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Treatment of Nephrotic Syndrome

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(1) DEFINITION OF NEPHROTIC SYNDROME:

The nephrotic syndrome is a clinical state in which gross proteinuria, always selective but to a varying degree is present with "mirror-image" hypoproteinemia. Edema, ascites and hyperlipemia are usually present. Systemic hypertension, azotemia, hypocomplementemia and excessive erythrocyturia are sometimes present.

Thus defined, the nephrotic syndrome can readily be classified into three groups, the treatment of which must be considered separately.

(1) Congenital Nephrotic Syndrome.

(2) Secondary Nephrotic Syndrome.

(3) Idiopathic Nephrotic Syndrome.

CONGENITAL NEPHROTIC SYNDROME: (CNS)

This consists of at least four types which may be defined thus:

(1) Finnish Type

(2) Mesangial Type

(3) Focal Glomerulosclerosis

(4) Congenital Syphilis

The Finnish type is inherited as a Mendelian recessive pattern; the infants are extremely vulnerable to infection and usually die aged 3-15 months. The histology is minimal change at first with smudging of foot processes on electron microscopy proceeding to glomerular obsolescence

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with progressive sequential microcystic changes in the renal tubules. The mesangial type is rarer and the patient usually dies of renal failure in the first year of life. The mesangium of the glomeruli shows a progressive hyalinization. The rare form with focal glomerulosclerosis may live for a number of years. Syphilitic nephrosis should be prevented by antenatal screening of the mother and treatment of the infection with penicillin and will not be considered further.

Treatment of all forms of CNS is overshadowed by the gross edema and the extreme hypogammaglobulinemia produced by the small molecular proteinuria. These two factors make such babies extremely vulnerable to lethal bacterial infection such as meningitis, pyelonephritis and peritonitis. Whilst it is tempting to give prophylactic antimicrobial therapy the end result of this is most likely to be infection with a resistant organism. If close supervision is *not* possible then sulphadimidine in dosage of 25 mg/Kg given three times daily is advised. If close supervision is possible, infection should be treated vigorously as it arises, usually by benzylpenicillin.

Unfortunately, administration of gamma globulins is of very transient value since the small molecules rapidly leak out in the urine. Similarly intravenous albumin is of transient value.

Treatment is therefore symptomatic, that is the avoidance and treatment of infection, the feeding by a low sodium milk (e.g. Edosol), and diuretic therapy as required. The diuretics used may be chlorothiazide (125-500 mg) and spironolactone-A (25 mg) given six-hourly, or frusemide (10-20 mg) six-hourly. The level of plasma potassium should be monitored carefully and supplementary potassium given as required during such diuretic therapy.

CNS is much commoner in Finland than anywhere else and Hallman and his colleagues have pioneered attempts to hemodialyse and then transplant such infants who are otherwise doomed to die. Such herotic efforts are somewhat improving the length of survival and life but research and further improvements are desirable.

SECONDARY NEPHROTIC SYNDROME: (SNS)

This term is used when a known primary clinical condition or disease is causal. The simple classification used is:

(1) Collagen Diseases

Disseminated lupus erythematosus, anaphylactoid purpura and polyartertis nodosa.

(2) **Quartan Malaria**

(3) **Toxic Substances**

These include calomel, envenomation, troxidone and other drugs, immunization and bee-sting.

(4) **Post Nephritic**

A rare sequel to acute nephritis.

(5) **Diverse Rare Causes**

These include amyloidosis, sickle cell disease, bacteremia, renal venous thrombosis and diffuse sarcomatosis.

The existence of an unknown cause of secondary nephrotic syndrome should always be suspected if the age incidence of the disease differs significantly from that of the classical series of Barnett et al. (1952). Prior to 1956 in the Glasgow area, some 20 % of children with nephrotic syndrome presented aged 3-12 months as opposed to 2 % in Barnett's series. Investigation incriminated intake of Calomel (HgCl) and removal of this from "teething powders" sold in local shops was followed by a return of the age incidence in Glasgow to standard. Later, Hendrickse applied this method of comparing age incidence in Nigeria where the older age incidence was found to relate to causal quartan malarial infection.

With so many diverse causes only a few brief notes on treatment are possible. In general the basic treatment is that of the primary illness (such as anaphylactoid purpura or diabetic glomerulosclerosis) with symptomatic treatment for the secondary nephrotic state using diet, diuretics and antimicrobials as for INS. Corticosteroids and cytotoxic drugs are rarely of help. An exception is in disseminated lupus erythematosus in which prolonged intensive prednisolone therapy may benefit both the primary DLE and secondary nephrotic syndrome for a considerable but limited period.

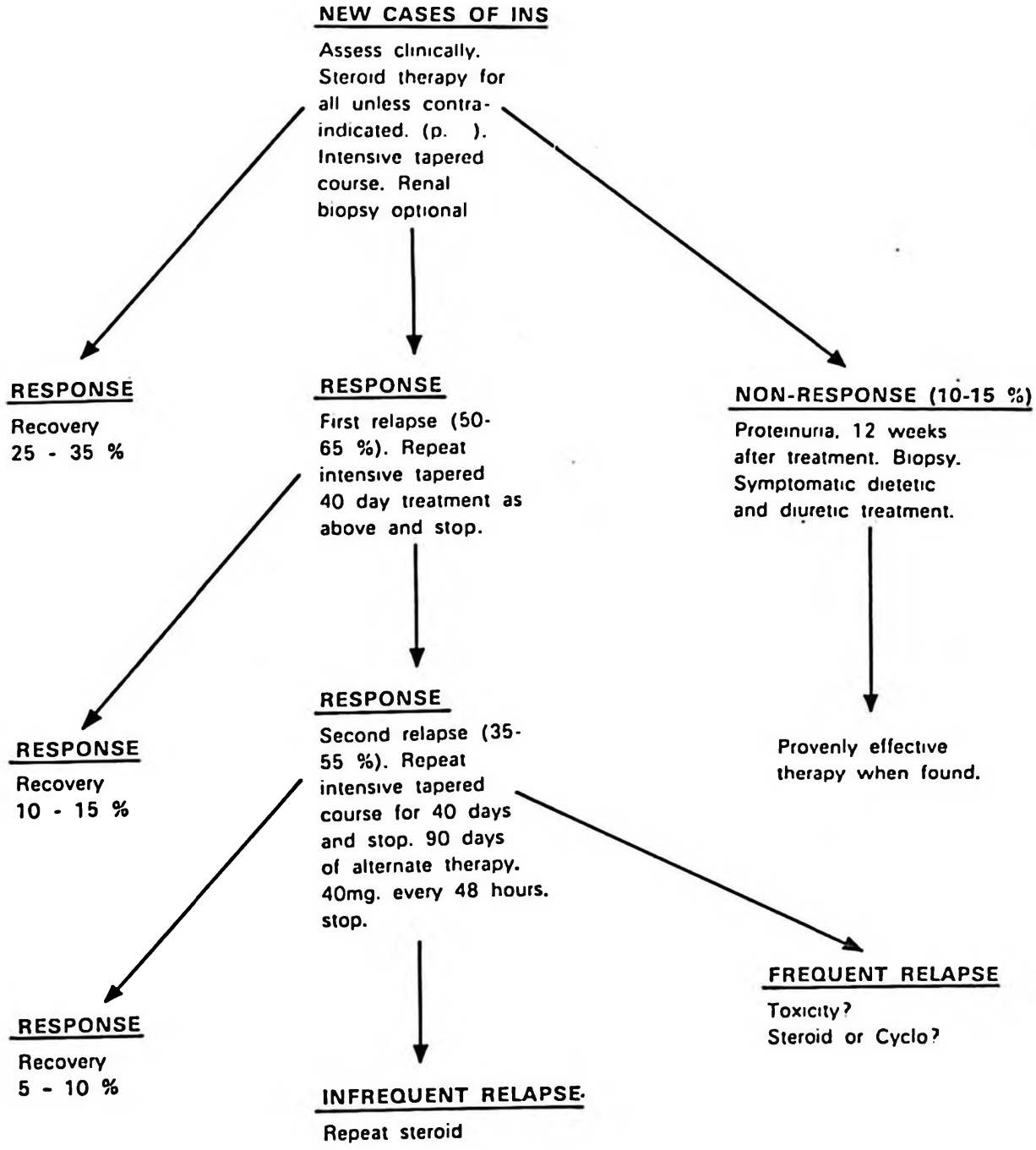
Optimal results for secondary nephrosis lie in elimination or avoidance of causel chemicals (e.g. calomel), drugs (e.g. troxidone), envenomation (e.g. snakes, spiders and bees) and pollens. The use of prednisolone may then precipitate recovery. Eventually these children will recover or die of the primary disease or proceed to chronic renal failure, the treatment of which will require to be reviewed in the light of the primary illness.

Quartan Malaria Nephrosis (QMN) seems to be an extremely complex subject which deserves separate consideration. It seems that

they vary in degree of severity (Hendrickse et al. 1972). Most patients have poorly selective proteinuria and respond poorly to anti-malarial and conticosteroid therapy. A characteristic finding on histology is segmental glomerular sclerosis and thickening of capillary walls. Globulin deposits are found on immunofluorescent examination. It seems that this disease is an immunologically mediated disorder caused by quartan malarial infection which once started can only be treated symptomatically if severe in type. Milder cases may respond to prednisolone therapy.

IDIOPATHIC NEPHROTIC SYNDROME: (INS)

This is by far the commonest type of nephrotic syndrome to occur in the children and probably accounts for 90% or more of the total,



save in countries such as Finland and Nigeria where a specific entity such as CNS or QMN is present. Treatment of this fascinating illness should be considered under the following headings:

(1) **Social Factors**

Home or hospital? Distance and travel. Financial considerations. Psychological aspects.

(2) **Dietetic Treatment**

(i) Initially: low sodium + high protein

(ii) On steroid: eucaloric, high protein and low carbohydrate.

(iii) Terminally: as for chronic renal failure.

(3) **Antimicrobial Therapy**

Prophylactic and therapeutic.

(4) **Diuretic**

Drugs and plasma expanders

(5) **Glucocorticosteroid therapy**

(6) **Cytotoxic therapy**

(7) **Chronic renal failure**

(8) **Dialysis and/or transplant**

All but the last two will be considered seriatim.

Social Factors

Supervision should desirably be by a local center close to home and school. Finance of travel and of drugs may be a problem. Costs to the individual may preclude optimal therapy in an affluent country and costs to the state in a poor one. Parents will require psychological support and should be warned from the beginning of the potentially protracted and/or relapsing course. Often they can accept steady progression to failure more easily than a relapse - treatment - response cycle with dramatic shifts of edema. Cyclophosphamide alopecia and steroid obesity can and should be predicted, earning plaudits as a

prophet rather than reproof for producing unexpected changes in a beloved child.

Diet

The initially brine-logged, olugiric, oligosaluric and edematous child should have both sodium and water intake moderately restricted to 50 m.Eq. and one litre daily, respectively. This will not stop edema increasing (since as little as lmEq. of sodium may be in the urine daily) but will *slow* the rate of edema formation whilst glucocorticosteroid and/or diuretic therapy is given. A high protein intake of say 80 g per day is desirable unless azotemia obtains.

When prednisolone therapy is started the low sodium, high protein diet is continued with the calorie intake restricted to 1,000 - 1,500 calories daily and the carbohydrate intake as low as practicable. Steroid obesity is caused by intake of *excess calories* and should not be accepted as inevitable. Calorie restriction is easy in the hospital and it is essential that adequate instruction be given to the parents prior to sending the child home. When diuresis and improvement occurs *keep* the child on a low salt diet (50 - 100 m.Eq. sodium daily in a temperate country). If he resumes normal use of salt he will dislike (and perhaps disobey) returning to a low sodium intake when he relapses, as most do. When chronic renal failure ensues, the high protein intake ceases as specific treatment for this chronic state begins.

Antimicrobials:

Because of the increased vulnerability to infection of the edematous nephrotic with a low level of circulating gammaglobulins there has been discussion as to whether or not prophylactic antimicrobial therapy should be given. De facto the common infecting organism is streptococcus pneumoniae (pneumococcus) which is easily killed of by penicillin or sulphonamide therapy. Peritonitis is a common lesion and should be readily diagnosed. Immediate high dosage intramuscularly of penicillin is indicated, prior to which (if ascites is present) as sample of ascitic fluid should be obtained by acupuncture. This should both be cultured and a sample stained and looked at under the microscope to confirm the presence of pneumococcus or alternatively E. Coli. Certainly surgical intervention is strongly contra-indicated. If the child is toxic a blood culture chould be made and ampicillin prescribed in full dosage in addition to benzylpenicillin. The same applies if abdominal pain fails to respond quickly to penicillin or if Gram-ve organisms are seen on

on the film of ascitic fluid. Gram -ve septicemia, shock and death can occur in a few hours. Prompt intravenous infusion may be required.

The use of penicillin prophylactically is not advised since the result will probably be infection with a penicillin resistant organism, whereas infection with pneumococcus can be dealt with easily. The only place for prophylactic therapy is where repeated upper respiratory tract infections or urinary tract infections occur producing relapses. Then prophylaxis with an agent such as sulphadimidine, 500 mg. twice daily can prove effective.

Diuretic Therapy:

The object of therapy is to reduce sodium reabsorption in the renal tubules and consequently release water and salt from the edematous extracellular fluid. The optimal diuresis in INS is that associated with glucocorticosteroid therapy since proteinuria synchronously ceases. Diuretics may be required in a number of differing circumstances.

(1) When the patient is grossly edematous and is distressed or if percutaneous renal biopsy is indicated.

(2) If the susceptible patient has been in contact with chicken-pox or measles.

(3) If urinary tract infection is present.

(4) If clinical, biochemical, immunological or histological date contra-indicate glucocorticosteroid therapy.

(5) When glucocorticosteroid therapy fails or results in unacceptable toxicity.

A wide range of diuretic drugs are available including thiazide diuretics, frusemide, aldosterone antagonists such as spinorolactone-A and triamterene, and plasma expanders.

The best known thiazide diuretics are chlorothiazide and hydrochlorothiazide which is ten times more potent. Basic treatment consists of 250 mg. chlorothiazide six-hourly for two days. If this fails, the dosage is doubled to 500 mg. six-hourly. If this fails or ceases to be effective, spironolactone-A is added in dosage of 25 mg. six-hourly. Should this still prove ineffective the chlorothiazide is increased to 1,000 mg. six-hourly. (In each case 25 mg. hydrochlorothiazide may be used as equal to 250 mg. of chlorothiazide). The potassium levels in plasma should be watched carefully, particularly if diuresis is produced and supplemental potassium (25-40 m.Eq. daily) should be given.

Frusemide (Lasix) is an alternative form of therapy which may be used. This has a very rapid action which resembles ethacrynic acid and is complete in four hours. Diuresis begins in one minute after an intravenous injection of frusemide. Begin with 10 mg. six-hourly orally and increase the dosage daily until diuresis occurs (to a maximum of 40 mg six-hourly). Less potassium loss occurs with frusemide than with thiazide diuretics but the plasma potassium should be monitored.

Spironolactone-A is an aldosterone antagonist which reduces sodium retention in the distal renal tubules and thus complements thiazide diuretics or frusemide. A dosage of 25 mg. six-hourly is used.

Hyperkaluria and hyporkalamia may complicate any effective diuretic therapy. In addition to measuring plasma potassium levels the ECG tracing is rapidly useful. Special care is required if the patient is on digoxin. Hyperuricemia occasionally occurs.

Plasma expanders are used sparingly today and their action is very transient. Continuous infusion of albumin may produce diuresis or complement diuretic therapy for resistant cases. One child in whom thiazide diuretics, frusemide, spironolactone-A and intravenous albumin failed was grossly edematous and had scrotal swelling which threatened to rupture. He was given continuous intravenous albumin, intravenous frusemide (500 mg) and aminophylline (250 mg) and waterfall diuresis resulted (1,800 ml. in six hours). He did however complain of backache but lost 6 Kg. of fluid in the next three days! Extreme therapy like this is rarely justifiable.

Corticosteroid therapy:

In 1951 we began 5-day "Go-Stop" therapy with cortisone acetate orally in daily dosage of 300 mg. Spectacular success occurred in a few and permanent improvement in a very few patients. In 1955 we were given a new substance to test, later to be known as prednisolone. At once the greater potency and lesser sodium retention paid off and by 1956 we had published our intensive tapered dosage for INS which has stood the test of time. This was as follows:

Day	Dosage of Prednisolone Daily
1 – 10	60 mg. (15 mg. 6 – hourly)
11 – 20	40 mg. (10 mg. 6 – hourly)
21 – 30	20 mg. (5 mg. 6 – hourly)
31 – 40	10 mg. (5 mg. 12 – hourly)

Dosage is irrespective of body weight which seems irrelevant· Corticotrophin gel (20 mg.) may be given intramuscularly on days, 30,35 and 40 to stir the sleeping adrenals.

Despite sophisticated techniques such as renal biopsy (with light, immunofluorescent and electron microscopy) and selectivity of proteinuria, there is still no test which indicates definitely that an *individual patient* will respond to glucocorticosteroid therapy. The dictum is therefore to give steroid therapy to all cases unless a contra-indication is present. Possible contra-indications are:

(1) Known persistent hypocomplementemia (Low C_3 level). In such a child biopsy is required to exclude membrano-proliferative disease in which intensive steroid therapy produces acute hypertension.

(2) Glomerulitis indicated by considerable hematuria, systemic hypertension, or azotemia when a proliferative lesion may be present.

(3) Exposure to chicken-pox or measles (temporary).

(4) Bacterial infection such as peritonitis or urinary tract infection (temporary).

(5) Other diseases such as peptic ulcer.

(6) Lack of adequate supervision.

Often the question is asked, "Is renal biopsy necessary before steroid therapy for INS?" The answer is "no", except under the conditions listed in (1) and (2) above. Contrary to popular belief renal biopsy is not a form of treatment and rarely helps an individual patient. It is doubtful if the thousands of renal biopsies carried out have improved prognosis significantly although they have greatly improved prognostication and knowledge of pathological histology.

There are indications for renal biopsy for INS (apart from research interest) and these may be listed as follows:

(1) **Clinical:**

Systemic Hypertension: Gross hematuria.

(2) **Immunological:**

Persistently low C_3 level is plasma.
Raised antistreptolysin titre.

(3) **Biochemical:**
Poorly selective proteinuria.
Azotemia.

(4) **Atypical Features:**
e.g. normal plasma lipids

(5) **Steroid Resistance:**
to adequate therapy

(6) **Frequent Relapsing:**
Two in six months.

The presence of any histology other than "minimal change" makes complete response to steroid therapy improbable and as mentioned, a membrano proliferative histology would rule it out. Results published by the International Collaborative Study of Kidney Disease in Childhood (ICSKDC) are interesting and indicate again that "minimal change" histology does not *always* indicate steroid response or a good prognosis.

Clearly where there is a high incidence of INS with "minimal change" lesions the results will be good, whereas with a high level of focal segmental glomerulosclerosis, proliferative, membranous or membrano proliferative lesions, the results will be less good.

In a series of patients seen in Glasgow from 1955-60 a five year follow-up was obtained on 100%. The results for uor intensive tapered steroid therapy were most interesting and may be shown as below:

No Response	– 7%
Diuresis, no relapse, recovery	– 40%
Diuresis, relapse – recovery	– 22%
– "unwell"	– 22%
– dead	– 9%

"Unwell" means that proteinuria, with or without edema had been detected in the previous two years. "Recovery" means at least two years free of proteinuria. These results include all INS presenting at the hospital where nearly all cases are found to have light negative histology. It is of great interest to compare the clinical state at five years of 186 consecutive cases all followed up and beginning between 1929 and 1960. The results are in Table I.

TABLE I

HISTOLOGY BY CLINICAL COURSE (ICSKDC)

Histology	Total	Clinical Response to Corticosteroid: No Response	Response and frequent relapses	Response and few or no relapses	Death
Minimal Change	103	5	36	62	3
Focal Segmental Glomerulosclerosis	13	10	1	2	3
Other	18	14	1	3	1
Total	134	29	38	67	7

It is perhaps as surprising that 33 % recovered in pre-sulphonamide days as that only 9 % died within five years of onset in the prednisolone era. There is no doubt that the really significant improvement in mortality (from 67 % to 22 %) was brought about almost entirely by the antimicrobials prior to the use of intensive steroid therapy in 1955. It would appear that steroid therapy accelerates recovery in those *who would have recovered in any case* but who prior to 1955 would have died of infection. A further effect has been to reduce death from renal failure from 21 % to 9 % after five years. Clearly these figures are applicable only in this region where there is no reason to suppose the types of INS presenting have changed significantly. Such results could not be applied directly to other areas with a differing incidence of the various clinical, immunological and histological patterns.

TABLE II

CLINICAL STATE 5 YEARS AFTER ONSET

Years of Onset	Effective Therapy	Clinical State: Well %	Proteinuria %	Dead %
1929–	None	33	0	67
	Sulphonamides	40	18	42
	Penicillin	54	11	35
	Cortisone ACTH	49	29	22
–1960	Prednisolone	69	22	9

These results clearly define the three problems of the future, namely, how to deal with the steroid resistant patient, the steroid sensitive but

frequently relapsing patient and how to reduce toxicity further for the steroid sensitive case and prevent a first relapse. It is to this end that our intensive tapered course is designed. The ICSKDC results help to indicate the likely underlying pathology of the steroid resistant and frequently relapsing cases - Table II

TABLE III

HISTOLOGY AND RESPONSE TO STEROID THERAPY (ICSKDC)

Histology	Total	Steroid	Deaths
Minimal Change	98	5	3
Focal Segmental Glomerulosclerosis	12	10	3
Proliferative:-			
Mesangial	4	1	0
With Crescents	4	4	0
Membranoproliferative	6	5	1
Membranous	2	2	0
Chronic Sclerosis	1	1	0
Total	127	28	7

The non-responders who should be biopsied after failed steroid therapy if this was not done previously will consist of two groups who will probably recover spontaneously ("minimal change and "minimal mesangial proliferation") and those who will not ("focal segmental glomerulasclerosis", "proliferation + crescents", "membranoproliferative", "membranous" and "chronic sclerosis"). There is no *good* evidence that flogging patients (whose kidneys reveal any of these histological pictures) with intensive prolonged therapy with glucocorticosteroids, azathioprine, clyclophosphamide or any combination makes any difference to the outlook. It is very tempting to go on treating such patients vigorously with these toxic drugs but until results of prospective controlled trials are to hand the physician should be cautious.

The toxic effects of glucocorticosteroid are many and varied but may be summarized thus:-

General : Cushingoid obesity with buffalo hump. Increased appetite. Altered psychological and emotional state with euphoria common.

Cutaneous	: Poor healing of wounds. Cutaneous striae which may lead to spontaneous weeping of skin. Hirsutism of trunk, face, pubes and moustache area. Acne.
Gastro-Intestinal	: Abdominal distention simulating obstruction due to fecal impaction, peptic ulceration, diabetes mellitus, hepatomegaly.
Immunological	: Decreased resistance to infection such as viral (e.g. varivella) bacterial or monilial. Flaring up of latent tuberculosis. Urinary tract infection common.
Skeletal	: Delayed growth, osteoporosis, compression fractures, reduced osteoporotix index (bicortical: transverse ratio of bones). Growth "rebound" provided treatment with steroid lasts less than one year.
Cardiovascular	: Systemic hypertension, acute left failure, thromboembolism.
Haematological	: Erythropoiesis, leucocytosis, lymphopenia.
Central Nervous System	: Convulsions due to hypokalemia, systemic hypertension of other unkown factor. Papilledema.

Clearly with such a list of potential toxic effects, glucocorticosteroids should not be used unnecessarily or promiscuously. It was hoped that cytotoxic therapy with cyclophosphamide or azothioprine might provide the answer.

CYTOTOXIC THERAPY:

Azothioprine was widely used in transplantation but results in nephrotic syndrome were disappointing and it is now little used. Cyclophosphamide proved of great value in the treatment of the steroid sensitive, frequently relapsing child. There is no doubt than an adequate course (8 weeks) of moderate dosage (2,5 - 3 mg/Kg/day) produces sustained remission in steroid sensitive frequent relapsers, so that even after one year less than 25 % relapse and after two years, less than 50%. The number of days of treatment is critical and short courses are ineffectual.

Unfortunately the drug has many toxic effects, the most severe of which are marrow depression, alopecia, vulnerability to infection of all kinds, hemorrhagic cystitis and gonadal damage causing temporary or permanent sterility. This may occur even in a post-pubertal boy who was treated several years before puberty. The situation in girls is less clear. For these reasons treatment with cyclophosphamide should be reserved for:

(1) Steroid-sensitive frequent-relapsing cases of INS with unacceptable steroid toxicity.

(2) Renal cases where life is threatened and cyclophosphamide is believed to be potentially beneficial.

In every case the potential gonadal hazard must be explained to the parents before therapy begins. By far the most important group are children with frequent-relapsing steroid sensitive INS because this group survive and reproduce and because cyclophosphamide is very effective. The transition from a dwarfed, obese, osteoporotic, frequent relapser to a rapidly growing healthy boy is very dramatic. The following system of usage for such cases is advised for edematous, oliguric, steroid toxic nephrotics:

(1) Provoke diuresis with prednisolone (40 mg. daily). This means a large output of urine and greatly reduces the risk of hemorrhagic cystitis particularly if the fluid intake is kept high (1.5 litres daily).

(2) Reduce prednisolone to 15 - 20 mg. daily and start cyclophosphamide in dosage of 2,5 to 3 mg/Kg./day given in divided doses. Maintatin for eight weeks. The prednisolone reduces the risk of marrow depression but the white count should remain above 2,500 per cm. Alopecia may occur and can be cloaked by a wig.

(3) Taper steroid therapy and stop over a period of two weeks.

This treatment would seem to combine optimal efficacy with minimized risks of toxicity.

The proposed treatment for INS as written here can be summarized as follows:

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