


Necrotizing Enterocolitis, Sepsis, and Diarrhea Due to Cow's Milk Allergy in A Full-Term Infant with Hypothyroidism

Runi Arumndari,[1] Asterisa Retno Putri,[1] Claudia Natasha Liman,[1] Putu Siska Suryaningsih[2]
[1]General Practitioner, [2]Paediatrician, Wangaya Regional Public Hospital, Denpasar, Bali, Indonesia

ABSTRACT

Necrotizing enterocolitis (NEC) remains one of the most common gastrointestinal diseases in neonates, with high morbidity and mortality. An 8-day-old full-term baby girl was admitted with an initial diagnosis of sepsis and acute diarrhea due to a cow's milk allergy. Her condition worsened on the 4th day of hospitalization with abdominal distention, bradypnea, and vomiting. An abdominal x-ray showed increased bowel gas. She had a slightly lowered FT4. The findings met Bell's criteria for the diagnosis of NEC. After being given meropenem and levothyroxine for 7 days, she was discharged on the 12th day of hospitalization in good condition. NEC is allegedly to be a multifactorial disease, with predisposing factors of cow's milk formula (CMF) feeding or not breast-fed since birth, sepsis, and hypothyroidism. The combination of clinical symptoms, radiologic findings, and risk factor tracing is important in the diagnosis and management of NEC.

Keywords: Cow's milk allergy, hypothyroidism, necrotizing enterocolitis, neonate, sepsis.

ABSTRACT

Necrotizing enterocolitis (NEC) masih merupakan salah satu masalah gastrointestinal yang paling sering pada neonatus dengan morbiditas dan mortalitas tinggi. Bayi perempuan berusia 8 hari dirawat dengan diagnosis awal sepsis dan diare akut akibat alergi susu sapi. Kondisi pasien memburuk pada hari ke-4 dengan gejala distensi abdomen, bradipnea, dan muntah-muntah. Foto polos abdomen menunjukkan adanya peningkatan gas usus. Penemuan di atas memenuhi kriteria Bell's untuk diagnosis NEC. Kadar FT4 juga menurun. Setelah diberi antibiotik *meropenem* selama 7 hari dan *levothyroxine*, pada hari ke-12 perawatan pasien dipulangkan dengan kondisi baik. Penyebab NEC diduga multifaktorial, dengan beberapa faktor predisposisi di antaranya pemberian susu formula atau tidak diberikannya ASI eksklusif, sepsis, dan hipotiroid. Kombinasi gejala klinis, temuan radiologis, dan penelusuran faktor risiko penting untuk diagnosis dan tata laksana NEC. **Runi Arumndari, Asterisa Retno Putri, Claudia Natasha Liman, Putu Siska Suryaningsih. *Necrotizing Enterocolitis*, Sepsis, dan Diare akibat Alergi Susu Sapi pada Bayi Cukup Bulan dengan Hipotiroidisme.**

Kata Kunci: Alergi susu sapi, hipotiroid, enterocolitis nekrotikans, neonatus, sepsis.

INTRODUCTION

Necrotizing enterocolitis (NEC), caused by intestinal tissue necrosis due to inflammation, is one of the most common gastrointestinal problems in the neonatal intensive care unit (NICU), with high morbidity and mortality.[1,2] It is estimated that 1-3 out of 1000 newborn babies suffer from NEC, with a mortality rate between 15% and 30%.[3] Recovered infants from NEC have an almost 25% chance of developing microcephaly and serious neurodevelopmental delays.[2]

The pathophysiology of NEC is still not fully understood. The cause is thought to be multifactorial, with antenatal and postnatal factors. Antenatal factors include infections and the use of antibiotics and/or steroids during pregnancy.[1,4] Postnatal factors may include immune system dysregulation, rapid introduction and progression of enteral feeding, formula feeding and/or not breast-fed from birth, and sepsis.[1,2,4,5] Hypothyroidism may also predispose to NEC by decreasing intestinal motility, which then plays a role in gut bacteria overgrowth.[6]

Diagnosis and staging of NEC are based on Bell's criteria modified by Kleigman, *et al*, which divide NEC into 5 grades based on clinical, gastrointestinal, and radiologic findings.[1,4] Clinical symptoms of NEC can be nonspecific, making the diagnosis of NEC challenging. On the other hand, the mortality and morbidity of NEC are high, and immediate treatment is required. This report presents a case of NEC in a full-term infant with risk factors of cow's milk allergy, sepsis, and hypothyroidism at Wangaya Regional Public Hospital, Denpasar, Indonesia.

CASE

An 8-day-old baby girl came with complaints of liquid stools 1 day before admission. The frequency was approximately 11 times within

Alamat Korespondensi *email: arumndariruni@gmail.com*

24 hours, initially greenish then becoming yellow in color with a little pulp; mucus and blood were absent. The complaints were accompanied by a fever with no cough. The urine color was dark yellow. She had vomited three days before admission. She was given 50–60 mL of cow's milk formula (CMF) every 3 hours. She had never been breastfed since birth because her mother was on epilepsy medication with phenobarbital.

The patient was born by caesarean section to a gravida 5 and para 2 mother with a gestational age of 37 weeks and premature rupture of membranes. She was born vigorous, with a birth weight of 3.250 grams, a birth length of 50 cm, a head circumference of 34 cm, and a chest circumference of 34 cm. Hepatitis B and polio vaccines had been given; she was discharged in good condition.

Examination at the emergency room showed a body weight of 3.285 grams and a body length of 50 cm. She had a fever with a temperature of 38.3°C, a heart rate of 170 beats per minute, a respiratory rate of 44 times per minute, and an oxygen saturation of 98% without oxygen support. On physical examination, she looked lethargic, had sunken eyes, was icteric with Kramer 4, had cutis marmorata almost all over the body, and had a decrease in skin turgor.

A blood test showed leukocytes of 6,280/ul, hemoglobin of 13.8 g/dl, hemocrit of 40.3%, platelet count of 477,000/ul, IT ratio of 0.06, and CRP of 114. The complete stool test showed fat.

CMF was replaced with a hypoallergenic formula, given through a nasogastric tube (NGT) at 30 ml per 3 hours. She was then given intravenous fluids with 10% dextrose at 12 drops/min, equivalent to 87 ml/kg/day. Cefotaxime 150 mg every 12 hours was also given intravenously (equivalent to 45 mg/kg/day), paracetamol drops 0.4 ml every 4 hours orally, zinc syrup 1x10 mg, and 1x2 drops of probiotic *Lactobacillus reuteri* supplement. She was then admitted to the perinatology room with an initial diagnosis of acute diarrhea with mild to moderate dehydration and sepsis due to a cow's milk allergy.

In the first 3 days of treatment, the patient still had liquid stool three times a day, and her body temperature was still fluctuating, with the highest peak at 38.5°C. Her condition worsened on the 4th day of treatment. She vomited with a yellowish color of approximately 10 ml. She was immediately fasted, but the next day she experienced another yellowish vomiting three times a day. There was approximately 30 ml of yellowish NGT residue. She also had abdominal distention, bradypnea, and 87% oxygen saturation, followed by a minimal chest retraction. She was then given nasal cannula oxygen at 0.5 liters/min, and the antibiotic regimen was changed to meropenem 130 mg every 12 hours intravenously plus metronidazole 50 mg every 12 hours intravenously. Laboratory investigations showed leukocytes 4,980/ul, hemoglobin 13.5 g/dl, hemocrit 44.1%, platelet count 54,300/ul, a positive fecal occult blood test (FOBT), and no growth of specific pathogenic bacteria in the blood culture. A plain abdominal radiograph showed an increase in an increase in intestinal gas. She was diagnosed with grade I NEC.

The patient also underwent a thyroid hormone screening due to the persistent cutis marmorata in a non-dehydrated condition and cold temperature intolerance. She had never gone through a thyroid hormone screening before. The result showed subclinical hypothyroidism with TSHs of 6.36 and FT4 of 1.23. There was no facial dysmorphia, macroglossia, hypotonia, or hyperbilirubinemia. Levothyroxine, 30 mcg per day (equivalent to 30 mcg/kg/day), was then given.

During hospitalization, she also had hyponatremia with an initial sodium level of 119 mmol/L. She was corrected with 8 mL of 3% NaCl in 2 hours and continued with 35 mL of 3% NaCl for the rest of the 22 hours. A repeat electrolyte examination 24 hours later revealed results of sodium 126 mmol/L, potassium 5.4 mmol/L, and chloride 94 mmol/L. The 5% dextrose maintenance fluid was replaced with 140 ml/kg/day isotonic crystalloid fluid containing 50 mEq/L sodium, 20 mEq/L potassium, and 50 mEq/L chloride.

Deterioration occurred on the 4th day of hospitalization; an electrolyte examination showed hyperkalemia with potassium 6.8 mmol/L, sodium 115 mmol/L, and chloride 83 mmol/L. She was given salbutamol inhalation to reduce her potassium level. Her electrolyte balance was achieved on the 8th day of hospitalization with sodium 137 mmol/L, potassium 3.7 mmol/L, and chloride 104 mmol/L.

The improvement was gradual. The patient was able to breathe room air on the 6th day and was active and crying vigorously on the 7th day of hospitalization. Cutis marmorata was no longer visible. Faeces consistency was back to normal on the 8th day. She was able to drink orally on the 8th day of hospitalization after fasting for 2 days, starting with 2 ml every 2 hours. The nasogastric tube appeared clear and was removed on the 10th day. After administration of meropenem for 7 days, blood test results on the 11th day were leukocytes 8,550/uL, hemoglobin 10 g/dL, hematocrit 28.7%, platelets 177,000/uL, and CRP 98.

The patient was discharged on the 12th hospitalization day in good condition. Three days later, she had a follow-up at the pediatric and endocrine clinic and was in good health. Levothyroxine was continued until the planned follow-up examination of thyroid hormones 1 month later.

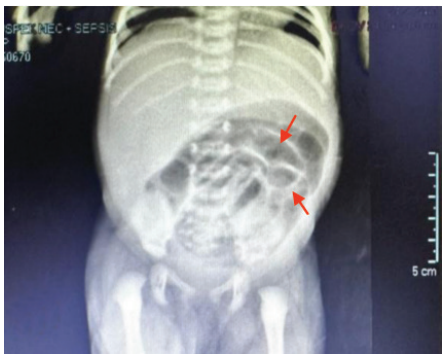

Figure. Plain abdominal radiograph on the 5th day of hospitalization showed an increased bowel gas.

DISCUSSION

NEC, an intestinal tissue necrosis due to inflammatory processes, is still one of the most common gastrointestinal problems found in the NICU, with high morbidity and mortality rates.[1,2] The pathophysiology of NEC is not fully understood; it is suspected that there are immune system dysregulation, changes in intestinal motility, decreased enzyme function, changes in mucus production and composition, decreased


innate defense mechanisms, the introduction and rapid progress of enteral feeding along with intestinal hypoxia-ischemia-reperfusion, formula feeding, and impaired colonization of the normal gut of the neonate.[1,2,4,5,7,11] These factors can trigger an inflammatory response, causing cytokine activation, decreased epidermal growth factor, increased platelet activation factor, and progressive mucosal damage due to free radical production, which will then lead to NEC. In addition, sepsis is also a predisposing factor for NEC.[1,4,5,7] An animal study showed that bacteria play an important role in the occurrence of NEC, as NEC will not occur in a germ-free environment but can only develop after exposure to microbes.[1,2]

This case arrived at the emergency room with complaints of liquid stools more than three times a day, fever, weakness, sunken eyes, decreased skin turgor, icteric appearance, and visible cutis marmorata throughout the body. The patient has been given CMF since birth because the mother was on epilepsy medication. The patient was hospitalized with an initial diagnosis of sepsis and acute diarrhea with mild to moderate dehydration suspected to be due to a cow's milk allergy. The cow's milk allergy was severe enough to trigger sepsis, which then became a predisposing factor for NEC.[8-10]

Clinical symptoms of NEC can be non-specific; abdominal distension and/or tenderness, bloody stools, lethargy, apnea, respiratory distress, or poor perfusion. Erythema of the abdominal wall is a strong predictor of NEC diagnosis but is only present in 10% of patients.[1] Symptoms of NEC can progress rapidly, often within hours, from nonspecific symptoms to abdominal discoloration, bowel perforation, and peritonitis, leading to systemic hypotension requiring intensive medical support, surgery, or both.[2] Laboratory examination may reveal leukocytosis or leukopenia (with left-shifted neutrophils), thrombocytopenia, metabolic acidosis, hypo- or hyperglycemia, and/or electrolyte imbalance. A non-specific radiographic examination may show bowel wall thickening, decreased intestinal gas, and dilated bowel loops.[1] Pathognomonic radiologic findings in NEC are pneumatosis intestinalis, portal venous gas, or both.[1,2] Pneumatosis intestinalis is usually found in the right lower quadrant.[1] Diagnosis and staging of NEC is established by Bell's criteria modified by Kleigman, *et al*, which divides into 5 grades based on clinical, gastrointestinal, and radiologic findings.[1,4]

This patient still had diarrhea, fever, and even deterioration in the first few days of treatment. A repeated complete blood test showed leukopenia and thrombocytopenia. A fecal-occult blood test also showed a positive result. A plain abdominal radiograph showed an increase in intestinal gas. The clinical and radiological findings met Bell's criteria for the diagnosis of grade I NEC.

During treatment, she also had an electrolyte imbalance, which is also one of the laboratory findings in NEC. The patient was also screened for thyroid function; the results were TSHs 6.36 and FT4 1.23; thus, she was also diagnosed with subclinical hypothyroidism and given levothyroxine. The relationship between hypothyroidism and NEC is not fully understood, but hypothyroidism is thought to be a predisposing factor for NEC.[6] In a study of hypothyroid animals, the electrical and mechanical activity of the gastrointestinal tract was found to be decreased. In humans, the frequency of basal electrical rhythms has also decreased.[6] In addition, hypothyroidism has been shown to cause peripheral neuropathy of the gut. This can lead to decreased intestinal motility, ileus, abdominal distension, and impaired mesenteric blood flow.[6] Decreased gut motility during feeding can lead to intestinal bacterial overgrowth. This, as mentioned earlier, is one of the predisposing factors for NEC.[1,2,6,7,11]

The management of NEC can be conservative or surgical. Conservative treatment may include abdominal decompression, bowel rest, intravenous antibiotics, and intravenous hyperalimentation.[2,3,7] Broad-spectrum antibiotics are given because several studies have not been able to explain the specific microbiota that causes or induces NEC.[3] There is not enough evidence regarding the recommended antibiotic regimen of choice, but the most commonly used is intravenous administration of ampicillin and gentamicin combined with metronidazole for 10–14 days.[3,11] Amoxicillin, clavulanic acid, and amikacin are also commonly used as the first line.[1,12] Antibiotic administration in suspected NEC cases is also recommended, with the combination of amoxicillin and meropenem or meropenem and vancomycin being the preferred choice. Administration of probiotics is also recommended, considering the gut microbiota dysbiosis in NEC.[1] The most common surgical procedure is laparotomy.[2,3,11]

In this case, a broad-spectrum antibiotic, cefotaxime, was already given since the

Table. Staging system of NEC with Bell's criteria modified by Kliegman, *et al.*[1]

Stage	I	IIa	IIb	IIIa	IIIb
Systemic signs	Temperature instability, apnea, bradycardia.	Similar to stage I.	Mild acidosis, thrombocytopenia.	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, DIC, oliguria.	Further deterioration, shock.
Intestinal signs	Increased gastric residuals, mild abdominal distention, occult blood in stool.	Marked abdominal distention with or without tenderness, absent bowel sounds, grossly bloody stools.	Abdominal wall edema and tenderness with or without palpable mass.	Worsening wall edema with erythema and induration.	Evidence of perforation.
Radiographic signs	Normal or mild ileus.	Ileus, dilated bowel loops, focal pneumatosis.	Extensive pneumatosis with or withour portal venous gas.	Prominent ascites, fixed bowel loop.	Pneumoperitoneum

first day of treatment, and probiotics were also given. After diagnosis of grade I NEC and worsened condition, the antibiotic was replaced with a combination of meropenem and metronidazole. The clinical condition began to improve after 3 days and was discharged after 7 days. The patient was in good health during follow-up two days later.

CONCLUSION

Diagnosis of NEC can be challenging as clinical symptoms can be non-specific. The combination of clinical symptoms, radiologic findings, and risk factor tracing is important in the diagnosis and management of NEC.

ACKNOWLEDGEMENT

We would like to thank Dr. dr. I Wayan Bikin Suryawan, Sp.A(K), Head of the Child's Health Department from Wangaya Hospital, for the opportunity to prepare this case report.

AUTHORS CONTRIBUTION

Runi Arumndari is involved in concepting, designing, literature searching, and data analysis. Asterisa Retno Putri and Claudia Natasha Liman are involved in literature searching. Putu Siska Suryaningsih is involved in supervising the manuscript. All authors prepare the manuscript and agree for this final version of the manuscript to be submitted to this journal.

FUNDING

None.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

REFERENCES

1. Niemarkt HJ, deMeij TGJ, vdVelden ME, van der Schee MP, van Goudoever JB, Kramer BW, et al. Necrotizing enterocolitis: A clinical review on diagnostic biomarkers and the role of the intestinal microbiota. Inflamm Bowel Dis. 2015;21(2):436-44. DOI: 10.1097/ MIB.0000000000000184.
2. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011;364(3):255–64. DOI: 10.1056/NEJMra1005408.
3. Gill EM, Jung K, Qvist N, Ellebæk MB. Antibiotics in the medical and surgical treatment of necrotizing enterocolitis. A systematic review. BMC Pediatr. 2022;22(1):66. DOI: https://doi.org/10.1186/s12887-022-03120-9/
4. Rose AT, Patel RM. A critical analysis of risk factors for necrotizing enterocolitis. Semin Fetal Neonatal Med. 2018;23(6):374–9. DOI: 10.1016%2Fj.siny.2018.07.005.
5. Gordon PV, Swanson JR, Attridge JT, Clark R. Emerging trends in acquired neonatal intestinal disease: Is it time to abandon Bell's criteria? J Perinatol. 2007;27(11):661–71. DOI: 10.1038/sj.jp.7211782.
6. Amer T, David R, Oberfield S. Necrotizing enterocolitis and hypothyroidism in a newborn infant: Treatment with intravenous L-thyroxine. Am J Perinatol. 1994;11(01):30–2. DOI: https://doi.org/10.1055/s-2007-994530.
7. Neu J. Necrotizing enterocolitis: The future. Neonatology 2020;117(2):240-4. DOI: 10.1159/000506866.
8. Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R. Cow's milk-induced gastrointestinal disorders: From infancy to adulthood. World J Clin Pediatr. 2022;11(6):437–54. DOI: 10.5409/wjcp.v11.i6.437.
9. Abdelhamid AE, Chuang SL, Hayes P, Fell JME. In vitro cow's milk protein-specific inflammatory and regulatory cytokine responses in preterm infants with necrotizing enterocolitis and sepsis. Pediatr Res. 2011;69(2):165–9. DOI: 10.1203/PDR.0b013e31820263e7.
10. Aceti A, Beghetti I, Martini S, Faldella G, Corvaglia L. Oxidative stress and necrotizing enterocolitis: Pathogenetic mechanisms, opportunities for intervention, and role of human milk. Oxidative Medicine and Cellular Longevity 2018;2018:1–7. DOI: 10.1155%2F2018%2F7397659.
11. Donà D, Gastaldi A, Barbieri E, Bonadies L, Aluvaala J, English M. Empirical antimicrobial therapy of neonates with necrotizing enterocolitis: A systematic review. Am J Perinatol. 2023;40(6):646-56. DOI: 10.1055/s-0041-1730364.
12. Heyne-Pietschmann M, Lehnick D, Spalinger J, Righini-Grunder F, Buettcher M, Lehner M, et al. Newborns with bloody stools—At the crossroad between efficient management of necrotizing enterocolitis and antibiotic stewardship. Antibiotics 2021 Dec 1;10(12):1467. DOI: 10.3390/antibiotics10121467.