CLINICAL RESEARCH

Bacterial contamination of the small intestine of infants with enteropathogenic Escherichia coli and other enteric infections: a factor in the aetiology of persistent diarrhoea?

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Abstract

The duodenal microflora was studied during the first week of diarrhoea in 40 infants with acute infectious diarrhoea of different aetiologies and compared with that in a convalescent group and a group in whom diarrhoea of known aetiology had persisted for more than 14 days after an acute onset. In the acute phase 16 of the 40 infants had more than 10^4 colony forming bacteria/ml, predominantly upper respiratory commensals. In over half of the infants infected with enteropathogenic Escherichia coli a faecal type flora was found in the duodenum. This flora included the enteropathogenic E coli serotype isolated from the stool in three quarters of cases.

Infants with persisting diarrhoea had significantly more faecal type bacteria in the duodenum than either those with acute diarrhoea or the convalescent group. In addition, there was a significant further increase in Enterobacteriaceae in infants whose persistent diarrhoea occurred after infection with enteropathogenic E coli.

Infections with enteropathogenic E coli may have a predilection for disturbing the duodenal microflora, which may contribute to the development of persistent diarrhoea.

Introduction

Increasing attention is being directed to the importance of persistent or chronic diarrhoea in young children as a cause of morbidity and mortality in the developing world.[1] The aetiological mechanisms are ill understood and are probably complex, and a "vicious cycle" of events has been proposed.[2] Bacterial contamination of the duodenum with Enterobacteriaceae is a feature of chronic diarrhoea,[3-5] and this provides a possible explanation for the attendant malabsorption of fat[6] and carbohydrate.[7] The aetiology of this bacterial overgrowth is unknown. Contamination of the upper small intestine with bacteria normally associated with the lower gut may also occur in acute enteric infections.[8-10] In the first week of infection this differs with different aetiologies; thus there was little disturbance of flora in patients with rotavirus and non-bacterial diarrhoea,[9 11] whereas in bacterial enteritis—especially when associated with *Escherichia coli* infection—high counts of bacteria have been recorded.[8 9] Rotavirus,[12] adenovirus,[13] enteropathogenic *E coli*,[8] enterotoxigenic *E coli*,[8] and salmonella[14] have all been isolated from the upper small intestine during acute infections.

It may be important to understand the relation between the intestinal bacterial overgrowth in acute diarrhoea and the overgrowth in persistent diarrhoea. We have therefore studied the duodenal microflora during and after acute infantile infectious diarrhoea of known aetiology, comparing the flora of convalescent infants with that in infants with persisting diarrhoea.

Patients and methods

STUDY GROUPS

Infants with acute diarrhoea—Forty infants aged 2-43 weeks who were admitted with a history of acute onset of diarrhoea (defined as three or more liquid stools a day, representing a change from previous bowel habit) were studied within the first week of diarrhoea. Infants taking antibiotics were excluded and all babies were rehydrated before the test.

Convalescent infants—Seven infants in the convalescent phase and free of diarrhoea (fewer than three stools a day for two consecutive days) were studied 14 days or more after the onset of diarrhoea. Two of these infants were from the group studied during the acute phase.

Infants with persisting diarrhoea—Fifteen infants with diarrhoea persisting 14 days or more after an acute onset were studied.

Permission to study the infants was obtained from all parents before the tests, and when possible they helped in the procedure. Ethical approval was given by the research and ethical committee of East Birmingham Hospital.

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DUODENAL INTUBATION AND LABORATORY INVESTIGATIONS

Duodenal intubation was performed usually on the morning after admission and three to six hours after the last drink, depending on the frequency of feeds. We did not think it justifiable to starve the babies for the test. A sterile 6 or 8 French gauge lubricated single lumen tube was passed through one nostril into the stomach, which was inflated with 20-30 ml of air, allowing the tube to be easily advanced into the duodenum. Aspirate was accepted if it had a pH of 6 or more and was stained with bile. No *x* ray positioning was used. The first aliquot of aspirate was discarded. Subsequent samples were collected for confirmation of pH, viral analysis, and the last sample for bacterial culture. The procedure was well tolerated by the children and was usually completed in 30 minutes.

The duodenal aspirate was taken directly to the microbiology laboratory, where it was serially diluted with peptone water and spread on pairs of blood agar plates incubated anaerobically and aerobically at 37°C. The number of colony forming bacteria per ml of aspirate was calculated by counting separate colonies on the dilution plates. Selective media, MacConkey's agar, and Sabouraud's agar were also inoculated. Colonies were classified as upper respiratory commensals after routine preliminary identification. Colonies from the MacConkey plates were Gram stained and *E coli* further identified by slide agglutination of a sweep of five colonies with polyvalent enteropathogenic *E coli* antisera for O antigen serotypes 26, 55, 111, 119, 126, 86, 114, 125, 127, 128, 18ac, 44, 112ac, 124, and 142 and confirmed by tube agglutination. One further strain (serotype O153) was examined in more detail by the Center for Vaccine Development, Baltimore, because it was present in the duodenum in such high numbers (10^{10} colony forming bacteria/ml aspirate). This was found to be an enterotoxigenic *E coli* producing ST toxin.[15] Non-lactose fermenting colonies were examined by standard techniques for salmonella and shigella, but none was found.

Stools were examined in all infants for bacterial pathogens including *Campylobacter* spp, salmonellas, shigellas, and enteropathogenic *E coli*. Aspirate and stool were examined by electron microscopy for virus particles and were tested by enzyme linked immunosorbent assay for rotavirus.

Results

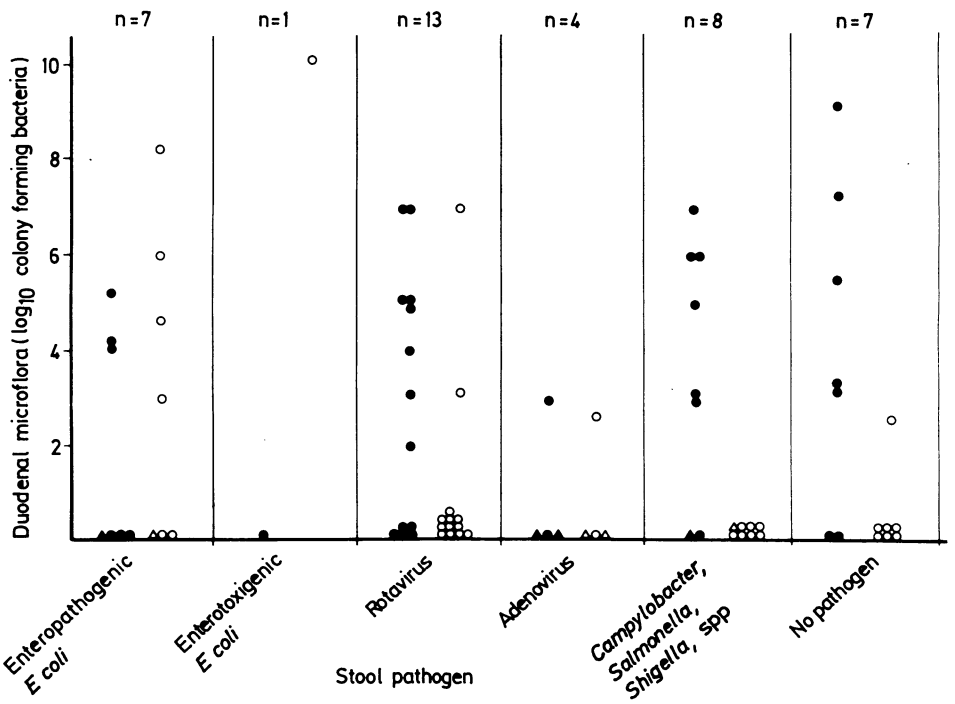
INFANTS WITH ACUTE DIARRHOEA

The figure shows the results of bacterial culture of duodenal aspirates from 40 infants with acute diarrhoea of less than seven days' duration. Infants are grouped according to the isolation of potential pathogens in their stools—enteropathogenic *E coli*, enterotoxigenic *E coli*, rotavirus, adenovirus, dysenteric bacteria (shigellas, campylobacters, salmonellas), and no pathogen isolated. Three infants had two possible pathogens identified: an enteropathogenic *E coli* and an enteric adenovirus; *Campylobacter jejuni* and an enteric adenovirus; and *C jejuni* and *Shigella flexneri*.

Sixteen of the 40 children had more than 10^4 colony forming bacteria/ml duodenal aspirate but there was no difference in the frequency of this occurrence among the different groups. Nine children (22·5%) had faecal type organisms isolated. More than half (57%) of the infants with enteropathogenic *E coli* serotypes identified in their stools had faecal organisms in the duodenum. In three of the four children the same enteropathogenic *E coli* was isolated from faeces and duodenum. Thus in the first week of acute infectious diarrhoea attributed to enteropathogenic *E coli* the putative pathogen could be cultured from the duodenum of nearly half of the patients and accounted for the excess of faecal type organisms isolated in this group.

CONVALESCENT INFANTS

Table I gives the results in seven diarrhoea free convalescent patients sampled 14 days or more after the onset of their diarrhoea. Only low numbers (10^4 or fewer colony forming bacteria/ml) of upper respiratory tract commensals were found and only two infants had faecal type bacteria.



Duodenal microflora in acute diarrhoea of different aetiologies less than seven days from onset of diarrhoea. n=Number of infants in each group. ▲●=Upper respiratory tract flora. △○=Faecal type flora. ▲△=Infant with dual pathogens.

INFANTS WITH PERSISTING DIARRHOEA

Table II shows the results in 15 infants sampled 14 days or more from the onset of diarrhoea who continued to have three or more loose stools a day at the time of the test. The initial results of stool microbiology and virology during the acute phase were used to attribute the aetiology. Two of the patients with enteropathogenic *E coli* (cases 18 and 19) had duodenal intubation during the acute phase. In both cases the enteropathogenic *E coli* serotype isolated from the duodenum and stool was the same.

During the persistent phase faecal type organisms were cultured from the duodenum of 12 of these 15 infants, which was a significantly higher proportion than in the acutely ill children ($\chi^2=13·7$; $p<0·001$). More faecal type organisms were found in the duodenum of infants with prolonged diarrhoea than in those who had recovered (Mann-Whitney U test, $p<0·002$). Mean ages of these two groups were 19·7 and 15·7 weeks respectively and mean times from the onset of illness 17·3 and 27·2 days. This last difference was partly accounted for by a single infant (case 2) sampled 60 days after the onset of diarrhoea.

Three of the six infants who had prolonged diarrhoea attributed to

TABLE I—*Duodenal microflora in asymptomatic convalescent infants intubated 14 days or more after onset of diarrhoea*

Case No	Age in weeks	Days from onset	Putative pathogen in stools in acute phase	Duodenal microflora (log_{10} colony forming bacteria/ml)	
				Upper respiratory tract flora	Faecal type flora
1	17	21	Rotavirus	NG	10^5 *Klebsiella* spp
2	23	60	Rotavirus	10^4 α Haemolytic streptococci, *Neisseria* spp, diphtheroids	NG
3	3	18	Rotavirus	10^4 α Haemolytic streptococci, *Neisseria* spp, diphtheroids	NG
4	37	24	Enteropathogenic *E coli* O114	10^4 *Str viridans*, *Neisseria* spp	NG
5	43	28	Enteropathogenic *E coli* O111	10^3 *Str viridans*	NG
6	3	22	None	NG	6×10^5 *E coli*
7	12	17	None	NG	NG

NG=No growth.

TABLE II—*Duodenal microflora in infants with persisting diarrhoea intubated 14 days or more after onset of diarrhoea*

Case No	Age in weeks	Days from onset	Putative pathogen in stools in acute phase	Duodenal microflora (log_{10} colony forming bacteria/ml)	
				Upper respiratory tract flora	Faecal type flora
8	14	25	Rotavirus	10^4 Streptococci, staphylococci	10^4 *E coli*
9	13	16	*Salm enteritidis*	NG	NG
10	11	18	*Sh flexneri, rotavirus*	NG	NG
11	12	15	None	10^5 Mixed	$1{\cdot}1\times10^5$:10^5 Streptococci, 10^4 *E coli*
12	7	14	None	NG	2×10^6 *Acinetobacter* spp
13	17	20	None	$1{\cdot}1\times10^4$:$4{\cdot}3\times10^3$ *Neisseria* spp, $2{\cdot}3\times10^3$ *Str viridans*, $4{\cdot}6\times10^3$ *H influenzae*	9×10^2 *Str faecalis*
14	8	21	None	NG	$1{\cdot}8\times10^3$:5×10^2 *Str faecalis*, $1{\cdot}3\times10^3$ coliforms
15	26	23	None	$8{\cdot}8\times10^6$:4×10^6 α Haemolytic streptococci, 4×10^6 *Str pneumoniae*, 8×10^3 *Staph aureus*	NG
16	35	14	None	$4{\cdot}4\times10^3$:$2{\cdot}8\times10^3$ *Staph aureus*, $1{\cdot}6\times10^3$ α haemolytic streptococci	$3{\cdot}4\times10^3$:3×10^3 Streptococci, 4×10^2 *Klebsiella* spp
17	2	16	Enteropathogenic *E coli* O127	NG	10^4 *Klebsiella* spp
18	37	14	Enteropathogenic *E coli* O114	NG	10^6 Enteropathogenic *E coli* O114
19	26	15	Enteropathogenic *E coli* O128	NG	$2{\cdot}4\times10^7$ Enteropathogenic *E coli* O128
20	15	15	Enteropathogenic *E coli* O128	NG	$2{\cdot}5\times10^4$ *E coli*
21	4	15	Enteropathogenic *E coli* O114	4×10^4 Mixed	$6{\cdot}0\times10^6$:$4{\cdot}5\times10^6$ Anaerobic bacilli, $1{\cdot}5\times10^6$ coliforms
22	8	19	Enteropathogenic *E coli* O126	$1{\cdot}4\times10^8$ Mixed including $4{\cdot}4\times10^5$ *Klebsiella* spp	$1{\cdot}3\times10^6$ Enteropathogenic *E coli* O126

NG=No growth.

enteropathogenic *E coli* infection had the same enteropathogenic *E coli* cultured from the duodenum when sampled 14 days or more after onset of diarrhoea. The other three had more than 10^4 faecal type organisms cultured. This represented significantly higher bacterial counts from prolonged infection due to enteropathogenic *E coli* compared with prolonged infections due to other pathogens (Mann-Whitney U test, $p<0{\cdot}002$).

Five of the 15 infants had more than 10^4 upper respiratory tract commensals/ml, which was not significantly different from the proportion in the group with acute diarrhoea.

Discussion

Bacterial culture of duodenal aspirate obtained using a single lumen open ended tube has been shown to give results comparable to those after direct sampling of the intestine at surgery.[16] The technique used was simple, quick, and caused little discomfort. Using similar open tubes other studies of comparable populations have found up to 10^4 upper respiratory commensals and no faecal type flora in the proximal small intestine of healthy children.[11 17]

In most of our infants intubated within seven days of onset of diarrhoea the aspirate was sterile or grew only upper respiratory tract commensals. The exception to this was that infants with diarrhoea associated with *E coli* (enteropathogenic or enterotoxigenic) tended to have a faecal type flora. This is consistent with findings from Ethiopia[8] and India,[9] showing that this phenomenon occurs not only in infants in countries where a contaminated environment and malnutrition may complicate the issue but also in relatively affluent countries.

Our findings confirm reports that the specific enteropathogenic *E coli* present in stools may also be isolated from the duodenum.[8 9] This accounted for the excess of faecal type duodenal bacteria in the patients with enteropathogenic *E coli* in our study. Probably organisms found in this site are pathogenic, because both in experimental infection with enteropathogenic *E coli* serotypes[18] and in detailed studies of severe infections[19 20] enteropathogenic *E coli* has been detected in the small intestine, and enteropathogenic *E coli* isolated from children with diarrhoea can be shown to adhere to small intestinal human enterocytes in vitro.[21] In four of the infants with enteropathogenic *E coli* serotypes isolated from the stools the same organisms were not found in the duodenum. Possibly in these patients the bacteria were missed either because sampling was proximal to the bacterial contamination or because the bacteria had already been cleared.

Until recently serotyping has been the only means of identifying members of this group of pathogens, but evidence now suggests that adherence to enterocytes in the small intestine, with brush border effacement, provides a better correlation with pathogenesis.[20 22] An alternative explanation for those cases where the enteropathogenic *E coli* was isolated only from stool is that these strains were not truly pathogenic. In one of the four infants an enteric adenovirus was also isolated.

There was an increase in total bacterial counts and especially in the Enterobacteriaceae isolated from infants who had diarrhoea persisting for 14 days or more. This was significantly greater than both the bacterial counts in acute diarrhoea and the counts in infants who were sampled at similar times after onset but who were symptom free. This non-specific effect of chronic diarrhoea was described by Challacombe *et al* in 1974[3] and has since been reported elsewhere.[4 5]

In our study an additional effect was identified. Infants with prolonged diarrhoea initially attributed to enteropathogenic *E coli* infection had significantly higher numbers of faecal type flora than were found in infants with prolonged diarrhoea of other aetiologies. Thus there seems to be a disturbance of small intestinal bacterial flora specific to enteropathogenic *E coli* infection which cannot be explained entirely by the effect of the diarrhoea itself. Nor can this effect be attributed solely to the persistence of the enteropathogenic *E coli* itself, since this was present in only half the cases. In the other three cases there were high counts of faecal type bacteria.

Little is known about the adherence and pathological characteristics of the organisms isolated from the upper gut in infants with persistent diarrhoea. Bacteria isolated from the jejunum of adults with tropical sprue have been shown to produce enterotoxins[23] and adhere to cells in tissue culture.[24]

Mucosal damage, fat malabsorption, carbohydrate malabsorption, and diarrhoea occur when there is bacterial contamination of the small intestine,[25] and a similar effect of an altered microflora occurring after acute enteritis might explain the persistence of diarrhoea and malabsorption. Until now studies of established diarrhoea documenting such a pattern have been unable to differentiate between cause and effect.[4 7] Even diarrhoea produced experimentally by infusion of sterile saline is known to result in bacterial overgrowth in the jejunum.[26] Our study shows, however, that, certainly in enteropathogenic *E coli* infections, there is a bacterial overgrowth which cannot be attributed to the presence of diarrhoea alone.

The aetiology of the initial infection is known to be a factor in determining the duration of diarrhoea. For instance, diarrhoea due to enterotoxigenic *E coli* or shigella infection lasts longer than that due to rotavirus.[27] Enteropathogenic *E coli* infections, in common with all other acute enteric infections, are usually short lived, but enteropathogenic *E coli* serotypes may be associated with persistent diarrhoea.[19 20 28] Our results suggest a possible explanatory mechanism for this persistence. Our understanding of the pathogenic mechanisms which determine the virulence of enteric pathogens has advanced rapidly in recent years following the application of advances in molecular genetics, electron microscopy, and immunology to the study of these organisms. We now need to apply these techniques to the bacterial flora of the duodenum to understand its role in the pathogenesis of prolonged diarrhoea.

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100 YEARS AGO

A movement on the part of brigade-surgeons of the Medical Staff Corps serving in India, the recognition of their rank on the part of the Government of India, is now in progress. It is alleged that, as the matter stands, the rank brings with it duties and responsibilities far in excess of those of surgeons-major when in charge of regiments under the old regulations. They are now always posted to the headquarters of a division, and hold charge of the station-hospital, frequently in two or more sections, and they perform duties formerly divided among several senior officers. In addition to this, they have to carry on the duties of the deputy surgeon-general during his absence on duty, and when absent on privilege-leave up to three months, without additional pay or allowances, doing, also, their own work. The only recognition of the rank of brigade-surgeon in India seems to be permission to wear a different uniform from that of a surgeon-major.

The Government of India have, over and over again, asserted their right to regulate the pay and allowances of medical officers of the British Services serving in India, irrespective of any warrants dealing with the rank and pay of the same officers when at home. This is a regulation which cuts both ways, sometimes to the advantage, at others to the disadvantage, of the officers. When the pay-regulations for the medical department in India were promulgated, promotion to the administrative rank was quicker by five years than it is now. Consequently, surgeons-major are now in this position, they have to serve from twenty years' service to over thirty, with but one small increment of pay—thirty-seven rupees *per mensem* after twenty-five years' service.

The position of brigade-surgeon is attained not by any means as a matter of course. On the contrary, it is one of selection in the strictest sense of the term; only about 25 per cent. of the grade of surgeon-major attain to it at all. There must first be evidence of physical fitness to serve in any climate; favourable reports both from medical and military superiors; foreign service of, as a minimum, eight years; and last, not least, a strict examination.

All this being so, we think, on the part of the Indian Government, there ought to be some substantial recognition of the fact. The Government get the advantage of superior qualification for posts of responsibility and importance, and it is only right and reasonable that the advantage should not be one-sided. At the same time, we think the Indian Government have a right to place a limit on the number of brigade-surgeons sent to India. Let their remuneration be more in proportion to work and responsibility than it is now, but they have a perfect right to regulate the number of brigade-surgeons in receipt of extra emoluments. We think, if it became the practice to send brigade-surgeons in excess of service-requirements, the wrong at present done to them would be shifted to the finances of India.

There is a good precedent for this act of justice. The majors of artillery, when promoted from the rank of captain, were all granted majors' pay, the grant being even made retrospective. The BRITISH MEDICAL JOURNAL has never been the advocate of unreasonable demands on the part of the medical officers of the public services, or the organ of grievance-mongers; all the more, when it speaks as the organ of 12,000 members of the profession, and asks for justice to deserving officers who serve the State in positions of great usefulness and responsibility, its voice should be listened to. (*British Medical Journal* 1886;ii:219.)