Colonic Perforation after Exchange Transfusion

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Summary: Four patients are reported in whom perforation of the colon followed exchange transfusion for haemolytic disease of the newborn. This association seems to be more than coincidental, and possibly the perforation is due to a vascular accident occurring as a mechanical result of the exchange transfusion. The insidious onset of colonic perforation may be recognized early by the passage of blood per rectum. There is no place for conservative treatment, and once the diagnosis has been made treatment must include broad-spectrum antibiotics and laparotomy.

Introduction

Spontaneous perforation of the colon in the neonate is a well-recognized but rare surgical emergency. We wish to report four cases treated at the Children's Hospital, Sheffield, in which the perforation followed exchange transfusion for haemolytic disease of the newborn, to suggest a way in which the transfusion may have led to the perforation, and to indicate some of the difficulties in early diagnosis.

Case 1

This patient was the eighth child of a rhesus-negative mother and a homozygous rhesus-positive father. Four of his siblings had had exchange transfusions because of erythroblastosis foetalis; he was delivered by caesarean section because of delay in the first stage (mother's history) and weighed 5 lb. 5 oz. (2,410 g.) at birth.

When he was 5 hours old an exchange transfusion was performed for haemolytic disease. The abdomen was noted to have been moderately distended at that time and the rectum was empty. At 48 hours a second exchange transfusion was performed because of a rising serum bilirubin. He tolerated this procedure well but six hours later passed blood per rectum. On the sixth day, because of abdominal distension, abdominal paracentesis was performed and gas and fluid were obtained. He was started on intravenous fluids and antibiotics. The following day he passed changing stools. On the eighth day he was transferred to the paediatric surgical unit of this hospital.

On examination he was moderately jaundiced though well hydrated. The abdomen was distended and there was oedema of the abdominal wall. No masses could be felt in the abdomen, and bowel sounds were absent. Rectal examination revealed a little blood-stained faeces. An x-ray film showed dilated loops of small bowel, but no free gas.

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At laparotomy a large collection of faeces was found in the left side of the peritoneal cavity. The small bowel was inspected, and no perforation was found. The proximal transverse colon contained gas. A narrowed segment of bowel was noted in the region of the splenic flexure, but owing to adhesions and soiling could not be examined thoroughly. The actual site of perforation was not located. Peritoneal lavage was performed, a proximal colostomy made, and the abdomen closed with drainage. A swab taken from the peritoneal cavity grew Pseudomonas pyocyanae and Escherichia coli. Postoperatively he was treated with antibiotics, and made a good recovery.

Two months later a barium enema showed "an extremely narrow" segment, about 2 cm. long, proximal to the splenic flexure (Fig. 1). At 10 weeks of age a second laparotomy was performed. Frozen section revealed normal innervation in the rectosigmoid region. The narrow segment of bowel at the splenic flexure was excised and an end-to-end anastomosis was performed. Macroscopic examination failed to reveal a lumen in this narrow segment. A month later his colostomy was closed, and he has made uneventful progress ever since. He was last seen at the age of 2½ years, when he was free of complaints and was developing normally.

Case 2

A female child, the second baby of a rhesus-negative mother and a homozygous rhesus-positive father, was born at the Jessop Hospital for Women, Sheffield, following induction of labour at 37 weeks' gestation. Her birth weight was 6 lb. 4 oz. (2,835 g.). The cord bilirubin was 4.6 mg./100 ml., and an exchange transfusion...
was performed at 3 hours of age. This procedure was uneventful. At 20 hours she passed normal meconium, and did so on two further occasions. Apart from a number of mucous vomits she remained well, but at 48 hours her general condition deteriorated rapidly. There was progressive abdominal distension, and she developed peripheral cyanosis and tachycardia. An x-ray film of the abdomen (Fig. 2) showed free gas in the peritoneal cavity, and she was transferred to the paediatric surgical unit.

![X-ray film of abdomen showing pneumoperitoneum.](image)

At that stage she was still slightly jaundiced, but was active and not acutely distressed. The abdomen was tensely distended and tympanitic. No masses could be felt. Rectal examination revealed normal meconium. At laparotomy a few hours after admission free gas, pus, and fibrinous exudate were found in the peritoneal cavity. There was no free meconium. A small pinhole perforation was found in the caecum on its antimesenteric border. Peritoneal lavage was performed and the caecal perforation exteriorized. The affected portion of caecum was excised for biopsy, but unfortunately was lost. A swab taken from the peritoneal cavity grew E. coli. Postoperatively antibiotics were continued, the caecostomy was closed after nine days, and, apart from a pseudomonal infection of her wound, she made a straightforward recovery. When last seen at 10 weeks of age she was gaining weight, and appeared normal in every way.

**Case 3**

A male infant, the third child of a rhesus-negative mother, was born at home at full term weighing 7 lb. 13 oz. (3,545 g). Cord blood bilirubin was 5.0 mg./100 ml., and the Coombs test was positive. Ten hours after birth he was noticed to be jaundiced, and was admitted to hospital. Shortly after this he passed normal meconium. At 24 hours an exchange transfusion was performed because of a rising serum bilirubin and a falling haemoglobin. He tolerated this procedure well, but four hours afterwards passed a small amount of blood and mucus per rectum. Over the next 24 hours his general condition began to deteriorate, and he began to vomit. At 48 hours he was admitted to the paediatric surgical unit.

On admission he was jaundiced (total bilirubin 12 mg./100 ml.) and lethargic. There was moderate distension of the abdomen, and a mass could be felt in the left hypochondrium. This was thought to be an enlarged spleen. An x-ray film of the abdomen (Fig. 3) showed some distended loops of gut with a suggestion of free peritoneal fluid but no free gas. These appearances were thought to represent a paralytic ileus in a septicæmic baby. The next day he developed twitchings due to hypocalcaemia, which was corrected with intravenous calcium gluconate. Because of persistent abdominal distension and aspiration of bile-stained fluid from the stomach, laparotomy was performed when he was 4 days old.

![X-ray film of abdomen showing distension of small bowel, with a few fluid levels and a suggestion of free peritoneal fluid. Note the absence of free intraperitoneal gas.](image)

A lot of clear yellow fluid was found in the peritoneal cavity. A large yellow mass in the region of the splenic flexure, corresponding to the mass felt preoperatively, proved to be faeces in the colon, covered only by an extremely thin layer of serosa. There was no trace of the muscular or mucosal layers in the region of the splenic flexure, over an area about 2.5 cm. in diameter. The serosal layer was so thin that immediately an attempt was made to mobilize the affected bowel it burst, and there was gross faecal soiling. There were numerous purplish red patches on the antimesenteric border of the descending colon distal to the splenic flexure and down to the mid-sigmoid colon. The affected segment of colon was resected. A terminal right transverse colostomy was performed. The distal end of the sigmoid colon was oversewn and dropped back into the peritoneal cavity. A swab from the peritoneal cavity grew E. coli. Culture of a segment of the umbilical vein grew E. coli (same sensitivities as the peritoneal one), Proteus vulgaris, and Streptococcus faecalis. Postoperatively he made a slow but steady recovery. At 6 weeks bowel continuity was restored, and he has remained perfectly well ever since.

**Case 4**

A male child was born to a multiparous rhesus-negative woman. Birth weight was 5 lb 2 oz. (2,340 g). Cord blood bilirubin was 4.5 mg./100 ml., and exchange transfusion was carried out when he was 4 hours old. He had one apnoic episode towards the end of this procedure, but recovered spontaneously. At 24 hours another exchange transfusion was done because of a bilirubin level of 24 mg./100 ml. There was no difficulty during this procedure. At 48 hours he passed some blood per rectum, together with normal meconium. At 65 hours a third exchange was done because the bilirubin was again rising. After a further 22 hours he was noted to have abdominal distension, and began to vomit. There were no further bowel movements. Oral fluids were withheld, and the abdominal distension was thought to decrease a little. The next day oral fluids were restarted and retained. There was, however, a slight increase in the degree of abdominal distension. The bilirubin was 24 mg./100 ml. at this stage, but exchange transfusion was not repeated because of his poor general condition. When he was 5 days old his serum bilirubin rose to 28 mg./100 ml., and a fourth exchange transfusion was performed. He seemed a little better after this, and tolerated feeds. On the sixth day the abdominal distension increased rapidly. The bilirubin then was 13.6 mg./100 ml. On the seventh day an x-ray film of his abdomen showed an extensive pneumoperitoneum, and he was transferred to the paediatric surgical unit. Since birth he had had a four-day course of oxytetracycline followed by a combination of penicillin and streptomycin up to the time of admission.
Laparotomy was performed on the seventh day of life. At operation a large amount of gas and faeces was found free in the peritoneal cavity. The whole of the anterior wall of the descending colon was necrotic (Fig. 4). In the sigmoid colon there were a few necrotic spots on the antimesenteric border. The cæcum and transverse colon were intact. The affected segment of bowel was excised, and proximal and distal colostomies were performed. A swab from the peritoneal cavity grew Str. faecalis and Proteus vulgaris. Postoperatively he had a very stormy course, and developed extensive sclerema. However, he eventually recovered, and his progress has been satisfactory. At 5 months of age the colostomy was closed and bowel continuity restored.

Histology
The histological appearance of the damaged bowel was similar in the three cases in which material was available for examination. The lesion showed progression from necrosis confined to the epithelium through necrosis involving epithelium and muscle and extending to full-thickness loss. In places there was a mild inflammatory reaction at the edges of the affected areas, together with scattered extravasation of red cells.

Discussion

Diagnosis
Spontaneous perforation of the colon in the newborn is rare, and its association with exchange transfusion in four cases seems more than coincidental. It is suggested that the perforations in these cases occurred after second, first, first, and third exchange transfusions, and in retrospect a distinct, diagnostic sequence of events can be recognized. All patients were well at birth apart from their haemolytic disease and a weight of just over 5 lb. (2.270 g.) in two of them; in three the first abnormal sign was the passage of blood per rectum 4 to 15 hours after exchange, and this was followed within 24 hours (in Case 2 within 40 hours of the sole transfusion) by general non-specific deterioration, with lethargy, poor peripheral circulation, abdominal distension, and usually vomiting. The pattern was so recognizable that in our fourth case the diagnosis was made over the telephone to the referring paediatrician 80 miles (130 km.) away. The diagnosis may be confirmed by x-ray films showing free intraperitoneal gas (Fig. 2) or less dramatically showing fluid levels in bowel and a suggestion of free intraperitoneal fluid (Fig. 3). Abdominal paracentesis does not seem to have a place in the diagnosis, though therapeutic aspiration of free intraperitoneal gas may greatly increase the respiratory reserve preoperatively.

Aetiology
Though rare, spontaneous neonatal colonic perforation has been reported in the literature with many suggested causes. In small-bowel and large-bowel perforations localized bowel wall defects (von Sur, 1912; Moretti, 1949), primary vascular insufficiency (Pultauf, 1888; Helbing, 1908), and hypertrophy of the crypts of Lieberkühn coupled with thinness of the bowel wall and lymphoid hyperplasia (Boikin, 1930; Baehr, 1935; Maguire and Moore, 1950) have been suggested. In the colon specifically bacterial and fungal infection (Levin and Isaacson, 1960; Waldbaum et al., 1963), meconium and faecal plugs (Zachary, 1957), and haemangiomatious malformations of the bowel wall (Haas, 1958) have been put forward as causes.

Linkner and Benson (1959) reported a neonatal gastric perforation in a child with erythroblastosis without exchange transfusion, and Nienhuis (1963) an intrauterine colonic perforation in a child with haemolytic disease who later required exchange transfusion. However, the association between exchange transfusion and colonic perforation has been noted by Waldbaum et al. (1963), Forshall (1964), and in particular in a well-documented case by Hermann (1965), who suggested that the Schwartzman phenomenon was an aetiologic factor. Thomas and Brockman (1966) could find no firm evidence for this theory, and agreed with Waldbaum et al. in placing bacterial infection as the most important causal factor.

That colonic perforation following exchange transfusion should not be grouped with all "spontaneous" perforations in the neonate is suggested by its apparently good prognosis. All our cases survived; so did Hermann's (1965) case and two of the three cases reported by Wagget (1968). The general mortality of neonatal colonic perforation is very different; of the seven cases of Waldbaum et al. (1963) the only survivor was one who had had an exchange transfusion, and both patients of Levin and Isaacson (1960) died. Thomas and Brockman (1966) found 26 cases of uncertain aetiology, 17 were operated on, and only eight survived, all after operation; there is no record of whether or not exchange transfusion was associated in these cases.

Studying some of the hazards of exchange transfusion, using a catheter inserted into the umbilical vein, Mintz and Vallbona (1960) demonstrated that in the presence of upper respiratory tract obstruction markedly negative pressures are obtained in the catherized vein during inspiration. It is common experience during the procedure of exchange transfusion that if the patient strains or cries and the fluid level in the umbilical catheter can be observed the pressure within the umbilical vein can be seen to be raised by forcible expiration. Farquhar and Smith (1958) noted disturbances in 7 out of 19 patients during exchange transfusion. In two patients in whom the catheter was inserted 11 cm. into the umbilical vein, cyanosis of the lower half of the body associated with pallor of the upper half was noticed; increased venous filling and retrograde flow in the superficial veins were observed. These indicated that at that time there was a functional obstruction of the inferior vena cava. On withdrawing the catheter these signs subsided spontaneously and apparently without having produced any ill-effects. "Shock" — that is, the infants suddenly became quiet, their body temperature dropped, and they developed some abdominal distension which was not due to hepatomegaly — was noted in three of these cases, and no blood chemistry changes explained this.

The umbilical vein runs, in the free border of the falciiform ligament, to join the left branch of the portal vein in the porta hepatis. From the point on the left portal vein opposite this junction the ductus venosus runs on the posterior surface of the liver to join the left hepatic vein just before it enters the inferior vena cava (Johnston and Whillis, 1949). Van Loghem et al. (1949), by catheterizing the umbilical veins of lambs under x-ray control, have shown that usually it is easy to pass a catheter through the umbilical vein into the inferior vena cava via the ductus venosus. When the catheter had been inserted to a length of about 12 to 14 cm. it had reached the inferior...
vena cava. They also demonstrated that it is sometimes difficult to thread the catheter through the ductus venosus owing to a "stricture" in the distal part of the latter. In these cases they noted that the catheter whose passage is so obstructed is apt to turn off to the left or right side into the branches of the portal vein. As a rough guide they state that if the passage of the umbilical catheter is obstructed at 11 cm. the tip of the catheter is probably in a branch of the portal vein. The technique of exchange transfusion in general use at the present time involves inserting, usually, between 5 and 7 cm. of catheter well short of the junction of the umbilical and portal veins.

Fig. 5.—Cadaver injection study. X-ray film after injection of 5 ml. of radio-opaque medium with 5 cm. of catheter in umbilical vein.

Most people who perform exchange transfusion assume that the exchange is of inferior vena cava blood. This may be so, but with the tip of the catheter proximal to the ductus venosus there can be little doubt that some at least of this exchange takes place in the portal circulation. Perhaps in a quiet child in whom there is a low central venous pressure this fraction may be very small, but if the central venous pressure is raised, say, in a restless child, much of the injected blood may enter the portal circulation. Some of this will flow centrally, but some will also flow peripherally and thus raise the portal pressure relatively suddenly. Similarly, a narrow ductus venosus will lead to higher portal pressures during exchange. A further possibility may be that in catheterizing the umbilical vein a small thrombus may be dislodged and forced in a retrograde direction along the portal vein. The impressive cyanosis of the distal half of the body noticed by Farquhar and Smith (1958) in two of their patients in whom 11 cm. of umbilical catheter was inserted should alert us to the possibility, and indeed the probability, that equally impressive changes may take place in the portal circulation if the catheter tip is in the appropriate place and there is some unusual increase in resistance to the flow of blood into the systemic circulation. If the tip of the catheter has actually strayed into the portal vein itself then profound changes in pressure and turbulence undoubtedly must occur in the portal circulation.

It is difficult to devise any experimental injection of the umbilical vein which would exactly mimic the situation during an exchange transfusion. However, experimental injection of an opaque medium into the umbilical vein of cadavers has indicated the ease with which the portal venous system may be outlined, as shown in Figs. 5 and 6. An umbilical vein catheter was inserted 5 cm. into the umbilical vein and an opaque medium as used in other cadaveric angiographic studies (Lister, 1964) was injected. X-ray studies indicate that in a cadaver in which the cardiovascular system has not been perfused it is very much easier for the opaque medium to run into the portal system than into the vena cava.

That a vascular lesion was primarily responsible for the perforations in the four cases reported here is suggested by the fact that in three of these the passage of blood per rectum was the earliest sign that something was amiss, as it was in two of Wagget's (1968) three cases. This would suggest that a haemorrhagic infarct had occurred at the time of the exchange transfusion. It is suggested that, for one of the reasons already referred to, a vascular catastrophe of some sort (such as severe arteriospasm, venospasm, or sudden occlusion of the venous drainage due to a small retrograde embolus) occurred, resulting in infarction of the bowel wall with perforation, and in Case 1 an ischaemic stricture was produced in the region of the splenic flexure in addition. Further support is lent to this suggestion.

Fig. 6.—Cadaver injection study. X-ray film taken after injection of 30 ml. of radio-opaque medium with 3 cm. of catheter in umbilical vein.

Key to Fig. 5.

Key to Fig. 6.
in that in the resected specimen in Case 3 there were numerous red patches on the antimesenteric border of the descending colon. These were acutely congested patches that had not actually infarcted, and in Case 4 similar patches in the sigmoid colon actually showed full-thickness necrosis which had not perforated, presumably because of the proximal perforation.

Why these lesions should be more common in the colon than in the small bowel is difficult to explain if the condition is due to vascular changes resulting from back pressure. Cases 1, 3, and 4 perforated in inferior mesenteric vein territory, but Case 2 involved superior mesenteric vein territory, and Schaffer (1960) described a case in which there was an "unexpectedly excellent result" in a "miracle baby" who had two ileal perforations closed at laparotomy, and these occurred after an exchange transfusion. More small-bowel perforations may be reported once the association between bowel perforation and exchange transfusion becomes more appreciated; but it may be that the more complex venous system of the small bowel dams down any sudden rises in portal pressure more effectively than the large-bowel venous system. Continuous monitoring of the injection pressure during exchange transfusion could avoid large and dangerous pressure variations.

Perforation of the Bowel in the Newborn as a Complication of Exchange Transfusion


Summary: Spontaneous perforation of the bowel without evidence of intestinal obstruction is reported in six infants who had exchange transfusions for rhesus incompatibility, and in a seventh who had prolonged intravenous fluids via the umbilical vein. The pathological findings resemble those found in acute necrotizing enterocolitis in adults, which is known to be associated with arterial hypotension. The cause in these infants may also be due to a period of hypotension during the transfusion, and hypoxia and superimposed infection may also play an important part.

Introduction

"Spontaneous" perforation of the bowel in the newborn, where perforation occurs in the absence of intestinal obstruction, was first described by Siebold (1826). Thelander (1939) reviewed the world literature up to 1939. Of her 85 cases 65 occurred in the neonatal period. Thomas and Brockman (1966) found 26 further cases in the colon between 1946 and 1965, and Fonkalsrud et al. (1966) reported 19 cases of "spontaneous" perforation in a study of neonatal peritonitis. Some of the earlier cases may have been associated with meconium ileus due to cystic fibrosis or Hirschsprung's disease.

We describe six cases of "spontaneous" perforation in newborn infants who had had exchange transfusions shortly beforehand.

Case 1

A male infant weighing 3.2 kg. was delivered normally following induction at 36 weeks. The mother's blood group was O negative with rhesus antibodies present 1 in 40. There was no asphyxia at birth. Cord blood results were: group O positive; Coombs test positive; Hb 70%; bilirubin 9.7 mg/100 ml. Three exchange transfusions were carried out without difficulty in the first 48 hours, calcium supplements being given. No antibiotics were used.

At the age of 54 hours he became reluctant to feed and passed small quantities of bright blood rectally. Abdominal distension developed. Bowel sounds were normal. At 72 hours peribulbar oedema and erythema developed. Portal vein thrombosis was suspected. An abdominal x-ray picture was suggestive of ileus. There was no gas under the diaphragm.

Laparotomy at 130 hours showed facial peritonitis with two perforations of the large bowel, in the cecum and descending colon. The affected bowel was resected and an ileostomy fashioned. Post-operative recovery was good. Microscopy (Fig. 1) showed an acute colitis with extensive necrosis of the mucosa and submucosa. Associated vessels were thrombosed, but it was not possible to say whether this was primary or secondary.

Case 2

A male infant weighing 3 kg. was delivered by lower segment caesarean section for foetal distress after induction at 38 weeks. The liquor was meconium-stained. The infant had white asphyxia and required endotracheal oxygen for resuscitation. Maternal blood group: A negative, with antibodies 1 in 20. Cord blood: group O positive; Coombs test positive; Hb 85%. Exchange transfusion was carried out at three hours with calcium supplements. Streptomycin was given.

At the age of 4 days the infant developed bilious vomiting and passed blood and mucus rectally. Abdominal distension, grunting respiration, and peribulbar oedema and erythema followed. Bowel sounds were absent and peritonitis was suspected. An x-ray film of the abdomen showed gas under the diaphragm. At operation three large perforations were found in the sigmoid colon. The affected bowel was resected with an end-to-end anastomosis.