Diagnostic imaging features of necrotizing enterocolitis: a narrative review

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Abstract: Necrotizing enterocolitis (NEC) is an inflammatory process, characterized by intestinal necrosis of variable extension, leading to perforation, generalized peritonitis and death. The classical pathogenetic theory focuses on mucosal damage related to a stress induced intestinal ischemia leading to mucosal injury and bacterial colonization of the wall. A more recent hypothesis emphasizes the role of immaturity of gastrointestinal and immune system, particularly of the premature, responsible of bowel wall vulnerability and suffering. NEC is the most common gastrointestinal emergency in the newborn, with a higher incidence in the preterm; improvement of neonatal resuscitation techniques enables the survival of premature of very low birth weight (VLBW) with prolongation of hospital stay for perinatal and neonatal care and a higher risk of NEC. Clinical presentation of NEC in newborn ranges from mild forms with moderate gastrointestinal tract disorder and that can heal spontaneously, to very serious forms with fulminant course characterized by perforation, peritonitis, sepsis, disseminated intravascular coagulation (DIC) and shock. Imaging modality in the diagnosis of NEC is historically represented by the plain-film abdominal radiographs which can be performed every 6 hours because of the rapid evolution that may occur in the patient's clinical condition. However ultrasound (US), in recent years, is playing an increasingly important role in the evaluation of early stages of the disease as it provides images in real time of the abdominal structures being able to assess the presence and validity of peristalsis of the bowel loops, detect the thickness of the intestinal wall and the presence of minimal amounts of fluid in the peritoneal cavity. In this paper we review the pathogenesis, clinical presentation and imaging of NEC with a particular attention to the emergent role of US in the diagnosis of the disease.

Keywords: Necrotizing enterocolitis (NEC); ultrasound (US); newborn; bowel disease

Introduction

Newborn necrotizing enterocolitis (NEC) is a term used to describe a common and devastating gastrointestinal neonatal pathology (1-3). NEC is an inflammatory process, characterized by intestinal necrosis of variable extension, leading to perforation, generalized peritonitis and death (1,4). It is the most common gastrointestinal emergency in the newborn (1-3,5,6), more frequent in the preterm infant, especially those of very low weight [newborns with birth weight <1,500 g or very low birth weight (VLBW)], although it affects term infants also (5,7-10). The incidence of NEC in VLBW infants, stable over the years, is between 5–7% (11,12); a slight increase over the period 2000–2009 was reported in the intensive care unit neonatal (NICU) of the Vermont Oxford Network (VON) (12). Recently in UK an incidence of around 3% in infants <32 weeks'

gestational age, between 2012 and 2013, was reported (13). Mortality from NEC varies depending from the degree of bowel involvement and comorbidities, up to 50% in those forms which require surgical treatment (1-3,6,14). The age of onset of NEC is inversely proportional to gestational age (15); those born at term develop NEC much earlier than pre-term infants, with the average age of the onset by the 1st week of life, particularly within the first 2–3 days (16).

Described for the first time in 1938 in a case of fetal peritonitis (17), the NEC is a disease linked to medical progress; its incidence increased with improvement of neonatal resuscitation techniques that enabled the survival of premature of VLBW. In addition, the dramatic prolongation of hospital stay for perinatal and neonatal care exposed the preterm at a higher risk of NEC (5).

According to the classical pathogenetic theory formulated in 1969 by Lloyd (18), the NEC in premature infant should be the final event of a "cascade" that, starting from a "stress induced" intestinal ischemia, leads to alterations of intestinal mucosa with translocation and bacterial colonization of the wall, perforation and death. A new pathogenetic hypothesis instead explains the NEC as a result of a series of imbalances caused by the immaturity of the gastrointestinal system, digestive system, circulatory regulation and of the immune system of the newborn. Intestinal immaturity leads to a compromised intestinal epithelial barrier, an underdeveloped immune defense, and altered vascular development and tone, so the newborn is more exposed to intestinal inflammation and sepsis (19,20).

Clinical presentation

Clinical presentation of NEC in newborn ranges from mild forms with moderate gastrointestinal tract disorder and that can heal spontaneously, to very serious forms with fulminant course characterized by perforation, peritonitis, sepsis, disseminated intravascular coagulation (DIC) and shock (21). First signs usually appear after start eating with nutritional intolerance: distension/abdominal discomfort, delayed gastric emptying and gastric retention and vomiting, first inconstant then biliary (8,22,23). Diarrhea, ematic or not, may occur (1,21). Furthermore, in almost all newborns a reduced peripheral circulation was noticed (24). Blushing, swelling and resistance of the abdominal wall are commonly described in the advanced stages of the NEC (25).

Nonspecific signs and symptoms such as worsening apnea, bradycardia, lethargy and instability of body temperature may be the first manifestations of the disease with insidious progression (26-28). General conditions become quickly compromised and, in the advanced stages, necrosis of the intestinal mucosa leads to perforation, peritonitis, sepsis with consequent persistent acidosis, clotting disorders, circulatory collapse and shock (29-31). Clinical suspicion is essential for an early recognition and an effective treatment to drastically reduce the morbidity and mortality of the disease. In 1978 Bell (26) proposed a clinical staging of the disease, modified in 1986 by Walsh and Kliegman (21), particularly useful in the evaluation of the patient and his treatment (*Table 1*).

According this classification, stage 1 (suspected NEC) is associated with clinical and radiological signs not specific such as body temperature instability, apnea, bradycardia, lethargy, moderate abdominal distension, fecal occult blood, dilated bowel loops with moderate ileus. Stage 2 (proven NEC) is characterized by rectal bleeding, moderate metabolic acidosis and thrombocytopenia together with radiological signs of ascites (due to the peritoneal inflammatory reaction to bacterial invasion) and intestinal pneumatosis. Typically, a linear strip of gas in the wall thickness of a limited portion of the intestine is observed. Rarely, it can involve both the small and large intestine. Moreover, often the bubble pattern is very similar to those infants with meconium retention; so, this sign is less specific than the former. In this stage it is also possible to observe an abdominal mass in the right lower quadrant. Finally, stage 3 (advanced NEC) is characterized by hypotension, DIC and often signs of generalized peritonitis. Respiratory acidosis associated with radiological signs of intestinal perforation can be present.

Imaging

Imaging modality in the diagnosis of NEC is historically represented by the plain-film abdominal radiographs (32) which can be performed every 6 hours because of the rapid evolution that may occur in the patient's clinical condition. Ultrasound (US), in recent years, is playing an increasingly important role in the evaluation of early stages of the disease. The basic premise for understanding the role of imaging is to know the pathophysiological "cascade" that leads to NEC. Reduction of bowel wall perfusion leads to local ischemia with damage of the mucosal barrier resulting in penetration of air (pneumatosis) and microorganisms.

Radiographic findings have been well described in the literature (33,34), ranging from completely unspecific

Table 1 Modified Bell criteria for NEC

Stage	Systemic symptoms	Intestinal symptoms	X-ray—US signs
IA—suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Increased gastric residuals, mild abdominal distension, emesis, occult blood in stool	Normal or intestinal dilatation, mild ileus
IB—suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Bright red blood from rectum	Normal or intestinal dilatation, mild ileus
IIA—proven NEC	Temperature instability, apnea, bradycardia, lethargy	Bright red blood from rectum, + absent bowel sounds, ± abdominal tenderness	Intestinal dilatation, ileus, intestinal pneumatosis
IIB—proven NEC	Temperature instability, apnea, bradycardia, lethargy, + mild metabolic acidosis, mild thrombocytopenia	Same as above, + absent bowel sounds, definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, with or without ascites
IIIA—advanced NEC (bowel intact)	Same as stage IIB, + hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia	Same as above, + signs of generalized peritonitis, marked tenderness and abdominal distension	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, + definite ascites
IIIB—advanced NEC (perforated bowel)	Same as stage IIIA	Same as stage IIIA	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, + definite ascites, + pneumoperitoneum

NEC, necrotizing enterocolitis; US, ultrasound; DIC, disseminated intravascular coagulation.

signs, such as a widespread bowel distension (*Figure 1*), up to more useful signs as wall thickening, fixation of the loops or reduction of intestinal air (*Figure 2*). X-ray abdomen examination shows a specific pattern only when there is the mucosal damage with pneumatosis of the intestinal wall and pneumoperitoneum (*Figure 3*). This is an already advanced stage of disease that may precede perforation and pneumoperitoneum, a condition that requires urgent surgical treatment and often leads to a negative outcome (35,36).

Recently a standardized evaluation of the plain-film X-ray of the abdomen using the Duke Abdominal Assessment Scale was proposed. It consists in a score based on radiological findings that increases with disease severity, ranging from 0 (normal gas pattern) to 10 (pneumoperitoneum) (37,38).

Despite the importance of the presence of pneumatosis there is a wide range of pathophysiological events related to bowel wall suffering that show a nonspecific radiographic pattern. So, the "goal" of the diagnostic path is to highlight precisely these early stages before bowel wall damage is determined. US is a fundamental tool to make an early

diagnosis.

US has certain advantages over conventional X-ray examination (39-42), as it (I) provides images, in real time, of the abdominal structures, thus being able to assess the presence and validity of peristalsis of the bowel loops; (II) allows to detect the presence of even minimal amounts of fluid in the peritoneal cavity not detectable with standard X-ray; (III) allows to accurately detect the thickness of the intestinal wall and evaluate the presence, absence or reduction of the wall perfusion (40,41,43,44).

In the early stages of NEC, when X-ray can show only an aspecific loop distension, US shows direct and more specific signs as the following:

(I) Wall thickening: in general it is considered pathological a wall thickness greater than 2.6 mm (36,43) (*Figure 4*);

(II) Abnormal bowel wall echoic pattern: the reduction of normal wall layering results in a progressive increase in the parietal US echogenicity (43,45) (*Figure 5*);

(III) Wall perfusion: in this stage there is an increase in vascularity of the wall and mesenterial perivisceral

Figure 1 Supine plain X-ray of the abdomen: aspecific distension of small bowel loops.

tissues (36,40,46) (*Figure 6*);

(IV) Initial signs of intestinal pneumatosis: the presence of air microbubbles inside wall thickness appears as hyperechoic spots, usually without signs of posterior reverberation (46). This finding represents the sign of the air passage from the intestinal lumen, as a result of the damage of the mucosal barrier (*Figure 7*). It should be emphasized that, at this stage, the small amount of air detected by US is not appreciable at radiographic examination (36).

In the intermediate stage of NEC, when radiographic examination indicates signs of intestinal pneumatosis, US can show the following:

(I) Extensive penetration of air in the wall thickness area: presence of air appears as multiple hyperechoic spots limited to some continuous wall portions (*Figure 8*) or with a circumferential pattern (*Figure 9*) and affects one or more loops (42,43,47);
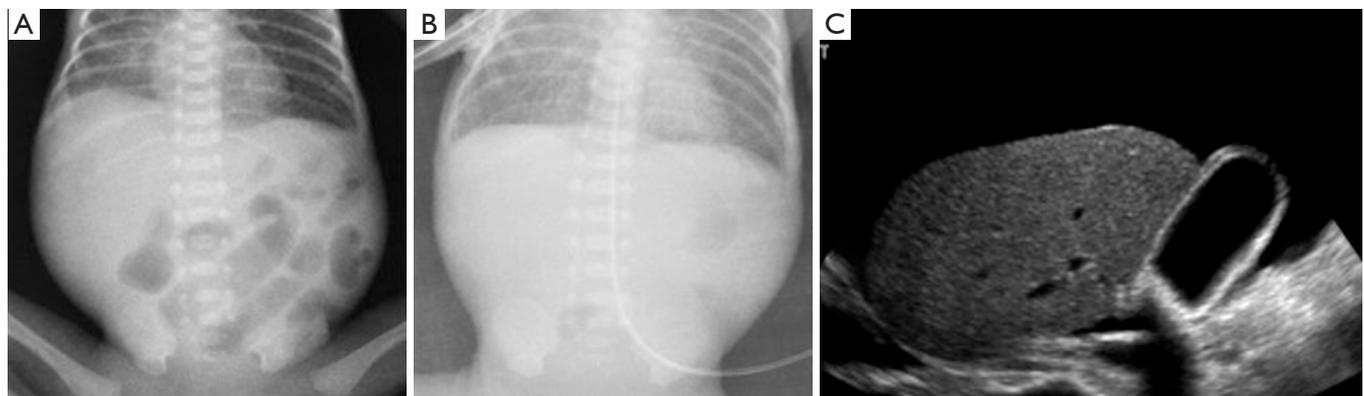

Figure 2 Supine plain X-ray showing bowel loops distension with progressive reduction of intestinal air. Ultrasound (US) examination showed an abundant ascites.
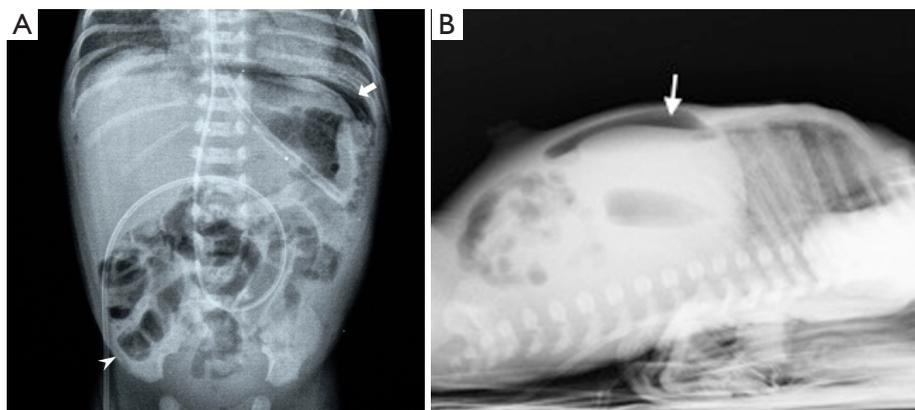

Figure 3 Plain X-ray of the abdomen in orthostasis: subdiaphragmatic air (arrow) and intestinal pneumatosis (arrow head).
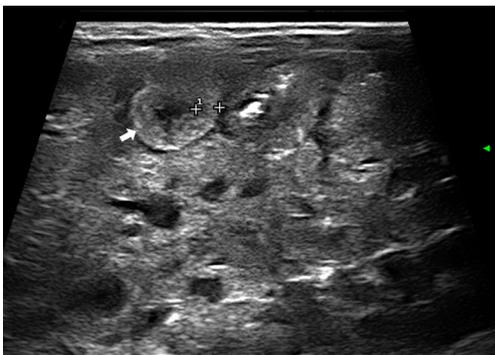
Figure 4 Bowel wall thickening (>2.6 mm) (caliper).

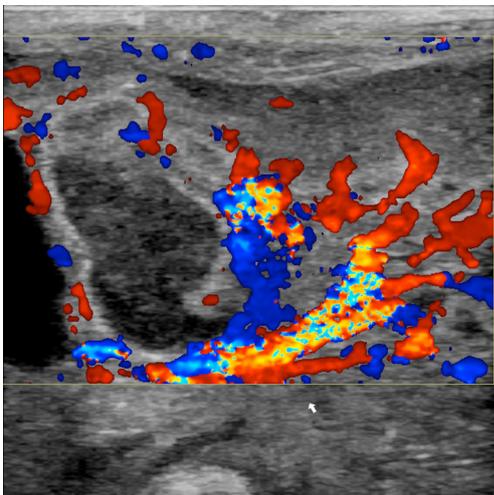**Figure 5** Disappearance of wall stratification with increased echogenicity (arrow).

Figure 6 Colour Doppler imaging showing increased wall vascularization (arrow) and of mesenterial vessels.
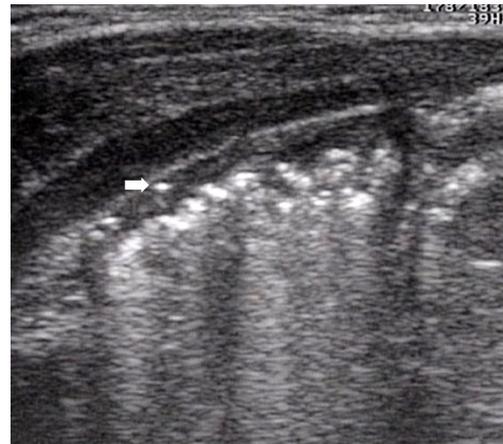

Figure 7 Intestinal pneumatosis (initial phase): presence of hyperechoic spots within the bowel wall (arrow).

(II) Portal pneumatosis: air is present in the main portal vein (*Figure 10*) and in the peripheral intrahepatic portal branches. In the latter case the pneumatosis manifests as a series of hyperechoic spots, irregularly distributed in the liver parenchyma, often moving during the examination (*Figure 11*) (39,40,46,48);

(III) Extraintestinal gas: presence of small hyperechoic spots, expression of small air bubbles between the front surface of the liver and the abdominal wall or between the intestinal loops (initial sign of intestinal perforation). Also in this case the US is more sensitive than X-ray examination. The small amount of extraintestinal air, detectable with US, is not detectable in direct radiography (36,40).

In advanced NEC, when radiographic examination demonstrates signs of pneumoperitoneum, US shows:

(I) Bowel wall ischemia: wall thinning (*Figure 12*). The real reduction in bowel wall thickness has to be distinguished from an apparent thinning due to "stretching" of the loop caused by fluid accumulation in the lumen in patients with and without NEC (40,42); significant reduction of the wall vascularization until its complete disappearance (40,43) (*Figure 13*);

(II) Significant amount of free fluid in the abdomen: in the newborn, a small amount of free fluid between the loops can be present (36). The
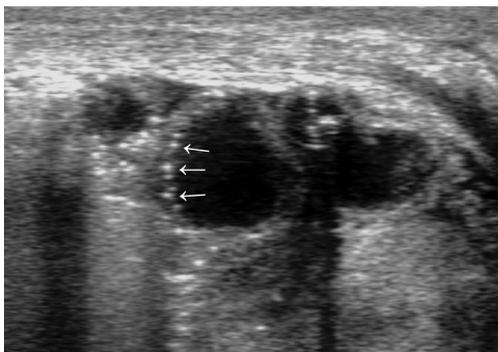
Figure 8 Bowel wall pneumatosis (advanced phase): multiple hyperechoic spots within bowel wall. Gas bubbles interest a limited portion of the wall (arrows).
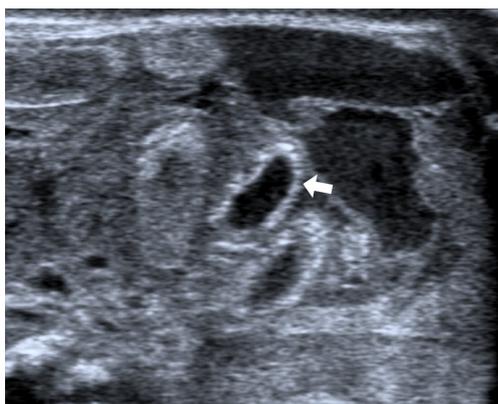

Figure 9 Bowel wall pneumatosis (advanced phase): multiple hyperechoic spots within bowel wall. Gas bubbles interest the entire wall (arrow).

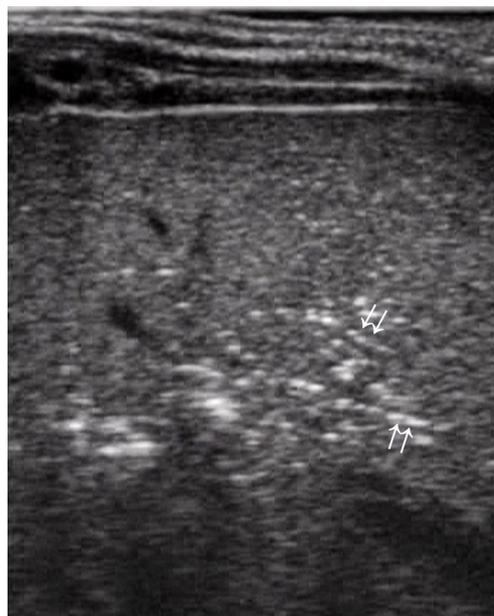**Figure 10** Presence of air microbubbles within the main portal vein (arrow).

Figure 11 Air microbubbles within intrahepatic portal branches as linear hyperechoic spots (arrows).

amount and echostructural aspect of the liquid can indicate disease. In fact, in the NEC, the presence of abundant amount of liquid that shows inhomogeneous echostructure with internal echoes and septa is suggestive of perforation (49) (*Figure 14*).

Conclusions

Since the NEC clinical signs, both early and late, are often non-specific (40), imaging plays an important role in the timing of diagnosis. While plain abdominal radiographs remain the main and most used modality in the evaluation and monitoring of the NEC, it is true that the most specific sign that defines the diagnosis is the presence of intramural gas (37,40,46,50,51). Unfortunately, this radiographic sign is present in the advanced stages of the disease when the damage of the wall has been consolidated leading perforation.

US offers several advantages that can potentially contribute to an earlier diagnosis or, at least, provide more timely information about the stage of the intestinal wall suffering. Timing of US follow-up is not yet standardized (40,42,45,46,51). However, greater results can occur in patients who present a worsening of the clinical symptoms
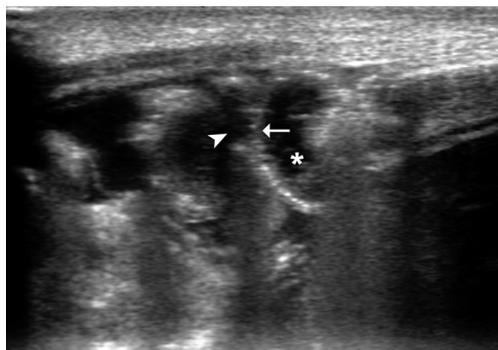
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Figure 12 Bowel wall thinning (arrow). Ultrasound (US) exam shows fine particulate bowel lumen content (*) surrounded by free clear fluid (arrowhead).

Figure 14 Intraperitoneal free fluid in a newborn with necrotizing enterocolitis (NEC) and perforation: inhomogeneous free fluid between bowel loops with internal echoes and septa (*). In some intestinal loops hyperechoic spots within the wall are present.
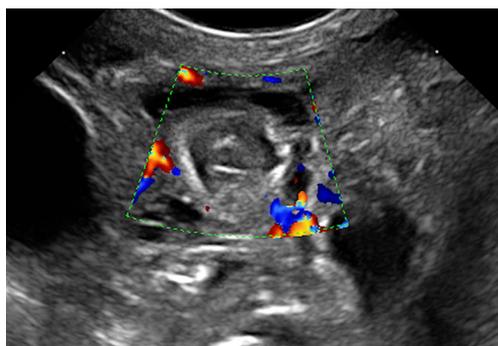
to declare.

Figure 13 Absence of bowel wall vascularization at Colour Doppler examination.

with no obvious signs of intestinal pneumatosis and/or pneumoperitoneum on X-ray plain film. In these patients US, with the possibility to assess the vitality of the intestinal wall (with colour Doppler), the damage of the bowel wall (by identifying early signs of pneumatosis) and to recognize the presence of free fluid in the abdomen, may provide a prompt guide to clinical management, since its findings have a good relationship with patients outcomes (36,41,44,46,49,51,52).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

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