Predictors of gangrenous necrotizing enterocolitis and extent of disease

Early laparotomy versus peritoneal drainage

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ABSTRACT

Objectives: Evaluation of known predictors of gangrene in neonates with necrotizing enterocolitis (NEC) and identification of those suggestive of severe disease, requiring expeditious laparotomy rather than primary peritoneal drainage as a definitive treatment.

Methods: This is a retrospective review of data collected from the medical records of newborns with confirmed NEC, treated at the Maternity and Children's Hospital, Dammam, Kingdom of Saudi Arabia, from May 1993 to May 2004. Fifty-five cases were selected for the study, 23 had successful medical management and 32 underwent laparotomy. Of this group, 15 had peritoneal drainage prior to laparotomy. Nine known clinical, radiological and laboratory features suspicious of bowel perforation or gangrene were evaluated. The operated group was classified according to the extent of disease into isolated, multifocal or pan intestinal and the distribution of these 9 criteria was calculated for each of the 3 groups. Comparison was then carried out between the group with isolated NEC and those with extensive disease.

Results: Isolated NEC was present in 8 (25%), multifocal NEC in 19 (59%) and pan intestinal NEC in 5 (16%) of the operated cases. Pneumoperitoneum and palpable abdominal mass were the most specific and predictive signs of perforated or gangrenous bowel in NEC. Severe pneumatosis intestinalis and gasless abdomen were also highly specific and predictive of the same but had a low prevalence. Abdominal wall erythema, persistent metabolic acidosis, portal vein air, gasless abdomen and severe pneumatosis intestinalis were found to be associated with severe or extensive gangrene. Palpable abdominal mass and fixed dilated loops were increased in cases of isolated NEC. Portal vein air was associated with the highest mortality.

Conclusion: Pneumoperitoneum, though the only absolute evidence of bowel perforation, cannot predict the extent of disease. Peritoneal drainage is a useful stabilizing procedure but the presence of any of the above mentioned criteria which are associated with severe disease necessitate a quick decision in favor of laparotomy. The absence of these signs, however, cannot rule out extensive or progressive NEC and failure to improve after peritoneal drainage also requires an emergency laparotomy, regardless of birth weight or gestational age.

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Neonatal necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency requiring surgical intervention in most neonatal units.[1] It is an acquired polymicrobial inflammation of the bowel wall, which starts in the mucosa and may progress to full thickness necrosis or bowel perforation. Neonatal necrotizing enterocolitis may be isolated, involving a single or short bowel

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segment or extensive (multiple segments) or a long segment of bowel may be involved. In pan intestinal NEC, the majority of small and large bowel is affected.

The only absolute evidence of perforated bowel in these babies is the presence of free air or, pneumoperitoneum on abdominal radiographs. This finding, however, may be absent in a high proportion of infants with NEC and gangrenous bowel. In this group, the decision to operate was difficult as other indications for example, abdominal wall erythema, pneumatosis intestinalis, clinical deterioration and others, are considered nonspecific for the presence of necrotic bowel. Recently, isolated or focal intestinal perforation (FIP), in newborns without NEC, has been described as a separate disease entity affecting very low birth weight babies.[2,3] The presence of pneumoperitoneum on its own cannot distinguish between FIP and NEC. In FIP, primary peritoneal drainage (PPD), alone has been reported to be sufficient in the majority of cases.[4,5] In neonates with NEC, a higher mortality has been reported in those who had PPD when compared to those who had primary laparotomy,[6,7] and a rescue or salvage laparotomy was required in many cases who had PPD.[4-6,8] Laparotomy after unsuccessful PPD is technically difficult due to inflammatory response and organized suppuration or abscess formation around necrotic and perforated bowel, and is associated with an increased morbidity.[9] Operating early, even if PPD was used initially, may improve the outcome by removing necrotic bowel, which is a focus of continuing systemic sepsis in the patient. The optimum waiting time between PPD and laparotomy is however, undefined.

In a previous study of 67 newborns with established NEC, we found a much higher mortality rate and 3 times longer time interval from onset of NEC to laparotomy in babies with failed PPD when compared to those who had primary laparotomy.[10] Assuming that the babies who recovered after PPD had only isolated perforation and who did not had extensive disease, we have attempted to evaluate known predictors of gangrene[11] so as to identify those suggesting advanced gangrenous NEC.

Methods. Data was collected from medical records of 68 newborns with confirmed NEC classified according to Modified Bells Staging Criteria.[12] All had been managed in the neonatal intensive care units of Maternity and Children's Hospital, Dammam, Kingdom of Saudi Arabia from May 1993 to May 2004. Included in this study were 23 neonates treated successfully with medical therapy, and 32 who underwent laparotomy. In this operated group, 15 had a peritoneal drainage procedure prior to laparotomy. The infants who recovered completely by medical management alone were assumed to have no gangrene or perforation. Two babies who died during medical therapy and 11 babies who underwent PPD only were excluded from the study as it was not possible to determine the extent of disease in them. Data collected included gestational age, birth weight, clinical, radiological and laboratory manifestations suggestive of advanced NEC, operative findings regarding extent of NEC, histopathological reports for confirmation of NEC and outcome (death or discharge from the hospital). Presence and prevalence of 9 indicators or predictors of

Table 1 - Predictors of gangrene, predictive values and associated mortality to NEC (N=55).

Predictors	Prevalence		Gangrene		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Mortality	
	n	(%)	n	(%)	(%)	(%)	(%)	(%)	n	(%)
Abdominal erythema	25	(45)	22	(68)	(87)	(88)	(67)		12	(48)
Abdominal mass	8	(15)	8	(25)	(100)	(100)	(49)		4	(50)
Persistent metabolic acidosis	24	(44)	22	(68)	(91)	(92)	(68)		12	(50)
Significant thrombocytopenia	29	(53)	21	(66)	(65)	(72)	(58)		12	(41)
Severe pneumatosis intestinalis	2	(4)	2	(6)	(100)	(100)	(43)		1	(50)
Portal vein air	8	(15)	6	(19)	(91)	(75)	(45)		6	(75)
Pneumoperitoneum	22	(40)	22	(68)	(100)	(100)	(70)		9	(41)
Fixed loop on serial x-rays	17	(30)	13	(41)	(83)	(76)	(50)		5	(29)
Gasless abdomen	2	(4)	2	(6)	(100)	(100)	(43)		1	(50)

NEC - necrotizing enterocolitis

perforated or gangrenous bowel such as abdominal wall erythema, abdominal mass, radiological signs like pneumoperitoneum, diffuse or severe pneumatosis intestinalis (SPI), portal vein air (PVA), fixed dilated loops on serial x-rays, gasless abdomen and, laboratory signs like significant thrombocytopenia and persistent metabolic acidosis (PMA), were determined for each group. Significant thrombocytopenia was defined as the presence of at least 3 consecutive platelet counts <100,000/mm^3. Persistent metabolic acidosis was defined as a metabolic acidosis with pH <7.25 on serial blood gas estimations. For each of these criteria we estimated sensitivity, specificity and predictive values, using standard epidemiological methods (**Table 1**).[13] In the 32 operated cases of NEC, we classified the extent of gangrene as isolated, multifocal, or pan intestinal according to criteria adopted by Fasoli et al[14] and determined the distribution of 9 signs of gangrenous gut mentioned above (**Table 2**) in each group. A comparison of these presumed predictors of gangrene was also carried out between the group with isolated NEC and the group with severe disease (multifocal + pan intestinal NEC) (**Table 3**).

Results. Fifty-five neonates with confirmed NEC were analyzed, 23 of them recovered completely with standard medical management and 32 had laparotomy, 15 of them after a failed PPD. The mean birth weight was 1994 gms and gestational age was 33.7 weeks for the medically treated group and for the operated group, the mean birth weight was 1835 gms and gestational age was 32.5 weeks. The total mortality in babies who underwent laparotomy was 15/32 (47%), due mainly to the very high mortality in infants with PPD, 67% of whom died compared to 29% of those who had primary laparotomy. Isolated NEC was present in 8 (25%) of the operated group, whereas 19 (59%) had multifocal and 5 (16%) had pan intestinal disease. The highest mortality was in babies with pan intestinal NEC (80%), followed by 47% in multifocal and 25% in isolated NEC.

Table 1 shows that only palpable abdominal mass, pneumoperitoneum, SPI and gasless abdomen had specificity and positive predictive values of 100% but the prevalence of SPI and gasless abdomen was only 4% in our series of cases. Persistent metabolic acidosis had 91% specificity and a positive predictive value of 92%. Portal vein air had high specificity (91%), but low positive predictive value (75%). However, babies manifesting with PVA on abdominal radiographs, had the highest mortality (75%). On correlating these 9 predictors of gangrene with extent of disease in **Table 2**, an abdominal mass was present in 38% of babies with isolated NEC as compared to 21% in the multifocal and 20% in the pan intestinal groups. Abdominal wall erythema was noticeable in babies with severe disease, 79% in multifocal and 80% in pan intestinal, as compared to only 38% of those with isolated disease. The percentage of babies having PMA increased proportionately to the extent of disease, manifesting in 100% of those with pan

Table 2 - Predictors of gangrene, extent of disease and outcome in 32 operated cases.

Predictors of gangrene and mortality	Isolated NEC n = 8 (25%)		Multifocal NEC n = 19 (59%)		Pan intestinal NEC n = 5 (16%)	
	n	(%)	n	(%)	n	(%)
Abdominal erythema	3	(38)	15	(79)	4	(80)
Abdominal mass	3	(38)	4	(21)	1	(20)
Persistent metabolic acidosis	4	(50)	13	(68)	5	(100)
Significant thrombocytopenia	5	(63)	12	(63)	4	(80)
Severe pneumatosis intestinalis	nil	nil	1	(5)	1	(20)
Portal vein air	nil	nil	3	(16)	3	(60)
Pneumoperitoneum	6	(75)	14	(74)	2	(40)
Fixed loop on serial x-rays	4	(50)	8	(42)	1	(20)
Gasless abdomen	nil	nil	1	(5)	1	(20)
Mortality	2	(25)	9	(47)	4	(80)

NEC - necrotizing enterocolitis

Table 3 - Predictors of gangrene in isolated versus severe NEC in 32 operated cases.

Predictors of gangrene	Isolated NEC n = 8		Severe NEC n = 24	
	n	(%)	n	(%)
Abdominal erythema	3	(38)	19	(79)
Abdominal mass	3	(38)	5	(21)
Persistent metabolic acidosis	4	(50)	18	(75)
Significant thrombocytopenia	5	(63)	16	(67)
Severe pneumatosis intestinalis	nil		2	(8)
Portal vein air	nil		6	(25)
Pneumoperitoneum	6	(75)	16	(67)
Fixed loop on serial x-rays	4	(50)	9	(38)
Gasless abdomen	nil		2	(8)

NEC - necrotizing enterocolitis

intestinal NEC. This group also had significant thrombocytopenia in 80% as compared to 63% in the multifocal group. Pneumoperitoneum was present in 74-75% of babies with isolated and multifocal NEC and in 40% of those with pan intestinal NEC. None of the babies with isolated disease manifested with either PVA, SPI or gasless abdomen. Sixty percent of infants with pan intestinal NEC had PVA and 20% had SPI and gasless abdomen when compared to only 16% PVA and 5% SPI as well as gasless abdomen in the multifocal group. Fixed dilated loops on serial abdominal radiographs presented in 50% of those with isolated disease, 42% in the multifocal group and only 20% of cases with pan intestinal NEC. A comparison between isolated NEC and severe NEC is shown in **Table 3**. Palpable abdominal mass and fixed dilated loops were increased in isolated NEC. Abdominal wall erythema, PMA, PVA, SPI and gasless abdomen were increased in severe NEC cases. Pneumoperitoneum and significant thrombocytopenia were not found to be useful in predicting the extent of disease.

Discussion. Surgical intervention in advanced NEC is essential to prevent life threatening complications and improve outcome. Well-defined objective criteria for laparotomy versus PPD are unavailable and the superiority of either procedure is debatable. Infants with isolated NEC or perforation may respond favorably to PPD but laparotomy with removal of necrotic bowel should ideally be carried out as early as possible in those with extensive disease. The problem lies in differentiating between isolated and extensive NEC. Kosloske[11] found that pneumoperitoneum, positive paracentesis and PVA were the most reliable indicators of bowel gangrene in NEC, followed closely by palpable abdominal mass, abdominal erythema and fixed intestinal loops on serial x-rays. She also considered SPI a fair indication for surgery and in her study of 147 cases, thrombocytopenia, clinical deterioration and gasless abdomen were nonspecific indicators of gangrene. Abdominal wall erythema was associated with advanced disease in 101 cases analyzed by Cikrit et al,[17] as was the case in our series. Persisting abdominal erythema in spite of PPD requires early operation as hemodynamic instability can supervene quickly in the presence of large amounts of necrotic bowel in these small, premature newborns. Abdominal mass in our study was associated with localized disease and this maybe due to walled off perforation and gangrene, with or without abscess formation. This, however, may or may not respond to PPD. Kosloske[11] considered a palpable abdominal mass to be a valid indication for operative intervention but in her series, PPD was not used and laparotomy was the treatment of choice.

In our study, PVA did not reliably indicate a need for surgical intervention, but a breakup of operated cases reveals it to be exclusively associated with severe NEC (**Tables 2 & 3**), and with the poorest outcome (**Table 1**). Tam et al[15] studied 80 neonates who had laparotomy for advanced NEC or FIP and observed that PVA was indicative of severe disease and a high mortality. Severe pneumatosis intestinalis in their series as in ours had a similar association with severe NEC. However, they have advised that the absence of radiological signs classically associated with NEC should be treated with caution as all of them have low sensitivities. Molik et al[16] found PVA to be a poor prognostic sign, particularly in babies with low birth weight. In their study, 25% of neonates with PVA had NEC totalis. Cikrit et al[17] noticed that neonates who had PVA and NEC, and were operated early, demonstrated increased survival. On analysis of 53 babies with PVA, Cikrit et al[18] found that NEC totalis was present in 55% of the group with PVA. They suggested that PVA is a sign of advanced disease needing early surgery. Kosloske[11] also considered PVA as an indication for operation. Tam et el[15] found that pneumoperitoneum was present in only 52% of their patients with perforation and gasless abdomen was sometimes the only sign of perforation in babies weighing <1000 gms, a finding corroborated in a recent study.[19] We have noticed that though pneumoperitoneum was 100% specific and predictive of bowel perforation it

could not predict the extent of disease. In fact, it was present in only 40% of those with pan intestinal disease. Gasless abdomen was present in only 2 babies in our study both were <1000 gms, one with multifocal and the other with pan intestinal NEC.

Fixed, dilated loops on serial abdominal radiographs, manifested in 41% of our babies, and were mostly associated with localized disease. They were also noticed in 4 of our medically treated babies who recovered completely. This sign was first described by Wexler[20] in 1978 in a group of 5 newborns who later developed gangrene. It is seen in 4–43% of babies with NEC, but does not always indicate bowel necrosis and, a clinically stable patient with this feature may be managed medically or undergo another diagnostic test to rule out necrotic bowel,[21] for example, abdominal paracentesis. Laparoscopy has been used in a group of 3 infants who were <1000 gms, with NEC and this radiological sign, and segmental colonic necrosis was detected in all of them.[22]

Significant thrombocytopenia showed a low specificity and predictive value for perforated bowel in our group of cases. Though it was present in 80% of the pan intestinal group (**Table 2**), it was more or less similarly distributed between the isolated and multifocal NEC groups. It could not differentiate between isolated and severe NEC in this study (**Table 3**). Ververides et al [23] demonstrated that though platelet counts <100,000/mm^3 or rapid reduction in platelet counts has a poor prognosis, it alone cannot predict the extent of disease. Sharma et al[24] found that when severe thrombocytopenia was present, outcome of laparotomy was better than that of PPD.

In our study, PMA was present in 75% of cases with severe NEC and in 100% of those with pan intestinal NEC. Cikrit et al[17] were of the opinion that PMA indicates advanced NEC and could adversely affect outcome. It represents clinical deterioration in those being managed medically or with PPD. Clinical deterioration is a relative indication for surgical intervention in infants with confirmed NEC and would also include increasing requirements for ventilatory or circulatory support. Persistent metabolic acidosis, especially in association with other signs like abdominal erythema or PVA, SPI and others, should be regarded as an indication for laparotomy.

The surgical approach to bowel perforation in NEC is often biased in favor of PPD due to extreme prematurity, very low birth weight and associated severe illnesses in the subset of infants prone to develop this disease.[7,10] With currently improved perioperative care, even small premature neonates respond favorably to primary laparotomy once necrotic bowel, which is a focus of severe sepsis is removed.[9] Limpert et al [25] have reported that in spite of the higher mortality associated with neonates undergoing surgery for NEC, the various morbid conditions of prematurity are not worsened by surgery. In a recent study of 78 infants with bowel perforation managed with either PPD or laparotomy, mortality was not affected by birth weight and survival improved in those with a shorter time interval between diagnosis of perforation and surgical intervention.[24] The same authors concluded that in the presence of signs of necrotic bowel, laparotomy is superior to PPD in improving outcome. Gollin et al[26] evaluated 29 extremely low birth weight infants with intestinal perforation treated with peritoneal drainage. They found that though the survival rates were more or less similar to those in series where primary laparotomy was used, the long term infectious and nutritional morbidity was considerably high.

In conclusion, the choice of PPD or laparotomy in managing infants with surgical NEC, should be based on assessment of extent of disease rather than birth weight or gestational age. In neonates being monitored for progressive NEC, abdominal wall erythema, PMA, PVA, SPI and gasless abdomen should be considered as indicative of extensive or severe disease and laparotomy should be planned without delay, even in those who have already had PPD. Prospective studies with larger numbers are however, required to support these conclusions objectively and statistically.

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