1-2022

Imaging for Diagnosis and Assessment of Necrotizing Enterocolitis.

Vinayak Mishra

Alain Cuna
Children's Mercy Hospital

Rachana Singh

Daniel M. Schwartz

Sherwin S. Chan
Children's Mercy Hospital

See next page for additional authors

Recommended Citation

Mishra V, Cuna A, Singh R, Schwartz DM, Chan S, Maheshwari A. Imaging for Diagnosis and Assessment of Necrotizing Enterocolitis. Newborn (Clarksville). 2022;1(1):182-189. doi:10.5005/jp-journals-11002-0002

Creator(s)
Vinayak Mishra, Alain Cuna, Rachana Singh, Daniel M. Schwartz, Sherwin S. Chan, and Akhil Maheshwari

REVIEW ARTICLE

Imaging for Diagnosis and Assessment of Necrotizing Enterocolitis

Vinayak Mishra[1], Alain Cuna[2], Rachana Singh[3], Daniel M Schwartz[4], Sherwin Chan[5], Akhil Maheshwari[6]

Abstract

Necrotizing enterocolitis (NEC) is inflammatory bowel necrosis of preterm and critically ill infants. The disease is seen in 6–10% of preterm infants who weigh less than 1500 g at birth and carries considerable morbidity, mortality, and healthcare cost burden. Efforts focused on timely mitigation remain restricted due to challenges in early diagnosis as clinical features, and available laboratory tests remain nonspecific until late in the disease. There is renewed interest in the radiological and sonographic assessment of intestinal diseases due to technological advances making them safe, cost-efficient, and supporting Web-based transmission of images, thereby reducing time to diagnosis by disease experts. Most of our experience has been with plain abdominal radiography, which shows characteristic features such as pneumatosis intestinalis in up to 50–60% of patients. Many patients with advanced disease may also show features such as portal venous gas and pneumoperitoneum. Unfortunately, these features are not seen consistently in patients with early, treatable conditions, and hence, there has been an unfulfilled need for additional imaging modalities. In recent years, abdominal ultrasound (AUS) has emerged as a readily available, noninvasive imaging tool that may be a valuable adjunct to plain radiographs for evaluating NEC. AUS can allow real-time assessment of vascular perfusion, bowel wall thickness, with higher sensitivity in detecting pneumatosis, altered peristalsis, and characteristics of the peritoneal fluid. Several other modalities, such as contrast-enhanced ultrasound (CEUS), magnetic resonance imaging (MRI), and near-infrared spectroscopy (NIRS), are also emerging. In this article, we have reviewed the available imaging options for NEC evaluation.

Keywords: Diagnostic imaging, Necrotizing enterocolitis, Neonatology, Prematurity, Preterm neonate, Ultrasonography.

Newborn (2022): 10.5005/jp-journals-11002-0002

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal (GI) complication secondary to preterm birth, with high morbidity and mortality. It is an acute inflammatory bowel disease of preterm infants, and it can affect 6–10% of very-low-birth-weight (VLBW) infants born before 32 weeks of gestation.[1–4] Despite significant advances in neonatal intensive care units (NICUs), the disease still has high mortality rates (30–50%).[5,6] The pathogenesis of NEC is complex, multifactorial, and challenging to predict clinically with sudden onset. Many risk factors for NEC have been identified, such as prematurity, genetic predisposition, chorioamnionitis, perinatal asphyxia, formula feeding, human milk fortifiers, feed thickeners, viral infections, gut dysbiosis, and severe anemia with red blood cell transfusions.[7] However, despite extensive research, a unifying pathophysiological mechanism remains unclear.

Unlike many other organ-specific diseases such as those affecting the brain, lungs, and the urogenital tract, diagnostic imaging of the neonatal gastrointestinal tract has had relatively limited accuracy, and this has constrained improvement in diagnostic efforts and measurement of severity in disorders such as NEC.[6,8] For many decades, the diagnosis for NEC has relied heavily on clinical presentation and abdominal radiographs. The easy availability of portable radiographic machines, cost-effectiveness, and clinicians' familiarity with interpreting results has made abdominal radiographs a definitive part of evaluating preterm infants with suspected NEC.[9] However, even in the best hands, the sensitivity of radiographical approaches has been limited to 55–60% of all patients.

More recently, sonography has emerged as a novel, exciting technological advance. The availability of handheld ultrasound (US) machines has further simplified these approaches and increased the accessibility of such evaluation.[8] These devices are highly portable, provide high-quality images, and can be used for frequent, sequential monitoring with no exposure to radiation. More recent efforts have focused on increasing the sensitivity of sonography by using contrast-enhanced ultrasound (CEUS). Other studies have used magnetic resonance imaging (MRI) or near-infrared spectroscopy (NIRS) for evaluating the anatomy, physiology, and perfusion of the GI tract in relation to NEC.

[1]Department of Pediatrics, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India

[2]Division of Neonatology, Children's Mercy, Kansas City, Missouri, United States of America

[3]Department of Pediatrics, Tufts Children's Hospital, Boston, Massachusetts, United States of America

[4]Department of Radiology, Tufts University School of Medicine, Boston, Massachusetts, United States of America

[5]Department of Radiology, Children's Mercy, Kansas City, Missouri, United States of America

[6]Global Newborn Society, Baltimore, Maryland, United States of America

Corresponding Author: Vinayak Mishra, Department of Pediatrics, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India, Phone: +91 8828079692, e-mail: vinayakmishra3009@gmail.com

How to cite this article: Mishra V, Cuna A, Singh R, *et al.* Imaging for Diagnosis and Assessment of Necrotizing Enterocolitis. Newborn 2022;1(1):182–189.

Source of support: Nil

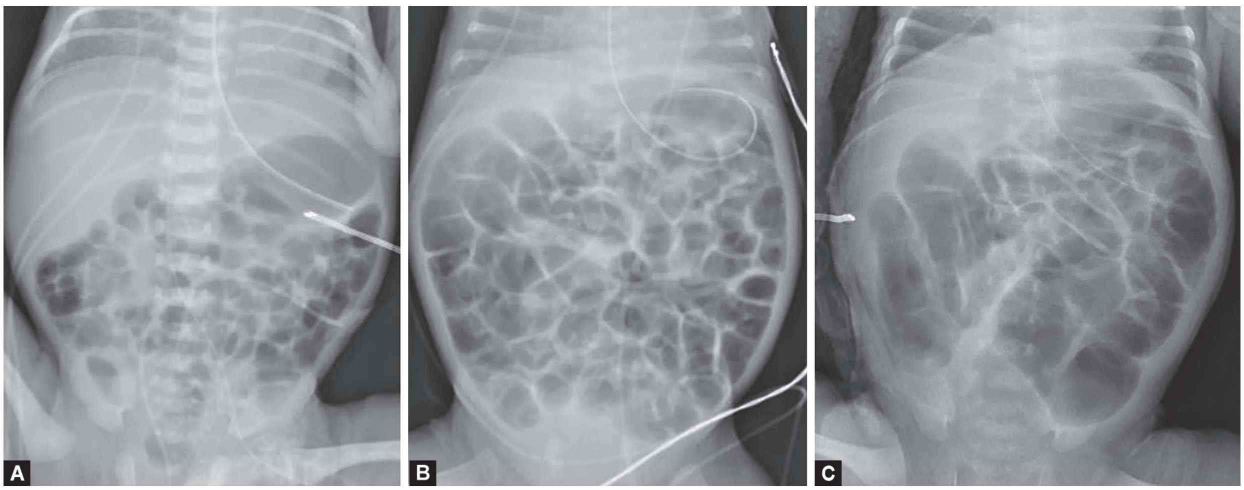
Conflict of interest: None

In this article, we have reviewed the evolving landscape of imaging modalities for NEC evaluation. We begin with a review of traditional abdominal radiographs, focus on the emerging role of abdominal ultrasound (AUS), and conclude with novel modalities for diagnosing and assessing NEC.

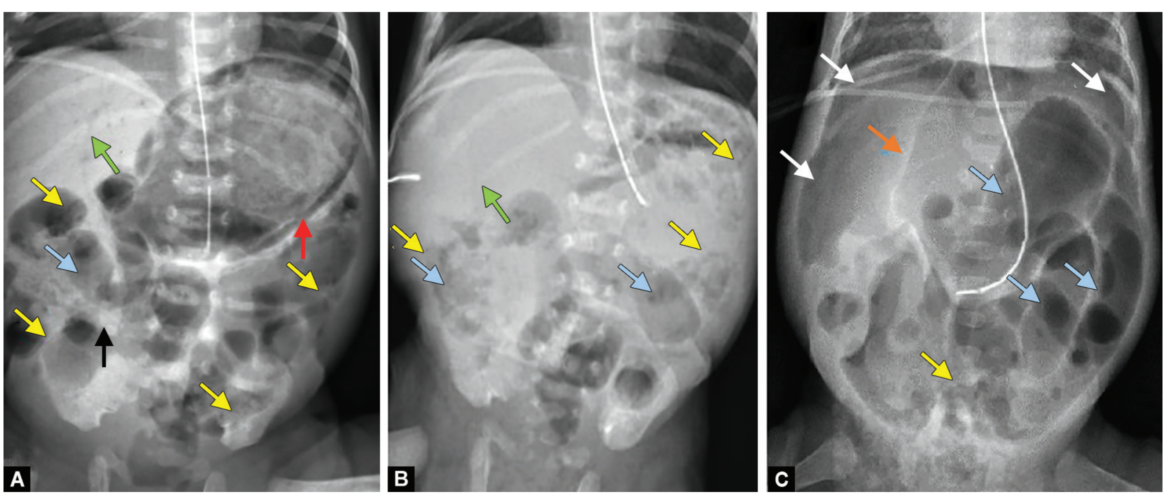
Radiographic Imaging in NEC

The traditional, most widely used technique for evaluation and diagnosis of NEC is plain abdominal radiography. Early, subtle radiographic signs are related to alteration in peristalsis with ileus, such as dilatation and, sometimes, apparent elongation of the bowel loops with the loss of the normal mosaic pattern[10] (Figs 1A to C). Distension of the bowel loops and bowel wall edema, especially if with an asymmetric pattern, is considered more ominous and may suggest impending necrosis in the bowel area.[11] More specific radiographic findings, which have been considered pathognomonic for NEC, include *pneumatosis intestinalis* and the detection of radiolucent gas in the portal venous system (Figs 2A to C). *Pneumatosis intestinalis* refers to gas bubbles/cysts in the mucosal, submucosal, subserosal, or all three bowel wall layers.[12]

Pneumatosis is believed to originate in abnormal bacterial colonization and overgrowth in the bowel wall. Other possibilities rooted in mechanical and biochemical reasons have been considered but never proven.[12] As currently believed, the disruption



Figs 1A to C: Plain anterior-posterior (AP) supine abdominal radiographs demonstrating normal versus abnormal bowel gas pattern; (A) Normal bowel gas pattern with no evidence of NEC; (B) progressively dilated bowel gas pattern, nonspecific for NEC as can be seen in many clinical settings such as swallowed air in a normal infant to inflamed bowel due to NEC and/or with postsurgical ileus. It could be more specific for NEC if bowel dilation is more localized and more severe (bowel lumen diameter measures greater than the width of one vertebral body), or it persists over many subsequent radiographs in the same place and; (C) Advanced dilatation of bowel loops with some evidence of bowel wall edema



Figs 2A to C: Sequential AP supine abdominal radiographs showing the evolution of NEC; (A) NEC totalis with linear lucent shadows in the gastric wall (red arrow), soap-bubble radiolucent intramural gas (pneumatosis intestinalis) in the abdomen (yellow arrows), portal venous gas (green arrow), dilated bowel loops (blue arrowhead) with bowel wall edema/thickening; (B) After 6 hours, the gastric distension seems to have decreased. Intestinal distension, pneumatosis, and a thin line of portal venous gas can still be noticed and; (C) 18 hours later, pneumoperitoneum (indicating intestinal perforation) (white arrows) can be seen with gas between both domes of the diaphragm and the liver and likely forming the relative radiolucency seen in front of the liver. The massive air collection in the peritoneal cavity accounts for the "football sign" (orange arrow). Pneumatosis can still be seen in some areas through the overlying intraperitoneal air of the mucosal layer allows bacterial translocation into the intestinal wall, and the gaseous products of bacteria metabolism then progressively dissect through the tissues to accumulate in the deeper layers of the injured bowel. Some of these collected gases gradually find their way into the local venules that drain into the portal venous system and can be seen as branching radiolucency against the relatively opaque background of the liver (Figs 2A to C). In severe cases, the necrotic bowel ruptures to release the intraluminal air into the peritoneal cavity. In this pneumoperitoneum, the collection of relatively large amounts of free air can be seen as a "football sign," or the "falciform ligament sign," where the oval abdominal cavity outlined by the lucent intraperitoneal air may be visualized as a football, the longitudinal falciform ligament as the ball's lace, and the transversely transecting ribs as the cross-stitches (Figs 2A to C).

Clinical Use of Abdominal Radiographs in NEC

Several clinical staging systems for NEC incorporate abdominal radiographic findings. Bell's staging, established in 1978, is the most widely used criteria for classifying and managing NEC.[13] Walsh and Kliegman subsequently modified this staging system to make it more contemporary by dividing each stage into two subcategories and incorporating clinical signs indicative of disease severity.[14] In Bell's stage I NEC (suspected NEC), abdominal radiographic findings include nonspecific signs such as intestinal dilatation or mild ileus. Bell's stage II NEC (definite NEC) requires the presence of more specific features such as *pneumatosis intestinalis* and/or portal venous gas. Lastly, Bell's stage III NEC (advanced NEC) includes the finding of pneumoperitoneum or "free" air. Gephart et al. recently described a simple, alternative bedside clinical tool for diagnosing preterm NEC called the "two out of three" rule.[15] This rule is comprised of (1) *pneumatosis intestinalis* and/or portal venous gas at presentation, (2) platelet count below 150,000 for 3 days after diagnosis, and (3) gestational age at disease onset more suggestive of NEC than spontaneous intestinal perforation. Gordon et al. also proposed a new system that utilizes *pneumatosis* and pneumoperitoneum as 2 of 11 diagnostic criteria for classifying NEC and other acute neonatal intestinal conditions.[16] However, it was not widely used in clinical practice, likely due to its complexity.

Limitations of Plain Abdominal Radiographs for NEC Evaluation

Although *pneumatosis* and portal venous gas can be highly specific for NEC, these pathognomonic signs are not always readily evident on plain radiographs. As mentioned above, *pneumatosis* is seen only in 55–60% of all infants with NEC. Occasionally, it also becomes challenging to distinguish between intramural air and air admixed with stool, specifically when the clinical presentation is equivocal. Moreover, nonspecific findings such as gaseous intestinal distension, air-fluid levels, bowel wall thickening, and ascites are common findings on plain radiographs but of unclear usefulness in diagnosing NEC. Sharma et al., in their study of 202 neonates, demonstrated that the clinical and radiographic presentations of NEC are different in extremely preterm infants (gestational age, 23–26 weeks) compared to infants with higher gestational age, highlighting the inadequacy of plain abdominal film in the diagnosis of NEC in extremely premature neonates.[17] Kosloske et al. corroborated this insufficiency by reporting that preterm neonates developed intestinal necrosis before developing diagnostic NEC features in serial abdominal X-rays.[18] Thus, the sole use of abdominal radiographs for the diagnosis and staging of NEC can have numerous demerits.[19,20] A readily available, noninvasive imaging modality that can characterize the state of the intestinal tract in more detail than plain radiographs would help evaluate infants for NEC.

Sonographic Assessment in NEC

Bowel US has been shown to be helpful for the evaluation of NEC since 1984 when Kodroff et al. described "abnormal bowel characterized by a hypoechoic rim with a central echogenic focus."[21] It was suggested that this sign could be used to help identify gangrenous bowel before perforation. Since then, many additional US findings associated with NEC have been identified. A few of these are visible on radiography, including *pneumatosis intestinalis*, portal venous gas, and free intraperitoneal air. However, US may be more sensitive to these findings, and they may be identified earlier in the disease course.[21–24]

US also allows for identifying many additional signs of NEC, which are not apparent on radiography, through real-time imaging of the bowel and peritoneum. The bowel wall can be directly characterized, demonstrating abnormal thickness (increased or decreased) and abnormal echogenicity. Bowel distension with fluid can be seen. Doppler imaging can assess perfusion of the bowel wall (increased or absent). Real-time cine imaging can detect the presence or absence of peristalsis. In addition to the bowel findings, small amounts of free intraperitoneal fluid can be identified, and the fluid can be described as simple or complex. Focal fluid collections or abscesses can be localized.[25–28]

Imaging Findings of NEC Common to Plain Abdominal Radiography and AUS

Pneumatosis Intestinalis

This finding is best identified using high-frequency linear transducers, which allow for higher spatial resolution US. *Pneumatosis* appears as tiny echogenic gas bubbles or granules along the circumference of the bowel wall (Figs 2A to C), dubbed as the "circle sign" with posterior reverberation artifacts.[29,30] When scanning, it can be challenging to differentiate pneumatosis from gas in the bowel lumen, so real-time evaluation and cine imaging can be beneficial in this regard. Kim et al. studied NEC in newborn rabbits and noted that echogenic dots and circumferential granular echogenicity might also correlate with the histopathologic features of ischemic enterocolitis.[31] Intramural gas does not shift position with alterations in the patient's position, bowel peristalsis, respiratory movement, or abdominal compression with the transducer.[32]

Portal Venous Gas

Portal venous *pneumatosis* in neonates can be iatrogenic, resulting from the passage of gas bubbles during umbilical venous catheterization.[33–35] However, portal venous gas is also a frequent finding in infants with NEC.[23,36] It appears as echogenic foci moving as microbubbles with the blood flow inside the lumen of the portal vein on grayscale ultrasonography.[37] These microbubbles in the small intraparenchymal portal vein branches can be seen as hyperechogenic foci in a dendriform granular pattern.[38] On spectral Doppler images, portal venous gas appears as a vertical line in the spectral Doppler waveform tracing and will sound like a popping sound if audio output is enabled on the US machine. In a study including 352 neonates, the presence of portal venous gas in AUS had an 86% specificity and a 45% sensitivity in

NEC diagnosis (Bell's stage II or above).[39] In a more recent study, the combination of portal venous gas on US and *pneumatosis intestinalis* on abdominal X-ray had a diagnostic sensitivity of 89% and specificity of 91%.[40]

Free Abdominal Gas

Bowel perforation in the final stages of NEC, most commonly in the distal ileum and proximal colon, results in free gas in the abdominal cavity. In AUS, free gas appears as bright, linear, or punctate echogenic foci between the anterior abdominal wall and the anterior surface of the liver, between loops of bowel, or floating on peritoneal fluid deep to the abdominal wall.[37,41] The finding of free abdominal gas can be harder to detect on AUS as compared to abdominal radiograph.[35]

Imaging Findings for NEC Unique to AUS

Bowel Wall Thickness and Echogenicity

Increasing bowel wall thickness reflects mucosal hemorrhage and edema at the initial phases of the pathogenesis of NEC. Usually, a bowel wall thickness of more than 2.6 mm is considered pathological.[42] In the later advanced stages, prominent bowel wall ischemia can cause bowel wall thinning. Thickness below 1.1 mm indicates bowel wall ischemia and consequent necrosis.[37,42] The normal echogenicity of the intestinal wall vanishes in case of bowel wall thickening or thinning.[43] The thickened bowel wall appears hypoechoic (black) and contrasts against the increased echogenicity (white) of the *valvulae conniventes*, giving rise to the characteristic grayscale "zebra" or "herringbone" pattern (seen as white stripes/branching surrounded by black) (Figs 3A to C).[43]

Bowel Wall Perfusion

Color Doppler US with the lowest possible pulse repetition rate and the highest Doppler gain settings can be used to assess bowel wall perfusion in NEC.[38] In color Doppler US, bowel wall inflammation in the initial stages of NEC is characterized by ring-shaped signals, a Y-shaped pattern in distal mesenteric and subserosal vessels, and a zebra pattern in longitudinal scans.[42] When there is no color Doppler signal at a velocity of or below 0.029 meters per second, bowel wall perfusion is said to be absent.[42]

Free Abdominal Fluid

In neonates with severe NEC with or without perforation of the bowel wall, free fluid can accumulate in the intraperitoneal cavity. Echogenic ascites is one of the typical findings associated with bowel wall necrosis in ischemic enterocolitis.[44] Low-level echoes and septations within the intraperitoneal fluid that indicates the presence of pus or intestinal contents are more suggestive of perforation of gangrenous bowel.[45] The echogenic foci between bowel loops suggest localized fluid accumulation with or without septations and indicate bowel perforation.[38] It is crucial to appreciate that a small amount of nonechogenic, free abdominal fluid is nonspecific and can be normal in neonates.[37]

Benefits of AUS Over Plain X-ray Examination

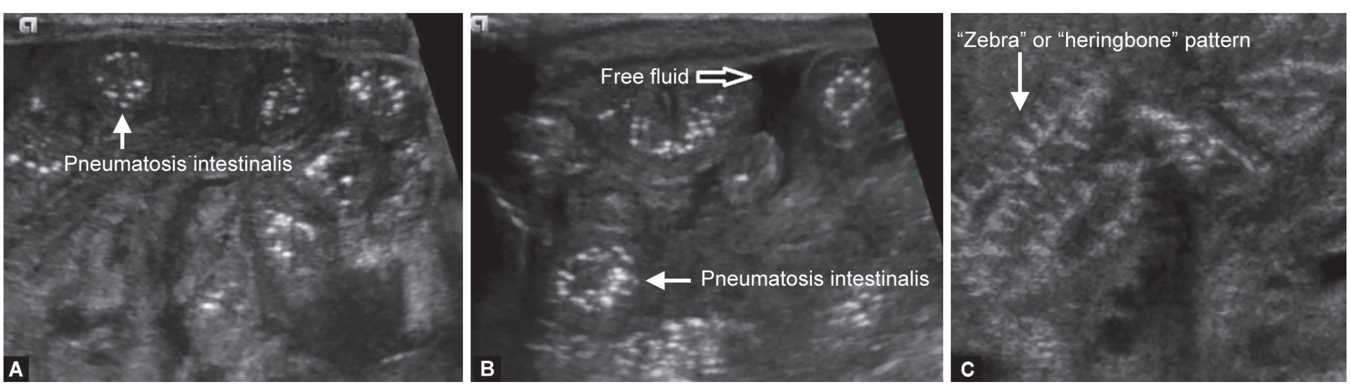
The US examination can display abdominal structures in real time, which allows the assessment of bowel peristalsis and viability. AUS also has significantly higher rates of detection of *pneumatosis* and portal venous gas than abdominal X-ray, permits a more precise assessment of bowel wall thickness, and is superior to plain X-rays in evaluating intraperitoneal fluid.[28] The added capability of color Doppler enables the evaluation of bowel perfusion to recognize bowel ischemia and necrosis.[45,46] Plain abdominal radiographs can also have significant interobserver variability in NEC diagnosis, and the frequent need for multiple serial X-rays exposes preterm neonates to potentially harmful radiation.[47–49]

Several single-center studies have reported the superiority of AUS over plain radiographs in NEC. Dilli et al. showed the benefits of AUS over plain abdominal X-ray as the better demarcation of portal venous gas, intraabdominal fluid, bowel wall thickness, and bowel wall perfusion.[50] Shebrya et al., in a study of 30 preterm neonates, substantiated the superiority of AUS in early diagnosis and detection of complications such as intestinal perforation and, hence, early surgical management associated with better morbidity and mortality rates.[51] Franco and Ramji, in their case report of a preterm neonate, highlighted the importance of AUS in the diagnosis of NEC when there are nonspecific clinical features and an inconclusive plain abdominal X-ray.[52]

Clinical Use of AUS in NEC Evaluation

Diagnosis or Exclusion of NEC

Because of widespread availability and familiarity with clinicians, plain abdominal radiography remains the current imaging modality of choice for the immediate evaluation of infants with suspected NEC. The current role of AUS in NEC evaluation is that of an adjunct to plain X-rays to aid in the diagnosis of infants with clinical suspicion



Figs 3A to C: Sonographic diagnosis of NEC; (A) Multiple punctate, echogenic foci seen within the bowel wall demonstrating pneumatosis (marked by the white arrow), which are distributed circumferentially and in multiple bowel segments; (B) Pneumatosis (white arrow), with some free fluid present between bowel segments (black arrow with white outline) and; (C) Increased echogenicity of the valvulae conniventes (also called the plicae circulares or small bowel folds) has been described as the "zebra" or "herringbone" pattern (white arrow) and is a nonspecific finding of bowel wall edema of NEC by providing a more detailed evaluation of the intestine. Studies have recommended that the cohesive application of plain abdominal radiographs and AUS in NEC management will improve the diagnostic accuracy and sensitivity.[53–55] The NEC group of the International Neonatal Consortium recommended utilizing AUS to locate pneumatosis and/or portal venous gas as a component of the "two out of three" rule.[56] AUS is also helpful in the differential diagnosis of necrotic bowel conditions. For instance, it can differentiate between NEC and food protein-induced enterocolitis syndrome; the decreased or absent bowel peristalsis is present in the entire gut in NEC, whereas it is present only in an isolated bowel segment in the latter.[57] AUS can also exclude conditions with overlapping clinical presentation, such as neonatal appendicitis and intussusception, better than radiographs.[58,59] Hashem et al. advocated applying color Doppler ultrasonography of the splanchnic circulation to detect NEC early in septic preterm neonates.[40]

Monitor Progression of the Disease

The US has the potential to identify the progression of the disease, with imaging findings ranging from early disease (wall thickening, minimal simple free fluid, and the presence of peristalsis), to more severe disease (increased blood flow, pneumatosis, and portal venous gas), to the most severe disease (bowel wall thinning, decreased perfusion of the bowel wall, and large volumes of complex fluid).[28] Signs of perforation include complex (echogenic) free intraperitoneal fluid and visible free air.[25]

Predicting Outcome with Ultrasonographic Parameters

Predicting patient outcomes is another potential use of AUS. Single-center studies[25,26,60,61] and a recent meta-analysis[62] have identified several ultrasonographic features associated with a strong or moderate association with surgery or poor outcomes, including death. Findings associated with poor outcomes (including surgery or death) include abnormal bowel wall thickness (increased or decreased), pneumatosis intestinalis, absent bowel wall perfusion, bowel dilatation with anechoic contents, complex ascites, a focal fluid collection, and free air. Lack of peristalsis may also predict a poor outcome, while anechoic (simple) free intraperitoneal fluid predicts a better outcome. Portal venous gas and increased bowel wall perfusion did not prove to be helpful with the prediction of outcomes. These studies suggest that AUS may be helpful in risk stratification and identification of infants who may benefit from more aggressive treatment, including surgery.

Technical and Practical Aspects of AUS

AUS to assess bowel viability in NEC is performed in two phases. At first, portal venous gas, free intraperitoneal fluid, free abdominal air, and the relationship between the superior mesenteric artery and superior mesenteric vein are evaluated. Secondly, grayscale and color Doppler AUS are used to assess the bowel loops in the four quadrants of the abdomen.[46] A linear array transducer of frequency 12–20 megahertz (MHz) is used.[48] Color Doppler AUS recommended settings and parameters include lowest possible pulse frequency without aliasing, highest color Doppler gain settings without flash artifacts, and velocity of 2–7 cm/second. Certain conditions can restrict the interpretation of color Doppler AUS signals. These include excessive bowel peristalsis, elevated bowel gas, use of high-frequency ventilation, decreased cardiac output, and use of vasopressors.[42,46]

There are also practical aspects of AUS to consider, as it may not be as readily available as plain abdominal radiographs and involves higher costs, and clinicians may not be as familiar with its use in NEC. AUS also requires sufficient expertise for adequate acquisition and interpretation of images. This expertise is primarily concentrated in pediatric hospitals where pediatric radiologists and US technologists are available. In contrast, most preterm infants at the highest risk for NEC are admitted in level 3 neonatal intensive care units (NICUs) housed within adult hospitals. Radiology services in this setting are often staffed by adult radiologists and US technologists who may not have sufficient expertise with AUS for NEC evaluation. Other practical limitations of AUS include potential intolerance to the procedure in labile, critically ill infants and poor image quality when excessive bowel gas is present.[8]

Emerging Modalities of Assessment in NEC

Several other noninvasive modalities for evaluating NEC have recently been reported in the literature. While not as well-studied as plain radiographs and AUS, these modalities have the potential to be clinically valuable for the assessment of NEC.

Contrast-enhanced US

CEUS is a novel imaging modality increasingly being used to assess pediatric bowel perfusion.[63] US contrast agent consists of microbubbles of gas suspended in a shell of various materials like sulfur hexafluoride, albumin, or lipid. The advantage of US contrast agents over the other more common radiological contrast agents is that they have no renal toxicity and have a lower rate of allergic reaction.

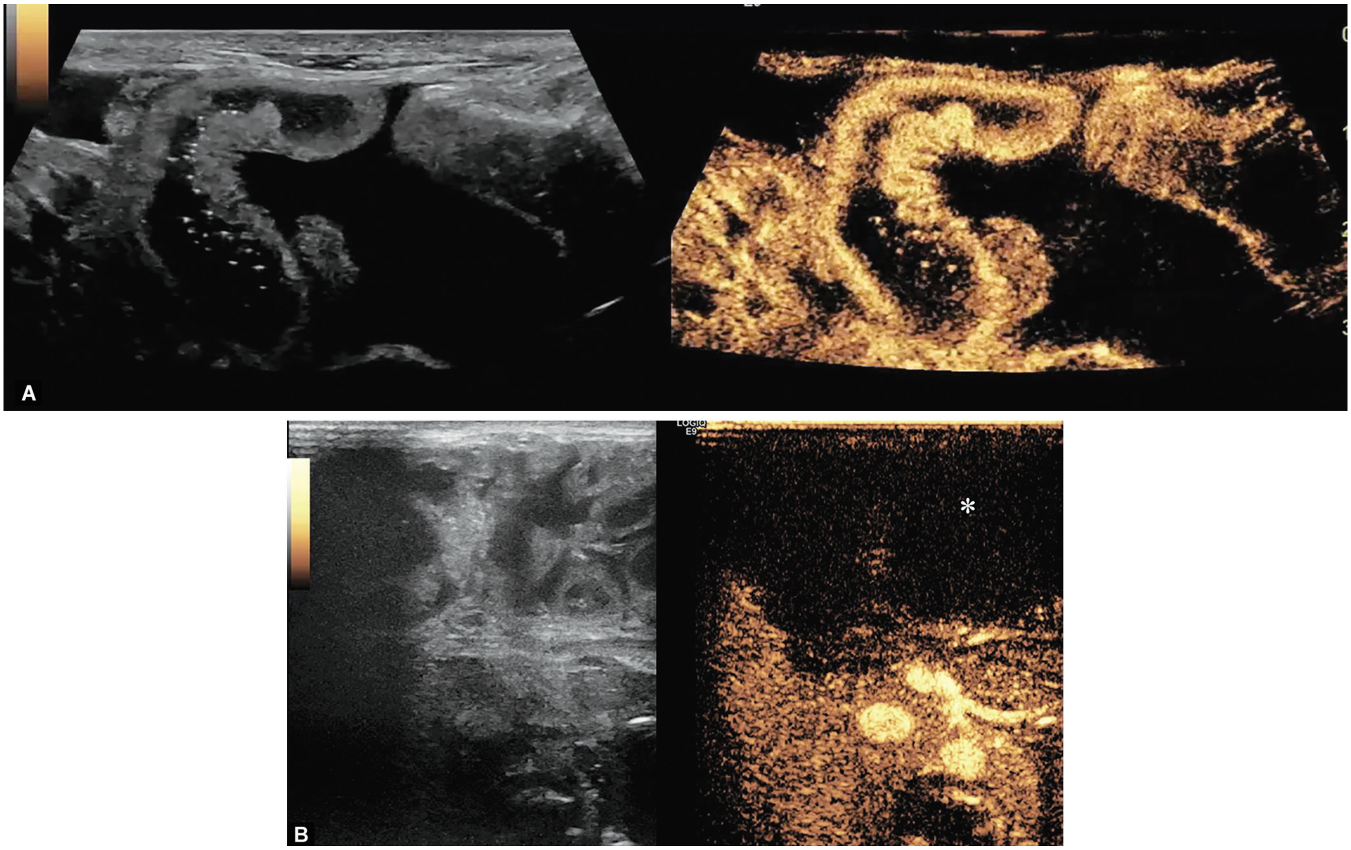
CEUS may act as an alternative to Doppler US to evaluate bowel perfusion, especially in neonates requiring mechanical ventilation, where there are disturbances due to the vibrations conducted from the ventilator to the body. During bowel wall inflammation in the early stages of NEC, CEUS displays hyperenhancement, and during progression to bowel wall ischemia and subsequent necrosis, there is hypoenhancement and eventually no perceptible enhancement in the CEUS (Figs 4A and B).[63,64] These findings are similar to those seen by color Doppler imaging, and the challenge for CEUS will be to prove that it provides increased value in return for the added complexity associated with the US contrast agent.

Magnetic Resonance Imaging

Mustafi et al. demonstrated that advanced magnetic resonance imaging (MRI) methods such as high-resolution magnetic resonance colonography and dynamic contrast-enhanced MRI could ascertain colonic injury in a mouse model.[65] MRI permits the noninvasive diagnosis of bowel necrosis, which appears bubble-like, in preterm neonates.[66] Mustafi et al. expanded the potential application of MRI by reporting its role in the early detection of NEC before clinical features in a neonatal rat model.[67] Although these studies show that NEC can be diagnosed on MRI, many barriers remain to widespread adoption. MRI examinations for NEC are not possible at the bedside, are expensive, and fail to identify any features over those imaged by US and radiograph.

Near-infrared Spectroscopy

Another promising modality is NIRS, which could help distinguish advanced stages of NEC from moderate disease by cerebral and splanchnic oxygenation measures; however, it may not be helpful in early-stage identification.[68,69] Fortune et al. demonstrated that



Figs 4A and B: (A) NEC in a 5-week-old premature infant who was admitted for abdominal distension and bloody stools. Dual-screen grayscale (left) and CEUS (right) still images from cine US show concentric wall thickening with surrounding ascites. The CEUS image shows marked hyperenhancement of the bowel wall compared with that of the surrounding mesentery and adjacent bowel loops, a finding compatible with the hyperperfusion phase of NEC and; (B) Total bowel necrosis in a premature newborn girl who was evaluated for possible in utero volvulus at prenatal US (not shown) and found to have duodenal atresia. Grayscale (left) and CEUS (right) images show that after administration of intravenous contrast material, no enhancement of the bowel wall is visible (*), which is consistent with diffuse bowel necrosis (Republished with permission from: Gokli A, Acord MR, Hwang M, et al. Contrast-enhanced US in pediatric patients: overview of bowel applications. RadioGraphics 2020;40:1743–1762. Copyright RSNA, 2020)

NIRS could be used to detect splanchnic ischemia by comparing cerebro-splanchnic oxygenation ratio (CSOR).[70] Cortez et al. established the feasibility of using NIRS in the early diagnosis of NEC in preterm neonates. They demonstrated that regional splanchnic oxygen saturation ($rsSO_2$) was lower, and fractional tissue oxygen extraction (FTOE) was higher in infants with feeding intolerance than those without feeding intolerance. Additionally, infants with NEC had persistently low $rsSO_2$ with a loss of variability preceded or followed by very high $rsSO_2$.[71] NIRS, alone or with other diagnostic modalities, holds the potential for facilitating early diagnosis and management of NEC[64,72] and may differentiate between complicated and uncomplicated NEC.[68]

Broad Optical Spectroscopy

NIRS involves oximeters that identify light absorbance and reflectance in a narrow wavelength range (700–850 nm); on the contrary, broad optical spectroscopy (BOS) involves spectroradiometers that can detect wavelengths in a much wider range (400–1800 nm).[73] BOS not only analyzes tissue oxygen levels but also evaluates biomarkers involved in the initial pathogenesis and progression of NEC. In a mouse model, it was able to diagnose NEC with 100% sensitivity and specificity.

Conclusion

NEC diagnosis and management continue to be challenging due to the lack of objective imaging methods for early detection with adequate sensitivity and specificity. The traditional use of abdominal radiographs for NEC diagnosis has poor specificity, leading to ambiguity in differentiating it from similar conditions, failure of early detection. By the time the specific diagnostic features become apparent, NEC has already progressed to an advanced, irreversible stage. Recent advancements in this field have identified ultrasonography, both with traditional and handheld probes, as a viable alternative with the potential for earlier diagnosis, improved management, and prognostication of outcomes for preterm infants with NEC. Despite the promising data, further studies are still needed due to lack of consensus, heterogeneous reporting, and a potential bias risk from observational studies. In addition to grayscale and Doppler US, several other modalities are under investigation, such as CEUS, MRI, NIRS, and BOS. Specific focus on optimum timing and frequency of US in preterm neonates with suspected NEC is needed.

Orcid

Rachana Singh https://orcid.org/0000-0001-7783-1214

References

1. Kosloske AM. Epidemiology of necrotizing enterocolitis. Acta Paediatr Suppl 1994;396:2–7. DOI: 10.1111/j.1651-2227.1994.tb13232.x.
2. Holman RC, Stoll BJ, Curns AT, et al. Necrotising enterocolitis hospitalisations among neonates in the United States. Paediatr Perinat Epidemiol 2006;20(6):498–506. DOI: 10.1111/j.1365-3016.2006.00756.x.
3. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. Journal of the American Medical Association 2015;314(10):1039–1051. DOI: 10.1001/jama.2015.10244.
4. Johnson TJ, Patel AL, Bigger HR, et al. Cost savings of human milk as a strategy to reduce the incidence of necrotizing enterocolitis in very low birth weight infants. Neonatology 2015;107(4):271–276. DOI: 10.1159/000370058.
5. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001;107(1):E1. DOI: 10.1542/peds.107.1.e1.
6. Zani A, Pierro A. Necrotizing enterocolitis: controversies and challenges. F1000Res 2015;4. DOI: 10.12688/f1000research.6888.1.
7. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med 2011;364(3):255–264. DOI: 10.1056/NEJMra1005408.
8. Alexander KM, Chan SS, Opfer E, et al. Implementation of bowel ultrasound practice for the diagnosis and management of necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2021;106(1):96–103. DOI: 10.1136/archdischild-2019-318382.
9. Gan X, Li J. [Research advances in necrotizing enterocolitis in neonates]. Zhongguo Dang Dai Er Ke Za Zhi 2018;20(2):164–168. DOI: 10.7499/j.issn.1008-8830.2018.02.016.
10. Rabinowitz JG, Siegle RL. Changing clinical and roentgenographic patterns of necrotizing enterocolitis. AJR Am J Roentgenol 1976;126(3):560–566. DOI: 10.2214/ajr.126.3.560.
11. Soni R, Katana A, Curry JI, et al. How to use abdominal X-rays in preterm infants suspected of developing necrotising enterocolitis. Arch Dis Child Educ Pract Ed 2020;105(1):50–57. DOI: 10.1136/archdischild-2018-315252.
12. Pear BL. Pneumatosis intestinalis: a review. Radiology 1998;207(1):13–19. DOI: 10.1148/radiology.207.1.9530294.
13. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187(1):1–7. DOI: 10.1097/00000658-197801000-00001.
14. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33(1):179–201. DOI: 10.1016/s0031-3955(16)34975-6.
15. Gephart SM, Gordon PV, Penn AH, et al. Changing the paradigm of defining, detecting, and diagnosing NEC: Perspectives on Bell's stages and biomarkers for NEC. Semin Pediatr Surg 2018;27(1):3–10. DOI: 10.1053/j.sempedsurg.2017.11.002.
16. Gordon PV, Swanson JR, Attridge JT, et al. Emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell's criteria? J Perinatol 2007;27(11):661–671. DOI: 10.1038/sj.jp.7211782.
17. Sharma R, Hudak ML, Tepas JJ 3rd, et al. Impact of gestational age on the clinical presentation and surgical outcome of necrotizing enterocolitis. J Perinatol 2006;26(6):342–347. DOI: 10.1038/sj.jp.7211510.
18. Kosloske AM, Musemeche CA, Ball WS, et al. Necrotizing enterocolitis: value of radiographic findings to predict outcome. AJR Am J Roentgenol 1988;151(4):771–774. DOI: 10.2214/ajr.151.4.771.
19. Raghuveer TS, Lakhotia R, Bloom BT, et al. Abdominal ultrasound and abdominal radiograph to diagnose necrotizing enterocolitis in extremely preterm infants. Kans J Med 2019;12(1):24–27. PMID: 30854167.
20. Daneman A, Woodward S, de Silva M. The radiology of neonatal necrotizing enterocolitis (NEC). A review of 47 cases and the literature. Pediatr Radiol 1978;7(2):70–77. DOI: 10.1007/BF00975674.
21. Kodroff MB, Hartenberg MA, Goldschmidt RA. Ultrasonographic diagnosis of gangrenous bowel in neonatal necrotizing enterocolitis. Pediatr Radiol 1984;14(3):168–170. DOI: 10.1007/BF01002304.
22. Malin SW, Bhutani VK, Ritchie WW, et al. Echogenic intravascular and hepatic microbubbles associated with necrotizing enterocolitis. J Pediatr 1983;103(4):637–640. DOI: 10.1016/s0022-3476(83)80605-2.
23. Robberecht EA, Afschrift M, De Bel CE, et al. Sonographic demonstration of portal venous gas in necrotizing enterocolitis. Eur J Pediatr 1988;147(2):192–194. https://doi.org/10.1007/bf00442221.
24. Bomelburg T, von Lengerke HJ. Intrahepatic and portal venous gas detected by ultrasonography. Gastrointest Radiol 1992;17(3):237–240. DOI: 10.1007/BF01888557.
25. Staryszak J, Stopa J, Kucharska-Miasik I, et al. Usefulness of ultrasound examinations in the diagnostics of necrotizing enterocolitis. Pol J Radiol 2015;80:1–9. DOI: 10.12659/PJR.890539.
26. Muchantef K, Epelman M, Darge K, et al. Sonographic and radiographic imaging features of the neonate with necrotizing enterocolitis: correlating findings with outcomes. Pediatr Radiol 2013;43(11):1444–1452. DOI: 10.1007/s00247-013-2725-y.
27. Chen S, Hu Y, Liu Q, et al. Application of abdominal sonography in diagnosis of infants with necrotizing enterocolitis. Medicine (Baltimore) 2019;98(28):e16202. DOI: 10.1097/MD.0000000000016202.
28. Esposito F, Mamone R, Di Serafino M, et al. Diagnostic imaging features of necrotizing enterocolitis: a narrative review. Quant Imaging Med Surg 2017;7(3):336–344. DOI: 10.21037/qims.2017.03.01.
29. Goske MJ, Goldblum JR, Applegate KE, et al. The "circle sign": a new sonographic sign of pneumatosis intestinalis – clinical, pathologic and experimental findings. Pediatr Radiol 1999;29(7):530–535. DOI: 10.1007/s002470050638.
30. Vernacchia FS, Jeffrey RB, Laing FC, et al. Sonographic recognition of pneumatosis intestinalis. AJR Am J Roentgenol 1985;145(1):51–52. DOI: 10.2214/ajr.145.1.51.
31. Kim WY, Kim IO, Kim WS, et al. Sonographic findings in a model of ischemia-induced necrotizing enterocolitis with pathological correlations. Invest Radiol 2007;42(5):312–318. DOI: 10.1097/01.rli.0000258681.14275.19.
32. Kim W-Y, Kim WS, Kim I-O, et al. Sonographic evaluation of neonates with early-stage necrotizing enterocolitis. Pediatr Radiol 2005;35(11):1056–1061. DOI: 10.1007/s00247-005-1533-4.
33. Arnon RG, Fishbein JF. Portal venous gas in the pediatric age group. Review of the literature and report of twelve new cases. J Pediatr 1971;79(2):255–259. DOI: 10.1016/S0022-3476(71)80110-5.
34. Schmidt AG. Portal vein gas due to administration of fluids via the umbilical vein. Radiology 1967;88(2):293–294. DOI: 10.1148/88.2.293.
35. Swaim TJ, Gerald B. Hepatic portal venous gas in infants without subsequent death. Radiology 1970;94(2):343–345. DOI: 10.1148/94.2.343.
36. Merritt CR, Goldsmith JP, Sharp MJ. Sonographic detection of portal venous gas in infants with necrotizing enterocolitis. AJR Am J Roentgenol 1984;143(5):1059–1062. DOI: 10.2214/ajr.143.5.1059.
37. Epelman M, Daneman A, Navarro OM, et al. Necrotizing enterocolitis: review of state-of-the-art imaging findings with pathologic correlation. Radiographics 2007;27(2):285–305. DOI: 10.1148/rg.272055098.
38. Bohnhorst B. Usefulness of abdominal ultrasound in diagnosing necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2013;98(5):F445–F450. DOI: 10.1136/archdischild-2012-302848.
39. Dordelmann M, Rau GA, Bartels D, et al. Evaluation of portal venous gas detected by ultrasound examination for diagnosis of necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 2009;94(3):F183–F187. DOI: 10.1136/adc.2007.132019.
40. Bohnhorst B, Kuebler JF, Rau G, et al. Portal venous gas detected by ultrasound differentiates surgical NEC from other acquired neonatal intestinal diseases. Eur J Pediatr Surg 2011;21(1):12–17. DOI: 10.1055/s-0030-1265204.

41. Buonomo C. The radiology of necrotizing enterocolitis. Radiol Clin North Am 1999;37(6):1187–1198, vii. DOI: 10.1016/s0033-8389(05)70256-6.
42. Faingold R, Daneman A, Tomlinson G, et al. Necrotizing enterocolitis: assessment of bowel viability with color doppler US. Radiology 2005;235(2):587–594. DOI: 10.1148/radiol.2352031718.
43. Wang MQ, Lee MY, El Teo H. Ultrasound in the evaluation of necrotic bowel in children: a pictorial essay. Ultrasound 2019;27(4):207–216. DOI: 10.1177/1742271X18814864.
44. Azarow K, Connolly B, Babyn P, et al. Multidisciplinary evaluation of the distended abdomen in critically ill infants and children: the role of bedside sonography. Pediatr Surg Int 1998;13(5–6):355–359. DOI: 10.1007/s003830050338.
45. Miller SF, Seibert JJ, Kinder DL, et al. Use of ultrasound in the detection of occult bowel perforation in neonates. J Ultrasound Med 1993;12(9):531–535. DOI: 10.7863/jum.1993.12.9.531.
46. Faingold R. Technical aspects of abdominal ultrasound and color Doppler assessment of bowel viability in necrotizing enterocolitis. Pediatr Radiol 2018;48(5):617–619. DOI: 10.1007/s00247-018-4077-0.
47. Iyer NP, Baumann A, Rzeszotarski MS, et al. Radiation exposure in extremely low birth weight infants during their neonatal intensive care unit stay. World J Pediatr 2013;9(2):175–178. DOI: 10.1007/s12519-013-0417-1.
48. Mata AG, Rosengart RM. Interobserver variability in the radiographic diagnosis of necrotizing enterocolitis. Pediatrics 1980;66(1):68–71. PMID: 7402793.
49. Coursey CA, Hollingsworth CL, Gaca AM, et al. Radiologists' agreement when using a 10-point scale to report abdominal radiographic findings of necrotizing enterocolitis in neonates and infants. AJR Am J Roentgenol 2008;191(1):190–197. DOI: 10.2214/ajr.07.3558.
50. Dilli D, Suna Oguz S, Erol R, et al. Does abdominal sonography provide additional information over abdominal plain radiography for diagnosis of necrotizing enterocolitis in neonates? Pediatr Surg Int 2011;27(3):321–327. DOI: 10.1007/s00383-010-2737-8.
51. Shebrya NH, Amin SK, El-Shinnawy MA, et al. Abdominal ultrasonography in preterm necrotizing enterocolitis. Is it superior to plain radiography? Egypt J Radiol Nucl Med 2012;43(3):457–463. DOI: 10.1016/j.ejrnm.2012.06.001.
52. Franco A, Ramji FG. Utility of abdominal sonography to diagnose necrotizing enterocolitis. Eur J Radiol Extra 2008;65(1):13–16. DOI: 10.1016/J.EJREX.2007.11.004.
53. Gwizdala D, Wilczynska M, Talar T, et al. [Ultrasound examination in diagnosis and monitoring of necrotizing enterocolitis in a group of newborns with birth weight below 2000 g–a preliminary report]. Ginekol Pol 2013;84(10):862–870. DOI: 10.17772/gp/1653.
54. Gao HX, Yi B, Mao BH, et al. Efficacy of abdominal ultrasound inspection in the diagnosis and prognosis of neonatal necrotizing enterocolitis. Clinics (Sao Paulo) 2021;76:e1816. DOI: 10.6061/clinics/2021/e1816.
55. Tracy SA, Lazow SP, Castro-Aragon IM, et al. Is abdominal sonography a useful adjunct to abdominal radiography in evaluating neonates with suspected necrotizing enterocolitis? J Am Coll Surg 2020;230(6):903–11e2. DOI: 10.1016/j.jamcollsurg.2020.01.027.
56. van Druten J, Khashu M, Chan SS, et al. Abdominal ultrasound should become part of standard care for early diagnosis and management of necrotising enterocolitis: a narrative review. Arch Dis Child Fetal Neonatal Ed 2019;104(5):F551–F559. DOI: 10.1136/archdischild-2018-316263.
57. Guo Y, Si S, Jia Z, et al. Differentiation of food protein-induced enterocolitis syndrome and necrotizing enterocolitis in neonates by abdominal sonography. J Pediatr (Rio J) 2021;97(2):219–224. DOI: 10.1016/j.jped.2020.03.001.
58. Raveenthiran V. Neonatal appendicitis (Part 1): a review of 52 cases with abdominal manifestation. J Neonatal Surg 2015;4(1):4. PMID: 26023528.
59. Martinez Biarge M, Garcia-Alix A, Luisa del Hoyo M, et al. Intussusception in a preterm neonate; a very rare, major intestinal problem--systematic review of cases. J Perinat Med 2004;32(2):190–194. DOI: 10.1515/JPM.2004.036.
60. Silva CT, Daneman A, Navarro OM, et al. Correlation of sonographic findings and outcome in necrotizing enterocolitis. Pediatr Radiol 2007;37(3):274–282. DOI: 10.1007/s00247-006-0393-x.
61. Garbi-Goutel A, Brevaut-Malaty V, Panuel M, et al. Prognostic value of abdominal sonography in necrotizing enterocolitis of premature infants born before 33 weeks gestational age. J Pediatr Surg 2014;49(4):508–513. DOI: 10.1016/j.jpedsurg.2013.11.057.
62. Cuna AC, Reddy N, Robinson AL, et al. Bowel ultrasound for predicting surgical management of necrotizing enterocolitis: a systematic review and meta-analysis. Pediatr Radiol 2018;48(5):658–666. DOI: 10.1007/s00247-017-4056-x.
63. Gokli A, Dillman JR, Humphries PD, et al. Contrast-enhanced ultrasound of the pediatric bowel. Pediatr Radiol 2021;51(12):2214–2228. DOI: 10.1007/s00247-020-04868-x.
64. Al-Hamad S, Hackam DJ, Goldstein SD, et al. Contrast-enhanced ultrasound and near-infrared spectroscopy of the neonatal bowel: novel, bedside, noninvasive, and radiation-free imaging for early detection of necrotizing enterocolitis. Am J Perinatol 2018;35(14):1358–1365. DOI: 10.1055/s-0038-1655768.
65. Mustafi D, Fan X, Dougherty U, et al. High-resolution magnetic resonance colonography and dynamic contrast-enhanced magnetic resonance imaging in a murine model of colitis. Magn Reson Med 2010;63(4):922–929. DOI: 10.1002/mrm.22229.
66. Maalouf EF, Fagbemi A, Duggan PJ, et al. Magnetic resonance imaging of intestinal necrosis in preterm infants. Pediatrics 2000;105 (3 Pt 1):510–514. DOI: 10.1542/peds.105.3.510.
67. Mustafi D, Shiou SR, Fan X, et al. MRI of neonatal necrotizing enterocolitis in a rodent model. NMR Biomed 2014;27(3):272–279. DOI: 10.1002/nbm.3060.
68. Schat TE, Schurink M, van der Laan ME, et al. Near-infrared spectroscopy to predict the course of necrotizing enterocolitis. PLoS One 2016;11(5):e0154710. DOI: 10.1371/journal.pone.0154710.
69. Le Bouhellec J, Prodhomme O, Mura T, et al. Near-infrared spectroscopy: a tool for diagnosing necrotizing enterocolitis at onset of symptoms in preterm neonates with acute gastrointestinal symptoms? Am J Perinatol 2021;38(S 01):e299–e308. DOI: 10.1055/s-0040-1710033.
70. Fortune PM, Wagstaff M, Petros AJ. Cerebro-splanchnic oxygenation ratio (CSOR) using near infrared spectroscopy may be able to predict splanchnic ischaemia in neonates. Intensive Care Med 2001;27(8):1401–1407. DOI: 10.1007/s001340100994.
71. Cortez J, Gupta M, Amaram A, et al. Noninvasive evaluation of splanchnic tissue oxygenation using near-infrared spectroscopy in preterm neonates. J Matern Fetal Neonatal Med 2011;24(4):574–582. DOI: 10.3109/14767058.2010.511335.
72. Robinson JR, Rellinger EJ, Hatch LD, et al. Surgical necrotizing enterocolitis. Semin Perinatol 2017;41(1):70–79. DOI: 10.1053/j.semperi.2016.09.020.
73. Goldstein SD, Beaulieu RJ, Nino DF, et al. Early detection of necrotizing enterocolitis using broadband optical spectroscopy. J Pediatr Surg 2018;53(6):1192–1196. DOI: 10.1016/j.jpedsurg.2018.02.083.