Risk factors of necrotizing enterocolitis in neonatal intensive care unit of Assiut University Children Hospital

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Background
Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the neonates. It is characterized by ischemic necrosis of the intestinal mucosa.

Objective
The aim of this work was to detect the most important risk factors of NEC in the Neonatal Intensive Care Unit of Assiut University Children Hospital to help in prevention of this condition.

Patients and methods
The present retrospective study included 36 neonates who were diagnosed as having NEC and admitted to Neonatal Intensive Care Unit during the period from April 2017 to March 2018. They were diagnosed by Modified Bell's staging criteria.

Results
Prematurity, cesarean section, formula feeding, neonatal sepsis, and respiratory distress syndrome have been identified as the most important risk factors for development of NEC in our study.

Conclusion
NEC is an important problem for our patients. Avoidance of the most important risk factors (prematurity, cesarean section, formula feeding, neonatal sepsis, and respiratory distress syndrome) may decrease the incidence.

Keywords:
necrotizing enterocolitis, neonatal intensive care unit, risk factors

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Introduction

Necrotizing enterocolitis (NEC) is the leading cause of death from gastrointestinal disease in preterm neonates, affecting newborn babies at a rate of 1–3 per 1000 births per year in North America [1,2]. Despite several decades of experience in treating neonates with NEC [3], the overall mortality and approach to treatment have remained largely unchanged since the initial description of the disease several decades ago [4,5].

Despite a lot of research conducted over many years, the etiology remains obscure. It involves serious intestinal injury following a combination of vascular, mucosal, toxic, and possibly other insults to a relatively immature gut [6,7].

NEC is one of the most common gastrointestinal emergencies in the neonates. It is characterized by ischemic necrosis of the intestinal mucosa, which is associated with severe inflammation, invasion of enteric gas-forming organisms, and dissection of gas into the bowel wall and portal venous system [3]. Although early recognition and aggressive treatment of this disorder has improved clinical outcomes, NEC accounts for substantial long-term morbidity in the survivors of neonatal intensive care units (NICU), particularly in preterm very low-birth-weight (VLBW) infants [birth weight (BW) below 1500 g] [8]. Intensive research efforts over the past decade have begun to clarify the molecular underpinnings of NEC and have identified several biologic strategies targeting the specific signaling pathways involved, which could potentially prevent and/or treat this disease in preterm neonates [1].

Although most cases of NEC occur among preterm neonates, a small subset of babies born at term or shortly before (i.e. ≥35 weeks of gestation) develop NEC-like gastrointestinal signs and symptoms, frequently in association with other conditions [9].

Aim

The aim of this work was to detect the most important risk factors of NEC in the NICU of Assiut University Children Hospital (AUCH) to help in prevention of this condition.

Patients and methods

The present retrospective study included 36 neonates who were diagnosed as having NEC and admitted to NICU of AUCH during the period from April 2017 to March 2018. They were diagnosed by Modified Bell's staging criteria [10].

Records of these cases were examined for history taking (age, sex, perinatal, family history, maternal risk factors, placental abnormalities, type, and rate of advancement of feeding), full clinical examination [vital signs, anthropometric measurements, general, and regional examination, and the following risk factors were investigated: BW, gestational age, perinatal asphyxia, sepsis, respiratory distress syndrome (RDS), mechanical ventilation (MV), patent ductus arteriosus (PDA), indomethacin treatment, gastroschisis, glucocorticoids in the first week of life, H2 receptor blocker therapy, prolonged empirical antibiotic use (≥5 days), polycythemia, anemia, transfusions, and presence of umbilical catheter (UC)], investigations (complete blood count, C-reactive protein, serum electrolytes, kidney function tests, plain erect abdominal radiograph, abdominal ultrasound, and capillary blood gases).

The IRB Assiut faculty of medicine approved the study. IRB no: 17100022, consent statement : patients signed informed consent).

Inclusion criteria

All neonates were diagnosed as having NEC by Modified Bell's staging criteria[10] in the NICU of AUCH.

Exclusion criteria

Patients with anatomic or functional conditions that cause intestinal obstruction and having disorders including Hirschsprung disease, ileal atresia, volvulus, meconium ileus, and intussusception were excluded.

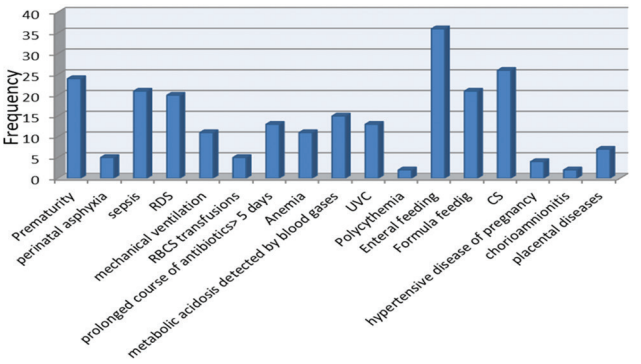
Statistical analysis

All data analysis was performed by using statistical analysis system software package (SPSS, version 17, IBM, Armonk, New York, Westchester County.) The frequency and percent were calculated.

Results

The study included 36 neonates who were diagnosed as having NEC and admitted to NICU of AUCH during the period from April 2017 to March 2018 (Fig. 1 and Tables 1–4).

Figure 1



Risk factors of NEC among the studied neonates. NEC, necrotizing enterocolitis.

Table 1 Characteristics and clinical data of the studied neonates diagnosed as having necrotizing enterocolitis (*n*=36)

Items	Frequency	Percentage
Sex		
Male	23	63.9
Female	13	36.1
Gestational age		
Full term	12	33.3
Preterm	24	66.7
Birth weight (kg)		
<1.5	15	41.7
>1.5	21	58.3
Method of delivery		
CS	26	72.2
Normal vaginal delivery	10	27.8
Place of delivery		
Assiut university hospital	14	38.9
General hospital	6	16.7
Private clinic	15	41.7
At home	1	2.8
Antenatal care		
Yes	23	63.9
No	13	36.1

CS, cesarean section.

Table 2 Distribution of the studied neonates diagnosed as having necrotizing enterocolitis according to their feeding regimen (*n*=36)

Items	Frequency	Percentage
Enteral feeding		
Yes	36	100
No	0	0
Type of milk		
Breastfeeding	11	30.6
Formula feeding	21	58.3
Both types of feeding	4	11.1
Advancement (ml/kg/day)		
<20	31	86.1
>20	5	13.9

Table 3 Frequency and percentage of maternal risk factors of the studied neonates diagnosed as having necrotizing enterocolitis (*n*=36)

Items	Frequency	Percentage
Hypertensive disease of pregnancy	4	11.1
Chorioamnionitis	2	5.6
Placental diseases	7	19.4
No illness	23	63.9

Table 4 Frequency and percentage of neonatal risk factors of the studied neonates diagnosed as having necrotizing enterocolitis (*n*=36)

Items	Frequency	Percentage
Perinatal asphyxia	5	13.9
Sepsis	21	58.3
RDS	20	55.6
Mechanical ventilation	11	30.6
PDA	0	0
Indomethacin treatment	0	0
Gastroschisis	0	0
Anemia	11	30.6
RBC transfusions	5	13.9
Polycythemia	2	5.5
Prolonged course of antibiotics ≥5 days	13	36.1
Glucocorticoid treatment in the first week of life	0	0
H2 receptor blocker	0	0
Metabolic acidosis detected by blood gases	15	41.7
UC		
Umbilical venous catheter	13	36.1
Umbilical arterial catheter	0	0

PDA, patent ductus arteriosus; RBC, red blood cell; RDS, respiratory distress syndrome.

Discussion

The present study presents a trial to get information about risk factors for development of NEC in NICU of AUCH.

In our study, we found that the incidence of NEC among the preterm neonates (66.7%) was more than in the full-term neonates (33.3%). This is in agreement with Mohammed *et al.* [11], who reported that most neonates who developed NEC were premature (87.5%) and only 12.5% were full-term neonates in NICU of CUPH. Moreover, this is a confirmed worldwide experience that NEC is predominantly a disease of prematurity, occurring infrequently in full-term baby [12]. This is in agreement with another study done by Ostlie *et al.*[13] who reviewed the charts of all infants with definitive NEC in NICU of the Children's Mercy Hospital, Kansas City, MO, USA, and they found that from 277 patients, 251 were premature infants and 26 were full-term ones.

In our study, we found that incidence of NEC among neonates more than 1500 g (58.3%) was more than in neonates less than 1500 g (41.7%). This is inconsistent with Guthrie *et al.*[14] whose study showed that neonates who developed NEC had a lower BW. Overall, 45% of the neonates with NEC weighed less than 1000 g in their study. Our result may be explained by death of the infants of the VLBW before the disease clinically manifested.

In the present study, the incidence of NEC was more in neonates delivered by cesarean section (CS) (72.2%) than in those delivered by NVD (27.8%). This is in agreement with Lee *et al.* [15], who found that 73.1% of infants who developed NEC were delivered by CS; Ahle *et al.* [16], who found that delivery by CS was associated with a greater incidence of NEC, except in gestational age more than 31 W; and Maayan-Metzger *et al.* [17], who found that delivery by CS was associated with a greater incidence of NEC.

In our study, enteral feeding had firm association with NEC; 100% of patients who were diagnosed as having NEC had received enteral feeding. This is in agreement with the study done by Pietz *et al.* [18], who reported that more than 90% of infants who developed NEC are seen after milk feeding, whereas less than 10% of cases occurred in infants without any enteral feeding, and Mohammed *et al.* [11], who reported that ~ 89.6% of patients who developed NEC had received enteral feeding, whereas 10.4% did not receive.

Rate of advancement of enteral feedings has been viewed as a risk factor for NEC. Clinicians have considered advancing enteral feeding less than 20 ml/kg/day as safe [19]. This is in contrary to the present study, where enteral feeds were advanced by increases of less than 20 ml/kg/day in 86.1% of patients with NEC. However, in 13.9%, daily enteral feeding was advanced by more than 20 ml/kg/day. This is in agreement with Mohammed *et al.*[11] who reported that enteral feeds were advanced by increments of less than 20 ml/kg/day in 84.6% of patients. However, in 14.4%, daily feeding volume increased by more than 20 ml/kg/day. Our results may be explained by that infants fed more slowly might have higher risk of acquiring a severe infection owing to prolonged hospital stay than infants fed more quickly.

In the present study, we found that 30.6% of the infants diagnosed as having NEC received exclusively breastfeeding, 58.3% of infants received exclusively formula feeding, and 11.1% of infants received both breastfeeding and formula feeding. This is in agreement with Berkhout *et al.* [20], who found that administration of predominantly formula feeding increased risk of NEC, and in agreement with Mohammed *et al.* [11], who found that 4.7% of infants who were diagnosed as having NEC received exclusively breastfeeding, 76.7% of infants received exclusively formula feeding,

and 18.6% of infants received both breast and formula feeding in NICU of CUPH.

In our study, we found that 11.1% of infants diagnosed as having NEC had mothers having hypertensive disease of pregnancy. This is in agreement with Mohammed *et al.*[11], who reported that preeclampsia was found to increase the incidence of NEC and 12.5% of NEC cases had mothers having hypertensive disease of pregnancy, and in agreement with Kirsten *et al*. [21], who reported an increase in NEC in premature infants who were born to mothers diagnosed with severe preeclampsia.

In the present study, we found that 5.6% of neonates diagnosed as having NEC had mothers with chorioamnionitis. This is in agreement with Lee *et al*. [15], who found that 3.8% of neonates diagnosed as having NEC had mothers having chorioamnionitis, whereas Ahle *et al.* [16], found that 26% of neonates who developed NEC had mothers having chorioamnionitis.

In the present study, we found that 19.4% of neonates diagnosed as having NEC had mothers having placental problems. This is in agreement with Luig *et al.* [22], who found that 13% of neonates who developed NEC had mothers having placental problems (placental abruption), and Ahle *et al.* [16], who found that 19% of NEC cases had mothers having placental problems.

In the present study, we found that 13.9% of neonates with NEC had perinatal asphyxia. This is in agreement with Mohammed *et al.* [11], who reported that 12.5% of patients with NEC had perinatal asphyxia in NICU of CUPH.

In the present study, we found that 58.3% of neonates with NEC had neonatal sepsis. This is in agreement with Stoll *et al.*[23] who found that late-onset sepsis significantly increased the risk of NEC in premature neonates.

In the present study, we found that there was an association between RDS and NEC, where 55.6% of the NEC cases were diagnosed as having RDS. This is in agreement with Ahle *et al.* [16], who found that 43% of infants with NEC had RDS. Moreover, Mohammed *et al.* [11], reported that there was an association between hyaline membrane disease and NEC, where 14% of the NEC cases were diagnosed as having hyaline membrane disease.

In the present study, we found that there was an association between MV and NEC, where 30.6% of NEC cases were mechanically ventilated. Moreover, Guthrie *et al.* [14], reported that 73% of neonates with NEC were mechanically ventilated.

In the present study, we found that there were no cases of PDA developed NEC. This is inconsistent with Mohammed *et al.* [11], who reported that 8.4% of cases with NEC have PDA; Ostlie and colleagues, who reported that underlying congenital heart disease has been identified as a major risk factor for the development of NEC, especially in full-term infant; and Ahle *et al.* [16], who found that 28% of neonates diagnosed as having NEC had PDA. This may be owing to increased deaths among the VLBW neonates.

In our study, none of our cases of NEC had PDA, so no indomethacin treatment was used. This is inconsistent with Ahle *et al.* [16], and Guthrie *et al.* [14], who found that the use of indomethacin for the closure of PDA was a significant risk factor for development of NEC, and Mohammed *et al.* [11], who found that 4.2% of neonates diagnosed as having NEC received indomethacin treatment.

In the present study, no cases of diagnosed NEC had gastroschisis, although other authors reported this condition, such as Jayanthi *et al.* [24], who found that clinical and radiological signs of NEC developed in 15% of neonates with gastroschisis, and Lusk *et al.* [25], who found that 1.6% of gastroschisis cases developed NEC.

In the present study, we found that the incidence of anemia among neonates diagnosed as having NEC was 30.6%. This is in agreement with Ahle *et al.* [16], who found that 22% of neonates who developed NEC had anemia.

In the present study, we found that there was an association between development of NEC and red blood cell (RBC) transfusion, where 13.9% of neonates diagnosed as having NEC received RBC transfusion. This is in agreement with Ahle *et al.* [16], who found that 22% of neonates diagnosed as having NEC received RBC transfusion, and Mally *et al.* [26], and Christensen *et al.* [27], who reported that 35% of patients with NEC received RBC transfusion.

In the present study, 5.5% of patients diagnosed as having NEC had polycythemia. This is in agreement with Lambert *et al.* [28], who have identified increased incidences of polycythemia in groups of infants who develop NEC compared with a control group.

In our study, we found that there was an association between development of NEC and prolonged course of antibiotics more than 5 days, where 36.1% of NEC cases received prolonged course of antibiotics more than 5 days. This is in agreement with Cotten *et al.* [29], who found that 53% of neonates in their study who received prolonged empirical antibiotic therapy had increased

risk of NEC, and Berkhout *et al.* [20], who found that 100% of neonates diagnosed as having NEC received prolonged empirical antibiotic therapy.

In the present study, we found that there were no cases of NEC that received glucocorticoid treatment in the first week of life because treatment protocols in our unit do not include this therapy. This is inconsistent with Guthrie *et al.* [14], who found that 5% of NEC cases received glucocorticoid treatment in the first week of life.

In the present study, no cases diagnosed as NEC received H2 receptor blocker therapy. This is inconsistent with Guillet *et al.* [30], who reported that premature infants developed NEC significantly more often when H2 receptor blockers were prescribed than did infants who did not receive H2 receptor blockers, and inconsistent with Mohammed *et al.* [11], who reported that 35% of neonates diagnosed as having NEC received H2 receptor blocker therapy.

In the present study, we found that the incidence of metabolic acidosis detected by blood gases among neonates diagnosed as having NEC was 41.7%. This is in agreement with Mohammed *et al.*[11] who found that 58% of neonates who developed NEC have metabolic acidosis detected by blood gases, and Hällström *et al.* [31], who reported metabolic acidosis was a common laboratory finding in patients with proven NEC in preterm neonates.

In our study, 36.1% of patients diagnosed as having NEC had UC. This is in agreement with Livaditis *et al.* [32], who reported that NEC is a potential complication after UC in particularly predisposed infants, and disorders may occur regardless of type of vessels used or indications for procedures, and Rand *et al.* [33], who reported that impairment of mesenteric blood flow owing to the use of UAC may increase the risk of NEC in newborn infants, although Bertino *et al.* [34], reported that there was no NEC in 50 patients who underwent exchange transfusion.

Conclusion

The most important risk factors for development of NEC in this study included prematurity, CS, formula feeding, neonatal sepsis, RDS, MV, anemia, RBC transfusion, prolonged course of antibiotics more than 5 days, metabolic acidosis, perinatal asphyxia, polycythemia, umbilical venous catheter, hypertensive disease of pregnancy, chorioamnionitis, and placental problems.

PDA, indomethacin treatment, glucocorticoid treatment in the first week of life, H2 receptor blocker therapy, and gastroschisis were not reported as risk factors for development of NEC in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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