DIARRHOEA IN PREMATURE INFANTS

PREVENTIVE AND BACTERIOLOGICAL ASPECTS

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Prevention of infection is a primary objective in all premature infant units. Epidemics of enteritis may occur suddenly and spread with alarming rapidity. Control of an epidemic is often so difficult that complete closure of the unit becomes necessary. Ideal methods of prevention include spacious wards, the use of an incubator for each infant, barrier nursing, ultraviolet light, and sufficient specially trained personnel. These methods are uneconomical and beyond the reach of those hospitals serving the underprivileged.

A cheap and simple method of preventing diarrhoea would therefore be most welcome. Drug prophylaxis was reported by Marie and Basset[1] to be of temporary benefit only. The prophylactic use of carob flour in the prevention of diarrhoea in infants has been recommended by Tolentino,[2] Vonderweidt and Klein,[3] Marie and Basset,[1] and Vianello and Baratella.[4] Smith and Fischer[5] used it with success in 30 patients. In 1959 we embarked on a clinical investigation to confirm this.

MATERIAL AND METHODS

The Premature Unit

This unit at the McCord Zulu Hospital has 10 cribs and one incubator in a specially heated room measuring 12 feet × 12 feet. The temperature was kept constant at 82 - 84°F. The humidity was not measured because of Durban's subtropical climate. The infants are barrier nursed in the nude, and are not bathed, but are weighed daily. Records are kept of every stool passed. The formulae are made up in an adjoining kitchen which interleads with the ward. Because the hospital is a training school for nurses, changes in nursing staff occur frequently; during the period of the investigation the sister-in-charge changed once. There was at all times at least one graduate nurse (a pupil midwife) in the nursery. Infants developing diarrhoea were transferred to an 'isolation nursery' (7 feet × 3 feet) on the same floor, and were attended by a nurse not working in the premature baby nursery.

An average of 2,400 babies are born annually in the obstetrics unit, and the prematurity rate is approximately 10%. Only infants weighing 5 lb. (2,400 G.) or less are treated as being premature and only these were therefore allotted to the series.

The overall survival rate of infants admitted to the premature unit over a 5-year period, 1957 - 1961, has been 70% (inclusive of infants weighing less than 1,000 G.). There was an unusually high incidence of diarrhoea during the period of the investigation.

The Investigation

Two unselected groups of patients were observed simultaneously, one group receiving 'arobon' in their feeds (arobon group) and the other not (control group). They were attended in the same nursery, by the same nursing and medical staff and with identical bacteriological facilities.

The Allotment of Cases

The infants were weighed within 2 hours of admission and were allotted to their respective weight groups as follows:

Group A: 2,001 - 2,400 G.
Group B: 1,501 - 2,000 G.
Group C: 1,001 - 1,500 G.
Group D: Less than 1,000 G.

The first patient in each weight group was allotted to the arobon group and the second to the control group. Thereafter alternate cases were allotted in strict rotation without selection. The investigation ran from February 1959 to July 1961.

Feeding Routine

1. Feeds were not offered for the first 36 hours — or longer if the patients were not restless, thirsty or overactive.

2. Trial feeds of sterile water (one drachm 3-hourly) were given for 24 hours, followed by ½-strength expressed breast milk (EBM) for a further 24 hours, followed thereafter by full strength EBM. The total feed for the day was normally increased by one ounce daily.

3. With the first ½-strength EBM feed, arobon (1%) was added to all feeds of the infants in the arobon group; at no time was arobon given to infants in the control group.

4. Vitamins and intramuscular iron ('imferon' 0·25 ml. bi-weekly for 6 doses) were given from the 21st day.

Bacteriological Investigations

Rectal swabs were collected as a routine on the 7th day of life and again at the time of discharge. Additional swabs were taken from any infant developing diarrhoea, and these were repeated when the diarrhoea was cured, or if recurrence took place.

Swabs were seeded on to the following media as soon as possible after collection: blood agar, MacConkey's agar, desoxycholate citrate agar, and selenite-F fluid medium. Subcultures from the selenite medium were placed on to desoxycholate agar after overnight incubation. Non-lactose-fermenting colonies were picked off in the usual way and identified. Possible enteropathic forms of *E. coli* were detected from colonies on the blood-agar plates, or, on occasion, from the MacConkey plates, where the blood plate was covered with a growth of a spreading organism.

Preliminary slide agglutination was carried out with a range of *E. coli* antisera (obtained from Standards Laboratory, Colindale, London, and containing somatic O antibody and antibody against the B type of K antigen).

A fairly heavy suspension was used and positive agglutination appeared rapidly. Eight colonies were examined from each plate. Occasional granularity was distinguished from true agglutination, the former disappearing on mixing with a platinum loop. Positive slide tests were checked by tube agglutination, using serial doubling dilutions of sera, and aliquot volumes of suspensions. These suspensions were prepared by heating an overnight broth culture in the boiling waterbath for 30 minutes, and then diluting in saline to an opacity corresponding to $2{\cdot}5 \times 10^7$ organisms per ml.

All tubes were incubated overnight at 50·0°C. in a waterbath. Agglutination at 50%, or better, of the standard titre of the serum was accepted as adequate confirmation of the strain type. Strains giving less than this degree of agglutination were excluded. Some of these probably represented strains with part of the antigen structure of the type strain used for antiserum production, although some may, in fact, be poorly agglutinating strains of the specific type.

Definition of Diarrhoea

A patient was said to have *diarrhoea* if:

1. Two consecutive 'pure-water' stools were passed. These often showed as a large watery patch on the napkin, being yellow or colourless at first and then turning green.
2. Seven or more variable loose stools (mucoid, watery or curdy) were passed in 24 hours.
3. There was an increase of 3 or more stools over the average 24-hour count, associated with weight loss or marked looseness of the stools.

The diagnosis in (1) or (2) was usually confirmed by an associated weight loss of 1 - 3 ounces in 24 hours.

An infant was classed as *severely ill* if 2 of the following criteria were fulfilled:

1. Weight loss of 5 ounces or more.
2. More than 7 loose stools in 24 hours.
3. Intravenous fluid therapy necessary.
4. Diarrhoea for 5 or more consecutive days.

Routine Treatment for Diarrhoea

1. *Darrow's solution** offered orally *2-hourly* for 12 - 24 hours, the quantity of each feed being unchanged, thus increasing the total fluid intake by 50%. Thereafter 3-hourly feeds of ½-strength EBM for 12 - 24 hours, before resuming routine 3-hourly feeds of EBM.

2. *Antibiotic therapy*. When deemed necessary chloramphenicol (50 mg. per lb. per day, divided into 6-hourly doses) was prescribed for a 7-day period. If this treatment was unsuccessful within 4 days it was replaced by neomycin (40 mg. per lb. per day). Six months after this investigation was started the order of therapy was reversed because of the possibility of chloramphenicol toxicity in the premature infant. Occasionally streptomycin sulphate was used as the 3rd antibiotic of choice.

3. *Intravenous therapy* where indicated.

RESULTS

A total of 337 premature infants were admitted to the series at birth, and the progress of those surviving the first week of life is analysed in this report.

For purposes of analysis groups C and D have been eliminated — because, of the 72 infants weighing under 1,501 G., 58 (80%) died (none from diarrhoea) in the first week and 4 had incomplete records, leaving only 10 cases for analysis. Groups A and B (1,501 - 2,400 G.), combined, comprised 277 infants. Thirty-six of these infants died (none from diarrhoea) in the first week of life, leaving 241. Of these, 120 belonged to the arobon group and 121 to the control group. Incomplete records, however, further reduced the numbers for analysis to 107 in the arobon group and 95 in the control group.

* With 2½% glucose.

TABLE I. SUMMARY OF RESULTS IN THE AROBON AND CONTROL GROUPS

	Arobon	*Contro*
Total patients in group	107	95
Patients with diarrhoea:		
1 attack	62	51
2 attacks	18	16
3 attacks	4	3
Patients with severe diarrhoea:	29	20
Prolonged attacks	9	12
Weight loss over 5 oz.	9	5
Patients requiring intravenous therapy	14	12
Patients requiring a second antibiotic	12	11
Average birth weight:		
Group A	4 lb. 11 oz.	4 lb. 11 oz.
Group B	3 lb. 15 oz.	3 lb. 11 oz.
Average age at which birth weight was regained:		
Group A	18 days	15 days
Group B	18 days	21 days
Deaths from diarrhoea	4	1

Table I compares the incidence and severity of the diarrhoea in the two groups, and also shows the average age at which the infants had regained their birth weights.

Results of Bacteriological Investigations

Apart from enteropathogenic strains of *E. coli* and salmonella strains, the only other predominant organism found in association with diarrhoea was *Candida albicans*. Table II shows the relationship of diarrhoea to the presence of potentially pathogenic organisms in the total of 202 infants (107 in the arobon group and 95 in the control group).

TABLE II. RELATIONSHIP OF DIARRHOEA TO THE PRESENCE IN THE STOOL OF POTENTIALLY PATHOGENIC ORGANISMS

	Arobon	*Control*
Number of patients	107	95
With diarrhoea	62	51
Without diarrhoea	45	44
E. coli:		
With diarrhoea	14	12
Without diarrhoea	1	1
Salmonella:		
With diarrhoea	6	3
Without diarrhoea	1	—
Candida albicans:		
With diarrhoea	2	4
Without diarrhoea	—	1

The distribution of the *E. coli* types and salmonella strains is shown in Table III.

E. coli infections: Enteropathogenic *E. coli* organisms were isolated from only 2 infants who at no time had evidence of diarrhoea. All those who had diarrhoea in

association with *E. coli* responded to treatment with antibiotics. In spite of this, however, 50% (13 of 26) still had the organism present in the stool at the time of discharge. Some cases appeared to show a quantitative increase in the number of organisms at the time of discharge as determined by the examination of 8 colonies

TABLE III. DISTRIBUTION OF THE *E. coli* TYPES AND SALMONELLA STRAINS

Organism and type:	*No. of infants*	*Total*
E. coli 0·26 : B. 6	2	28
E. coli 0·111: B. 4	5	
E. coli 0·119: B. 14	7	
E. coli 0·125: B. 15	5	
E. coli 0·126: B. 16	7	
E. coli 0·127: B. 8	1	
E. coli 0·128: B. 12	1	
S. abony	2	10
S. anatum	8	

from each plate. This increase, however, may be more apparent than real since antibiotic therapy may have caused a selectively greater reduction in the numbers of other organisms. In one case, strain O.119: B.14 was isolated on 2 occasions during 2 attacks of diarrhoea, and strain O.126: B.16 was found in the swab taken at the time of discharge.

Salmonella infections: Two infants developed infection with *S. abony* during the early stage of the investigation. Diarrhoea was present in both and severe in one. Following recovery the organisms disappeared from the stools. At a later stage an outbreak of *S. anatum* infection involved 8 infants and was traced to a nurse who was a carrier. Seven of the 8 had diarrhoea. In the eighth case the salmonella was isolated from the discharge swab after the infant had left hospital, and it is not known whether diarrhoea subsequently developed. There was one death among these 8 infants and 2 were still excreting the organism at the time of discharge.

Candida albicans infection: This fungus predominated in the stool in 7 cases; in 5 it was present at the onset of the first attack of diarrhoea. In one it was present at the onset of a second attack, and it was also found in the discharge swab of an infant who had had an attack of diarrhoea 14 days previously. Neomycin had been used in the treatment of diarrhoea in both these infants.

DISCUSSION

Although diarrhoea in our premature infants was a constant threat and occurred frequently (Table I) it was apparently responsible for only 5 deaths. Many others survived despite the need for intravenous therapy and second courses of antibiotics.

Under the conditions pertaining in our unit we were unable to demonstrate any benefit from the prophylactic use of 1% arobon (Table I). It was also hoped that arobon, in changing the consistency of the stools, would prevent fluid loss. Daily weighings of our patients did not provide any such proof.

The exact cause of the diarrhoea in prematures is often difficult to identify and in this series, unfortunately, virus studies could not be included. Consequently one must be circumspect in drawing conclusions. However, pathogenic *E. coli* organisms are known to cause epidemics of diarrhoea. We believed that in our unit they were probably a common aetiological factor, but from this investigation it is evident that they did not play a significant role in our patients with diarrhoea (Table II), because in by far the largest number no organisms were found at all. Nor were parenteral causes discovered in these patients. A few cases may have been caused by monilia, and some we know were due to salmonella. One must beware of drawing conclusions with regard to causative organisms which on occasion may be cultured in the absence of clinical disease.

SUMMARY

1. An investigation into the prophylactic use of carob flour (arobon) in the prevention of diarrhoea in prematures is reported. No benefit was demonstrated.

2. A total of 202 unselected premature infants was observed in a controlled study.

3. Routine bacteriological examination of the stools in all cases is recorded. In many with diarrhoea no organisms could be isolated.

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REFERENCES

1. Marie, J. and Basset, M. (1956): Sem. Hôp. Paris, **33,** 3580.
2. Tolentino, P. (1950): Ann. paediat. (Basel), **175,** 201.
3. Vonderweidt, P. and Klein, M. L. (1955): Sem. Hôp. Paris, **31,** 3950.
4. Vianello, A. and Baratella, B. (1958): Clin. pediat. (Bologna), **40,** 532.
5. Smith, A. E. and Fischer, C. C. (1949): J. Pediat., **35,** 422.