

Comparison between X-ray and Abdominal Ultrasound Findings of Necrotizing Enterocolitis, its Usefulness in Early Diagnosis, Prognosis, and to Assess, is this is the Time to Change our View of Surgeon's Intervention According to the Bell's Criteria

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Abstract

Introduction: Comparison between X-ray and abdominal ultrasound (AUS) findings of necrotizing enterocolitis (NEC), its usefulness in early diagnosis, prognosis, and to assess, is this is the time to change our view of surgeon's intervention according to the Bell's criteria.

Objective: To compare between X-ray and AUS findings, its usefulness in the early diagnosis, detection, assessment, and prognosis of NEC in preterm babies.

Patients and Methods: This is a prospective study of 60 premature newborns (January 2010 - January 2014) with all signs and symptoms of NEC. Biochemical and radiological changes were taken into consideration for Bell's staging. Our study includes birth weight as per Bell's staging. Antenatal, prenatal, and postnatal findings were noted. Abdominal X-ray and AUS were done and compared for early diagnosis and management. Then our findings were correlated with complications ("surgery and/or death" and "stenosis"). We have also taken 30 premature neonates as a control and done uni- and multi-variate analyses. Sonographic findings as per Dr. Feingold and Dr. Epelman technique were followed. Informed consent from parents was taken.

Results: In our study, AUS done in 30 normal premature newborns and their findings were taken as a reference, normal values of Dr. Feingold and Dr. Epelman were also considered; with these basics we have done AUS in premature neonates with Stages 1, 2, and 3 of NEC. Grouped into those who survived with medical therapy alone (63.3%), medical therapy with complications (10%), medical and surgical therapy without complications (5%), medical and surgical therapy with complications (5%), died before surgery (8.3%), and died after surgery (8.3%). We compared AUS findings with X-ray, AUS showed important features like bowel wall thickening in Stage 1 (80.8%), whereas none by X-ray (0%).

Conclusion: Our study concludes that AUS is superior to plain radiography in the early detection of NEC. Complications like pneumatosis intestinalis, portal venous gas, free fluid collection, intestinal thinning, perforation, and pneumoperitoneum were detected earlier by AUS than by X-ray. Hence, AUS is a reliable tool for early detection, assessment, and prognosis of NEC in preterm infants.

Keywords: Abdominal ultrasound, Bell staging, Necrotizing enterocolitis, Pneumatosis intestinalis

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INTRODUCTION

Necrotizing enterocolitis (NEC) is an inflammatory gastrointestinal disease of unknown etiology that primarily affects the preterm neonate and carries a high mortality rate.¹ NEC is a leading cause of morbidity in neonatal intensive care units (NICU). The pathologic features of NEC

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resemble those of ischemic necrosis, with inflammation beginning in the mucosa and often extending through the bowel wall. The distal ileum and proximal colon are most commonly affected. The incidence of NEC is inversely proportional to the gestational age. Infants of 28 weeks or less gestational age and those of extremely low birth weight (<1000 g) are at a greater risk for NEC.² However, approximately 10% of neonates with NEC are born at term, and congenital heart disease is the main risk factor in this group. Other risk factors include perinatal asphyxia, patent ductus arteriosus, indomethacin therapy, and decreased umbilical flow in utero. NEC most commonly manifests within the 1st or 2nd week of life. However, the time of presentation varies with the gestational age; in very premature neonates, NEC may manifest only in the 2nd or 3rd week of life. The symptoms referable to the gastrointestinal tract include feeding intolerance, vomiting, diarrhea, and blood in the stool. However, there may also be non-specific generalized symptoms including lethargy, temperature and blood pressure instability, and apnea. Physical signs include abdominal distention and in more advanced cases, palpable, distended bowel loops, and abdominal wall erythema and edema. Neonates with severe disease may even present in shock. Bell's classification of NEC, which was modified by Walsh and Kliegman in 1986, relates to the worsening of these clinical and radiological abdominal signs.³ These staging criteria help pediatricians in the diagnosis, management, and prognostic assessment of NEC, but they are exclusively based on plain abdominal radiography, which remains the "gold standard" for the diagnostic assessment (Figure 1).

Plain abdominal radiography is the current standard imaging modality for evaluation of NEC. Sonography is still not routinely used for diagnosis and follow-up, as it is not widely recognized that it can provide information that is not provided by plain abdominal radiography and that may affect the management of NEC. However, the major advantages of abdominal sonography over plain abdominal radiography are that it can depict intra-abdominal fluid, bowel wall thickness, and bowel wall perfusion. Sonography may depict changes consistent with NEC when the plain abdominal radiographic findings are nonspecific and inconclusive. Thinning of the bowel wall and lack of perfusion at sonography are highly suggestive of nonviable bowel and may be seen before visualization of pneumoperitoneum on plain abdominal radiography. The mortality rate is higher after perforation; thus, earlier detection of severely ischemic or necrotic bowel loops, before perforation occurs, could potentially improve the morbidity, and mortality in NEC. The information provided by sonography allows a complete understanding of the state of the bowel in patients with NEC and may thus make management decisions easier and potentially change the outcome.⁴

Prompt institution of therapy, which includes bowel rest with a nasogastric tube, antibiotics, and adequate hydration (total parenteral nutrition), is essential to limit the clinical progression and the development of complications. Clinical deterioration may result from generalized sepsis or bowel necrosis, which may progress to perforation and the development of peritonitis or intra-abdominal abscesses. Bowel perforation occurs in 12-31% of patients.

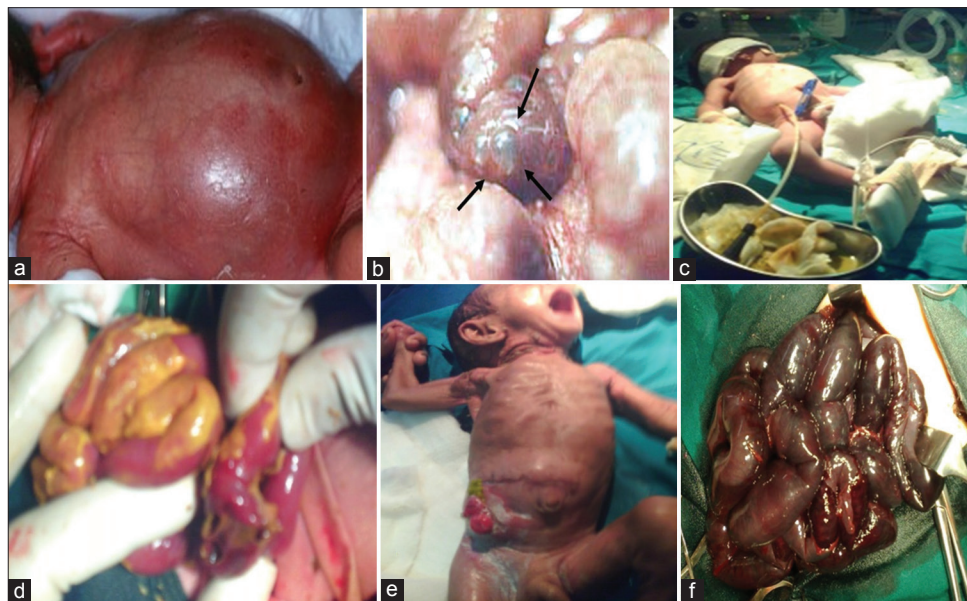


Figure 1: (a) Abdominal wall distension, erythema and cellulitis, (b) pneumatosis bullae with thinning of intestine, (c) peritoneal drainage, (d) bowel wall perforation, (e) colostomy procedure, (f) severe necrotizing enterocolitis with ischemic necrosis and gangrene, (picture B courtesy: Henri R. Ford. MD Vice President and Chief of Surgery)

A continuing challenge to the surgeon and radiologist alike is determining the most appropriate time for surgical intervention in those neonates who are not responding to medical therapy or who have developed complications.

Pneumoperitoneum is the only radiological sign that has been universally agreed on as an indication for surgical intervention, and this is complicated by the fact that not all neonates with bowel necrosis and perforation have free gas at plain abdominal radiography. In abdominal ultrasound (AUS) by using color flow, Doppler study of superior mesenteric artery (SMA) and celiac trunk, flow velocities can be known. It is an early sign of increased blood flow in ischemic and hypoxic intestinal valvulae conniventes. This allows us to study perfusion and non-perfusion areas, helps in detection of ischemic and necrotic bowel walls, thinning and non-perfused bowel walls for the early diagnosis and to know impending perforation.⁵

The overall mortality rate in NEC is between 20% and 40% and is higher in neonates of very low birth weight. Mortality climbs to 64% for the very low birth weight infant once perforation has occurred. Because of the higher mortality rate following perforation, earlier detection of severely ischemic or necrotic loops of the bowel before perforation occurs could potentially improve the morbidity and mortality in NEC. Imaging may, therefore, play an important role in this regard (Figure 2).⁶

There are cases where the abdominal radiograph may show no bowel gas. In others, necrotic bowel and perforation may occur without any radiographic signs. In these circumstances the diagnosis and follow up of nec based on clinical and radiological basis sometimes will be deficient. AUS provides a more detailed understanding of the state of the bowel in patients with NEC and may thus make management decisions easier and potentially change the outcome.⁷ In this study, we aimed to prospectively analyze abdominal sonographic findings of premature infants with NEC to investigate whether AUS is superior to abdominal plain radiography in the diagnosis of NEC.

PATIENTS AND METHODS

Patients

This was a single-centric, prospective study conducted in a level 3 neonatal unit in a teaching medical college hospital.

Clinical Data and Management

Inclusion criteria

1. Premature infants of <36 weeks of gestation, born between January 2010 and December 2013 hospitalized in the NICU
2. Absence of congenital malformations

3. Clinical symptoms suggestive of NEC as defined by the presence of abdominal distension, increased gastric residuals (N20% of enteral feeding volume), or blood in the stools (macroscopically or microscopically)
4. Confirmation of the NEC episode using abdominal imaging examinations, including two views (supine view and cross table view) abdominal radiography, and ultrasonography, performed as soon as NEC was suspected and serial follow-up with both.

Antenatal, perinatal, and postnatal data of these preterm babies were taken. The mean gestational age was between 30.5 ± 0.5 and 25% were outborn babies. Also, data regarding umbilical vein catheterization, blood culture positivity before admission were noted. Modified Bell's staging was used to categorize these neonates into Stages 1A, 1B, 2A, 2B, 3A, and 3B. This staging was based on clinical signs, symptoms (vomiting, abdominal distension, abdominal tenderness, bloody stools, and increased gastric residues, generalized features of sepsis), biochemical changes (metabolic or respiratory acidosis, thrombocytopenia), X-ray changes (abnormal shaped distended loops, bowel wall thickening), and ultrasound changes (free or focal fluid collection, free intra-abdominal air, portal venous gas [PVG]). In all these 60 preterm neonates with NEC, their clinical signs, symptoms, biochemical changes, X-ray changes were studied and grouped according to those who survived with medical therapy with or without complications, those who survived with medical and surgical therapy without complications or with complications (like stenosis or malabsorption) and also these neonates were followed to see those who died before surgery and those who died after surgery.⁸⁻¹¹

Also, in our study, these preterm neonates were categorized based on their weight ranging from 600 to 2400 g and then divided into outborn and inborn, again staging done (as 1A, 1B, 2A, 2B, 3A, and 3B) separately. Mainly, the various changes in X-ray and AUS were studied in detail with their contribution in determining the survival, morbidity, and mortality. It was found that AUS was more sensitive and specific in identifying many features of NEC like bowel wall thickening, free or focal fluid, and PVG. Also, SMA flow could be determined which is a prognostic factor in NEC. Most importantly the percentage of cases of bowel wall thinning found out using NEC were high which indirectly determined impending necrosis and need for surgery along with other indicators like fluid collection, absent peristalsis, pneumatosis intestinalis (PI), and free intra-abdominal air.

Management of these cases were done as in Stage 1, neonates were kept NPO and antibiotic coverage given for 3 days. In Stage 2, neonates were kept NPO and given antibiotics for 10 days and in Stage 3, neonates were kept

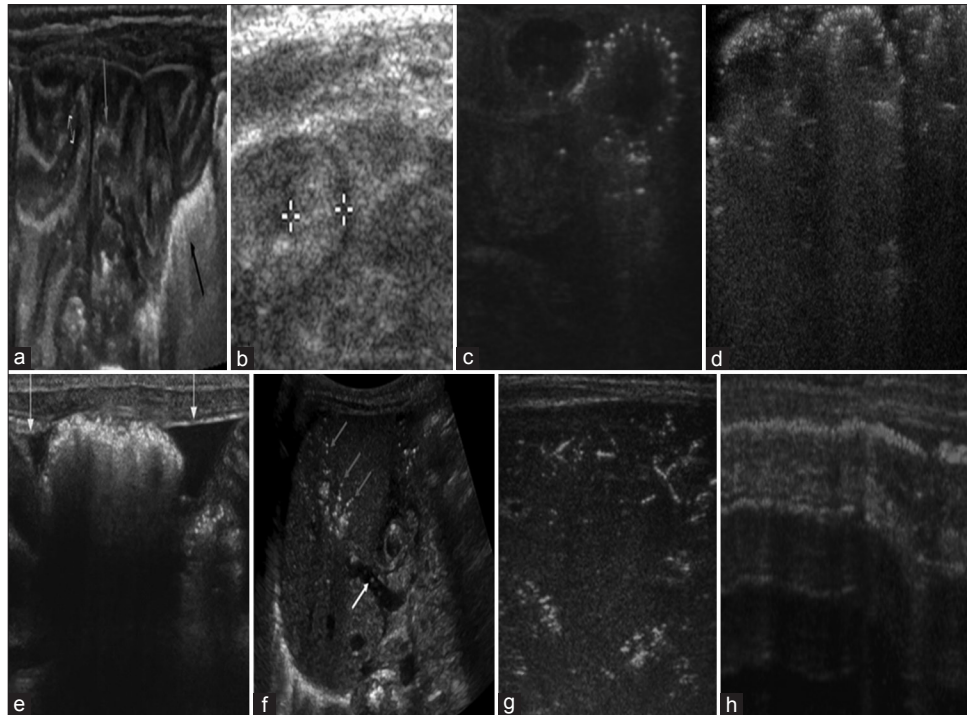


Figure 2: (a) Normal intestinal gut signature (pattern), (b) thickened intestinal wall, (c) pneumatosis intestinalis (PI), (early appearance), (d) massive PI, (e) massive PI, with local fluid collection (white arrows), (f) portal venous gas in portal vein appears as hyperechogenic dots (bold white arrow), hyper echogenic linear dendriform white dots in peripheral portal venous branches in the liver (white arrows), (g) Hyper echogenic linear dendriform white dots in peripheral portal venous branches in the liver, (h) Reverberation artefacts on the liver suggestive of pneumoperitoneum

NPO and were given antibiotics for 14 days and, especially when surgical indications like failure to respond to medical therapy, intestinal perforation, abdominal wall erythema, or abdominal wall thinning surgery was done. Post-surgery, preterm neonates were followed and for those presenting with strictures re-surgery was done and followed up. Post-surgery complication like malabsorption was treated by supplementation with vitamins (especially vitamin D).

Imaging examinations

Plain abdominal radiographs were performed according to the following protocol at the bedside, anteroposterior view, patient in supine position, vertical X-ray beam, and cross table view with a portable X-ray system multi mobile 2.5 Siemens and Fuji film dry computed radiography systems, exposition data we used 45-50 kV, 4-5 mAs. AUS examinations were carried out at the bedside, by a radiologist and trained neonatologist together, both were aware of clinical staging, baby's condition, X-ray, and ultrasound were looked into twice before giving radiological or AUS report (because we wanted to compare the clinical condition, X-ray, and ultrasound findings), with mobile ultrasound units and high-frequency linear ultrasound transducers (Philips HD 11, 3-12 MHz probe; Son site M-turbo, and 6-13 MHz probe). Sonographic findings as per Dr. Feingold and Dr. Epelman technique

were followed. Ultrasound examinations were performed according to the following protocol: Quadrant by quadrant, swipe-scanning in transverse, and sagittal planes. Color Doppler US was used to evaluate intestinal mural blood flow with a standard protocol and parameters included the lowest possible pulse repetition frequency without aliasing, a low wall filter, and the highest Doppler gain settings without flash artifacts. Velocity was set at 0.029-0.11 m/s. For each premature baby, we first read the radiograph and then did the ultrasound examination.

The following items were assessed on plain abdominal radiographs: Only gaseous distension, abnormal shaped distended intestinal walls, bowel wall thickening, intramural air (PI), soapy bubble appearance, fixed bowel loops, and free intra-abdominal air (pneumoperitoneum). In AUS, we looked in detail about Bowel Wall thickening (>2.6 mm) and echo texture striated echogenicity internal halo ("gut signature"), thinning (<1 mm), intramural air (PI, hyper echoic shadow in the mural layers), absent peristalsis (normal 10/min in one quadrant), PVG or punctate and linear, branching areas of echogenicity in the portal branches within the liver, free fluid, focal fluid collection,¹² dirty echogenic fluid collection, free intra-abdominal air (pneumoperitoneum),¹³⁻²⁰ color flow increased over all in bowel wall (compared to normal control group they were having enhanced color flow signals, ring or y,

zebra stripes-shaped abnormal flow pattern, and mural flow with a velocity of 0.085 m/s). Color Doppler signals ranged from 1 to 9 dots/cm². There were no significant differences between quadrants with dots per square centimeter, color flow decreased selective bowel wall (no color flow signal in spite of decreasing velocity to 0.015 m/s) or Doppler flow pattern extracted, SMA flow (>80-100 cm/s, if >120 cm/s severe).²¹⁻²⁵

Statistical Analysis

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean \pm standard deviation (min-max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made,

Assumptions:

1. Dependent variables should be normally distributed
2. Samples drawn from the population should be random
3. Cases of the samples should be independent.

Chi-square/Fisher exact test was used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software

The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0, and R environment version 2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables, etc.

RESULTS

Description of Study Population

Total admissions to our NICU over 4 years between January 2010 and December 2013 were 2304. In that 800 (34.5%) were preterm babies, of whom only 60 (7.5%) of preterm babies with signs, symptoms, biochemical changes, X-ray changes, or AUS changes of NEC were taken into study.

Description of the Included Preterm Neonates

Over 4 years, total admissions to the NICU were 2304, among these 800 (34.7%) were premature babies. We have taken only 60 (7.5%) of premature babies, presenting with symptoms of NEC for our study (gastrointestinal symptoms, biochemical changes, and radiological abnormality were taken into consideration in staging).

These neonates were divided based on modified Bell's staging as shown in Table 1. X-ray was done and serially

Table 1: Grouped according to Bell's staging

Bell's staging	Number of patients	Percentage
1A	14	23.3
1B	15	25.0
2A	12	20.0
2B	8	13.3
3A	6	10.0
3B	5	8.3
Total	60	100.0

repeated. X-ray changes were gaseous distension, abnormal shaped distended intestinal walls, bowel wall thickening, intramural air, PVG, soapy bubble appearance, free intra-abdominal air, whereas AUS picked up features such as bowel wall thickening, thinning, intramural air (PI), PVG, free fluid, and free intra-abdominal air. All these findings were done in neonates belonging to different groups like those who improved with medical or surgical therapy or both and those with or without complications and those who died before or after surgery. AUS was found to be more superior than X-ray like in those who survived with medical therapy, 10.5% had Bowel wall thickening seen on X-ray, but in AUS 55.2% were detected. PI seen in X-ray was 10.5%, whereas 23.5% by AUS. Bowel wall thinning could be detected only by AUS, which was a predisposing factor for impending necrosis and indication for Surgery. AUS Doppler identified many cases with increased color flow over all or decreased in selective area. SMA flow which was done also aided in diagnosis.

Keeping Bell's staging, X-ray and AUS findings were compared. Of 60 preterm neonates, 29 belonged to Stage 1, in that 1A were 14, 1B were 15. 20 belonged to Stage 2, 12 to Stage 2A, and 8 to Stage 2B. 11 belonged to Stage 3, in that 6 to Stage 3A, and 5 belonged to Stage 3B. X-ray showed Bowel wall thickening in 0% of cases in Stage 1, whereas 14.2% were identified using AUS. In Stage 2 by X-ray, 33.3% of cases of Bowel wall thickening were identified, whereas by AUS, it was 66.6%. In Stage 3A by X-ray, 66.6% of neonates with PVG were identified compared to ultrasound which was 100%. Also by ultrasound other important features like free fluid, focal fluid, and dirty echogenic fluid collection were identified. Incidence of bowel wall thinning cases identified were very high using AUS, additional things like color flow either increased overall, or decreased selective by Doppler as well as SMA flow were identified. Based on birth weight and Bell's staging, the incidence of NEC was classified. In neonates between 600 and 999 g, 21 were there, in that 11 were inborn and 9 were outborn. In neonates between 1000 and 1249 g, 14 were there, among them 8 were inborn and 6 were outborn. In neonates between 1500 and 1749 g, 6 were there, in that 4 were inborn and 3 were outborn. In

neonates between 1750 and 1999 g, 5 were there, in that 4 were inborn and 1 was outborn. In neonates between 2000 and 2400 g, 4 were there, in that 2 were inborn and 2 were outborn. Further, these outborn and inborn were again classified into 3 stages based on modified Bell's classification (Tables 2-7 and Figure 3).

Prognostic Value of Sonography

Plain abdominal radiography is the current standard imaging modality for evaluation of NEC. Sonography is still not routinely used for diagnosis and follow-up, as it is not widely recognized that it can provide information not provided by plain abdominal radiography and which may affect the management of NEC. However, the major advantages of abdominal sonography over plain abdominal radiography are that it can depict intra-abdominal fluid, bowel wall thickness, and bowel wall perfusion. Sonography may depict changes consistent with NEC when the plain abdominal radiographic findings are nonspecific and inconclusive. Thinning of the bowel wall and lack of perfusion at sonography are highly suggestive of nonviable bowel and may be seen before visualization of pneumoperitoneum by plain abdominal radiography. The mortality rate is higher after perforation, thus earlier detection of severely ischemic or necrotic bowel loops, before perforation occurs by AUS, which could potentially improve the morbidity and mortality in NEC. The information provided by sonography allows a complete understanding of the state of the bowel in patients with NEC and may thus make management decisions easier and potentially change the outcome.

We compared AUS findings with X-ray, AUS showed important features like bowel wall thickening in Stage 1 (80.8%), whereas none by X-ray (0%). In Stage 2 AUS detected bowel wall thickening in all cases were 100%, whereas 33.3% by X-ray. In Stage 3A, AUS detected bowel wall thickening in all cases were 100%, whereas 50% by X-ray. In Stage 3B, AUS detected bowel wall thickening in all cases were 100%, whereas 60% by X-ray. Intramural air (PI) detected by AUS in Stages 1A (0%), 1B (28.5%), 2A (66.6%), 2B (100%), 3A (100%), 3B (100%), respectively, whereas in X-ray, it was in Stages, 1A (0%), 1B (0%), 2A (33.3%), 2B (73%), 3A (83.3%), 3B (100%), respectively. PVG identified by AUS in Stages 1A (0%), 1B (0%), 2A (0%), 2B (87.5%), 3A (100%), 3B (100%), respectively, whereas by X-ray, it was in Stages 1A (0%), 1B (0%), 2A (0%), 2B (50%), 3A (66.6%), 3B (100%), respectively. Free intra-abdominal air (pneumoperitoneum) identified by AUS in Stages 1A (0%), 1B (0%), 2A (0%), 2B (12.5%), (66.6%), 3B (100%), respectively, whereas in X-ray, it was in Stages (0%), 1B (0%), 2A (0%), 2B (0%), 3A (33.3%), 3B (100%), respectively.

Table 2: Premature babies grouped according to the survival, morbidity, and mortality

Groups	Number of patients	Percentage
Survived with medical therapy	35	63.3
Survived with medical therapy associated with complications (stenosis)	6	10.0
Survived with medical and surgical therapy without complications	3	5.0
Survived with medical and surgical therapy associated with complications (stenosis or malabsorption)	3	5.0
Died before surgery	5	8.3
Died after surgery	5	8.3
Total	60	100.0

Table 3: Antenatal, perinatal, postnatal data of the 60 premature babies

Data	Number of patients (n=60)	Percentage
Antenatal data		
Antenatal corticosteroid therapy received	14	23.3
Oligohydramnios	20	33.3
Fetal heart rate abnormal rhythm	10	16.6
IUGR	16	26.6
Perinatal data		
Gestational age (weeks, mean±SD) (25-36 weeks)	30.5±0.5	
Male gender	35	58.3
Outborn	25	41.6
Apgar score at 5 min (mean±SD)	8±1.2	
Birth weight (grams, mean±SD) (600-2400)	1500±201	
Small for gestational age+IUGR	22	36.6
Postnatal data		
Surfactant received	45	75.0
Respiratory distress	50	83.3
Patent ductus arteriosus (>5 days) (>1.4 mm)	12	20.0
Minimal enteral feeding started	57	95.0
Age of onset (days, mean±SD)	8±2	
Given formula/bovine milk	14	23.3
Starting day of enteral feeding (days, mean±SD)	3±5.1	
Venous umbilical catheterization	15	25.0
Both venous and arterial umbilical catheterization	7	11.6
Severe polycythemia	1	1.6
Blood culture positive cases	8	13.3
Gastrointestinal symptoms started after indomethacin	5	8.3
Gastrointestinal symptoms started after ibuprofen	2	3.3
Death	10	16.6

SD: Standard deviation, IUGR: Intrauterine growth restriction

Cases with bowel wall thinning identified by AUS in Stages 1A (0%), 1B (0%), 2A (0%), 2B (25%), 3A (100%), 3B (100%), respectively, whereas none could be detected by X-ray also by AUS we could detect free fluid in Stages 1A (0%), 1B (0%), 2A (0%), 2B (37.5%), 3A

Table 4: Clinical signs, symptoms and biochemical changes according to the survival, morbidity, and mortality

Clinical signs and symptoms	Survived with medical therapy (n=38) (%)	Survived with medical therapy associated with complications (stenosis) (n=6) (%)	Survived with medical and surgical therapy without complications (n=3) (%)	Survived with medical and surgical therapy associated with complications (stenosis or malabsorption) (n=3) (%)	Died before surgery (n=5) (%)	Died after surgery (n=5) (%)	P value
Increased gastric residuals	35 (92.1)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	1.000
Abdominal distension	30 (78.9)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	0.761
Vomiting	27 (71.1)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.518
Bloody stools	24 (63.2)	4 (66.7)	3 (100)	3 (100)	5 (100)	5 (100)	0.219
Apnea	25 (65.8)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.313
Respiratory distress	22 (57.9)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.099+
Generalized features of sepsis	10 (26.3)	2 (33.3)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Abdominal tenderness	6 (15.8)	4 (66.7)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Abdominal cellulitis	0 (0)	1 (16.7)	2 (66.7)	1 (33.3)	5 (100)	3 (60)	<0.001**
Absent bowel sounds	1 (2.6)	2 (33.3)	2 (66.7)	2 (66.7)	5 (100)	4 (80)	<0.001**
Biochemical changes							
Metabolic acidosis	38 (100)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.367
Respiratory acidosis	15 (39.5)	4 (66.7)	3 (100)	3 (100)	5 (100)	5 (100)	0.001**
Neutropenia	19 (50)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.017*
Thrombocytopenia	28 (73.7)	5 (83.3)	3 (100)	3 (100)	5 (100)	5 (100)	0.650
Hyperkalemia	19 (50)	4 (66.7)	3 (100)	3 (100)	5 (100)	5 (100)	0.027*
Hyponatremia	23 (60.5)	3 (50)	3 (100)	3 (100)	5 (100)	5 (100)	0.111

Chi-square test/Fisher exact test, significant figures, + Suggestive significance (P value: 0.05<P<0.10), * Moderately significant (P value: 0.01<P≤0.05), ** Strongly significant (P value: P≤0.01)

Table 5: X-ray and AUS feature according to the survival, morbidity, and mortality

Clinical signs and symptoms	Survived with medical therapy (n=38) (%)	Survived with medical therapy associated with complications (stenosis) (n=6) (%)	Survived with medical and surgical therapy without complications (n=3) (%)	Survived with medical and surgical therapy associated with complications (stenosis or malabsorption) (n=3) (%)	Died before surgery (n=5) (%)	Died after surgery (n=5) (%)	P value
X-ray changes							
Only gaseous distension	22 (57.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<0.001**
Abnormal shaped distended Intestinal walls	20 (52.6)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	0.011*
Bowel wall thickening	4 (10.5)	2 (33.3)	2 (66.7)	2 (66.7)	2 (40)	3 (60)	0.004**
Intramural air (PI)	4 (10.5)	1 (16.7)	2 (66.7)	3 (100)	5 (100)	5 (100)	<0.001**
PVG	0 (0)	2 (33.3)	1 (33.3)	2 (66.7)	4 (80)	4 (80)	<0.001**
Soapy bubble appearance	0 (0)	0 (0)	1 (33.3)	2 (66.7)	4 (80)	5 (100)	<0.001**
Fixed Bowel loops	0 (0)	2 (33.3)	1 (33.3)	2 (66.7)	5 (100)	2 (40)	<0.001**
Free intra-abdominal air	0 (0)	0 (0)	1 (33.3)	1 (33.3)	2 (40)	3 (60)	<0.001**
Ultrasound abdomen							
Bowel wall thickening	21 (55.3)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	0.022*
Thinning	0 (0)	1 (16.7)	1 (33.3)	2 (66.7)	4 (80)	2 (40)	<0.001**
Intramural air (PI)	9 (23.7)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Peristalsis absent	0 (0)	1 (16.7)	1 (33.3)	3 (100)	5 (100)	5 (100)	<0.001**
PVG	6 (15.8)	2 (33.3)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Free fluid	0 (0)	0 (0)	1 (33.3)	2 (66.7)	5 (100)	5 (100)	<0.001**
Focal fluid collection	0 (0)	0 (0)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Dirty echogenic fluid collection	0 (0)	0 (0)	0 (0)	1 (33.3)	4 (80)	3 (60)	<0.001**
Free intra-abdominal air	0 (0)	0 (0)	1 (33.3)	2 (66.7)	3 (60)	4 (80)	<0.001**
Colour flow increased overall (bowel wall)	5 (13.2)	6 (100)	3 (100)	3 (100)	5 (100)	5 (100)	<0.001**
Colour flow decreased selective (bowel wall)	0 (0)	0 (0)	1 (33.3)	2 (66.7)	5 (100)	4 (80)	<0.001**
SMA flow (>80-100 cm/s)	3 (7.9)	5 (83.3)	2 (66.7)	3 (100)	5 (100)	5 (100)	<0.001**

Chi-Square test/Fisher exact test, significant figures, +Suggestive significance (P value: 0.05<P<0.10), *Moderately significant (P value: 0.01<P≤0.05), **Strongly significant (P value: P≤0.01), SMA: Superior mesenteric artery, PVG: Portal venous gas, PI: Pneumatosis intestinalis

(83.3%), 3B (100%), respectively. Along with this by AUS we could also detect focal fluid collection and dirty

echogenic fluid collection. AUS guided Doppler showed either increased overall flow or decreased selective

Table 6: Comparison of X-ray finding and ultrasound features with modified Bell's staging

X-ray features	NEC Stage 1 (n=29) (%)		NEC Stage 2 (n=20) (%)		NEC Stage 3 (n=11) (%)	
	1A (n=14)	1B (n=15)	2A (n=12)	2B (n=8)	3A (n=6)	3B (n=5)
Only distended intestinal loops	10 (71.4)	8 (53.3)	4 (33.3)	0 (0)	0 (0)	0 (0)
Abnormal shaped Distended loops	1 (7.1)	10 (66.6)	12 (100)	8 (100)	6 (100)	5 (100)
Bowel wall thickening	0 (0)	0 (0)	1 (8.3)	2 (25)	3 (50)	3 (60)
Intramural gas/PI	0 (0)	0 (0)	4 (33.3)	6 (73)	5 (83.3)	5 (100)
PVG	0 (0)	0 (0)	0 (0)	4 (50)	4 (66.6)	5 (100)
Soapy bubble appearance	0 (0)	0 (0)	0 (0)	2 (25)	5 (83.3)	5 (100)
Fixed bowel loops	0 (0)	0 (0)	0 (0)	2 (25)	5 (83.3)	5 (100)
Pneumoperitoneum	0 (0)	0 (0)	0 (0)	0 (0)	2 (33.3)	5 (100)
Ultrasound features						
Bowel wall thickening	2 (14.2)	10 (66.6)	12 (100)	8 (100)	6 (100)	5 (100)
Bowel wall thinning (some areas)	0 (0)	0 (0)	0 (0)	2 (25)	4 (66.6)	4 (80)
Intramural air (PI)	0 (0)	4 (28.5)	8 (66.6)	8 (100)	6 (100)	5 (100)
Peristalsis absent	0 (0)	0 (0)	0 (0)	5 (62.5)	5 (83.3)	5 (100)
PVG	0 (0)	0 (0)	0 (0)	7 (87.5)	6 (100)	5 (100)
Free fluid	0 (0)	0 (0)	0 (0)	3 (37.5)	5 (83.3)	5 (100)
Focal fluid collection	0 (0)	0 (0)	2 (16.6)	5 (62.5)	4 (66.6)	5 (100)
Dirty echogenic fluid collection	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)	5 (100)
Free intra-abdominal air (pneumoperitoneum)	0 (0)	0 (0)	0 (0)	1 (12.5)	4 (66.6)	5 (100)
Colour flow increased over all (bowel wall)	0 (0)	0 (0)	8 (66.6)	8 (100)	6 (100)	5 (100)
Colour flow decreased selective (bowel wall)	0 (0)	0 (0)	0 (0)	3 (37.5)	4 (66.6)	5 (100)
Superior mesenteric artery flow (>80-100 cm/s)	0 (0)	0 (0)	5 (41.7)	7 (87.5)	6 (100)	5 (100)

NEC: Necrotizing enterocolitis, PVG: Portal venous gas, PI: Pneumatosis intestinalis

Table 7: Incidence of NEC according to the birth weight, grouped according to Bell's classification

Weight in grams	Cases	Stage 1A (n=14) (%)	Stage 1B (n=15) (%)	Stage 2A (n=12) (%)	Stage 2B (n=8) (%)	Stage 3A (n=6) (%)	Stage 3B (n=5) (%)	P value
600-999	Inborn	3 (21.4)	4 (26.6)	2 (16.6)	1 (12.5)	1 (16.6)	1 (20)	0.987
Total=21	Outborn	1 (7.1)	0 (0)	3 (25)	3 (37.5)	0 (0)	2 (40)	0.027*
I/O=11/9								
1000-1249	Inborn	3 (21.4)	2 (13.3)	1 (8.3)	1 (12.5)	1 (16.6)	0 (0)	0.949
Total=14	Outborn	0 (0)	0 (0)	2 (16.6)	1 (12.5)	2 (33.3)	1 (20)	0.053+
I/O=8/6								
1250-1499	Inborn	1 (7.1)	2 (13.3)	1 (8.3)	0 (0)	1 (16.6)	0 (0)	0.887
Total=10	Outborn	1 (7.1)	1 (6.6)	1 (8.3)	1 (12.5)	0 (0)	1 (40)	0.867
I/O=5/5								
1500-1749	Inborn	1 (7.1)	1 (6.6)	1 (8.3)	0 (0)	1 (16.6)	0 (0)	0.889
Total=6	Outborn	0 (0)	1 (6.6)	0 (0)	1 (12.5)	0 (0)	0 (0)	0.419
I/O=4/3								
1750-1999	Inborn	2 (14.2)	1 (6.6)	1 (8.3)	0 (0)	0 (0)	0 (0)	0.922
Total=5	Outborn	0 (0)	1 (6.6)	0 (0)	0 (0)	0 (0)	0 (0)	1.000
I/O=4/1								
2000-2400	Inborn	1 (7.1)	1 (6.6)	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Total=4	Outborn	1 (7.1)	1 (6.6)	0 (0)	0 (0)	0 (0)	0 (0)	1.000
I/O=2/2								

Chi-square test/Fisher exact test, significant figures, +Suggestive significance (P value: 0.05<P<0.10), *Moderately significant (P value: 0.01<P≤ 0.05), **Strongly significant (P value: P≤0.01), NEC: Necrotizing enterocolitis

flow. Also, SMA flow were detected in Stage 1A (0%), 1B (0%), 2A (41.7%), 2B (87.5%), 3A, and 3B (100%), respectively (Table A).

Babies survived with medical therapy, surgical therapy or both treatment modalities is 63%. of these neonates survived only with medical therapy without complications (e.g., Stenosis) whereas 5% survived with complications after medical and surgical therapy. The deaths before and after surgery were 8.3% (Table 2).

Certain antenatal factors such as antenatal steroids, oligohydramnios, and fetal heart rate abnormal rhythm and intrauterine growth restriction contributed to NEC. The mean gestational age was found to be $30.5 \pm 5\%$. Of the total neonates with NEC, 41.6% were outborn. The mean birth weight was 1500 ± 201 g. Almost half of these neonates had respiratory distress and had received surfactants. The mean age of onset of NEC was found to be 8 ± 2 days. 23.3% were given formula/bovine milk. The mean day of starting enteral feeds were $3 \pm$ days. In these,

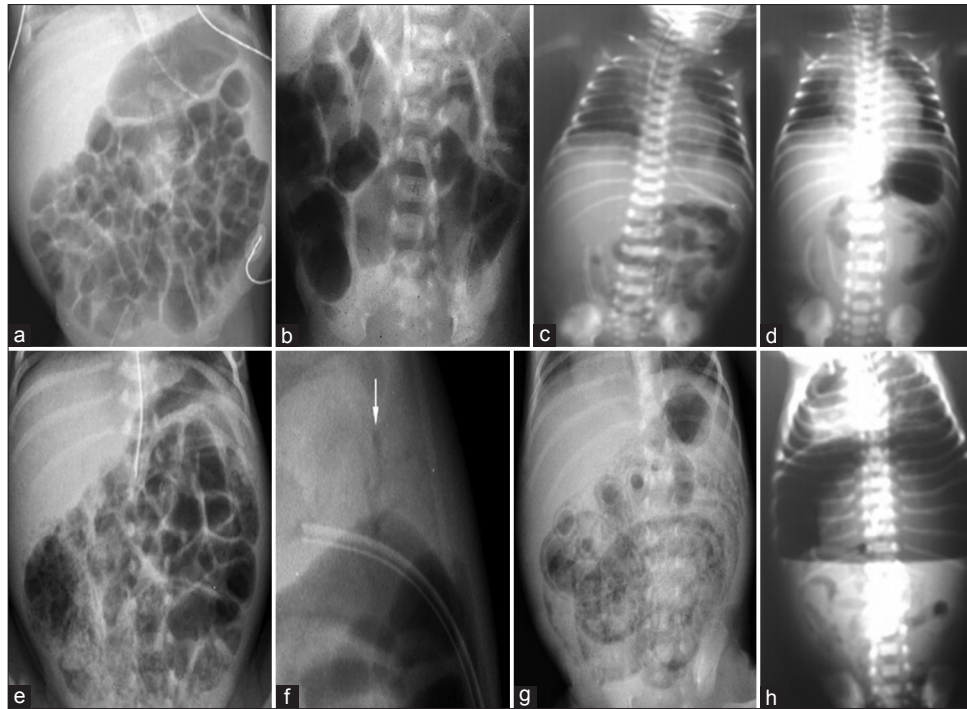


Figure 3: X-ray shows: (a) normal mosaic intestinal patterns, (b) abnormal distended bowel loops, (c) elongated intestinal loops, (d) gasless abdomen with distended loops, (e) pneumatosis intestinalis, (f) portal venous gas, (g) soapy bubble appearance, (h) pneumoperitoneum

Table A: Sensitivity and specificity of sonography and abdominal X-ray

Findings	Stage I	Stage II	Stage III
Sample size-	29	20	11
Bowel wall thickening			
X-ray	0	3	6
Ultrasound	12	20	11
P value	<0.001	<0.001	<0.01
Significance	Difference is very highly significant	Difference is very highly significant	Difference is highly significant
Intramural gas			
X-ray	0	10	10
Ultrasound	4	16	11
P value	<0.05	<0.05	>0.05
Significance	Difference is significant	Difference is significant	Difference is not significant
PVG			
X-ray	0	4	9
Ultrasound	0	7	11
P value	-	>0.05	>0.05
Significance		Difference is not significant	Difference is not significant
Pneumoperitoneum			
X-ray	0	0	7
Ultrasound	0	1	9
P value	-	>0.05	>0.05
Significance		Difference is not significant	Difference is not significant

PVG: Portal venous gas

one-fourth had undergone umbilical vein catheterization and blood culture was positive (Table 3).

Clinical signs, symptoms like increased gastric residuals, abdominal distension, vomiting, bloody stools, apnea, respiratory distress, generalized features of sepsis, abdominal tenderness, abdominal cellulitis, and absent bowel sounds were taken. About 92% of these neonates who survived with medical therapy had increased gastric residuals, whereas it was 100% in neonates with both medical and surgical therapy (Table 4).

DISCUSSION

The importance of AUS have become particularly evident with its usefulness in the assessment of bowel viability especially with color Doppler sonography in neonates with NEC along with other findings like bowel wall thickening or thinning, lack of peristalsis, and abnormalities of perfusion more often found in the lower abdomen, particularly in the right lower quadrant. Although there are limited data available, on the basis of our recent experience we believe that if meticulous attention is paid to technique, abdominal US is, in fact, more sensitive in detecting intramural gas and PVG and possibly even free gas than plain abdominal radiography. Intramural gas is also an early sign that may precede clinical signs. Although intramural gas may be present in other neonatal conditions, it is most commonly seen in NEC, and thus has been considered a virtually pathognomonic sign of NEC.^{26,27}

In our study, out of total admissions of 2304 to our NICU over 4 years, from 2010 to 2014, 800 (34.7%) premature infants were taken, among them 60 (7.5%) who had signs, symptoms, biochemical changes, X-ray and AUS changes of NEC were studied. 48.3% belonged to Stage 1, 33.2% belonged to Stage 2, and 18.3% belonged to Stage 3, whereas a study done by Buch. N. A, Ahmed. S. A (an epidemiological study of NEC) Saudi medical journal, 42 babies with NEC showed that 24% belonged to Stage 1, 33% belonged to Stage 2, and 43% belonged to Stage 3.

In another study done by Katherine E. Gregory *et al.* showed that 37% belonged to Stage 1, 28% belonged to Stage 2, and 15% belonged to Stage 3. Statistics of both these studies were close to our study.

The major advantage of AUS in NEC is that it is possible with this modality to visualize the bowel wall directly and assess bowel wall thickness, echogenicity, and peristalsis. In the 30 normal neonates studied by Faingold *et al.*, bowel wall thickness ranged from 1.1 to 2.6 mm.

A clue to differentiating intramural gas from overlapping loops is the white lines that often accompany the black lines of intramural gas. The white lines represent the mucosa and submucosa, which are lifted off the serosa and are contrasted by the subserosal intramural gas and the intraluminal gas. A search for white lines rather than the black lines may often be more fruitful in helping one confirm the presence of intramural gas.^{26,27}

In our study, preterm neonates were grouped according to their survival, morbidity, and mortality, and it was found that 63.3%.

Whereas a study done by Oneil *et al.* 1975 showed that 69% premature infants survived with medical therapy alone which correlated with our study.

Resolution of NEC is associated with the dilated bowel gradually returning to a more normal appearance. Persistence of dilatation or a change other than in the normal direction suggests a failure of response to medical therapy or deterioration. An ominous sign is a change from generalized dilatation to an asymmetric distribution where dilatation is confined to a more localized area of the abdomen. The degree and pattern of bowel dilatation are the most important signs for early diagnosis and for follow-up. It is even more worrisome if the asymmetric pattern persists and the dilated loops maintain the same appearance as fixed loops on follow-up plain abdominal radiographs. This suggests the development of full-thickness necrosis and may precede clinical deterioration including signs of peritonitis.^{26,27}

In our study, we predominantly compared X-ray findings with AUS findings and we noted that X-ray could identify gaseous distension in 57.5% of neonates who had survived with medical therapy alone and also abnormal shaped distended intestinal walls in 100% of cases with medical or surgical therapy with or without complications. X-ray could identify around 60% of cases with bowel wall thickening, whereas AUS could identify 100% of cases. Only a few cases of PI and PVG could be identified by X-ray, but AUS picked up 100% of cases, especially those with medical and surgical therapy with complications.

Similarly, a study done by Epelman *et al.* showed that AUS could identify free fluid, bowel wall thickening better compared to X-ray.

In our study, we also grouped neonates with NEC based on Bell's staging and compared their X-ray and AUS findings.

AUS also aided in color flow Doppler either increased flow or decreased selective flow. SMA flow could also be identified. Similarly, a study done by Shebrya *et al.* showed that 37.3% could be picked up by X-ray compared to 63.2% by AUS. Color Doppler sonography was found to be more accurate than clinical examination and plain abdominal radiography in the prediction of necrosis in neonates with NEC. Our study also grouped the incidence of NEC according to the birth weight ranging from 600 to 2400 g as per Bell's staging, and further classified into inborn and outborn.

The other advantage of AUS is the ability of this modality to directly assess the arterial perfusion of the bowel wall, as this is not possible with plain abdominal radiography.

Limitations

AUS does have some relative limitations:

1. Abdominal US should not be attempted in any neonate who is labile or unstable, and we have refrained from performing AUS if abdominal tenderness is present such that holding the transducer on the abdomen causes the patient severe discomfort. However, using a large amount of gel on the abdominal wall may facilitate performance of the study by enabling images to be obtained without the transducer actually touching the abdominal wall.^{26,27}
2. Large amounts of bowel gas may make a sonographic evaluation of the abdomen difficult, although we have found this to be a problem in only small numbers of neonates with NEC. Feingold *et al.* found that the gray-scale and color Doppler sonograms were not interpretable because of large amounts of bowel gas in only two of 32 neonates with NEC or at risk for NEC.^{26,27}

CONCLUSION

Our study concludes that AUS is superior to plain radiography in the early detection of NEC. Complications like PI, PVG, free fluid collection, intestinal thinning, perforation, and pneumoperitoneum were detected earlier than X-ray. Early findings in AUS, changes the treatment modality like implementing early advanced medical treatment, early surgical intervention which reduces the morbidity like stenosis, malabsorption (reducing gross resection of intestines), thereby facilitating better outcome and providing good long-term quality of life. Hence, AUS is a reliable tool for early detection, assessment, and prognosis of NEC in preterm infants.

At presentation, the presence of intramural gas in the clinical setting of NEC virtually clinches the diagnosis. In the absence of intramural gas, diagnosis may be much more difficult, especially if the clinical findings are mild and nonspecific. In such patients, interpretation of the plain abdominal radiograph may be a frustrating experience, if the only finding is mild gaseous distention or if there is a suggestion of bowel wall thickening. It is in these patients with mild symptoms and nonspecific findings on plain abdominal radiography that abdominal US may be extremely useful, as it may be able to depict intramural gas not visible on plain abdominal radiographs as well as depict changes in bowel wall thickness, echogenicity, peristalsis, and perfusion that may enable one to confirm or exclude the diagnosis of NEC.^{26,27}

Once the diagnosis of NEC has been established, interval plain abdominal radiographs are essential for appropriate follow-up. The disappearance of intramural gas and PVG is not always associated with clinical improvement, and these are thus poor indicators of progress. When to perform abdominal US during follow-up and how often has not been established. In those neonates who respond promptly to medical therapy, abdominal US probably has no role. However, it may play a significant role in two groups of patients. The first group includes those neonates in whom the evolution of changes seen on plain abdominal radiography is not keeping up with the clinical course, and the second group includes those who are deteriorating clinically but have no evidence of pneumoperitoneum seen on plain abdominal radiography. In the latter group, it is always a challenge to decide whether to operate in the absence of Pneumoperitoneum.^{26,27} We have found that in both of these groups, AUS provides valuable information regarding the bowel wall and peritoneal cavity that may influence management especially detection of bowel wall thinning which indicates impending necrosis and the need for immediate surgery.

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