

# Surgical treatment of infants with necrotizing enterocolitis

Agostino Pierro\*, Nigel Hall

Department of Paediatric Surgery, The Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, University College London, London, UK

## KEYWORDS ;

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**Summary** With the improvements in neonatal intensive care, necrotizing enterocolitis (NEC) has become the most common gastrointestinal emergency amongst infants in neonatal intensive care units. The incidence of NEC varies between 1 and 8% of neonatal intensive care unit admissions and the disease has a mortality rate between 20 and 40%. There are a number of surgical options available to the paediatric surgeon depending on the clinical condition of the infant and the extent of the disease. However owing to a paucity of prospective data in this field and a lack of randomized controlled trials there is little consensus as to which is the most appropriate. Primary peritoneal drainage has become very popular in North America and Europe for the treatment of perforated NEC in very low-birthweight infants. It is a useful manoeuvre in the resuscitation of critically ill infants and in some of these infants, further operation may be avoided completely by inserting a peritoneal drain. Others however remain too unwell to undergo laparotomy and may die. Two randomized controlled trials are currently underway to determine the real benefit of peritoneal drainage. Laparotomy in very small neonates has become safer with improvements in anaesthesia and intensive care management. Resection and primary anastomosis has been proposed as a valid treatment modality in neonates with both focal and multifocal disease. The advantage of resection and primary anastomosis over stoma formation is still controversial. Different surgical techniques such as diverting jejunostomy or 'clip and drop' have been described to deal with extensive disease and avoid massive small bowel resection. Prospective studies and randomized controlled trials are needed to define the best operative treatment for neonates with severe NEC.

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## Introduction

Necrotizing enterocolitis (NEC) is the most common surgical emergency in the neonatal period. With advances in neonatal intensive care, the incidence is increasing and the disease affects up to 0.5% of all live births and 3–5% of low-birthweight live births. Whilst primarily a disease of pre-term infants, it is also observed in term infants, particularly those with co-existing morbidities and recog-

nized risk factors such as congenital heart disease. The majority of cases respond to intensive medical treatment, which involves treatment of sepsis with parenteral broad-spectrum antibiotics, correction of hypovolaemia and acidosis, ventilatory support of respiratory failure and other supportive measures. The intestine is decompressed by means of a nasogastric tube and rested for a period of at least 7–10 days during which time nutritional intake is maintained by means of total parenteral nutrition (TPN). Despite excellent medical attention, a number of infants develop more severe NEC requiring surgical intervention. This group of infants represents a major challenge for paediatric surgeons. Despite increasing experience of this disease, there

\* Corresponding author: Department of Paediatric Surgery, Institute of Child Health, 30 Guildford Street, London WC1N 1EH, UK. Tel.: +44-20-7905-2175/2641; fax: +44-20-7404-6181

E-mail address: a.pierro@ich.ucl.ac.uk (A. Pierro).

remains little consensus as to the most appropriate timing and nature of surgery. In addition to surgery in the acute phase, a number of infants develop late complications of NEC, either following medical or previous surgical treatment, and these complications require surgical intervention.

### Paucity of evidence

Whilst there are a number of surgical techniques in use for the management of NEC, there is little agreement amongst paediatric surgeons as to the approach most beneficial to the child. This stems primarily from the lack of quality prospective data or randomized controlled trials concerning this condition. Although the disease is not rare, the share of cases seen in each individual centre is sufficiently small to preclude large-scale studies on a local basis. The majority of published data comparing treatment modalities are retrospective reviews of relatively small series of patients. There is inevitable bias within these studies and the numbers involved are too small to draw reliable conclusions. In order for one surgical method to be proven superior to another, large-scale, multicentre, prospective, randomized controlled trials are required. To date, these have been particularly sparse in the field of paediatric surgery. This article focuses on the operative management of infants with severe NEC and on the recent advances in this field.

### Indications for surgery

Severity of NEC is classified according to the Bell criteria which have been modified by Walsh and Kliegman.<sup>1</sup> Whilst this system may aid some therapeutic decisions and provide limited prognostic information, it does not take into account the extent of disease on an anatomical basis which would permit planning of surgery.

There is great controversy surrounding the indications for surgery in infants with NEC. Table 1 summarizes the indications reported in the literature. The indications for operation in a recent study of neonates with NEC included pneumoperitoneum in 45% of the neonates, clinical deterioration in 37% and intestinal obstruction in 18%.<sup>2</sup> The most widely accepted indication for surgery is the presence of pneumoperitoneum. Unfortunately, pneumoperitoneum is not always demonstrable in neonates with intestinal perforations.<sup>3-5</sup> Other absolute indications for surgery in acute NEC include continued deterioration of an infant that is refractory to maximal medical treatment, and an abdominal mass or abscess secondary to intestinal

**Table 1** Indications for surgery in infants with NEC

<i>Absolute indications</i>
Pneumoperitoneum
Clinical deterioration despite maximal medical treatment
Abdominal mass with persistent intestinal obstruction or sepsis
Intestinal stricture
<i>Relative indications</i>
Increased abdominal tenderness, distension and/or discolouration
Fixed intestinal loop
Portal vein gas
Positive paracentesis
Thrombocytopenia

perforation associated with persistent signs of intestinal obstruction and/or sepsis.<sup>6</sup>

Various authors have suggested other indications for surgery, some of which remain controversial. Occasionally, a laparotomy is performed because of increased abdominal tenderness and distension and/or discolouration of the abdominal wall. The differential diagnosis in these cases include midgut volvulus, Hirschsprung's enterocolitis and, rarely, intussusception.<sup>6</sup> Similarly, a fixed dilated intestinal loop defined by persistent location and configuration for more than 24 h has been a proposed indication for surgery. However, approximately half of the patients with this finding recover without undergoing an operation.<sup>5,7</sup> The presence of gas in the portal vein on abdominal radiograph has been proposed as an indication for surgery, although this is not accepted universally it does appear to carry a relatively poor prognosis.<sup>8</sup> Rowe et al.<sup>5,9</sup> suggested that more than 90% of infants with portal vein gas will develop intestinal necrosis, and approximately half will have panintestinal involvement. These authors suggest operative intervention on appearance of portal vein gas on plain abdominal radiographs. Finally, according to Kosloske et al.,<sup>3</sup> a positive paracentesis (defined as aspiration of more than 0.5 ml of brown or yellow-brown fluid with visible bacteria on Gram stain) is suggestive of gangrenous bowel thereby indicating surgical intervention. However, false-negative paracentesis have been reported on the presence of sealed intestinal perforations.<sup>10</sup>

Thrombocytopenia is commonly observed in infants with severe NEC<sup>11</sup> and its prevalence is particularly high in neonates requiring laparotomy.<sup>12</sup> The value of thrombocytopenia in defining the extent of the disease and the need for an operation is controversial. The trend of the platelet count during the course of the disease is

considered particularly important. A sudden, profound drop in the platelet count appears to predict the presence of gangrenous bowel<sup>13</sup> and may indicate the need for operative intervention.<sup>14</sup> Platelet consumption in combination with one or more other factors, such as abdominal mass or radiographic evidence of fixed abnormal bowel loops, is considered an important criterion to determine the need for surgery.<sup>15</sup> Persistent thrombocytopenia<sup>16</sup> or decreasing platelet count<sup>17</sup> is considered important in diagnosing clinical deterioration and the need for surgery. A study of risk factors and severity indices in NEC showed that infants that were operated had significantly lower platelet counts pre-operatively than the ones managed conservatively.<sup>18</sup> Ververidis et al.<sup>2</sup> showed that the greater the extent of the disease, the lower the platelet count. The nadir platelet count was significantly lower in infants who died than in survivors. None of the patients with platelet count  $>100 \times 10^9/l$  died. In predicting intestinal gangrene, severe thrombocytopenia has a sensitivity of 69%, specificity of 60% and positive predictive value of 89%, whilst a rapid fall in platelet count has a sensitivity of 32%, specificity of 89% and positive predictive value of 92%. Therefore, the presence of thrombocytopenia cannot reasonably predict the extent of the disease or indicate the need for laparotomy; however, a very low platelet count or a rapid fall in platelet count is a negative prognostic sign.

## Surgical treatment

Up to 50% of neonates with NEC develop advanced disease that requires operative treatment.<sup>19</sup> Butter et al.<sup>20</sup> reported an increase in operative rate from 46% between 1990 and 1994 to 69% between 1995 and 1999. According to this study, the increase was due to an increase in the percentage of stage III patients and an increase in referrals of post-NEC strictures. To some it may be surprising that small, unstable, critically ill infants are able to tolerate major surgical interventions. In a recent study investigating safety of the operative procedure itself, investigators found that even very low-birthweight infants with NEC tolerated the procedure well.<sup>21</sup>

There is no general consensus concerning the ideal surgical management of NEC. Current surgical options include primary peritoneal drainage (PPD) or laparotomy (Table 2).

The principal surgical objectives of laparotomy in acute NEC are to control sepsis, remove gangrenous bowel and to preserve as much bowel length as possible.<sup>5,22,23</sup> Within these objectives, a

**Table 2** Surgical options for advanced NEC

Primary peritoneal drainage
Laparotomy
Resection with enterostomy
Resection with primary anastomosis
Proximal jejunostomy
'Clip and drop' technique
'Patch, drain and wait'

number of options exist, including resection with enterostomy, resection with primary anastomosis, proximal jejunostomy, 'clip and drop' technique and 'patch, drain and wait'.

The patient's weight and clinical status as well as the extent of the disease influence the choice of surgical intervention. At laparotomy, the extent of the disease can be classified as *focal* when it is limited to a single intestinal segment; *multifocal* if it includes two or more intestinal segments with more than 50% of the small intestine viable and *panintestinal* when the majority of small and large bowels are involved with less than 25% viable bowel remaining.<sup>7,23</sup>

### Primary peritoneal drainage

The management of intestinal perforation related to NEC in extremely low-birthweight infants (ELBW), defined as  $<1000$  g, remains controversial. In 1975, Marshall and Ein presented at the meeting of the Canadian Association of Paediatric Surgeons, Winnipeg, Manitoba, Canada, the use of percutaneous peritoneal drainage before laparotomy, as a method of stabilizing and improving the systemic status of premature infants with intestinal perforation secondary to NEC. Initially, it was hoped that the drainage of air and stools from a child too unstable for a laparotomy would relieve symptoms of abdominal compartment syndrome and infection, and subsequently improve tolerance of a laparotomy. Two years later, Ein et al.<sup>24</sup> from the Hospital for Sick Children in Toronto reported the use of peritoneal drainage without laparotomy (PPD) in the management of newborn infants with complicated NEC. Since then, there have been several reports, which have suggested that PPD may serve as a definitive therapy rather than an intermediary for laparotomy. In 1990, the same authors<sup>25</sup> presented their 13-year experience with PPD in 37 patients with bowel perforation secondary to NEC. Sixty-five percent of these patients weighed less than 1000 g and 88% less than 1500 g. These patients were all septic, acidotic and too

unstable to undergo a primary laparotomy. Of the 37 reported patients, one-third completely recovered with PPD and did not require any further operative intervention. In the remaining two-thirds (26 patients), nine (24%) died rapidly before laparotomy, nine (24%) underwent an early laparotomy (within 24 h) for continued clinical deterioration, and seven (22%) underwent a delayed laparotomy for bowel occlusion or fistula formation. The authors concluded that laparotomy with resection and bowel anastomosis or stoma could be the preferred treatment for NEC and perforation, but they recommended PPD for ELBW infants too unstable for laparotomy.<sup>25</sup>

In 1988, Cheu et al.<sup>26</sup> reported their experience with PPD in 51 of 92 infants with perforated NEC. They concluded that PPD was useful in resuscitating ELBW infants with intestinal perforation secondary to NEC, but considered PPD a stabilizing procedure and not an alternative to laparotomy. Other authors have advocated the use of PPD as primary treatment for NEC and perforation for all children weighing less than 1500 g and for unstable babies more than 1500 g.<sup>27</sup> In this study, 79% of patients survived after PPD and 17 out of 23 survivors required no further operative intervention. In addition, the Toronto group<sup>28</sup> reported a survival rate of 69% in neonates less than 1000 g treated with peritoneal drainage compared with a survival rate of only 22% in neonates who underwent laparotomy without drainage.

We recently conducted a systematic review of the topic and failed to discover any randomized trial on the usage of PPD in the management of NEC. In spite of the lack of conclusive evidence, peritoneal drainage has become a popular method of treatment of ELBW infants with complicated NEC, whilst other surgeons still prefer to perform a laparotomy, resection of the diseased bowel, with either a primary anastomosis or stoma creation and peritoneal toilet for this disease.<sup>29–32</sup> Resection of the necrotic bowel is considered by some authors to be the key factor in improving the condition of the neonate.<sup>32</sup> Moss et al.<sup>33</sup> recently performed a meta-analysis on this topic reviewing the results of 10 published studies. The combined probability of survival was similar for PPD (55%) and laparotomy (67%). A marked bias in treatment assignment was found, with a greater proportion of smaller babies undergoing PPD compared with laparotomy (931 vs. 1615 g). However, correction for the effect of birthweight on survival did not show a significant difference in survival between PPD and laparotomy. In addition, there were significant variations in outcomes between institutions for the

same treatment modality (PPD/laparotomy). The authors concluded that, using the current available data, it is not possible to determine whether PPD is associated with improved survival, and that only a randomized controlled trial could identify the best treatment of perforated NEC.<sup>33</sup>

In light of relatively poor quality evidence from retrospectively collected data, it is not surprising that there is little consensus amongst paediatric surgeons. In an attempt to resolve this issue, there are currently two multicentre, prospective, randomized controlled trials in progress comparing peritoneal drainage with primary laparotomy in infants less than 1000 g (Pierro: NET trial) or 1500 g (Moss: NECSTEPS trial).

Two recent studies seem to indicate that PPD is more advantageous in neonates with isolated perforations of the gastrointestinal tract not related to NEC.<sup>34,35</sup> These perforations are usually isolated, idiopathic or related to indomethacin treatment for patent ductus arteriosus. The infants affected have neither pneumatosis intestinalis nor portal vein gas.

### Resection of affected bowel and enterostomy formation

The resection of affected bowel and exteriorization of remaining segments was once thought to be the only safe surgical approach to the infant with gangrenous bowel. This technique remains widely used but has been superseded by more novel approaches in some centres. Resection of necrotic bowel in neonates with NEC has the theoretical advantage of reducing bacterial translocation and correcting the septic state of the patients. The conventional view is that it is safer to exteriorize the bowel ends as the presence of peritonitis, inflammation of the bowel wall and the reduced intestinal blood supply in patients with NEC are unfavourable factors for the healing of the anastomosis.<sup>36</sup> In addition, the stoma allows adequate healing and rests the distal bowel prior to subsequent re-anastomosis.<sup>23</sup>

There are, however, several disadvantages to this approach. It is often difficult to re-establish adequate enteral feeding sufficient for adequate weight gain. High output stomas, in particular, carry a risk of dehydration and electrolyte imbalance, and the importance of early closure to avoid chronic salt and water loss has been highlighted. Enterostomies have been associated with significant morbidity whilst present, including stenosis, prolapse and excoriation of the surrounding skin. Stoma closure involves a second anaesthesia and is

usually performed once the infant is thriving and fully recovered from the acute stage of the illness. Metabolic or physical problems, however, may demand earlier surgery. In one series, the incidence of complications in infants with enterostomies for NEC was 68%.<sup>37</sup> This high rate has prompted the search for alternative strategies which may avoid the need for repetitive surgery and complications associated with stomas, whilst ensuring that the underlying surgical principles of treating NEC by means of laparotomy are adhered to.

### Resection and primary anastomosis

Resection and primary anastomosis was once considered a hazardous option because of the risk of anastomotic leakage due to poor healing of intra-peritoneal anastomoses in the presence of peritonitis, inflammation of the bowel wall and compromised intestinal blood supply. In recent years, a number of centres have published retrospective reviews of infants treated with intestinal resection and primary anastomosis. Kieswetter et al.<sup>38</sup> showed that in patients with localized NEC, an 89% survival rate can be achieved with resection and primary anastomosis. Harberg et al.<sup>39</sup> reported minimal morbidity and low mortality (11%) with resection and primary anastomosis in patients with localized or multiple areas of the disease regardless of the degree of peritoneal contamination. Sparnon and Kiely<sup>32</sup> reported an uncomplicated and rapid recovery in seven of 10 neonates with primary anastomosis. Griffiths et al.<sup>40</sup> reported 76% survival after resection and primary anastomosis compared with 39% in patients who underwent resection and enterostomy. A similar favourable experience with resection and primary anastomosis has been reported by Pokorny et al.<sup>15</sup> and Parigi et al.<sup>41</sup>. In contrast, Cooper et al.<sup>42</sup> showed that the survival rate of neonates that underwent primary anastomosis was lower (64%) than that of neonates that had an enterostomy (79%). Ade-Ajayi et al.<sup>43</sup> reported 89% survival after resection and primary anastomosis for advanced NEC. Recurrence of NEC and strictures occurred in 22 and 17% of the neonates, respectively. Fasoli et al.<sup>23</sup> reported that in neonates with localized NEC, resection and primary anastomosis had similar results to resection and stoma formation.

Whilst resection and primary anastomosis was initially described in selected patients with focal disease and good general condition, it is also now gaining acceptance as a valid treatment option for severe NEC and even for multifocal disease.<sup>22</sup> In a study of 46 neonates with multifocal disease, Fasoli

et al.<sup>23</sup> found that resection and primary anastomosis was associated with a higher survival rate than enterostomy. In addition, resection and primary anastomosis was not associated with higher incidence of intestinal strictures and longer duration of PN compared with resection and enterostomy. None of the studies, on this controversial issue,<sup>15,23,32,38–40,44–46</sup> were prospective, randomized controlled trials. It is possible that the more critical patients with multifocal disease were allocated to enterostomy in preference over resection with anastomosis, as indicated by the relatively high incidence of post-NEC strictures after enterostomy. It is notable, however, that in the study by Fasoli et al.,<sup>23</sup> resection and primary anastomosis was associated with acceptable morbidity and mortality even in patients with NEC spread to multiple intestinal segments. The results of intestinal resections and multiple primary anastomoses for preservation of bowel length have not been reported in the literature. Hall and Pierro (unpublished data) have treated seven neonates (weight 800–1800 g) with resection and multiple intestinal anastomoses: four neonates, who had two intestinal anastomoses, had no complications, two, who had three and four intestinal anastomoses, had anastomotic leaks and one neonate who had three anastomoses developed an anastomotic stricture. The results of this small series are encouraging, however, more than two intestinal anastomoses may carry an increased risk of anastomotic complications.

Most paediatric surgeons would agree that every effort should be made to preserve the ileocaecal valve in neonates with NEC. Ladd et al.,<sup>47</sup> in a retrospective review of infants with NEC, found no difference in duration of TPN, post-operative stay and growth between infants with or without a ileocaecal valve. Similarly, in a more recent study, there were no significant differences in duration of TPN, incidence of NEC recurrence and hospital stay between 40 neonates with NEC who had the ileocaecal valve resected and 43 who did not.<sup>23</sup> However, the incidence of post-NEC strictures was significantly lower in neonates who had the valve resected compared with neonates who retained the ileocaecal valve, possibly indicating that not resecting bowel of questionable viability in order to spare the ileocaecal valve could be less advantageous than resecting the valve itself. Survival rate was not affected by the removal of the valve. These results seem to indicate that neonates adapt well to the loss of the ileocaecal valve. The critical issues in performing an intestinal resection are the length of the retained small bowel and the

gestational age of the neonate. It is well known that pre-term neonates have potential for bowel growth<sup>48</sup> and the earlier findings<sup>23,47</sup> appear to indicate that their bowel adaptive capacity to the loss of the ileocaecal valve is remarkable.

### Operations for panintestinal disease

The techniques described thus far are of particular use for the infant with one or more short segments of NEC. Multiple resections and primary anastomoses may be appropriate for some infants with more widespread disease, provided careful attention is paid to the viability of resection margins. Infants with NEC affecting a large proportion of the gastrointestinal tract pose a particularly difficult problem, and treatment of this group remains particularly controversial. The surgical principles in these children are difficult if not impossible to fulfil. Due to the length of bowel involved, it is often not possible to fully remove all gangrenous intestine whilst salvaging adequate length for sustainable life. It is for these reasons that in the infant with panintestinal NEC who is unstable and critically ill, some surgeons would forego further treatment. However, when there is doubt, a number of techniques have recently been reported with the aim of allowing time for stabilization of the infants' general condition and the possibility of some healing of the gastrointestinal tract to occur. Due to the severity of the disease, the mortality with these strategies remains high.

### Proximal jejunostomy

Initially proposed by Martin and Neblett,<sup>30</sup> surgical creation of a high jejunostomy in the presence of panintestinal disease has been reported in one series of 10 infants.<sup>49</sup> This technique allows decompression and defunctioning of the diseased intestine but does not remove gangrenous segments and may permit continued bacterial translocation. A second-look laparotomy and intestinal reconstructive surgery are performed after 6–8 weeks and the aim is once again to preserve as much bowel length as possible. In this series, eight infants survived to undergo a second procedure; in these, resection of necrotic segments and anastomosis was performed to restore intestinal continuity. There was, however, a significant incidence of TPN-related complications and only a 50% long-term TPN-free survival rate. This procedure is useful in neonates with NEC affecting the majority of the intestine, but the high morbidity and mortality rate should be carefully considered.

### Clip and drop technique

This method complies with surgical principles and also avoids stoma formation. For the infant with extensive bowel necrosis, Vaughan et al.<sup>50</sup> advocated the resection of all segments of grossly non-viable or perforated bowel, irrigation and aspiration of peritoneal contamination, clipping the ends of remaining bowel and returning them to the abdomen. This is followed by a second-look laparotomy with delayed anastomosis 48–72 h later. In their small series, all three infants with NEC survived,<sup>50</sup> and in a subsequent report of four infants in whom this technique was employed, one died and the remaining three required stoma formation at the second look.<sup>8</sup> This technique has the advantages of preserving bowel length and intends to avoid stoma formation.

### Patch, drain and wait

The basic principle of this technique, reported by Moore,<sup>51</sup> is to resect no bowel and do no enterostomies. The technique is characterized by laparotomy, insertion of bilateral Penrose drains from the undersurface of the diaphragm into the pelvis with exit sites in both lower quadrants. Waiting is important and post-drainage laparotomy should not be performed before 14 days. The bilateral Penrose drains capture faecal fistulas and function as de-facto enterostomies. Moore's 15-year personal experience indicates no mortality with this approach during the first 60 post-operative days, no major morbidity and no second operations required in 70% of patients, possibly due to spontaneous 'auto-anastomosis'. The author<sup>51</sup> advocates this technique for infants with extensive gut necrosis (NEC totalis). There are no reports from other centres employing the same technique.

### Authors' preferred surgical strategy

The authors' preferred approach to the operative management of infants with NEC is illustrated in Fig. 1.

In infants with focal disease involving a small length of small or large bowel, a resection and primary anastomosis is usually performed, with the exception of patients unstable during the operation who are managed with a stoma at the level of the affected bowel.

In infants with multifocal disease (>50% of the bowel assumed to be viable), various surgical options are available. Resection and one or more intestinal anastomoses (preferably not more than two) are performed when it is possible to ascertain

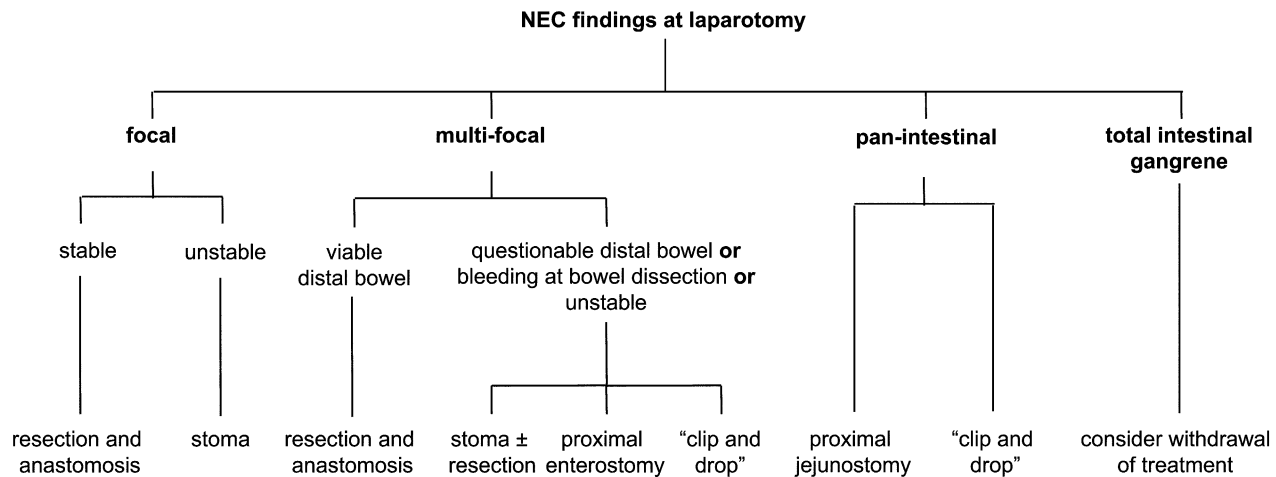


Fig. 1 Authors preferred operative management of advanced NEC.

the viability of the bowel distal to NEC without causing significant bleeding. Stoma (with or without intestinal resection), proximal enterostomy or clip and drop technique are performed when: (a) it is not possible to ascertain the status of the bowel distal to the NEC; (b) the distal bowel is of dubious viability; (c) attempts to dissect the distal bowel cause significant bleeding and (d) the patient is unstable peri-operatively. In these circumstances, a stoma with or without intestinal resection(s) is the preferred surgical option. However, if this would lead to massive intestinal resection, the clip and drop technique described earlier will be adopted in an attempt to salvage as much intestinal length as possible. If the mobilization of the bowel loops affected by NEC causes significant bleeding, a high diverting jejunostomy is preferred.

In patients with panintestinal disease (>75% of small and large bowel involved), two options are considered: (a) proximal diverting jejunostomy when the intestinal resection would cause significant bleeding or loss of the majority of the small bowel and (b) clip and drop technique in the attempt to salvage some of the affected bowel and avoid a short bowel syndrome. In neonates with total intestinal gangrene, closure of the abdomen and treatment withdrawal are considered.

### Pre- and post-operative management

Infants with NEC are amongst the most critically ill and most difficult patients to care for in paediatric surgery. Commonly, they are small premature neonates who require intensive care support and a team approach combining the expertise of paediatric surgeons, neonatologists, intensivists, cardiologists and microbiologists. A nasogastric or

orogastric tube is inserted to decompress the stomach. Broad-spectrum antibiotics including anaerobic coverage are given intravenously for at least 7 days. Ventilatory and circulatory support are of utmost importance in these patients. Advances in neonatal intensive care have been substantial in recent years, and this article is not intended to cover this vast topic.

The metabolic insult of the necrotic bowel and sepsis contributes to stress the neonate's homeostatic mechanisms. Sepsis is an intriguing pathological condition associated with many complex metabolic and physiological alterations.<sup>52</sup> Studies in adults have shown that the metabolic response to sepsis is characterized by hypermetabolism as documented by an increase in resting energy expenditure by up to 49%.<sup>53</sup> In addition, increased tissue catabolism,<sup>53</sup> gluconeogenesis and hepatic release of glucose<sup>54</sup> have been described. The existing knowledge on the metabolic response to sepsis in infants is limited. A recent metabolic study in septic neonates with NEC by Powis et al.<sup>55</sup> failed to show any increase in whole body protein turnover, synthesis and catabolism. This data suggests that the calorific requirement of infants with NEC is not increased. The metabolic rate and hormonal response to stress and sepsis in infants may be different from that of adults, and therefore, it is not possible to adapt recommendations made for adults to the neonatal population. It is possible that neonates divert the products of protein synthesis and breakdown from growth into tissue repair. This may explain the lack of growth commonly observed in infants with critical illness or sepsis. Further studies are needed in this field to delineate the metabolic response of newborn infants to NEC and severe sepsis by exploring the relationship between

nutrition and immunity. The standard practise in most paediatric surgical centres is to avoid enteral feeding during the acute stage of the disease, and provide calories by TPN.

In addition to requiring nutritional support, neonates with NEC may present with clotting abnormalities and require repeated transfusions of platelets and clotting factors. The Thomsen–Freidenreich (T) cryptantigen is a naturally occurring antigen found on the surface of all human erythrocytes, and is normally concealed by a layer of *N*-acetylneuraminic acid. This antigen is described as activated when the *N*-acetylneuraminic acid layer is cleaved from the cell surface by neuraminidase, thus exposing the underlying antigen. T cryptantigen activation has been reported in some cases of neonatal NEC.<sup>56–61</sup> Activation of the T cryptantigen renders erythrocytes susceptible to haemolysis following the transfusion of blood products containing anti-T antibodies. In a recent study of 104 neonates with advanced NEC,<sup>62</sup> the incidence of T cryptantigen activation was 22% and was significantly higher in infants with stage III disease (30%) compared with those with stage II disease (4%). Screening of neonates with advanced NEC for T cryptantigen activation is advised to identify those at risk of haematological complications.

The only direct implication of T cryptantigen activation for the management of NEC is that a selective transfusion policy has been recommended in order to reduce the risk of haemolysis. This has been identified in a number of infants when NEC is complicated by T cryptantigen activation and carries a poor prognosis.<sup>63–65</sup> In one series of 128 infants with NEC, the mortality rate was 40% following post-transfusion haemolysis compared with 6% when post-transfusion haemolysis did not occur.<sup>63</sup> When infants with T cryptantigen activation require blood products, the use of packed red cells, washed platelets and low titre anti-T FFP is advisable.<sup>62,66,67</sup> Should haemolysis occur, exchange transfusion may abolish the haemolytic process and allow survival.<sup>60</sup>

### Outcome of surgical intervention

Approximately half of the neonates with NEC who receive non-operative treatment demonstrate clinical resolution of the disease. The most common complication in this group of infants is post-NEC intestinal stricture. Butter et al.<sup>20</sup> reported an incidence of post-NEC strictures of 48% in neonates treated medically. The time, from the onset of NEC until the diagnosis of intestinal stricture, ranged

from 26 to 48 days. The usual management of post-NEC strictures is intestinal resection and primary anastomosis. Other complications of NEC include intestinal malabsorption, short bowel syndrome, hepatic cholestasis and recurrence of NEC. Malabsorption can derive from various causes including enzyme depletion, intestinal dysmotility, hypersecretion of gastric acid and bacterial overgrowth.<sup>5</sup> Short bowel syndrome is the most serious long-term gastrointestinal complication of NEC with an incidence of up to 23% in NEC survivors.<sup>68</sup> Hepatic cholestasis is a common complication of infants with NEC requiring long-term PN. The factors contributing to the development of this complication are likely to be multifactorial, and are not yet fully determined. Neonates, especially those born pre-term, with low-birthweight are particularly at risk. Infection, intestinal bacterial overgrowth, and lack of enteral stimulation contribute significantly to the development of the disease.<sup>5,69</sup> Introduction of minimal bolus enteral feeding in the recovery phase of the disease is important because it stimulates gallbladder contractility,<sup>5,70,71</sup> promotes bile flow and aids in bowel adaptation.<sup>5</sup> The recurrence rate of NEC varies between 4 and 6%.<sup>72,73</sup> The presence of an intestinal stricture may further promote the recurrence of NEC.

The neurodevelopmental implications of NEC have not been fully investigated. Approximately 50% of the neonates with NEC are neurodevelopmentally normal.<sup>5,74</sup> The neurological sequelae in children with NEC seems to be correlated with underlying prematurity and other associated medical diseases rather than with NEC itself.

The mortality rate of neonates with NEC depends on the severity of the disease, associated anomalies and gestational age. Over the past three decades, the survival rate of neonates with NEC has improved progressively. This has been most apparent in very low-birthweight infants.<sup>5</sup> In a study of 83 neonates who required a laparotomy for advanced NEC (Bell's stage II and III), the overall mortality rate was 30%. Causes of death included multisystem organ failure ( $n=10$ ), sepsis ( $n=14$ ) and congenital cardiac abnormality ( $n=1$ ). Seventeen deaths (68%) occurred within 30 days from the diagnosis of NEC. The mortality rate was higher (67%) in patients with panintestinal involvement of the disease compared with patients with focal (12%) or multifocal NEC (30%) (Fig. 2).

### Conclusions

The fact that so many infants with NEC survive is testimonial to the advances in medical and surgical

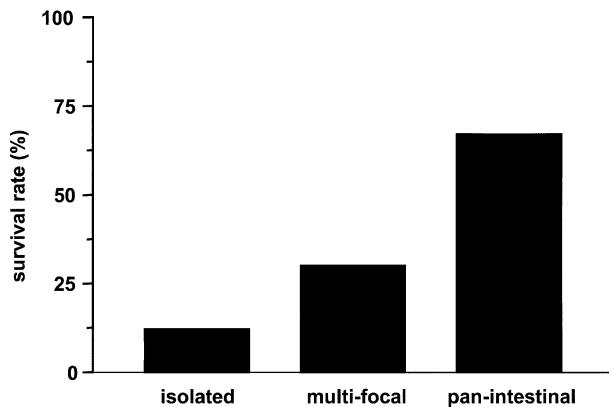


Fig. 2 Mortality rate according to extent of the disease in 83 neonates with NEC who required laparotomy (adapted from Fasoli et al.<sup>23</sup>).

care. Surgical intervention plays a vital role in the treatment of a proportion of infants with NEC, and is undoubtedly essential for their survival. However, the selective patients who would benefit most from surgery and the precise nature of that surgery remain largely unclear. Despite the introduction of new surgical techniques in recent years and a general improvement in morbidity and mortality rates, there remains little consensus amongst paediatric surgeons as to the most appropriate way to treat many of these children. Prospective, multicentre, randomized controlled trials are required to enable us to answer these questions fully.

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