CORTICOSTEROIDS AND VARICELLA

SIX-YEAR EXPERIENCE IN AN ASTHMATIC POPULATION

BY

CONSTANTINE J. FALLIERS and ELLIOT F. ELLIS

*Children's Asthma Research Institute and Hospital, Denver, Colorado, and Department of Pediatrics,
University of Florida College of Medicine, Gainesville, Florida, U.S.A.*

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The ubiquitous nature of certain viral exanthematous diseases, particularly varicella and rubeola, results in the occasional occurrence of these illnesses in patients with disorders of a more chronic character (Gordon, 1962). This fortuitous association offers an opportunity to detect possible reciprocal influences and presents clinical problems, the solution of which may lead to a better understanding of both coexisting disorders. Moreover, it is frequent that a chronic illness requires the administration of a pharmacological agent which in itself can modify the patient's response to an infective disease. One such situation that has aroused considerable interest during the past decade has been the occurrence of varicella in patients receiving corticosteroids for a variety of diseases. This event has been looked upon ominously since the report of Haggerty and Eley (1956) of fatal outcome of varicella in steroid-treated patients. Since our experience with varicella in a large group of chronic asthmatic patients was at variance with this view, we undertook a review of the material published on this subject both here and abroad. The result of this review plus our own experience in this area over a six-year period forms the basis of this report.

Material

Fifty-nine cases of varicella came under one or another of the authors' personal attention during the six-year period from July 1, 1957, to June 30, 1963. All patients were children in residence at the Children's Asthma Research Institute and Hospital (C.A.R.I.H.) (formerly the Jewish National Home for Asthmatic Children) in Denver, Colorado, for intractable asthma.

Bibliographical Survey

In the decade from July 1953 to June 1963, 31 published reports appeared (Josserand, De L'Hermuzière, and Vacher, 1953; Shee and Fehrsen, 1953; Crisalli and Terragna, 1956; Cheatham,

Weller, Dolan, and Dower, 1956; Bernheim, Larbre, Mouriquand, and Germain, 1956; Haggerty and Eley, 1956; Moulinier, Lartigaut, Cantonné, Martin, Geindre, and Traissac, 1956; Nichols, 1957; Le Tan Vinh, Canlorbe, Gentile, and Lelong, 1957; Gillot, Clausse, and de Peretti, 1958; Monnet, 1958; Kuipers and Van der Mei, 1958; Kaplan, 1958; Siegel, Lovin, Ely, and Kelley, 1959; Bernheim, Larbre, and Germain, 1959; Thoenes, 1959; Combe, Boineau, and Zannettacci, 1959; Kredba and Bradáčová, 1959; Hennemanne, 1960; Kirchhoff, 1960; Johnson and Nelson, 1960; Breton, Ponté, and Boniface, 1960; Falliers, Halberstein, and Bukantz, 1961; Pinkel, 1961; Finkel, 1961; Guazzelli and Calzolari, 1961; Celinska, Goledzinowska, Szpakowska, and Zychowicz, 1961; Viklický, Doutlík, and Kottová, 1961; Krajewska, 1961, 1962; Gerbeaux, Couvreur, Baculard-Beauchef, and Joly, 1963), describing cases of varicella in steroid-treated children (from 3 months to 16 years of age). There were several other reports where mention of this clinical problem was made, and others where some of the same cases were included for the second time. Such articles were noted but not included in the present bibliographical survey. The first reported fatal outcome of varicella 'during therapy with cortisone-ACTH' was in 1953, in France, by Josserand *et al.* (1953). This fatality occurred in a 6-year-old girl with rheumatic fever, in whom therapy with cortisone, 150 mg. daily, was stopped four days before varicella, because of 'marked obesity'. Following this, the patient received ACTH for three days. The disease terminated fatally in three days. In the same year, Shee and Fehrsen (1953) reported that cortisone, 100 mg. daily, given to an 11-year-old boy for urticaria, was associated with reactivation of varicella a month after the initial illness. Both courses of varicella were mild with the second one occurring immediately after discontinuation of cortisone.

TABLE 1
CORTICOSTEROIDS AND VARICELLA: REPORTED FATALITIES

	Number of Publications*	Total Cases Reported	Deaths	Steroid Therapy in Cases Terminating Fatally			
				Maintained	Increased	Decreased	Stopped
1953-57	9	21	16	6	3	3	4
1958-63	22	253	22	13	3	4	2

* Editorials, reviews, or duplicate presentations excluded.

The incidence of relapses or second episodes of varicella attributable to corticosteroid therapy was further studied by Crisalli and Terragna (1956). These authors gave cortisone to 22 patients at varying time intervals (10-60 days) after varicella. Typical signs of varicella reappeared in 11 cases, but always after the sudden discontinuance of steroid therapy. These observations were considered as 'due to cortisone'. However, the significance of the steroid withdrawal was not discussed.

The literature of the decade following the reports of Josserand *et al.* and Shee and Fehrsen contained articles with diametrically contrasting data on the question of the effect of steroid therapy on varicella. While sound judgements are difficult to make under such circumstances, the bibliographical review does give an estimate of the magnitude of the problem and, in addition, provides data from which one may decide whether the severity of varicella in a steroid-treated patient is dependent upon (a) the nature of the initial disorder for which corticosteroids were administered, (b) the duration and dosage of steroid therapy, and (c) the therapeutic manipulations of the clinician in managing the situation (abrupt discontinuation, increase or decrease of steroid therapy) during both the incubation period and the acute phase of varicella.

A marked difference in the mortality figures in the reports appearing before and after 1958 was noted (Table 1). This may be attributed to several factors. (1) The intent of the early publications were seemingly to call attention to the life-threatening hazard of varicella in the steroid-treated patient. (2) Subsequent reports appeared to present a more comprehensive survey of the situation in which both mild and fatal cases were reported. (3) Management of the clinical situation and the therapeutic attitudes of the attending physicians may have been different during the two periods. Although cortisone was used more commonly before 1958, and prednisone more often thereafter, no significant differences in daily dosage were noted if dose equivalents were considered (Aceto, Blizzard, and Migeon, 1962). Of the 21 cases reported before 1958, 16 terminated fatally. The remaining 5 represent too small a number to permit meaningful comparisons with the

231 cases reported in articles published after 1958 that recovered uneventfully. It appeared, however, that there was no significant difference in the dose and duration of therapy in these two groups. To permit a χ^2 analysis of the data (not possible otherwise with numbers of cases as small as these) the distribution was limited to two items: (1) therapy maintained or increased, and (2) therapy decreased or stopped. Considering only these two points, the difference in management before and after 1958 was not found to be statistically significant ($\chi^2 = 1.12$, $p = 0.1$).

Table 2 relates the outcome of varicella to the manner in which steroid therapy was managed before or during this illness. The majority of the reported cases were maintained on hormonal therapy. This fact was not always positively stated, but if no mention was made to the contrary it was assumed that the steroids were continued. It is of interest that in 49 of the 195 mild or average cases (25%) the dosage was increased, while in the 38 fatal cases an increase in steroid therapy was reported in 6 (16%). The daily dose of steroids was decreased in 21 cases, fairly evenly distributed among the various illness categories. In many more cases (excluding the instances of reactivation) therapy was abruptly discontinued.

The influence of the initial illness on the mortality rate is clearly shown in Table 3. Although in many instances the total number of cases is small, the data indicate that the deaths in cases of leukaemia, other haematological disorders, and in the rheumatic and connective tissue diseases significantly exceeded the mean of 14% for the total of the 274 cases reported. The dosage of steroid therapy varied considerably from case to case, and also within the groups of illnesses reviewed. In many cases the information available was only fragmentary. Calculations based on the available data indicated that the mean daily dose, expressed in milligrams of cortisone, was, in the cases of leukaemia and other haematological disorders, 160 mg. of cortisone or its equivalent.* The

* Equivalents were calculated by multiplying the given dose of the inflammatory steroid by an appropriate factor, as described elsewhere (Aceto *et al.*, 1962; Falliers, Tan, Szentivanyi, Jorgensen, and Bukantz, 1963).

TABLE 2
CORTICOSTEROIDS AND VARICELLA, 1953-1963: RELATIONSHIP OF OUTCOME OF
VARICELLA TO STEROID MANAGEMENT

	Corticosteroid Therapy						Total	
	Maintained	Increased or Resumed		Reduced		Stopped		
		A	B	A	B	A	B	
Mild or average cases	116	12	37*	8†	1	27†	2	195
Reactivation	—	—	—	—	—	11	1	12
Atypical or complicated cases	26	—	—	2	3	8	2	41
Fatalities	19	1	5	4	3	3	3	38

A: Incubation period. B: Acute phase of varicella.

* Steroids stopped in incubation period and resumed during varicella in three cases.

† In the majority of these cases steroids were reduced or stopped as part of the therapeutic programme for the original illness and not because of the supervening varicella.

TABLE 3
CORTICOSTEROIDS AND VARICELLA, 1953-1963: IMPORTANCE OF THE PRIMARY DISEASE

Disease	Total Cases Reported	Prolonged or Atypical Eruption	Complications	Deaths	Mortality (%)	References
Asthma	11	0	0	1	9	Haggerty and Eley (1956)
Allergic disorders (other than asthma) ..	8	1	0	1	12	Haggerty and Eley (1956)
Leukaemia	30	1	3	14	46	Haggerty and Eley (1956); Nichols (1957); Le Tan Vinh <i>et al.</i> (1957); Kredba and Bradáčová (1959); Hennemanne (1960); Pinkel (1961); Finkel (1961); Krajewska (1962)
Other haematological disorders	16	2	1	6	37	Haggerty and Eley (1956); Kuipers and Van der Mei (1958); Celinska <i>et al.</i> (1961)
Rheumatic and connective tissue diseases	30	1	3	9	30	Josserand <i>et al.</i> (1953); Cheatham <i>et al.</i> (1956); Bernheim <i>et al.</i> (1956); Haggerty and Eley (1956); Kirchhoff (1960); Finkel (1961)
Nephrosis and nephritis	13	0	0	0	0	Viklický <i>et al.</i> (1961)
Infectious hepatitis	10	0	3	0	0	
Metabolic and endocrine	4	1	0	1	25	Gillot <i>et al.</i> (1958); Thoenes (1959); Johnson and Nelson (1960)
Nutritional and gastro-intestinal disorders	4	0	0	0	0	
Tuberculosis	115	8	11	3	2.6	Viklický <i>et al.</i> (1961)
Misc. bacterial infections	20	2	3	1	5	Haggerty and Eley (1956)
Neurological disorders	11	1	0	0	0	
Diagnosis not stated	2	0	0	2	100	
Totals	274	17	24	38	14	

duration of therapy was not indicated in all cases. The figures reported ranged from two weeks to 'several years'. The period during which steroid therapy had been given continuously did not seem to have influenced the management of therapy during varicella nor was it found to bear a close relation to the outcome.

The ages of the patients varied considerably with a range from 3 months to 16 years, and median of 6 years. Age alone did not have any bearing on the mortality or morbidity figures.

Experience at C.A.R.I.H. in Denver

Table 4 shows the total number of admissions during the six-year period of this survey and indicates the frequency of pre-admission therapy with anti-inflammatory steroids, as reported in the protocols of the physicians and in the parents' application

forms. It can be seen that almost half of these children came to the Institute receiving daily steroid therapy for periods ranging from 1 month to 8 years with a mean of 16 months. Steroid therapy given for less than one month was not considered as

TABLE 4
CORTICOSTEROID THERAPY IN INTRACTABLE ASTHMA
PRE-ADMISSION RECORDS OF CHILDREN AT C.A.R.I.H.
JULY 1, 1957-JUNE 30, 1963

	No. of Patients	%
Total admissions	515	
One or more previous courses of steroids	470	91.3
No previous steroid therapy	45	8.7
Maintenance, daily therapy (months or years)	242*	47.0

* In 118 patients or 48.5% of the 242, steroid therapy was gradually reduced and stopped 3 to 12 weeks after admission to C.A.R.I.H.

TABLE 5
VARICELLA AT C.A.R.I.H. FEVER IN RELATION TO STEROID THERAPY

	Maximum Temperature Elevation (°C.)			Duration of Fever (days)		
	Range	Median	Mean	Range	Median	Mean
(A) No steroid therapy (N = 34)	37.8-40.2	39.0	38.7	2-6	3	3.23
(B) Steroids* taken daily (N = 21)	37.4-40.0	38.6	38.3	1-5	3	3.50
(C) Steroids stopped 4-19 days before varicella (N = 4)	38.8-39.2	38.8	38.9	3-5	3	3.75

* Prednisone, 2.5-15 mg. (mean 7.5 mg.) daily, or betamethasone, 0.3-1.8 (mean 1.0 mg.) daily, or dexamethasone phosphate inhalations, 2-9 daily.

TABLE 6
VARICELLA AT C.A.R.I.H. 1958-1963. MULTIPLE CORRELATIONS

Steroids	Fever			Asthma	Fever			Exanthema	Fever			Age (yr.)
	A	B	C		A	B	C		A	B	C	
I	0 1 0	3 6 4	0 2 5	M S L	0 1 0	1 8 4	0 5 1	+ ++ +++	0 1 0	8 4 1	4 2 1	6-9 9½-12 12½-16
II	0 1 0	3 6 3	1 2 1	M S L	0 0 1	4 6 2	1 3 0	+ ++ +++	1 0 0	10 1 1	1 2 1	6-9 9½-12 12½-16
III	0 0 3	5 3 3	2 3 2	M S L	0 0 3	2 8 1	2 5 0	+ ++ +++	3 0 0	6 2 3	2 4 1	6-9 9½-12 12½-16
Total ..	5	+ 36	+ 18 = 59 Pts.									

Steroids: I, none; II, stopped within past 12 months; III, daily therapy.

Fever: A, 37.0-38.0; B, 38.1-39.0; C, 39.1-40.0 (°C.).

Asthma: M, more; S, same; L, less than before.

Exanthema: +, mild; ++, average; +++, severe.

Analysis of Variance

Steroids vs. fever	F* = 0.20 (not significant)
Fever vs. asthma	F = 0.015 (not significant)
Steroids vs. exanthema	F = 0.81 (not significant)
Steroids vs. age	F = 0.58 (not significant)

* F = 3.23 would be needed to achieve a 5% level of significance, with 2 and 56 degrees of freedom ($F = 0.05(2, 56) = 3.23$).

maintenance therapy, and such cases were included under the category of 'one or more previous courses of steroids'. A cautious but persistent effort is made to withdraw therapy in as many cases as possible. It can be seen from the Table that this effort was successful in about half the children. In several more, therapy was discontinued several times, but only temporarily and had to be resumed as it provided the only means for acceptable control of the asthma. Of the 59 children at C.A.R.I.H., 21 were taking steroids daily at the time of varicella. There were two complications in the steroid group, a bacterial pneumonitis and a pyoderma. In the non-steroid group there was one case of pneumonitis and two of pyoderma. In all cases oral antimicrobial therapy was given, and recovery was uneventful. No fatalities, atypical eruptions, or any other reported complications were noted among the steroid-treated children during or after varicella.

There were 17 children in whom steroid therapy

had been discontinued during the 12 months preceding varicella, and in 4 of them the therapy had been stopped during the incubation period. The course of these patients during the exanthematous disease was followed very closely with special attention to possible signs or symptoms of adrenal insufficiency. All of these children ran an uneventful course.

Despite the absence of obvious complications, the possibility was considered that the over-all severity of varicella might be different in the three groups of patients described, i.e. children who had not received steroid therapy for at least one year before varicella, children who were on maintenance therapy with steroids, and children in whom therapy was stopped within the 12 months preceding varicella. The magnitude of the febrile response and the duration of fever were thought worth investigating in view of the well-known antipyretic effect of the adrenocortical hormones. Table 5 relates the febrile responses

noted to the steroid treatment state. The differences among the three treatment groups are not significant.

In order to carry out multiple statistical correlations between the severity of varicella (extent of eruption), febrile responses, steroid therapy, changes in asthma, and age of the patient, each one of the children observed was placed in an appropriate box, as shown in Table 6. The analysis of variance technique, used to evaluate the differences observed, was that of a single variable of classification, with unequal-sized subgroup samples (Dixon and Massey, 1957). The over-all severity of varicella and the extent and duration of the exanthema were not found to be affected by steroid therapy ($F = 0.81$). Fever was also not affected by steroids in the dosage range employed ($F = 0.20$). It was also noted that fever in these children was not accompanied by a consistent reduction in the severity of asthma, as had been noted and reported previously (Falliers *et al.*, 1961).

The initial inspection of the data gave the impression that older children, on steroid therapy, appeared more susceptible to varicella. In fact, the relation between age and steroid therapy was not found to be statistically significant ($F = 0.58$). The three oldest children had a history of having had varicella in the past. This historical information could not be confirmed with absolute certainty, but the possibility exists that in these three the varicella observed by us represented a second attack in a steroid-treated child.

In all cases except one steroid therapy was maintained or slightly increased during varicella. The sole exception was the first case in this series seen by the authors. At this time we were influenced here by the grave prognosis indicated in the early published reports, and a discontinuance of therapy on the third day of the illness was considered advisable. A more 'physiological' thinking has prevailed since, and, summarizing an experience with 21 cases, we have found that varicella pursued its ordinary course in children in whom the daily dose of prednisone was maintained at the low levels usually sufficient for reasonable control of asthma.

Discussion

Despite the great interest in the nature of viral agents and the diseases caused by them during the past few decades, the precise mechanisms of resistance to viral infection are unclear. One is still unable to assess the relative importance in viral immunity of humoral factors such as antibody, cellular factors, e.g. the interferons, and hypersensitivity of the delayed type (Friedman, Baron, Buckler, and Steinmuller, 1962; Wagner, 1963; Hale, 1961). Superimposing the effects of corticosteroids

upon this already complex problem further beclouds the issue. There is a voluminous literature on the effects of corticosteroids on resistance to infection (Kass and Finland, 1958). In attempting to evaluate the experimental data that bear upon this question, it is well to consider the following points.

(1) The species of animal with which one deals is of great significance. The effects of cortisol on resistance to infection in the mouse, rat, and rabbit, whose major adrenal cortical hormones are not the 17-OH corticoids (Bush, 1951), may be quite different from the effects of these same steroids in the guinea-pig, monkey, and man. Experiments in the former group of animals, receiving 17-OH corticosteroids, which show heightened susceptibility to infection, must be interpreted in the light of the possibility that these 'foreign corticosteroids' have a more profound effect on their metabolism in general, and specifically on their resistance to infection. In species such as man, whose major corticosteroids are the 17-OH derivatives, the effect of addition of these hormones may be a quantitative one only (Long, 1960).

(2) The timing of the administration of the corticosteroids in relation to the giving of the antigenic stimulus (either natural or artificial) influences the effect of the steroid on antibody production. Given after antibody production is already underway, corticosteroids have little, if any, effect and are similar in this regard to the effect of x-irradiation and cytotoxic drugs (Berglund, 1956).

(3) As with other agents that affect antibody production, the factor of dosage is of great importance. The corticosteroid dosage used in many of the animal experiments was, when related to body weight, many times in excess of what ordinarily would be used in man.

Recent brief reports have indicated that the viral exanthematous diseases, rubeola and rubella, usually run an uneventful course when occurring in children treated with corticosteroids (Falliers *et al.*, 1961; Gerbeaux *et al.*, 1963). The opposite has been the case with varicella, where an increase in mortality has been alleged to occur and be a direct result of the steroid hormones. It seems clear that the corticosteroid-varicella combination may be lethal in those disorders in which an underlying defect in the immune mechanism is known to exist, e.g. malignancy (Miller, 1962). However, when the immune mechanism is not compromised by the primary disease, a corticosteroid-varicella hazard is unproven. In reviewing the deaths reported in this latter group, one is impressed by the lack of specific details, especially regarding the dose of corticosteroid at the time of death (Haggerty and Eley, 1956; Eley, 1961). It has been accurately noted that 'at the

present time we are conditioned to associate the administration of corticosteroids or ACTH with an increased susceptibility of man to infectious agents' (Raffel, 1961). Since it has been recommended that corticosteroids be stopped in the face of varicella (Eley, 1961), it is quite possible that this course of action was followed in a number of the fatal cases. Death, then, may have resulted from adrenal insufficiency (Aceto *et al.*, 1962), precipitated by the stress of varicella, in a patient dependent upon exogenous corticosteroids. Mortality more likely occurred as a result of *not* using steroids rather than using them. Some of the catastrophic deaths occurring in steroid-treated asthmatics may likewise have resulted from a similar reluctance to reinstitute or increase steroid therapy in stressful situations, which, of course, would include severe asthma.

Summary

Two hundred and seventy-four cases of varicella occurring in children who were receiving corticosteroids have been reported from all over the world between the years 1953 and 1963. Mortality was higher in the period before 1958 than thereafter. The reasons for this have been discussed. A significantly higher mortality was found in cases treated with steroids for leukaemia and other haematological disorders, as well as for rheumatic and connective-tissue diseases, than in illnesses in which the immune mechanism is not thought to be compromised.

Of the 59 cases of varicella seen at C.A.R.I.H. during a six-year period, 21 were on corticosteroid therapy. No fatalities and no serious complications attributable to the adrenal cortical hormones were noted; indeed, steroid therapy did not influence the degree of duration of pyrexia, nor the extent or severity of the exanthematous eruption, as compared to a group of controls. When a child receiving steroids for a chronic disorder is exposed to or becomes ill with varicella, therapy at physiological levels equivalent to 25-50 mg./day of cortisone should be continued. Abrupt withdrawal of corticosteroids in the face of any potentially stressful disease, such as varicella, is unphysiological and hazardous.

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