Eight and 12 week courses of cyclophosphamide in nephrotic syndrome

Sir,—We read with great interest the report on cyclophosphamide treatment of steroid dependent nephrotic syndrome recently published in this journal by Ueda et al.1 Surprisingly the authors could not find any difference in the outcome of patients who remained in sustained remission after treatment with cyclophosphamide for either eight or 12 weeks, contrary to our previous findings.2 We would like to make a few comments on this study, as we find considerable differences in the treatment procedures used in their study and ours, in addition to the age differences in patients described by the authors.

Most notable is the difference in the initial treatment of nephrosis. All of our patients were treated initially according to the standard treatment protocol of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN), that is, 60 mg/m²/day continuously for four weeks, followed by treatment on alternate days with 40 mg/m²/48 hours prednisone. In contrast, the duration of the initial treatment of patients in the study by Ueda et al was significantly longer, that is, four weeks of continuous steroid administration, followed by three to four months' treatment with tapered down prednisone dose (reduction of 5 to 10 mg/m² every two weeks). Thus the total amount of prednisone in the initial treatment was 2240 mg/m² in the APN study, but about 4620 mg/m² in the study of Ueda et al. It has been shown recently that the intensity of the initial treatment is a critical factor in the outcome and prognosis of steroid sensitive nephrotic syndrome—that is, the longer and more intensive the initial treatment is, the lower the number of patients who relapse, and the number of relapses and frequent relapsers.3 We therefore would assume that the patients of Ueda and his colleagues represent a highly selective group, who suffer from a more severe nephrotic syndrome than the patients treated by the APN protocol, and where steroid dependency could not be prevented by any intensive initial treatment. Otherwise it could not be explained why the cumulative percentage of sustained remission rates after eight or 12 weeks' cyclophosphamide were only 24% or 25%, respectively, which is lower than all other published results of cytotoxic drug treatment for steroid dependent nephrotic syndrome.4,5 We therefore strongly suppose that the differences in the results of the two studies are due to the selection of patients who were treated with cyclophosphamide. The longer duration of the trial (five years Ueda et al v 2 years in the APN study) and the higher number of patients in the study by Ueda et al seem to play only a minor part in these results (see table) as all but one of the patients of Ueda et al relapsed within two years after treatment with cyclophosphamide. Therefore our study was sufficient to judge the effectiveness of cyclophosphamide treatment, which was later confirmed in a five year evaluation of APN study groups.6

In summary, we cannot agree with the general conclusion of Ueda et al that the effect of an eight week course of cyclophosphamide appears to be the same as that of a 12 week course in children with steroid dependent minimal change nephrotic syndrome. This is probably only true for such a high proportion of patients who were as intensively treated initially as in the study of Ueda et al. For those who were treated less intensively, by the conclusion of the initial treatment of Ueda et al, the remission rate in their patients treated for eight weeks is similar to those reported by us. I might add that the longer steroid treatment seems not to affect the subsequent course when it is followed once nephrotic patients are steroid dependent, although this has an impact on the outcome when it is used as initial treatment.7

Perhaps the important differences may relate to the criteria for steroid remission and the age of the patients studied. The criteria for steroid dependence they adopted is somewhat different from ours as they included the patients other than those relapsed while receiving steroids or within 14 days after stopping steroids ('fast' relaper). Such patients could be more responsive to cyclophosphamide than those with 'fast' relapse. In addition, the most striking difference is the age at which cyclophosphamide was instituted. The age at entry into the study of their patients treated for 12 weeks, who had higher relapse-free rate, is higher than that of those treated for eight weeks and of our patients with relapse, but is similar to that of our patients without relapse. Cyclophosphamide appears more effective in older patients than in the younger,8 thus the distribution of the age at entry should be strictly the same in a comparative trial of such a drug. Finally, I am sure that Oemar and Brodehl would agree with me that their data must be interpreted with caution because of the retrospective nature of their study and the small number of patients in their study group. Thus in their study if the only two patients treated for 12 weeks relapsed, the differences in the efficacy of the two regimens would be insignificant.

In summary, if the data including the total time off steroids, the number of the patients who relapsed after 'fast' relapse before cyclophosphamide, the age at entry into the study of patients with and without relapse, and the recent outcome after the completion of their study are known and published, the conclusion and our results could be more clarified. We believe that the two regimens have an equivalent efficacy when a patient selection is carefully performed as described above.


Dr Ueda comments: I read with interest the comments by Dr Oemar and Professor Brodehl, and I wish to thank them for their thoughtful remarks. There are indeed some differences between their study and ours. However, I cannot agree with the suggestion that we had a highly selective group of patients as a result of different initial steroid treatment, because the remission rate in their patients treated for eight weeks is similar to those reported by us. I might add that the longer steroid treatment seems not to affect the subsequent course when it is followed once nephrotic patients are steroid dependent, although this has an impact on the outcome when it is used as initial treatment.1

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Acute wheezy bronchitis—lumping and splitting

Sir,—Mertola and colleagues have carried out a very comprehensive and worthwhile study on the association between viral infection and wheezing in childhood.1 However, their terminology 'wheezy bronchitis' as an appropriate diagnostic term for their study population should be reconsidered. It is an emotive term, and its definition far from clear.

Characteristics of steroid dependent patients in study groups

<table>
<thead>
<tr>
<th>Ueda et al</th>
<th>APN²</th>
<th>12 Weeks</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>28/13</td>
<td>26/6</td>
<td>7/1</td>
</tr>
<tr>
<td>Mean age at onset of nephrosis (years)</td>
<td>6-40</td>
<td>6-40</td>
<td>5-80</td>
</tr>
<tr>
<td>Mean steroid dose for initial treatment (mg/m²)</td>
<td>4620</td>
<td>4620</td>
<td>2240</td>
</tr>
<tr>
<td>Mean duration of nephrosis before cyclophosphamide (months)</td>
<td>7-80</td>
<td>7-80</td>
<td>4-15</td>
</tr>
<tr>
<td>No of relapses (12) or (6) months before entry</td>
<td>19-20</td>
<td>18-80</td>
<td>24-80</td>
</tr>
<tr>
<td>Total cumulative dose of prednisone before relapse (12 months)</td>
<td>5-1 (12) 4-5 (12)</td>
<td>4-4 (12) 4-6 (12)</td>
<td></td>
</tr>
<tr>
<td>No of patients with relapse after cyclophosphamide/totall patients</td>
<td>4/41</td>
<td>24/32</td>
<td>6/18</td>
</tr>
</tbody>
</table>

Cumulative % of sustained remission
to our present practice, the inclusion criteria
used in the study (two or more wheezy
bronchitis attacks) do not permit an asthma
diagnosis in all these children. At present
many authors regard wheezy bronchitis and
asthma as the same disorder and children with
wheezing attacks are treated with the prin-
ciples of asthma therapy (as was the case in
our study). These terms of congenital wheezy bronchitis
should not lead to undertreatment of patients.

About one third of the children in our study
had regular prophylaxis and we agree that this
might have prevented wheezing attacks in
some children, although not all in the paper.
Recently we re-evaluated the importance of
allergen exposure as a cause of wheezing in
these children. Although many of the
symptoms were atopic, allergen exposure
was not often suspected or proved as a precipitat-
ating factor for wheezing. This was probably
due to the effective allergen avoidance
routinely advised to parents of young children
in child health centres in Finland. The early
preventive measures are helpful for the
patients but make the analysis of these kind of
studies even more complex.

Vanto T, Ziegler T, Mertoja S, Ruuskanen O,
Koivivko A. Allergen exposure and respiratory
virus infections in young wheezy children

Spontaneous resolution of congenital
nephrotic syndrome in a neonate

Sir,—We were interested to read the article by
Banton et al referring to a baby with con-
genital nephrotic syndrome whose condition
resolved.1 We too have observed a child with
congenital nephrotic syndrome who made a
spontaneous recovery, and whose case raises
important ethical considerations.

The mother had a raised serum α-feto-
protein concentration on routine screening in
pregnancy and aminocentesis, performed at 21
weeks' gestation, shown an α-fetoprotein
concentration of 325 mg/l (normal <20)
with normal cholesteroïne. An ultrasound scan
showed no gross fetal abnormalities. A
diagnosis of congenital nephrotic syndrome
was made and the mother was offered ter-
mination of her pregnancy but declined on
religious grounds. A baby was born at term weighing
3750 g, the placenta weighing 1000 g. He had
gross proteinuria (Albustix 4+) at birth but no
haematuria. He also became hypoalbuminae-
mic, with a serum albumin of 18 g/l at 2
weeks. He had mild pitting oedema in the first
week but none subsequently and at no time
did he become hypertensive. The selectivity
index (i.e. the protein: creatinine ratio in
urine: serum ratio) was initially 7% (highly
selective proteinuria) but rose to
17% at 7 weeks. The proteinuria fell back to 9
at 10 weeks of age and the proteinuria had
resolved by 10 months. A renal biopsy speci-
men at 2 months of age showed normal glomeruli by light microscopy with the excep-
tion of one obsolescent glomerulus. The
tubules, interstitium, and blood vessels
appeared normal. Immunofluorescent stains
for complement components and immunoglo-
bulins were all negative. These findings
were compatible with a 'minimal change'
nephrotic syndrome. He was treated with
a high protein diet (6 g/kg/day), replacement
immunoglobulin, and penicillin prophylaxis
up to 5 months of age; neither steroids nor
diuretics were used. The child is now 6 years
old, has not relapsed, and is entirely well.

The congenital nephrotic syndrome is
heterogeneous and various types can be
recognised histologically. The Finnish type,
and the forms exhibiting diffuse mesangial
scarring, or focal segmental glomeruloscle-
orosis all have a poor prognosis. A policy of
antenatal diagnosis is therefore justified in
families with a previously affected child whose
clinical course or histology makes it known to
be adverse. However from time to time
screening for neural tube defects by maternal
α-fetoprotein in serum and amniotic fluid will
lead unexpectedly to the diagnosis of congeni-
tal nephrotic syndrome which is a fairly
common congenital nephrotic syndrome and the actual
prognosis will not be known. In view of the
benign course of our patient, and the one
reported by Banton et al, the re-evaluation of
such families can be extremely difficult.

A review of patients with congenital
nephrotic syndrome at this hospital over a
period of 24 years (S Yoshita, RHR White, F
Raafat, unpublished data) showed that, of 26
cases proved at biopsy, eight were of the
Finnish type, three had the form exhibiting
diffuse mesangial sclerosis, 12 had focal
segmental glomerulosclerosis and the histo-
logical appearances compatible with minimal
change nephrotic syndrome. Of the latter,
two siblings were steroid resistant and
continue to have mild proteinuria at 19 years
of age, with normal renal function, although
one is hypertensive. The other child
responded to prednisolone 60 mg/m²/day
and remained in complete remission until 5 years
of age, when proteinuria recurred; a further
biopsy specimen taken at this time showed
type 1 mesangiopelaryglomerulosclerosis.
One of the 12 infants with focal segmental
glomerulosclerosis was partially steroid
resis-
tant and is currently on treatment after
administration of cyclophosphamide.

The distinction between the histological
subtypes can sometimes present difficulties.
Although the glomeruli in Finnish nephrotic
syndrome show mild mesangial hypercellu-
larysthis can also be a feature of minimal
change nephrotic syndrome. Moreover the
cystic tubular dilatation which characterises
Finnish nephrotic syndrome can be caused by
cystic dilatation of the renal parenchyma and
may be an idiopathic process. In the latter
condition one could perhaps make a diagnosis
of minimal change nephrotic syndrome.

If the differential diagnosis remains in
doubt, it is reasonable to offer a trial of corti-
coestroid treatment, with antibiotic prophy-
laxis because of the increased risk of infection,
rather than to dismiss the possibility of a
more treatable condition. The counselling of
a woman who had not previously had a child with
genital nephrotic syndrome requires an awareness
that there is, perhaps, as much as a 10% prospect
of sporadic renal insufficiency if she
produces an affected, liveborn infant.

The authors are grateful to Dr James Partridge
for permission to report this patient.

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Dr Mertoja, Ruuskanen, Vanto, et al: comment

We appreciate the comments of our colleagues
and agree that many of our patients can be
regarded as asthmatics. However, according

1 Mertoja T, Ziegler T, Ruuskanen O, Vanto T,
Partridge MP. Recurrent wheezy bronchitis and
viral respiratory infections. Arch Dis Child

2 Speight AMT, Lee DA, Hey EN. Underdiagnosis
and undertreatment of asthma in childhood.

3 Wilson NM. Wheezy bronchitis revisited.

4 Turner-Warwick M. On observing patterns of
airflow obstruction in chronic asthma. Br J Dis
Child 1977;77:87-93.

It is important to consider the possibility
of wheezy bronchitis in the absence of
viral respiratory infection. The condition
was noted to be present in children with
respiratory viral infection during the recent
year of viral vaccine usage. It is possible
that the diagnosis was not always made
accurately, as the terms 'bronchitis' and
'wheezing' are often used interchangeably.

In conclusion, the terms 'wheezing'
bronchitis and 'wheezing attacks' are
imprecise and do not allow for a clear
understanding of the underlying biological
processes. Further research is needed to
establish the pathophysiological basis of
these conditions and to develop more
specific diagnostic tools for their
management.