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CHLORAMPHENICOL IN PROPHYLAXIS OF INFANTILE GASTRO-ENTERITIS

BY

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Infantile gastro-enteritis is a condition which usually affects infants under the age of 1 year. It is characterized by diarrhoea and vomiting, but other features such as anorexia and loss of weight may be present. In some cases diarrhoea may be the only symptom, in others toxæmia and dehydration may be marked, and in others diarrhoea and vomiting tend to recur. After reviewing the recorded outbreaks of neonatal gastro-enteritis, Kirby *et al.* (1950) concluded that the term "gastro-enteritis" had been applied to at least six different clinical syndromes.

In some patients with clinical gastro-enteritis, *Salmonella* or dysentery organisms may be the causative agents, but in others no specific organisms have been isolated. Since 1945 increasing attention has been paid to the occurrence of specific serological types of *Bacterium coli* in both sporadic and epidemic infantile diarrhoea and vomiting. In some outbreaks there has been a relatively high correlation between the incidence of the disease and the isolation of these specific types of *Bact. coli*. Kirby *et al.* studied an epidemic of neonatal gastro-enteritis associated with *Bact. coli* O 111 (D433) and showed that this organism might appear in the stools one to nine days before the onset of symptoms. Preliminary reports (Rogers *et al.*, 1949; Smellie, 1950) suggested that chloramphenicol was of value in the treatment of gastro-enteritis, and our own experience over the past two years has confirmed the value of the drug in established gastro-enteritis.

Present Investigation

This paper records our experiences with chloramphenicol as a prophylactic agent in infants from whom *Bact. coli* O 111 had been isolated, but in whom diarrhoea had not

developed. The investigations were undertaken between November, 1950, and August, 1951, in two of the wards of the Liverpool University Department of Child Health, at Alder Hey Children's Hospital, Liverpool. These wards, each containing 14 single cubicles, are used primarily for the treatment of infants under the age of 1 year suffering from gastro-enteritis, but infants with other diseases such as respiratory-tract infections are also admitted when beds are available.

Rectal swabs taken from all infants on admission, and at intervals of not more than four days thereafter, were examined for *Bact. coli* O 111 according to the technique employed by Kirby *et al.* (1950). Patients becoming cross-infected with this organism but who had not developed diarrhoea were included in the investigation, and alternate patients ("trial" group) were given chloramphenicol in a dosage of 75 mg. per lb. (165 mg. per kg.) body weight per day, in divided doses three- or four-hourly, for a period of seven days. The remaining cases ("control" group) received no chloramphenicol. The day on which *Bact. coli* O 111 was first isolated is referred to as day 0.

Sixty patients were observed, 30 in each group, but four patients in the trial group were subsequently excluded because chloramphenicol was not given until more than three days after the rectal swab became positive for *Bact. coli* O 111.

The first dose of chloramphenicol was given on day 0 in one case, on day 1 in 15 cases, and on day 2 in 10 cases. In the one patient who received chloramphenicol on day 0 the drug was initially prescribed because of symptoms suggestive of whooping-cough. The details of age, diagnosis on admission, antibiotic therapy, etc., are recorded in Tables I and II.

TABLE I.—Control Group

Age	Diagnosis on Admission	Specific Therapy for Primary Illness	Days Between Admission and First Rectal Swab <i>Bact. coli</i> O 111	Days Between First Positive Swab and Onset of Gastro-enteritis	Gastro-enteritis
3 wks	Respiratory infection	Streptomycin; penicillin	4	6	Severe
5 "	U.R. tract infection	—	16	3	Mild
6 "	Acute otitis media	Penicillin	13	—	—
7 "	Bronchopneumonia	Sulphadimidine; streptomycin	4	7	Mild
7 "	Bronchitis	Penicillin	12	4	"
8 "	Congenital pyloric stenosis	—	15	14	"
8 "	Meningococcal meningitis	Sulphadiazine	8	5	"
10 "	Diarrhoea and vomiting	Aureomycin	20	—	—
10 "	Vomiting, ? cause	—	8	3	Severe
10 "	Hypoplastic anaemia	—	32	8	Mild
10 "	Bronchitis	—	12	1	"
10 "	Feeding disorder	—	23	2	Severe
3 mths	Diarrhoea and vomiting	—	9	2	Mild
3 "	Pylorospasm	—	12	2	"
3 "	Oral thrush and conjunctivitis	Sulphadimidine	8	5	"
3 "	Diarrhoea and vomiting	—	12	2	"
4 "	"	—	12	—	—
4 "	Bronchopneumonia	Aureomycin	36	—	—
4 "	Pylitis	Streptomycin	8	5	Mild
5 "	L.U.L. pneumonia	Streptomycin; penicillin	9	—	—
6 "	Acute bronchitis	Sulphadimidine	8	4	Mild
6 "	Hydrocephalus	—	30	—	—
6 "	Bronchopneumonia	Penicillin; streptomycin	8	1	Severe
6 "	Meningococcal meningitis	Sulphadiazine; penicillin	8	6	Mild
7 "	Acute bronchitis; acute otitis media	Sulphamerazine; penicillin	4	—	—
7 "	Intussusception	—	12	3	Mild
9 "	Tuberculous meningitis	Streptomycin	12	—	—
9 "	Primary tuberculosis	—	12	3	Severe
11 "	Hydrocephalus	—	12	1	Mild
12 "	Oesophageal chalasias	—	28	2	"

TABLE II.—Trial Group

Age	Diagnosis on Admission	Specific Therapy for Primary Illness	Days Between Admission and First Rectal Swab <i>Bact. coli</i> O 111	Days Between First Positive Swab and Onset of Gastro-enteritis	Gastro-enteritis	First Dose of Chloramphenicol*
3 wks	Laryngo-tracheitis	Streptomycin; sulphamerazine	4	—	—	Day 2
3 "	Thrush; prematurity	—	12	—	—	" 2
3 "	Haemolytic disease	—	12	—	—	" 1
3 "	Septicaemia	—	12	—	—	" 2
3 "	Bronchopneumonia	Penicillin; sulphadimidine	12	—	—	" 2
3 "	R.M.L. pneumonia	Streptomycin	8	19	Mild	" 1
6 "	Feeding problem	Sulphadimidine; streptomycin	4	—	—	" 2
6 mths	Meningococcal meningitis	Penicillin; sulphadiazine	12	—	—	" 2
2 "	Feeding problem	—	4	—	—	" 1
3 "	R.L.L. pneumonia	Sulphadimidine; penicillin	3	1	Mild	" 0†
3 "	R.L.L. pneumonia; thrush	Sulphadimidine; penicillin	8	12	"	" 1
3 "	U.R. tract infection	—	5	—	—	" 2
3 "	Primary tuberculosis	—	28	—	—	" 1
3 "	Bronchitis	—	12	—	—	" 1
3 "	U.R. tract infection	—	4	—	—	" 1
4 "	Acute bronchitis	Sulphadimidine; penicillin	8	—	—	" 1
4 "	Pyelitis	Sulphadiazine	8	11	Mild	" 1
4 "	Diarrhoea and vomiting	—	12	—	—	" 1
4 "	Bronchopneumonia	Penicillin	13	—	—	" 1
5 "	Acute otitis media	Penicillin; streptomycin	9	1	Mild	" 2
6 "	Tuberculous meningitis	Penicillin; sulphadimidine	12	—	—	" 2‡
6 "	Hirschsprung's disease	Streptomycin	7	—	—	" 1
7 "	Meningococcal meningitis	Sulphadiazine; penicillin	15	—	—	" 1
7 "	Bronchitis	Sulphadimidine	10	—	—	" 1
9 "	Bronchopneumonia	Penicillin; sulphadimidine	20	—	—	" 2

* Day 0 = day of first positive swab for *Bact. coli* O 111. † Given chloramphenicol for spasmodic whoop: ? whooping-cough. ‡ Developed no diarrhoea, but lost weight from day 3 to day 12; vomited twice on days 3, 4, and 5; anorexia days 3 and 4.

Of the 26 cases in the trial group, 21 (80%) did not develop gastro-enteritis and 5 developed a mild form. The onset of symptoms in three of these five cases was 11, 12, and 19 days after the first rectal swab positive for *Bact. coli* O 111, and 3, 4, and 10 days after chloramphenicol had been discontinued. In two cases diarrhoea developed before the second day of chloramphenicol therapy. In a further case, although no diarrhoea occurred, there was anorexia on days 3 and 4, loss of weight from days 3 to 12, and vomiting twice daily on days 3, 4, and 5. We have found that these symptoms often precede diarrhoea in patients from whom the organism *Bact. coli* O 111 is isolated.

Of 30 cases in the control group, 8 (26.6%) did not develop gastro-enteritis and 22 did; of the latter, 17 were mild at the onset and 5 were severe. Patients with mild symptoms were those in whom dehydration was not pronounced and who responded to oral glucose-saline followed by graduated milk-feeding, whereas severe cases received intravenous fluid therapy. In addition, some cases in both mild and severe groups received chloramphenicol after the development of diarrhoea. Statistical analysis shows that the difference between the trial and control groups is highly significant ($\chi^2=14.2$, $P<0.001$) and indicates that chloramphenicol had a marked therapeutic effect. The clinical features of the 22 patients in the control group who developed diarrhoea are recorded in Table III. This table

TABLE III.—Time of Appearance of Symptoms and *Bact. coli* O 111 in Stools in Relation to Onset of Diarrhoea in 22 Cases of the Control Group who became ill

Day:	No. of Cases													
	-14	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2
Diarrhoea												22	5	2
Loss of weight		1	1	2		1	2	5	3	1	1	3	2	
Anorexia							1	1	1	1	1	3	1	
Vomiting		1	1	1	1	2	3	2	4	5	3	7	3	1
<i>Bact. coli</i> O 111	1			1	1	2	3	2	4	5	3	7	3	1

shows that loss of weight and anorexia preceded the onset of diarrhoea in a high percentage of cases. Loss of weight was recorded in 20 patients, and in 13 of these it was observed before the onset of diarrhoea. Anorexia occurred before the diarrhoea in 5 out of 9 cases. In only 7 out of 18 cases did vomiting occur before diarrhoea.

Bacteriology

It is interesting to compare in the two series the variations both in the total *Bact. coli* flora and in the isolation of *Bact. coli* O 111. The day on which *Bact. coli* O 111 was

first isolated being day 0, further swabs were taken so far as was possible on days 2, 4, 6, 9, 13, and subsequently at four-day intervals thereafter until the patient was discharged. If diarrhoea and vomiting developed, swabs were taken at more frequent intervals. In the trial series, five patients were not swabbed after day 13, as they had been discharged well and remained so. In the control series, two patients did not develop symptoms and were discharged before day 13, and 12 were treated with antibiotics because they developed diarrhoea. The remaining 21 patients in the trial group and 16 in the control group were followed up until three consecutive negative swabs had been obtained.

In the trial group, the seven-day course of chloramphenicol was begun as soon as preliminary identification of the organism had been made.

A rough assessment of the number of colonies of *Bact. coli* type (as profuse, moderate, or scanty) was made visually from the initial MacConkey plates. Disproportionate inhibition was not observed at the site of inoculation when examining plates from patients under treatment, and it was not thought that carry-over of antibiotic from the faeces appreciably affected the results, an opinion reinforced by our repeated failure to detect the antibiotic in the tubes of broth in which the swabs were dispersed after inoculation of plates.

Of 121 swabs on days 0-13 inclusive in the control series, 8 gave a scanty growth of *Bact. coli* type colonies, and from 149 swabs in the trial series 32 gave a scanty growth.

From the fourth to the ninth day, at a time when one might expect any effect due to chloramphenicol to be most noticeable, there was a considerable difference between the two groups, in the proportions of swabs falling into the three classes mentioned above. In the control series 54 swabs were taken, 45 showing profuse, 6 moderate, and 3 scanty growths of *Bact. coli* type colonies; in the treated series the corresponding figures were 70-23, 28, 19.

The two series showed differences in the isolation of *Bact. coli* O 111 similar to the differences in the total *Bact. coli* flora. These are shown in Table IV. From the fourth to the ninth day, only 5 of the 54 swabs in the control group were negative for *Bact. coli* O 111, compared with 36 of 70 in the trial group.

In the control group 16 patients were followed up after the thirteenth day. Of these, three were already negative for *Bact. coli* O 111, and remained so; the other 13 were positive for varying periods up to day 40. In the trial group, of the 21 patients, only 11 were positive after day 13, and later remained so for periods up to day 37. The average

TABLE IV.—Incidence of Isolation of *Bact. coli* O 111 from Rectal Swabs at Similar Periods in Control and Trial Groups

Day:	0	1-2	3-4	5-6	7-8	9-10	11-13
Control series:							
No. of swabs ..	30	11	25	10	15	12	18
No. positive for <i>Bact. coli</i> O 111 ..	30	11	23	9	14	10	16
Percentage positive ..	100	100	92	90	93	83	89
Trial series:							
No. of swabs ..	26	17	25	25	9	23	24
No. positive for <i>Bact. coli</i> O 111 ..	26	15	18	12	5	4	6
Percentage positive ..	100	88	72	48	56	17	25

period for which cases in the control series were positive for *Bact. coli* O 111 was 22 days; in the treated series it was 14 days.

These results suggest that the administration of chloramphenicol was associated with a moderate reduction of the total *Bact. coli* flora and a more striking reduction in the isolation rate of *Bact. coli* O 111. It is worthy of note that all except one of the trial group became negative for *Bact. coli* O 111 on one or more occasions during the days when chloramphenicol was given, but 11 of these became positive again shortly after the end of treatment.

Discussion

The dangers to the life and health of young babies which result from their admission to hospital are well known, and usually follow the development of respiratory, gastro-intestinal, skin, or mucous membrane infections. Epidemic diarrhoea is often the most serious of these infections, and may carry a high mortality, especially in babies who are already debilitated by their primary illness. In our experience during the past three years, in Liverpool, there has been a fairly close correlation between bacteriological cross-infection with *Bact. coli* O 111 and the development of gastro-enteritis. In addition, certain clinical features such as loss of weight and anorexia may be observed before the onset of diarrhoea, and often before the rectal swab is positive for *Bact. coli* O 111.

In spite of the application of the measures recommended for the prevention and control of cross infections (Medical Research Council, 1951) we have experienced from time to time small outbreaks of diarrhoea and vomiting. Our experience with chloramphenicol in established gastro-enteritis has been encouraging enough to warrant the trial of this drug as a prophylactic agent. Though in an attempt to obtain representative control and treated cases we used as the criterion the appearance of *Bact. coli* O 111 in the stools, this was done only because at the time there was a clear association between cross-infection with *Bact. coli* O 111 and the onset of diarrhoea. We do not suggest that this is always so. In other circumstances the value of prophylactic chemotherapy would be much more difficult to assess. The administration of chloramphenicol is not a substitute for other precautions, but is an additional measure which might be tried when the generally accepted methods for control of cross-infection have failed.

No toxic effects from chloramphenicol have been observed with a dosage of 75 mg. per lb. (165 mg. per kg.) per day for seven days, but it is probable that a lower dosage for a rather longer period might prove equally effective. Three of our cases which received chloramphenicol developed mild diarrhoea 3, 4, and 10 days after the drug had been discontinued, and rectal swabs were positive for *Bact. coli* O 111 during this period. In the light of this experience we suggest that chloramphenicol should be given for 10 to 14 days in a daily dosage of 50 mg. per lb. (110 mg. per kg.).

The bacteriological data, though compatible with the suggestion that *Bact. coli* O 111 may be the cause of one form of infantile gastro-enteritis, are equally explicable on the basis that their occurrence is non-specific and that their suppression during treatment with chloramphenicol is merely a reflection of the general effect of this drug on the *Bact. coli* group. In our experience, so far, the occurrence

of *Bact. coli* O 111 has been so closely associated with the disease that we have felt that infants cross-infected with this organism should be closely observed for prodromal signs of gastro-enteritis.

Recent experience with small numbers both of clinical cases of gastro-enteritis and of those cross-infected with *Bact. coli* O 111 suggests that sulphadiazine may be as effective as chloramphenicol.

The prophylactic use of chloramphenicol or sulphadiazine is not considered necessary when isolated cases of cross-infection (both clinical and bacteriological) arise, but in the presence of widespread cross-infection not prevented by the usual measures the use of these drugs may be valuable.

Summary

Chloramphenicol was given to alternate patients in a consecutive series of 56 infants under 1 year who became cross-infected with *Bact. coli* O 111 after admission to hospital. The results in this small series suggest that this antibiotic might be of value in preventing the development of clinical gastro-enteritis.

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TESTS FOR GLYCOSURIA

A COMPARISON OF BENEDICT'S TEST, CLINITEST, AND GLUCOTEST

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Benedict's qualitative test is extensively used in clinical medicine, but its accuracy depends on the correct proportions of urine and Benedict's solution and on heating without "bumping" for the correct time. While these form no obstacle in a laboratory, many years' experience in our large diabetic clinic has shown how dubious the results may be when the test is performed by nursing staff, medical officers, and practitioners not connected with the clinic. Reducing substances have been found to be absent in innumerable urines referred to us for confirmation of a positive Benedict test found elsewhere. Such errors have been diminished but not eliminated by heating for five minutes in a boiling water-bath instead of two minutes over a flame.

In recent years the detection of reducing substances in urine has been simplified still further by the commercial production of tablets containing copper sulphate, sodium hydroxide, citric acid, and sodium bicarbonate in such proportions that when a tablet is dissolved in a measured amount of diluted urine enough heat is generated by solution of the sodium hydroxide, and by neutralization of part of it with the citric acid, for reduction of the copper to take place, giving green, yellow, or orange cuprous oxide colours, just as in Benedict's test. Such a test has many advantages, for with the commercial set of tablets a glass dropper is provided of such a size that the requisite volume is given by 5 drops of urine and 10 drops of tap-water. Under these conditions