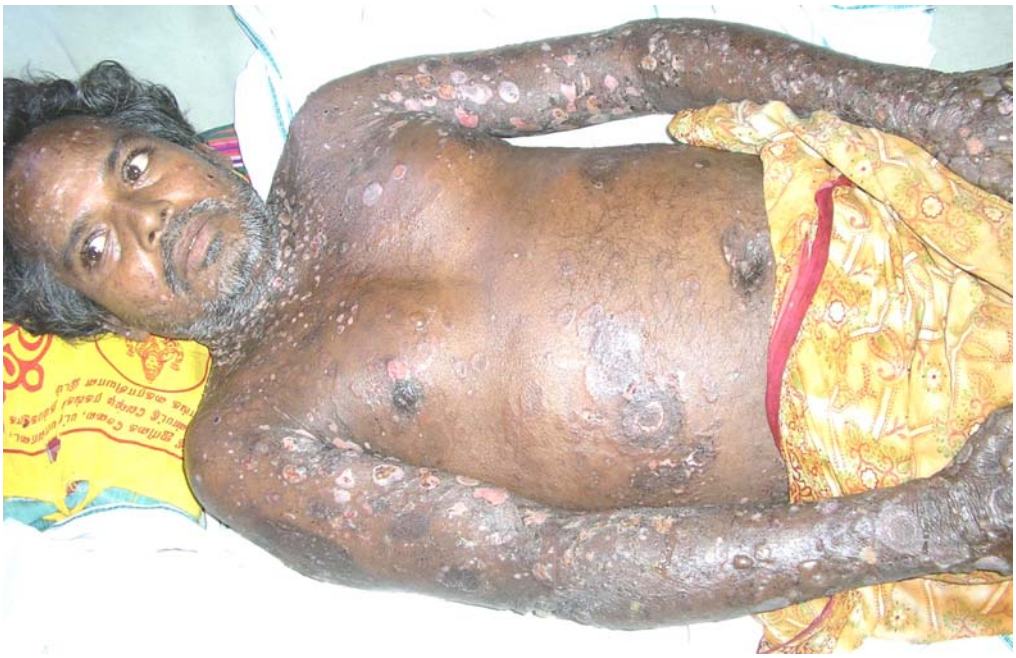


SAME PATIENT WITH ORAL LESION

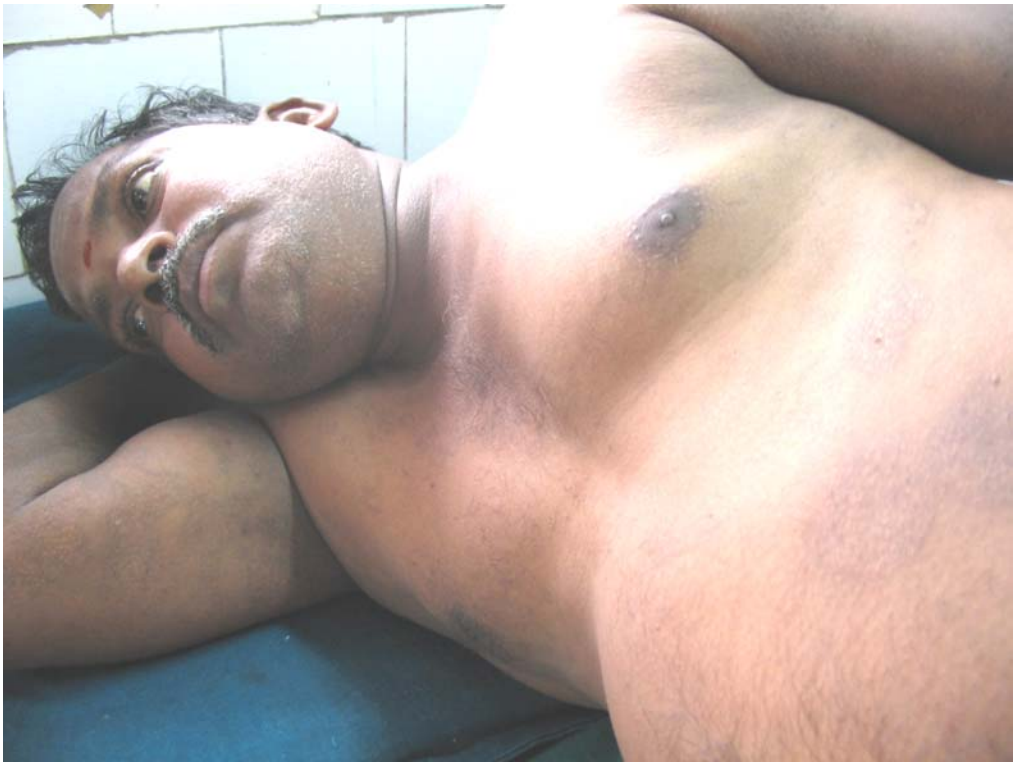


SAME PATIENT AFTER THERAPY

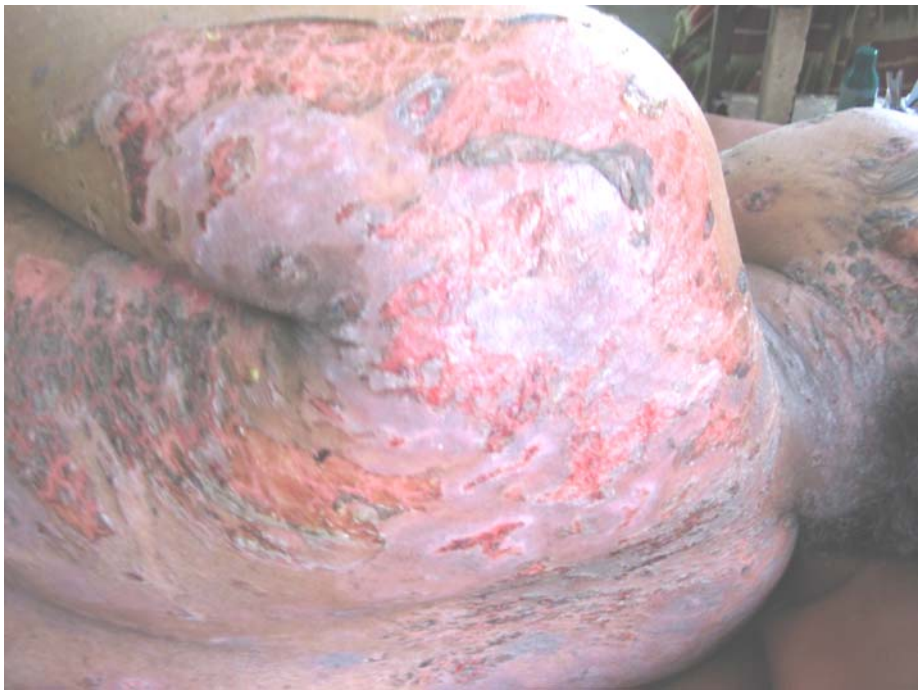




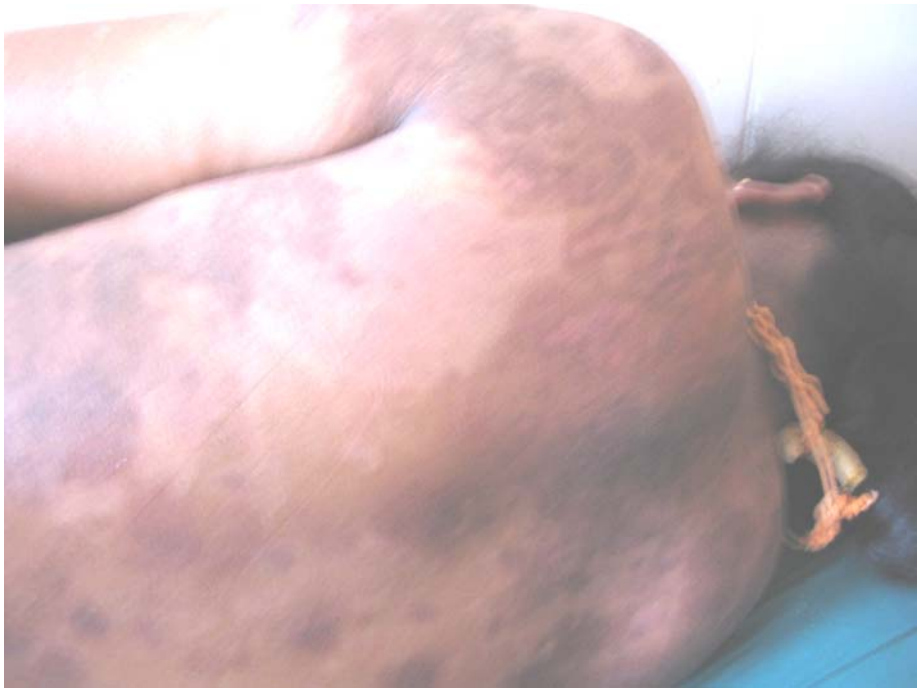
PATIENT WITH BULLOUS PEMPHIGOID BEFORE THERAPY



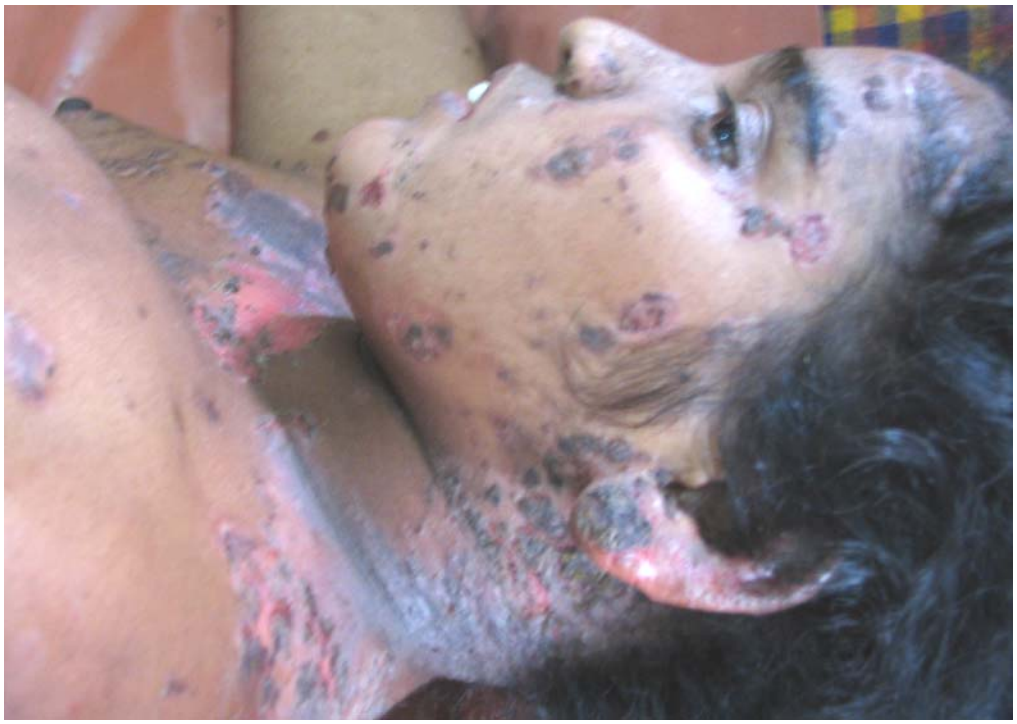
SAME PATIENT AFTER THERAPY



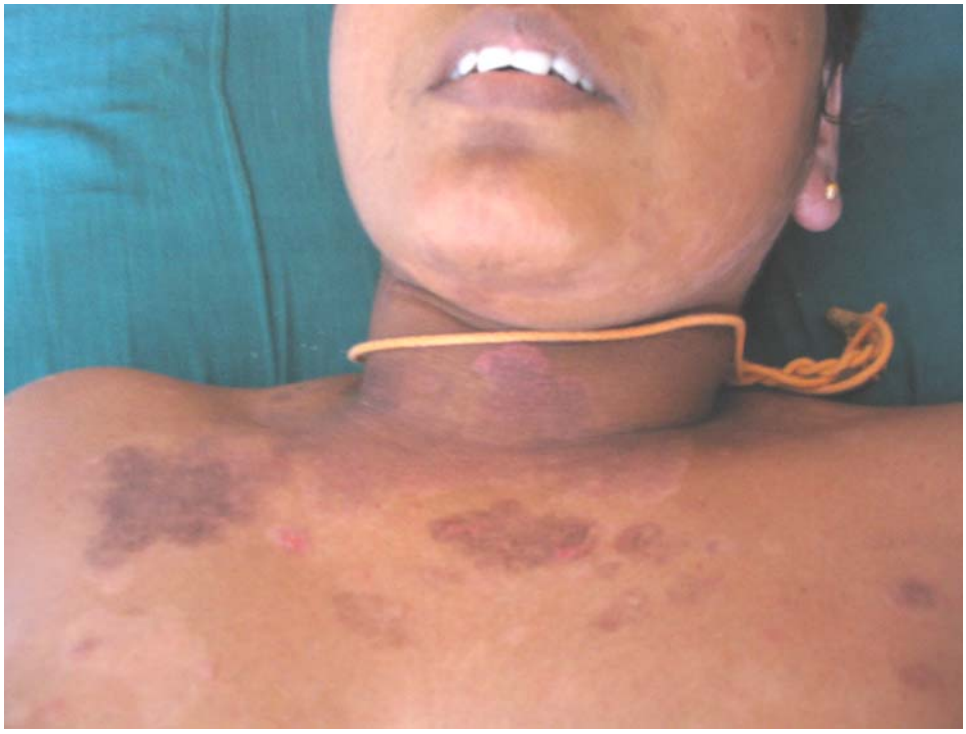
PATIENT WITH PEMPHIGUS VULGARIS BEFORE THERAPY



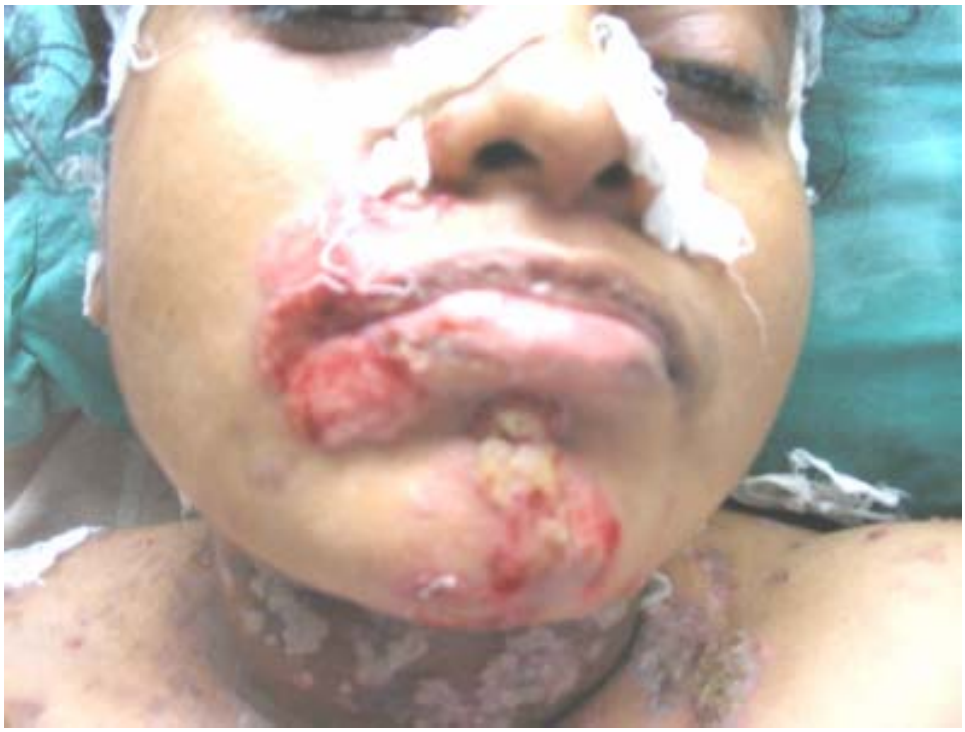
SAME PATIENT AFTER THERAPY



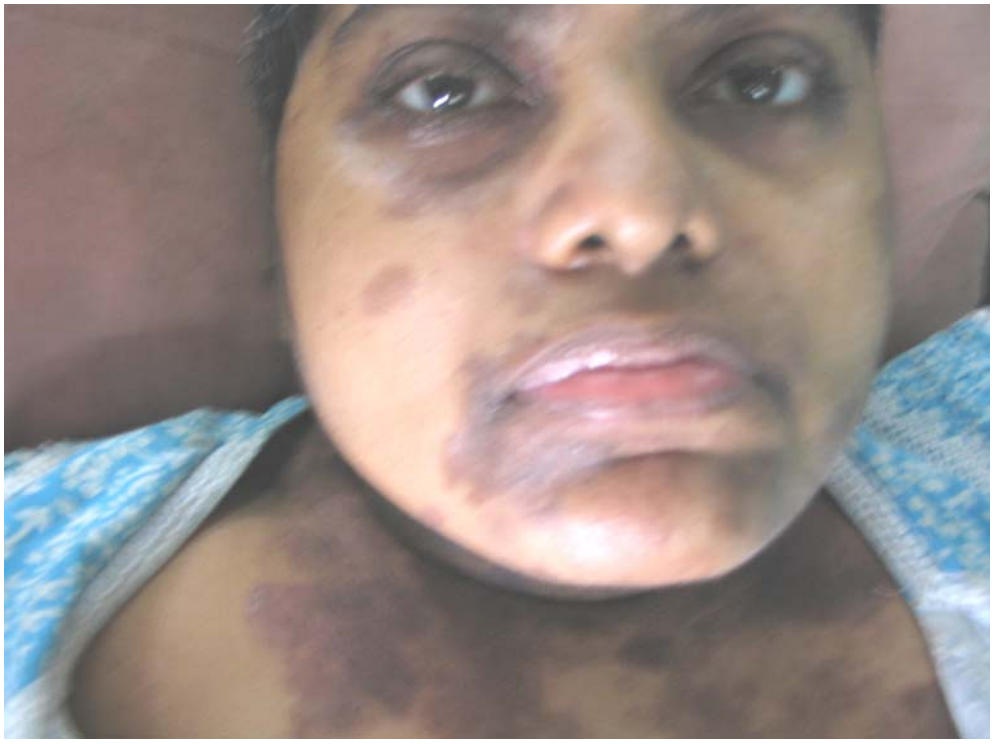
PATIENT WITH PEMPHIGUS VULGARIS BEFORE THERAPY



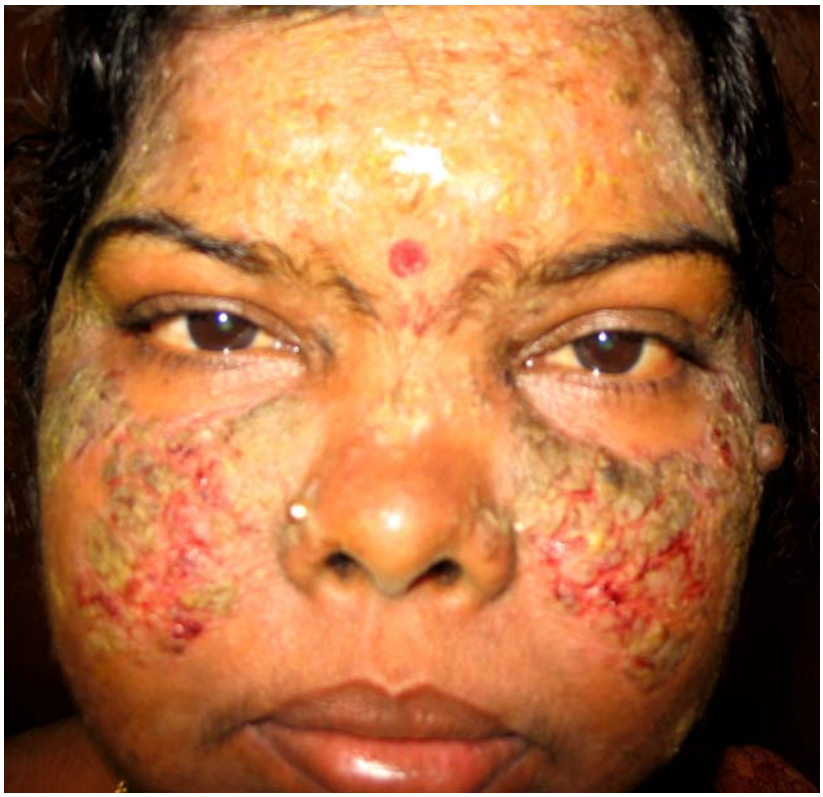
SAME PATIENT AFTER THERAPY



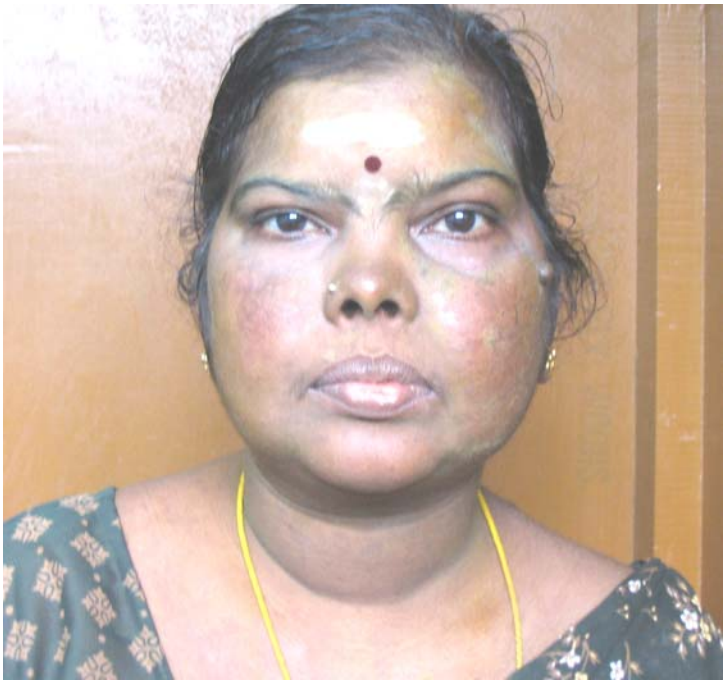
PATIENT WITH PEMPHIGUS VULGARIS BEFORE THERAPY



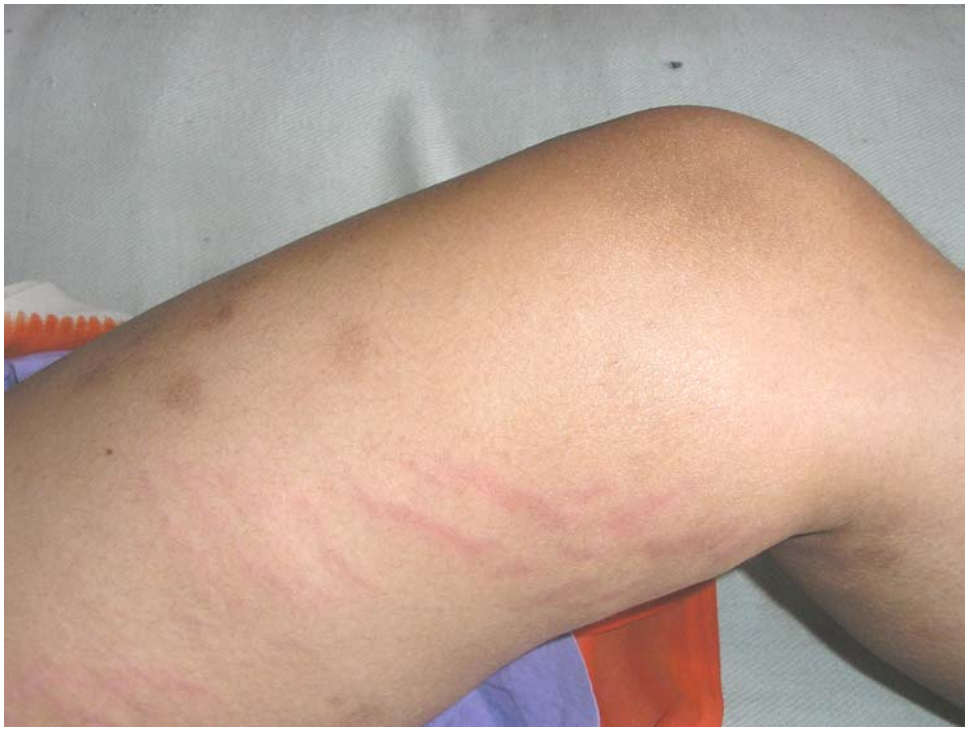
SAME PATIENT AFTER THERAPY



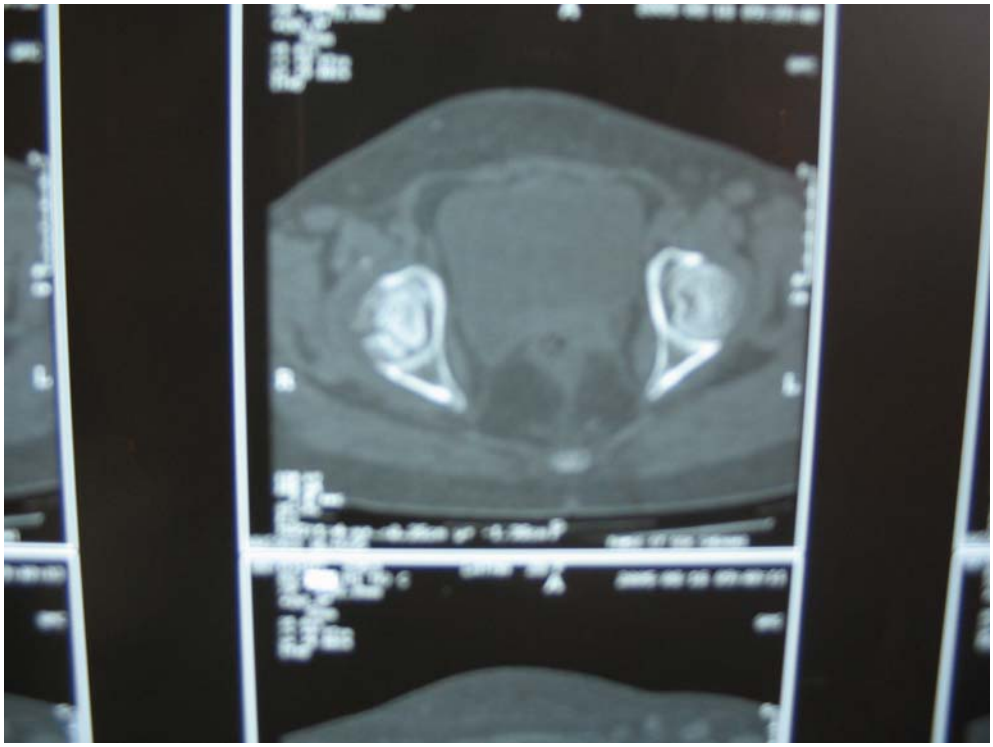
PATIENT WITH PEMPHIGUS VULGARIS BEFORE THERAPY



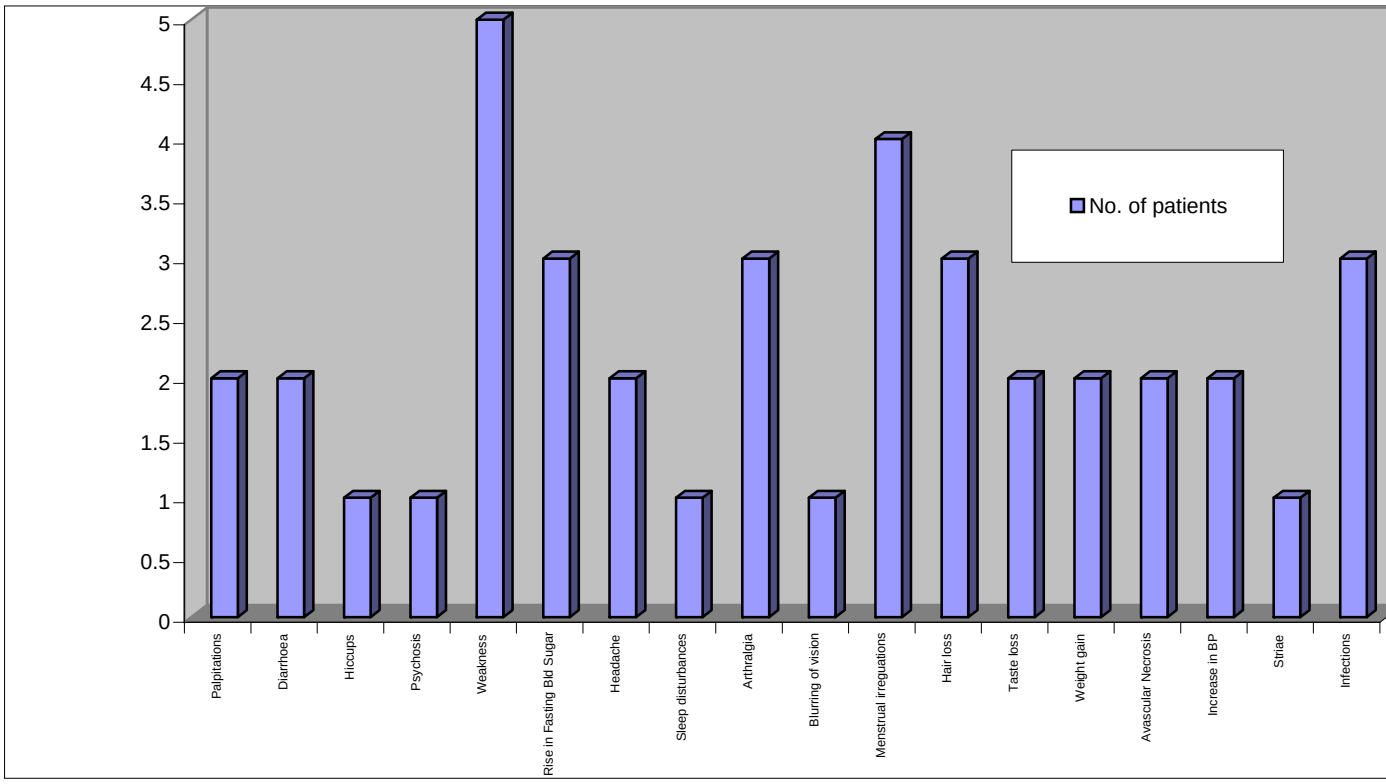
SAME PATIENT AFTER THERAPY



STREOID INDUCED STRIAE



AVSCULAR NECROSIS OF THE HEAD OF THE FEMUR


5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
No. of patients
Palpitations
Diarrhoea
Hiccups
Psychosis
Weakness
Rise in Fasting Bld Sugar
Headache
Sleep disturbances
Arthralgia
Blurring of vision
Menstrual irreguations
Hair loss
Taste loss
Weight gain
Avascular Necrosis
Increase in BP
Striae
Infections

INDEX TO MASTER CHART

DUR	:	Duration (Months)
S	:	Skin Lesions
MM	:	Mucous Membrane Lesions
ST	:	Steroids
C	:	Cytotoxic Drugs
V	:	Vesicle
B	:	Bulla
P	:	Pustule
E	:	Erosion
O	:	Oral
C	:	Conjunctival
G	:	Genital
N/E	:	Normal/Erythematous Skin
T/F	:	Tense/Flaccid
NS	:	Nikolsky Sign
D	:	Direct NS
M	:	Marginal NS
BSS	:	Bulla Spreading Sign
GR	:	Grading
MO	:	Moderate Grade
SE	:	Severe Grade
TZ	:	Tzanck Smear
HPE	:	Histopathological Examination
PV	:	Pemphigus Vulgaris
BP	:	Bullous Pemphigoid
IS	:	Intermittent Steroids
PI	:	Phase I
PII	:	Phase II
PIII	:	Phase III

AI	:	Area of Involvement
PR	:	Pattern of Remission
IC	:	Immediate complication
DC	:	Delayed Complication
Pa	:	Palpitation
H	:	Hiccup
Di	:	Diarrhoea
Ps	:	Psychosis
Mi	:	Menstrual irregularities
Rs	:	Rise in Fasting Blood Sugar
H	:	Headache
Sl	:	Sleep Disturbance
Ar	:	Arthralgia
Bv	:	Blurring of Vision
Hl	:	Hair Loss
Ts	:	Loss of Taste
Wg	:	Weight Gain
A	:	Avascular Necrosis
RB	:	Rise In Blood Pressure
St	:	Striae
In	:	Infection
W	:	Weakness

PROFORMA

NAME : **AGE:** **SEX:**

OCCUPATION: **IP.NO:**

ADDRESS:

COMPLAINTS: Skin Lesions : Duration
Oral Lesions : Duration

HPI: Blistering Skin Lesions : Duration

- Blisters Over Normal/Erythematous skin
- Ruptures immediately/after 2-3 days
- H/O Pruritis

H/O Oral Lesions : Duration
H/O Difficulty in swallowing
H/O Hoarsenses of voice
H/O Discharge/watering of eyes
H/O Burning micturition
H/O Loss of Weight/Apetite
H/O Drug Intake

Treatment H/O:

Diet H/O :

Past H/O : H/O Diabetes Mellitus/Hypertension/Tuberculosis/Myocardial Infection/Liver or kidney disease

Personal H/O: Married/Unmarried

No of Children

H/O Sterlisation

Menstrual H/O: Cycles
Regular/Not

Family H/O : Similar H/O among family members

GENERAL EXAMINATION:

- FEBRILE
- ANAEMIC
- JAUNDICE
- GEN LYMPHADENOPATHY
- PEDAL EDEMA

WEIGHT: **PULSE:** **BP:**

SYSTEMIC EXAMINATION :

CVS :

RS :

P/A :

D/E :

SKIN LESIONS :

Vesicles/Bulla/Pustules/Erosion

Vesicles / Bulla : Distribution
Over normal or erythematous skin
Tense or Flaccid
Clear or haemorrhagic
Nikolsky Sign: Direct or marginal
Bulla spreading Sign

Area of Involvement :

Post inflammatory Hypopigmentation or hyperpigmentation

Oral Lesions :

Ocular Lesions :

Genitalia :

Scalp :

Palms, Soles :

Nails :

Hair :

INVESTIGATIONS:

- Tzanck
- Histopathological Examination
- Complete Hemogram
- Blood Sugar
- Renal Function Test
- Serum Electrolytes
- Liver Function Test
- Urine – Routine
- Motion – Occult Blood
- ECG
- Chest X-ray
- Mantoux Test
- Pus C & S
- Urine C & S
- VDRL
- ELISA for HIV
- Scraping for Candida

COMPLICATIONS:

COMPLICATIONS	**PHASE I**	**PHASE II**	**PHASE III**
IMMEDIATE			
DELAYED			

BIBLIOGRAPHY

1. KOUNTZ SL, Cohn R, Initial treatment of renal allografts with large intrarenal doses of immunosuppressive drugs Lancet 1969:338-40

2. Cathcart ES, Idelson BA Schienberg MA, Courser WG. Beneficial effects of methyl Prednisolone Pulse therapy in diffuse proliferative lupus nephritis.Lancet 1976; 1:163-6.

3. Liebling MR McLaughlin K Blocka, K. Furst DE et al. Pulse Methyl Prednisolone in Rheumatoid Arthritis. Ann. Int med. 1981,94: 21-6.

4. Johnson RB Lazarus GS: Pulse therapy; Arch Dermatol 1982; 118;76-84.

5. Pasricha JS,Gupta. R Pulse therapy with dexamethasone Cyclophosphamide in Pemphigus. IJDVL 1990;56: 40-2.

6. Pasricha JS. Pulse therapy in Pemphigus, 2nd edition. New Delhi. Pulse therapy and Pemphigus Foundation.2000.

7. Esteban NV et al. Daily cortisol production rate in man determined by stable isotope dilution/ mass spectrometry.

8. Baldwin AS Jr. NF Kappa B and I Kappa B proteins. New discoveries and insights; Annual Rev Immunol 14:649, 1996.

9. Auphan N. Didonate JA Rosette et al: Immunosuppression by Glucocorticoids Science 270: 286,1995.

10. Flower RJ, Rothwel. NJ: Lipocortin l: Cellular mechanism and clinical relevance. Trends Pharmacol Sci 15:71,1994.

11. Croxtall JD etal: Lipocortin and control of cPLA2 Activity in A549 cells. Glucocorticoid block EGF stimulation of phosphorylation. Biochem Pharm 52: 351, 1996.

12. Pepinsky RB et al: 5 distinct calcium and phospholipids binding proteins share homology with lipocortin I. J. Biol Chem 263: 10799, 1988.

13. Wallner BP et al: cloning and expression of human lipocortin, a phospholipase A2 inhibitor with potential anti inflammatory activity. 320.77, 1986.

14. Cupps TR, Fauci AS: Corticosteroid mediated immunoregulation in man. Immunol Rev 65:133,1982.

15. Amano Y et al: Inhibition of Glucocorticoids of the formation of IL-1A, IL-1B, IL-6: Medication by decreased mRNA stability. Mol Pharmacol 43: 176, 1993.

16. Kilajima Tet al: A novel mech of Glucocorticoid induced immunosuppresion: the inhibition of Tcell mediated terminal maturation of a murine dendritic cell line J clin Invest 98: 142, 1996.

17. Baylis EM Williams IA, English J, MarksV, Chakaraborty J. High dose intravenous pulse methyl prednisolone therapy in patients with rheumatoid arthritis. Eur J Clin Pharmacol 1982:21:385-8.

18. Miller JJ. Prolonged use of intravenous steroid pulses in the rheumatic diseases of children. Paediatrics 1980:65:989-94.

19. Bijlsma JWJ, dursma SA,Bosch R, Raymakers JA, Huber Bruning O. Acute changes in calcium and bone metabolism during methyl prednisolone pulse therapy in rheumatoid arthritis. Br J rheumatol 1988:27:215-7.

20. Bijlsma JWJ, Dursma SA, Huber Bruning O. Bone metabolism during methyl prednisolone pulse therapy in rheumatoid arthritis. Ann Rheumatol Dis.1986:45:757-60.

21. Silverman ED, Myones BL, Miller JJ. Lymphocyte subpopulation alterations induced by intravenous megadose pulse methyl prednisolone. JRheumatol 1984:11:287-90.

22. Fan PT, Yu DTV, Clemente PJ,Fowlston. Effect of corticosteroids on the human immune response. Comparison of 1 and 3 daily 1gm intravenous pulses of methyl prednisolone. J Lab Clin Med 1978:91:625-34.

23. Ahmed AR Hombal SM. Cyclophosphamide: A review on relevant pharmacology and clinical uses. J Am Acad Dermatol 1984: 11: 1115-26.

24. Fox LP.Pandya AG. Pulse intravenous cyclophosphamide therapy for dermatologic disorders. Dermatol clin 2ooo: 18: 459-473.

25. Pan TD, McDonald CJ. Cytotoxic agents in comprehensive Dermatologic Drug Therapy. Edited by wolverton SE. W.B. Saunders Co. Pp.180-204.

26. Ho V, Zloty D. Immunosupressive agents in dermatology. Dermatol Clin. 1993:11:73-85.

27. J.S Pasricha, Pulse therapy as a cure for autoimmune diseases. IJDVL, Sep – Oct 2003 Vol 69, Issue 5.

28. Pulse therapy and its modification in Pemphigus, a six years study: P.Narasimha Rao, Lakshmi, IJDVL, Sep – 2003, Vol.69, 5:329 - 334

29. Long term efficacy of Dexamethasone Cyclophosphamide Pulse Therapy in Pemphigus. Amrinder J.Kanwar, Sukhjot Kaur. Dermatology 2002: 204: 228 – 231

30. Raman. Dexamethasone pulse therapy in Dermatology. IJDVL, 2003, Vol-69, Issue 5, 1-3.

31. Vikram K.Mahajan, Twelve year clinico therapeutic experience in Pemphigus: retrospective study of 54 cases.

32. Pasricha JS. AIIMS experience. Pulse therapy in pemphigus and other diseases. New Delhi: Pulse therapy in pemphigus Foundation; 2000,p21-40.

33. Chiou YM, Lan,Heish TY,etal. Spontaneous Achilles tendon rupture in a patient with SLE due to ischemic necrosis after methyl prednisolone pulse therapy. Lupus 2005;14:321-5.

34. Immediate and delayed complications of Dexamethasone Cyclophosphamide pulse therapy, Rajesh Jain and Bushan Kumar. Journal of Derm Vol 30: 713 – 718, 2003.

35. Kanwar AJ,Kaur S, Dhar S, Hiccup- a side effect of pulse therapy. Dermatology 1993;187:279.

36. Dhar S, Kanwar AJ, Facial flushing-a sidfeeffect of pulse therapy. Dermatology 1994;188:332.

37. Chrousos GA, Kattah JC,Beck RW, Side effects of Glucocorticoid treatment. Experience of the optic neuritis treatment trial. JAMA, 269;21102112,1993.

38. Kennedy B, Ziegler MG: Cardiac epinephrine synthesis. Regulation by a glucocorticoid, Circulation, 84: 891-895,1995.

39. Wilson KS, Gray CE, Parker AC: Recovery of HPA axis after intermittent high dose prednisolone and cytotoxic chemotherapy, Post Grad Med J, 53:745,1977.

40. Pentikainen PJ: Pharmacological aspects of corticosteroid pulse therapy, Scand J Rheumatology,54:6-9,1984.

41. Reckart MD, Eisendrath SJ: Exogenous corticosteroid effects on mood and cognition, Int Psychosom, 37:57-61,1990.

42. Kaufman M,Kahaner K, Peselow ED: Steroid psychoses: A case report and brief over view, J clin Psychiatry, 43: 75-76,1982.

43. Born J, Dekloet ER, Wenz H, etal. Glucocorticoid and mineralocorticoid effects on human sheep: A role of central corticosteroid receptors, Am J Physiol, 260:E183-E188, 1991.

44. Gardner DG, Hane S, Trachowsky D,et al: Atrial natriuretic peptide mRNA is regulated by glucocorticoids in vivo, Biochem Biophys Res Commun,139:1047-1054,1986.

45. Shields PP,Dixon JE, Glembotski CC: The secretion of atrial naturietic factor by cultured cardiac myopcytes is regulated by glucocorticoids, J Biol Chem,263;12619-12628,1988.

46. Bonnote B, Chauffert B: Side effects of High Dose Intravenous Methyl Prednisolone therapy cured by potassium infusion. Br.J Rheu 37: 109, 1998

47. Pasricha JS, Gupta R. Pulse therapy with dexamethasone cyclophosphamide in pemphigus. Indian J Dermatol Venereol Leprol 1984;50:199-203.

48. Pasricha JS, Srivastava G. Cure in pemphigus a possibility. Indian J Dermatol Venereol Leprol 1986;52:185-6.

49. Pasricha JS, Thanzama J, Khan UK. Intermittent high dose dexamethasone cyclophosphamide pulse therapy for pemphigus. Br.J Dermatol 1988;119:73-7.

50. Pasricha JS, Seetharaman KA, Das U. Further studies on pemphigus patients treated with dexamethasone cyclophosphamide pulse therapy for pemphigus,.IJDVL 1989;55;98-104.

51. Pasricha JS, Das SS. Curative effect of dexamethasone cyclophosphamide pulse therapy for the treatment of pemphigus vulgaris. Int J Dermatol 1992;31;857-82.

52. Pasricha JS, khaitan BK, Raman SR, Chandra M. Dexamethasone cyclophosphamide pulse therapy for pemphigus vulgaris.Int J Dermatol 1995;34;875-82.

53. Sachidanand, NC. Hiremath. Dexamethasone Cyclophosphamide pulse therapy for auto immune vesiculobullous disorder at Victoria Hospital, Bangalore, Dermatology online journal Vol 9, No.5.

54. Kreuter A, Gambichler T,Breukmann F, et al. Pulsed high dose corticosteroids combined with low dose methotrexate in severe localized scleroderma. Arch Dermatol 2005;141;847-52.

55. Pasricha JS, Reddy R, Nandakishore TH, Khera V, Pyodema gangrenosum treated with dexamethasone pulse therapy. Indian J Dermatol Venreolo Leprol 1991;57:225-8.

56. Gettler S,Rotho M,Grin C, et al. Optimal treatment of pyoderma gangrenosum.Am J Clin Dermatol2003;4:597-608.

57. Sharma V K, Murlidhar S, Treatment of widespread alopecia areata in young patients with monthly oral corticosteroid pulse. Pediatr dermatol 1998:15:313-7.

58. Seiter C, Ugurel S, Tilgen W, et al. High dose corticosteroid therapy in the treatment of severe alopecia areata. Dermatology 2001;202:230-4

59. Al Mutairi N, Joshi A, Zaki,etal. Acute generalized lichen planus treated with weekly betamethasone 5mg oral minipulse therapy.J Drugs Dermatol 2005;4:218-20.

60. Verma KK, Prurigo nodularis treated with dexamethasone pulse therapy. African J Dermatol 1994;1;27-8.

61. Singh OP, Verma KK. Discoid lupous erythematosus treated with dexamethasone pulse therapy.IJDVL 1991;57:311.

62. Verma KK, Singh OP, Dexamethasone pulse treatment in disseminated porokeratosis of Mibelli. J Dermatol Sci 1994;7:71-2.

63. Pandhi RK, et al. Multicentric Reticulohistocytosis. Response to Dexamethasone pulse therapy. Arch Dermatol 1990; 126: 251-2

64. Worm M,muche M, Schulze P,Sterry W, Hypocomplementemic urticarial vasculitis. Successful treatment with cyclophosphamide dexamethasone pulse therapy. Br J Dermatol 1998;39:704-7.

65. Vandermeer JB, et al. Successful Dexamethasone Pulse therapy in toxic epidermal necrolysis patient. Clin Exp dermatol 2001; 26: 654-6.

66. Shada B,Kumar A, Kakker R, Adya CM,Pande I,Uppal SS, et al.Intravenous dexamethasone pulse therapy in diffuse systemic sclerosus.

A randomized placebo controlled study. Rheumatol Internal 1994;145:91-4.

67. Pai BS et al. Efficacy of Dexamethasone pulse therapy in progressive systemic sclerosis. Int J Dermatol 1955; 34: 716-8.

68. Kanekura T. A case of Lupus Meningitis treated successfully with methyl prednisolone pulse therapy. J Dermatol 1993; 20: 566 – 71.

69. Vaisman M, Violante Alice HD, Conceicao Flavia L, et al. High dose intravenous pulse therapy with methylprednisolone and orbital irradiation in Grave's ophthalmopathy. The Endocrinologist 2001; 11:53-56.

70. Chen Hsin-Hsu, Liu Po-Mai, Bong Chin-Nam, et al. Methylprednisolone pulse therapy for massive lymphadenopathy in a child with intravenous immunoglobulin- resistant Kawasaki disease. J.Microbial Immunol Infect 2005; 38:149 – 52.

71. Hotta. O. Tonsillectomy combined with steroid pulse therapy: A curative therapy for IgA nephropathy. Acta Oto-Laryngologica 2004; 124:43-8

72. Sood A, Midha V, Sood N, et al. A prospective open-label trial assessing Dexamethasone pulse therapy in moderate to severe ulcerative colitis. J Clin Gastroenterol 2002; 35: 328-31

73. Wilson C, Mehra NK et al. Pemphigus in oxford, U.K & New Delhi a comparative Study of disease characteristics and HLA antigen dermatology 1994; 189: 108-10

74. Adam BA, Bullous diseases in Malaysia. Epidemiology and natural history. Int J dermatol 1992; 31: 42-5

75. Korman NJ. Pemphigus. Dermatol Clin 1990., 8:689 – 700

76. Miyagawa S, et al. HLA DRB1 Polymorphisms and auto immune responses to Desmogliens in Japanese with Pemphigus. Tissue antigen 1999; 54: 333-40.

77. Memar OM, et al. Human herpes virus 8 DNA sequences in blistering skin from patients with Pemphigus. Arch dermatol 1997; 133: 1247 – 51

78. Lateef et al. Pemphigus vegetans in association with HIV. Int J Dermatol 1999; 38: 778-81
79. Amagai et al. Auto antibodies against the aminoterminal cadherin like binding domain of Pemphigus Ag are pathogenic J.Clin. Invest 1992; 90: 919-26

80. Bhol Ahmed AR. Correlation of subclasses of IgG with disease activity Pemphigus vulgaris. Dermatology 1994; 189: 85-9

81. Kawana S, et al. Deposition of membrane attack complex of complement in pemphigus vulgaris. Invest dermatol 1989; 92: 588-92

82. Kraine LS. Pemphigus: epidemiological & survival characteristics of 59 patients. 1995-73. Arch Dermatol 1974; 110: 862-5

83. Hale EK. Laryngeal and nasal involvement in Pemphigus vulgaris. J. Am acad dermatol 2001; 44: 609-11

84. Goodman H. Nikolsky sign. Arch dermatol 1953; 68: 334-5

85. Fleischi ME. Pulse Cyclophosphamide therapy in Pemphigus. Arch dermatol 1999; 135: 57 – 61.

86. Lever W. Pemphigus & Pemphigoid. Spring field; Thomas, 1965

87. Anhalt H, et al. Pathogenic effects of Bullous pemphigoid auto antibodies on rabbit corneal epithelium. J.Clin Invest 1981; 68:1097-101

88. Muller S Stanley J. A 230 KD basic protein is the major Bullous pemphigoid antigen. J Invest dermatol 1989; 92: 33-8

89. Guidice, Diaz I. Cloning and primary structural analysis of Bullous pemphigoid auto antigen BP 180. J Invest dermatol 1992; 99: 243-50

90. Liu Z, et al., A major role for neutrophils in experimental Bullous pemphigoid J Clin Invest 1997; 100: 1256-63.

91. Hausten UF. Localised non scarring bullous pemphigoid of vagina. Dermatological 1998; 176: 200-1