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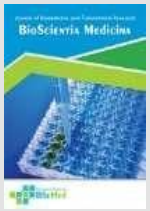

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The Complex Interplay of Prematurity, Respiratory Distress Syndrome, and Necrotizing Enterocolitis: Insights from a Case Study

Putu Cahya Chandranita[1*], I Gede Deden Susma Sugara[2]

[1]General Practitioner, Tabanan General Hospital, Tabanan, Indonesia

[2]Pediatrician, Tabanan General Hospital, Tabanan Indonesia

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***Corresponding author:**
Putu Cahya Chandranita

E-mail address:
cahyachandranita93@gmail.com

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A B S T R A C T

Background: Necrotizing enterocolitis (NEC) remains a devastating inflammatory bowel disease predominantly affecting premature infants, carrying significant morbidity and mortality risks. Respiratory distress syndrome (RDS), common in this population, is increasingly recognized not just as a comorbidity but as a potential contributor to NEC pathogenesis, possibly through mechanisms involving gut hypoperfusion. Understanding the clinical progression and management challenges when these conditions coexist is crucial. **Case presentation:** We present the case of a female infant born prematurely at 33-34 weeks gestation with a birth weight of 2280g. The infant developed early RDS, requiring Continuous Positive Airway Pressure (CPAP) support shortly after birth. On the second day of life, while RDS symptoms were improving, the infant developed signs suggestive of NEC, including abdominal distension, bilious gastric residuals, and subsequent irritability and feeding intolerance. The diagnosis of NEC (suspected Bell's stage II) was supported by clinical findings and radiological evidence of bowel wall thickening. Blood cultures identified *Klebsiella pneumoniae*. Initial antibiotic therapy proved insufficient, necessitating a change to meropenem and amikacin based on sensitivity testing. The infant was managed conservatively with bowel rest, parenteral nutrition, and targeted antibiotics, showing gradual clinical improvement. Enteral feeding with breast milk was successfully reintroduced, and the infant was discharged in good condition after 15 days of NICU care. **Conclusion:** This case highlights the challenging clinical scenario where early-onset RDS in a premature, low-birth-weight infant precedes the development of NEC. It underscores the importance of high clinical suspicion for NEC even as respiratory status improves, the utility of microbial surveillance and sensitivity testing in guiding antibiotic therapy, and the potential for successful conservative management in NEC Bell's stage II. The interplay between RDS-induced physiological stress and intestinal vulnerability likely contributed to NEC development in this patient.

1. Introduction

Necrotizing enterocolitis (NEC) represents a grave and acute inflammatory condition characterized by bowel necrosis, predominantly affecting premature and low-birth-weight (LBW) infants. This devastating disease process is a leading cause of morbidity and mortality within neonatal intensive care units (NICUs) across the globe. The pathophysiology of NEC involves a complex interplay of intestinal inflammation, ischemia, and necrosis, which can progress to perforation and sepsis, posing a substantial challenge to neonatologists and the overall care of these vulnerable patients. The incidence of NEC, while estimated to be relatively low in the general population at 1-3 per 1000 live births, exhibits a disproportionate predilection for premature infants. Very low birth weight (VLBW) infants, defined as those weighing less than 1500g at birth, are particularly at heightened risk, with NEC occurring in 5-10% of this specific population. In fact, premature birth accounts for

approximately 90% of all NEC cases, highlighting the profound impact of prematurity on the development of this disease. Despite significant advancements in neonatal care that have led to improved survival rates among even extremely premature infants, the incidence of NEC has not shown a commensurate decline. Paradoxically, in some cohorts, the incidence has remained stable or even increased, a finding that underscores the intricate and still incompletely understood nature of NEC pathogenesis. This persistent challenge emphasizes the critical need for continued research aimed at developing more effective preventive and therapeutic strategies to combat this disease. The clinical consequences of NEC are severe, with mortality rates ranging from 20-30%. This already significant mortality risk escalates dramatically to over 50% in cases where intestinal perforation occurs, a serious complication of NEC. Moreover, infants who survive NEC, particularly those who require surgical intervention, often face a multitude of long-term complications that can profoundly affect their quality of life. These complications include the development of intestinal strictures, malabsorption issues, short bowel syndrome, and neurodevelopmental impairment. The potential for such debilitating sequelae further emphasizes the importance of understanding NEC and optimizing its management to minimize both mortality and long-term morbidity.[1-3]

The etiology of NEC is multifactorial, and the precise mechanisms underlying its development are not yet fully elucidated. However, it is widely accepted that a convergence of several key risk factors contributes to the pathogenesis of this disease. Prematurity stands out as the single most consistent and significant risk factor for NEC. The increased susceptibility of premature infants to NEC is directly linked to the immaturity of their gastrointestinal tract. This immaturity manifests in various ways, including structural immaturity, impaired digestive function, abnormal intestinal motility, dysregulation of circulatory control, and deficiencies in immune defenses. Each of these factors plays a crucial role in the vulnerability of the premature infant's gut to the necrotizing processes characteristic of NEC. In addition to prematurity, several other factors have been identified as contributing to the risk of NEC. The mode of feeding is one such factor, with formula feeding associated with a higher risk compared to the use of human milk. Human milk provides numerous protective factors, including immunoglobulins and other bioactive components, that help to support the developing intestinal barrier and immune system. Hypoxia-ischemia events, which can occur due to perinatal asphyxia or other conditions leading to systemic hypoperfusion, also increase the risk of NEC. These events can compromise blood flow to the intestines, predisposing them to ischemic injury. Furthermore, abnormal intestinal microbial colonization, or dysbiosis, is implicated in NEC pathogenesis. The establishment of a healthy gut microbiome is critical for intestinal development and function, and disruptions in this process can increase the risk of NEC. Finally, there may be potential genetic predispositions that contribute to an infant's susceptibility to NEC, although these are not yet fully understood. Specific pathogenic bacteria have been frequently implicated in NEC outbreaks and individual cases. These bacteria, including *Klebsiella pneumoniae*, *Escherichia coli*, *Clostridium* species, and coagulase-negative Staphylococci, can exert their pathogenic effects by acting on a compromised intestinal barrier. In premature infants, whose intestinal barrier function is already immature, the presence of these bacteria can trigger an exaggerated inflammatory response, leading to the development of NEC.[4-6]

Respiratory distress syndrome (RDS) is another major cause of morbidity in premature infants, often requiring intensive care. RDS is primarily caused by a deficiency of surfactant, a substance that reduces surface tension in the alveoli of the lungs, in the immature lungs of premature infants. The immaturity of the lungs in premature infants leads to an inability to produce sufficient surfactant, resulting in alveolar collapse and respiratory distress. Intriguingly, a

clinical association between RDS and the subsequent development of NEC has been frequently observed in clinical practice. The nature of this association has been the subject of much investigation, and several pathophysiological links have been proposed to explain this connection. The proposed pathophysiological link between RDS and NEC often involves the physiological stress induced by RDS, which can have systemic effects that compromise intestinal integrity. One of the key mechanisms by which RDS may contribute to NEC development is through hypoxia and the resultant "diving reflex." The diving reflex is a physiological response to hypoxia that leads to a redistribution of cardiac output. In this reflex, blood flow is preferentially directed to vital organs such as the brain and heart at the expense of the mesenteric circulation, which supplies blood to the intestines. This reduction in blood flow to the intestines can result in intestinal hypoperfusion and subsequent ischemia-reperfusion injury. Ischemia-reperfusion injury occurs when blood flow is restored to tissue after a period of ischemia, paradoxically leading to further tissue damage. This process can damage the intestinal mucosa, impairing its barrier function and increasing susceptibility to bacterial translocation and inflammation – key events in the initiation and progression of NEC. The inflammatory cascade that is triggered by microbial invasion of the intestinal wall involves a complex interplay of signaling pathways. These pathways include the activation of Toll-like receptor 4 (TLR4), a key component of the innate immune system, and the release of pro-inflammatory cytokines such as TNF-α and IL-1β. Vasoactive mediators are also released, further contributing to the intestinal injury. The combined effects of these inflammatory processes exacerbate the damage to the intestinal tissue and contribute to the development of NEC. This case report details the clinical course of a premature, low-birth-weight infant who initially presented with RDS requiring Continuous Positive Airway Pressure (CPAP) support and subsequently developed NEC. The diagnosis of NEC in this case was confirmed by a combination of clinical and radiological findings, and the infant's condition was further complicated by *Klebsiella pneumoniae* sepsis. The report provides a detailed account of the diagnostic process, the challenges encountered during the management of this complex case, and the importance of targeted antibiotic therapy guided by susceptibility testing. It also highlights the successful outcome that was achieved through conservative, non-surgical management.[7-10] By thoroughly examining the interplay between prematurity, RDS, and NEC in this specific case, this report aims to provide valuable insights into the complex pathophysiology of these conditions. It also seeks to emphasize key considerations for the timely diagnosis and effective management of this challenging neonatal condition, ultimately contributing to improved outcomes for affected infants.

2. Case Presentation

The patient was a female infant. At the time of admission, her age was recorded as 7 days. She was born prematurely, with a gestational age of 33 to 34 weeks. The infant's birth weight was 2280 grams. The delivery method was via cesarean section (CS). Anthropometric measurements at birth included a length of 46 centimeters, a head circumference of 32 centimeters, and a chest circumference of 28 centimeters. Growth assessments using the Fenton Chart indicated that her birth weight was between the 10th and 50th percentile, her length was at the 50th percentile, and her head circumference was between the 50th and 90th percentile. These growth parameters provide a baseline assessment of the infant's size and development in relation to gestational age. The primary complaint that led to the infant's evaluation was abdominal distension. The maternal history was significant for a third pregnancy, one prior live birth, one preterm birth, and one abortion (G3P1101). The mother also experienced threatened preterm labor and preterm premature rupture of membranes (PPROM) for a duration exceeding 12 hours prior to delivery. The birth history noted that

the infant cried immediately after birth and demonstrated good initial activity. The amniotic fluid was described as clear. The history of the present illness (HPI) revealed a complex clinical course. The infant developed respiratory distress syndrome (RDS) approximately 10 minutes post-birth, characterized by gasping, grunting, and pallor. Initial management included continuous positive airway pressure (CPAP), intravenous fluids (IVF), and orogastric tube (OGT) decompression. Over the subsequent days, specifically on day 2, the infant developed jaundice and mild abdominal distension. The abdominal distension progressively worsened, accompanied by abdominal erythema, irritability, and greenish, then brownish OGT aspirates, with an approximate volume of 3 milliliters, observed over days 2 to 7. Due to the worsening symptoms and a poor response to initial antibiotic therapy, the infant was referred to a tertiary hospital on day 7. The initial treatments administered at the referring hospital consisted of a multifaceted approach. Respiratory support was provided with CPAP, with a fraction of inspired oxygen (FiO_2) of 25%, a flow rate of 8, and positive end-expiratory pressure (PEEP) of 7. The infant also received intravenous fluids, OGT decompression, and was kept nil per os (NPO). Phototherapy was initiated to manage the jaundice. Antibiotic therapy included ampicillin and gentamicin. Additional medications administered were aminophylline, ranitidine, tranexamic acid, vitamin K, cefoperazone, metronidazole, albumin, and probiotics. These treatments reflect the initial attempts to address the infant's respiratory distress, potential infection, and other associated complications. Upon physical examination on day 8, the infant's general appearance was described as moderately ill but conscious, with a Glasgow Coma Scale score of E4V5M6, indicating eye-opening to speech, verbal response of cooing, and motor response of purposeful movement. The vital signs revealed a heart rate of 142 beats per minute, a respiratory rate of 64 breaths per minute, a temperature of 36.7 degrees Celsius, and an oxygen saturation of 97% on room air. Examination of the abdomen revealed distension and erythema, particularly in the epigastric area. No abnormal bowel loops were visible. Auscultation of the abdomen revealed decreased bowel sounds. Percussion of the abdomen elicited a tympanic sound, indicating the presence of excessive gas. Palpation of the abdomen revealed tenderness, but no guarding or rigidity was noted, suggesting the absence of peritonitis at that time. Other findings included the absence of retractions, clear lung sounds, no murmurs, warm extremities, and a capillary refill time of less than 3 seconds. The fontanelles were open and flat, and the eyes were non-icteric and non-anemic. These findings provided a comprehensive assessment of the infant's overall condition, including respiratory, cardiovascular, and neurological status. Laboratory investigations conducted on day 8 revealed several abnormalities. The complete blood count (CBC) showed a white blood cell count of 15.8 x $10^3/\mu L$, with 72% neutrophils, indicating neutrophilia. The platelet count was 79 x $10^3/\mu L$, suggestive of thrombocytopenia. The hemoglobin level was 13.6 g/dL, indicating mild anemia, and the hematocrit was 38.1%, which was low. The blood glucose level was 87 mg/dL, slightly elevated. Bilirubin levels were also elevated, with a total bilirubin of 6.85 mg/dL, a direct bilirubin of 1.14 mg/dL, and an indirect bilirubin of 5.71 mg/dL, consistent with jaundice. The albumin level was 3.0 g/dL, indicating hypoalbuminemia. The blood culture yielded a positive result for *Klebsiella pneumoniae*, confirming bacteremia. Antibiotic sensitivity testing revealed that the *Klebsiella pneumoniae* isolate was sensitive to meropenem (with a minimum inhibitory concentration (MIC) of ≤0.25) and amikacin (MIC ≤2). However, the isolate was resistant to ampicillin, gentamicin, cefazolin, third and fourth-generation cephalosporins, and ciprofloxacin, indicating the presence of extended-spectrum beta-lactamase (ESBL) production. Imaging studies included a Babygram performed on day 5, which revealed patchy infiltrates in the chest, suggestive of bronchopneumonia. The abdominal component of the Babygram showed normal gas distribution but thickened bowel walls, raising

suspicion for Necrotizing Enterocolitis (NEC). An abdominal X-ray (Abd XR), specifically a Blank Abdominal X-ray (BOF), was performed on day 8. This imaging study demonstrated persistent thickened bowel walls, gas intermixed with fecal material, and a ground-glass appearance in the right abdomen, potentially indicative of hepatomegaly or ascites. Notably, there was no definite pneumatosis intestinalis or pneumoperitoneum observed. The orogastric tube was confirmed to be in place. The conclusion drawn from this imaging was that the thickened bowel walls were suggestive of NEC. The final diagnoses for this infant were: preterm infant appropriate for gestational age (AGA), low birth weight (LBW) infant, respiratory distress syndrome (RDS) secondary to neonatal pneumonia, Necrotizing Enterocolitis (NEC) (Bell's stage II implied), neonatal jaundice, and neonatal sepsis due to *Klebsiella pneumoniae*. These diagnoses comprehensively summarize the infant's complex medical condition, encompassing prematurity, respiratory compromise, gastrointestinal involvement, and systemic infection (Table 1).

The management and subsequent follow-up of the infant involved a structured and dynamic approach, adapting to the evolving clinical picture. The timeline can be broadly divided into initial management, antibiotic therapy adjustments, nutritional strategies, adjunctive therapies, and clinical follow-up, culminating in the patient's outcome at discharge. Upon arrival at Tabanan General Hospital on day 8, the infant was admitted to the Neonatal Intensive Care Unit (NICU). This admission to the NICU reflects the need for a high level of care, continuous monitoring, and the availability of specialized interventions for critically ill neonates, particularly those with conditions like Necrotizing Enterocolitis (NEC) and sepsis. Supportive care was immediately initiated, focusing on the critical aspects of stabilizing the infant's condition and addressing the gastrointestinal compromise. The infant was kept nil per os (NPO), meaning all oral or enteral feeding was withheld. This is a cornerstone of NEC management, allowing the inflamed bowel to rest and minimizing further intestinal stimulation. Orogastric (OGT) decompression was employed, involving the placement of a tube through the nose or mouth into the stomach to continuously or intermittently remove gastric contents. This decompression helps to alleviate abdominal distension, reduce the risk of vomiting and aspiration, and prevent further intestinal distension. Intravenous fluids (IVF) were administered to maintain hydration and electrolyte balance. The specific fluid used was D5 ¼ NS (dextrose 5% in 0.225% normal saline), and the rate was adjusted daily, starting at approximately 14 ml/hr, based on the infant's clinical status, fluid balance, and electrolyte levels. Continuous monitoring was essential, encompassing vital signs (heart rate, respiratory rate, temperature, oxygen saturation) and abdominal girth measurements. Frequent monitoring of vital signs allows for the early detection of deterioration or improvement in the infant's condition. Abdominal girth measurements are crucial in NEC management, as increasing abdominal distension is a key indicator of worsening intestinal inflammation and potential complications. Initial medications at Tabanan General Hospital consisted of intravenous antibiotics and an analgesic. Inj. Meropenem 90 mg IV q8h (every 8 hours) was initiated, guided by the antibiotic sensitivity results, which identified the causative organism, *Klebsiella pneumoniae*, as sensitive to meropenem. Meropenem is a broad-spectrum carbapenem antibiotic, often reserved for serious infections caused by multidrug-resistant bacteria. Inj. Amikacin 20 mg IV q12h (every 12 hours) was added later, starting on day 13, also based on sensitivity testing. Amikacin is an aminoglycoside antibiotic, providing synergistic activity against *Klebsiella pneumoniae* and further broadening the antibiotic coverage. Paracetamol 30 mg IV q8h prn (as needed) was administered for pain or fever management. The antibiotic therapy timeline illustrates the dynamic adjustment of antimicrobial agents based on the evolving microbiological data. In the pre-referral period, from day 1 to 4, the infant

received ampicillin and gentamicin. This combination is a common empirical therapy for neonatal sepsis, providing broad coverage against both gram-positive and gram-negative bacteria. However, the lack of clinical improvement necessitated a change in antibiotics. From day 6 to 7, still in the pre-referral phase, the antibiotic regimen was switched to cefoperazone and metronidazole. Cefoperazone is a third-generation cephalosporin, while metronidazole provides anaerobic coverage. This change suggests a concern for worsening infection or the possibility of anaerobic involvement in the NEC process. The post-referral antibiotic management, from day 8 onwards, involved meropenem and amikacin. This crucial switch was guided by culture and sensitivity results, which revealed that the *Klebsiella pneumoniae* isolate was resistant to the previous regimens but sensitive to meropenem and amikacin. This targeted antibiotic therapy was pivotal in effectively combating the infection. Nutritional management was carefully staged, progressing from complete bowel rest to the gradual reintroduction and advancement of enteral feeds. The initial phase, spanning approximately from day 8 to 11, involved NPO with IVF support. This period of complete bowel rest is essential in NEC to reduce intestinal workload, minimize further inflammation, and promote healing of the affected bowel. Intravenous fluids provided the necessary hydration and nutrients during this period. Enteral introduction began on day 12. Once the clinical condition stabilized and signs of peritonitis resolved, minimal enteral feeding was initiated with breast milk (ASI - Air Susu Ibu, Indonesian for breast milk) via a gavage tube. Gavage feeding involves delivering breast milk directly into the stomach through a tube. The initial feeds were extremely small in volume, starting with 2 ml every 3 hours, then increased to 10 ml every 3 hours. This cautious introduction minimizes the risk of exacerbating intestinal inflammation. Advancement of enteral feeds occurred from day 13 onwards. The volume of breast milk feeds was gradually increased, and the mode of feeding transitioned to ASI on demand (direct breastfeeding) as tolerated. Based on the removal of the OGT on day 12, breastfeeding attempts likely started around day 11 or 12. Intravenous fluids were gradually weaned as the infant tolerated increasing enteral feeds, demonstrating the successful transition to primarily enteral nutrition. In addition to antibiotics and nutritional support, several adjunctive therapies were used to support the infant's recovery. Probiotics were administered in the form of L. Bio. The dosage varied, initially 2 x ½ sachet orally (PO), and later increased to 2 x 1 sachet PO. Probiotics aim to promote the restoration of a healthy gut microbiome, which can be disrupted in NEC. Vitamins and minerals were supplemented. Apialys 0.3 ml PO daily provided multivitamins. Zinc syrup 10 mg PO daily was started later in the course, specifically for diarrhea, as zinc has been shown to reduce the duration and severity of diarrheal episodes. Fervit drops (iron) 0.3 ml PO daily were prescribed at discharge to prevent iron deficiency anemia. Other medications included paracetamol prn for pain or fever, Darm Boise, which was discontinued, and Busmin Syrup 3 x 1 ml PO, administered temporarily. Close clinical follow-up was crucial to monitor the infant's progress and guide ongoing management. Abdominal status was closely assessed. The initial distension and erythema gradually resolved. By days 14-16, the abdomen was soft and non-distended. Tenderness persisted but improved over time. These findings indicate the resolution of the acute inflammatory process in the intestine. Activity and feeding were also monitored. The initial lethargy improved, and the infant became more active, with a strong cry. The infant tolerated the gradual increase in ASI feeds and was feeding well at the breast by day 16, demonstrating successful recovery of feeding ability. Bowel function was tracked. Initially, there was a lack of stool. Subsequently, greenish mucoid stools were observed from days 11-15, which resolved by day 16. The change in stool characteristics likely reflects the intestinal inflammation and its resolution. Monitoring involved daily clinical assessments, documented in SOAP (Subjective, Objective, Assessment, Plan) notes. Vital signs remained stable,

and abdominal girth was monitored regularly. Repeat imaging was not documented after day 8, suggesting that the clinical and physical examination findings were sufficient to guide management. The duration of hospitalization was 15 days, from day 1 of life to day 16. The infant's condition at discharge on day 16 was clinically well, with NEC resolved. The infant was feeding well with ASI and was active. Discharge medications included Apialys (multivitamin), zinc syrup, and Fervit drops (iron). These medications aimed to support the infant's continued growth and development after discharge (Table 2).

Table 1. Summary of patient's clinical findings.

Category	Finding	Details
Demographics	Patient IDE	By. UH
	Gender	F
	Age at Admission	7 Days
	GA	33-34 weeks
	BW	2280 g
	Delivery Method	CS
	Anthropometry (Birth)	Length: 46 cm; HC: 32 cm; CC: 28 cm
	Growth (Fenton Chart)	BW: 10-50th percentile; Length: 50th percentile; HC: 50-90th percentile
Anamnesis (History)	Chief Complaint	Abdominal Distension
	Maternal History	G3P1101; Threatened Preterm Labor; PPROM >12 hours
	Birth History	Immediate cry; good initial activity; clear amniotic fluid
	HPI	- Developed RDS ~10 mins post-birth (gasping, grunting, pallor); - Required CPAP, IVF, OGT decompression; - RDS improved Day 2, onset jaundice & mild abdominal distension; - Worsening distension, abdominal erythema, irritability, greenish then brownish OGT aspirates (~3ml) over Days 2-7; - Referred to tertiary hospital Day 7 due to worsening symptoms & poor response to initial antibiotics.
	Initial Treatments (Referring hospital)	CPAP (FiO_2 25%, Flow 8, PEEP 7); IVF; OGT Decompression; NPO; Phototherapy; Ampicillin; Gentamicin; Aminophylline; Ranitidine; Tranexamic Acid; Vit K; Cefoperazone; Metronidazole; Albumin; Probiotics.
Physical exam (Day 8)	General Appearance	Moderately ill; conscious (Compos Mentis E4V5M6)
	Vital Signs	HR: 142/min; RR: 64/min; Temp: 36.7°C; SpO_2: 97% (RA)
	Abdomen – Inspection	Distended (+); Erythema (+) esp. epigastric area; No abnormal bowel patterns visible
	Abdomen - Auscultation	Bowel sounds decreased
	Abdomen - Percussion	Tympanic
	Abdomen - Palpation	Tenderness (+); No guarding/rigidity (-)
	Other	No retractions; Clear lungs; No murmur; Warm extremities; CRT < 3 sec; Fontanelles open/flat; Eyes non-icteric/non-anemic
Laboratory (Day 8)	CBC	WBC: 15.8 x 10^3/µL; NE%: 72 (Neutrophilia); PLT: 79 x 10^3/µL (Thrombocytopenia); Hgb: 13.6 g/dL (Mild Anemia); Hct: 38.1% (Low)
	Blood Glucose	87 mg/dL (Slightly Elevated)
	Bilirubin	Total: 6.85 mg/dL; Direct: 1.14 mg/dL (Elevated); Indirect: 5.71 mg/dL (Elevated)
	Albumin	3.0 g/dL (Hypoalbuminemia)
	Blood Culture	*K. pneumoniae (Positive)*
	Antibiotic Sensitivity	Sens: Meropenem (MIC ≤0.25), Amikacin (MIC ≤2); Res: Ampicillin, Gentamicin, Cefazolin, 3rd/4th Gen Cephalosporins, Ciprofloxacin (ESBL Positive)
Imaging	Babygram (Day 5)	Chest: Patchy infiltrates (Bronchopneumonia); Abdomen: Normal gas distribution, Thickened bowel walls (Suggestive of NEC)
	Abdomen XR (BOF, Day 8)	Persistent thickened bowel walls; Gas mixed with fecal material; Ground-glass appearance (right abdomen - ?hepatomegaly/?ascites); No definite pneumatosis or pneumoperitoneum; OGT in place; Conclusion: Thickened bowel walls suspect NEC.
Diagnosis	Final Diagnoses	- Preterm Infant (AGA); - LBW Infant; - RDS secondary to Neonatal Pneumonia; - NEC (Bell's Stage II implied); - Neonatal Jaundice; - Neonatal Sepsis (K. pneumoniae)

Abd XR: Abdominal X-Ray; AGA: Appropriate for Gestational Age; BOF: Blank Abdominal X-ray (Kor: Boro Fluoroscopy - often used locally for plain film); BW: Birth Weight; CC: Chest Circumference; cm: centimeter; CBC: Complete Blood Count; CPAP: Continuous Positive Airway Pressure; CRT: Capillary Refill Time; CS: Cesarean Section; dL: deciliter; ESBL: Extended-Spectrum Beta-Lactamase; F: Female; FiO_2: Fraction of Inspired Oxygen; g: grams; G: Gravida; GA: Gestational Age; Hct: Hematocrit; HC: Head Circumference; Hgb: Hemoglobin; HPI: History of Present Illness; HR: Heart Rate; IVF: Intravenous Fluids; K.: Klebsiella; LBW: Low Birth Weight; mg: milligram; MIC: Minimum Inhibitory Concentration; min: minute; ml: milliliter; µL: microliter; NEC: Necrotizing Enterocolitis; NE: Neutrophil; NPO: Nil Per Os (Nothing by Mouth); OGT: Orogastric Tube; P: Parity; PEEP: Positive End-Expiratory Pressure; PLT: Platelet; PPROM: Preterm Premature Rupture of Membranes; RA: Room Air; Res: Resistant; RDS: Respiratory Distress Syndrome; RR: Respiratory Rate; Sens: Sensitive; SpO_2: Oxygen Saturation; Temp: Temperature; Vit K: Vitamin K; WBC: White Blood Cell.

Table 2. Treatment course and follow-up summary.

Phase / Timing	Intervention / Observation	Details
Initial management (Day 8 at Tabanan General Hospital)	Admission Location	NICU
	Supportive Care	NPO; OGT decompression; IVF (D5 ¼ NS, rate adjusted daily starting ~14 ml/hr); Monitoring (Vitals, Abdominal girth)
	Initial Medications (RSUD)	Inj Meropenem 90 mg IV q8h (based on sensitivity); Inj Amikacin 20 mg IV q12h (started Day 13, based on sensitivity); Paracetamol 30 mg IV q8h prn
Antibiotic therapy timeline	Pre-referral (Day 1-4)	Ampicillin + Gentamicin
	Pre-referral (Day 6-7)	Cefoperazone + Metronidazole
	Post-referral (Day 8 onwards)	Meropenem + Amikacin (guided by culture & sensitivity results showing K. pneumoniae resistant to previous regimens, sensitive to these)
Nutritional management	Initial Phase (Day 8-11 approx.)	NPO with IVF support
	Enteral Introduction (Day 12)	OGT removed; Minimal enteral feeding initiated with breast milk (ASI) via gavage tube (initially 2ml then 10 ml q3h)
	Advancement (Day 13 onwards)	Gradual increase in breast milk volume; Transitioned to ASI on demand (direct breastfeeding attempts likely started Day 11/12 based on OGT removal); IVF weaned
Adjunctive therapies	Probiotics	L Bio (dose varied, e.g., 2 x ½ sachet PO, later 2 x 1 sachet PO)
	Vitamins/Minerals	Apialys 0.3 ml PO daily; Zinc syrup 10 mg PO daily (started later for diarrhea); Fervit drops (Iron) 0.3 ml PO daily (at discharge)
	Other	Paracetamol prn; Darm boise (discontinued); Busmin Syrup 3 x 1 ml PO (temporary)
Clinical follow-up (Day 8-16)	Abdominal Status	Initial distension & erythema gradually resolved; Abdomen soft, non-distended by Day 14-16; Tenderness persisted but improved.
	Activity / Feeding	Initial lethargy improved to active with strong cry; Tolerated gradual increase in ASI feeds; Feeding well at breast by Day 16.
	Bowel Function	Initial lack of stool, then greenish mucoid stools (Days 11-15), resolved by Day 16.
	Monitoring	Daily clinical assessment (SOAP notes), vital signs stable, abdominal girth monitored. Repeat imaging not documented after Day 8.
Outcome	Duration of Hospitalization	15 days (Day 1 of life to Day 16)
	Condition at Discharge (Day 16)	Clinically well, NEC resolved, feeding well with ASI, active.
	Discharge Medications	Apialys (Multivitamin); Zinc syrup; Fervit drops (Iron)

Notes: Abd: Abdominal; AGA: Appropriate for Gestational Age; ASI: Air Susu Ibu (Breast Milk); BW: Birth Weight; CBC: Complete Blood Count; CPAP: Continuous Positive Airway Pressure; CRT: Capillary Refill Time; CS: Cesarean Section; dL: deciliter; ESBL: Extended-Spectrum Beta-Lactamase; F: Female; FiO_2: Fraction of Inspired Oxygen; g: grams; GA: Gestational Age; Hct: Hematocrit; HC: Head Circumference; Hgb: Hemoglobin; HPI: History of Present Illness; HR: Heart Rate; IVF: Intravenous Fluids; K.: Klebsiella; LBW: Low Birth Weight; mg: milligram; MIC: Minimum Inhibitory Concentration; min: minute; ml: milliliter; µL: microliter; NEC: Necrotizing Enterocolitis; NE: Neutrophil; NICU: Neonatal Intensive Care Unit; NPO: Nil Per Os (Nothing by Mouth); OGT: Orogastric Tube; PEEP: Positive End-Expiratory Pressure; PLT: Platelet; PO: Per Os (By Mouth); PPROM: Preterm Premature Rupture of Membranes; prn: pro re nata (as needed); q8h: every 8 hours; q12h: every 12 hours; q3h: every 3 hours; RA: Room Air; Res: Resistant; RDS: Respiratory Distress Syndrome; RR: Respiratory Rate; RSUD: Rumah Sakit Umum Daerah (Regional General Hospital); Sens: Sensitive; SpO_2: Oxygen Saturation; Temp: Temperature; Vit K: Vitamin K; WBC: White Blood Cell; XR: X-Ray.

3. Discussion

The infant in this report was born prematurely, between 33 and 34 weeks of gestation, and exhibited low birth weight. These factors, prematurity and low birth weight, are unequivocally established as the most significant non-modifiable risk factors for both RDS and NEC. The premature infant's gastrointestinal system is inherently vulnerable due to a constellation of factors stemming from its incomplete development. This immaturity affects various critical aspects of gut function and structure, predisposing these infants to a higher risk of developing NEC. One of the primary vulnerabilities is the reduced digestive and absorptive capacity of the premature gut. The production of digestive enzymes, which are essential for breaking down nutrients into absorbable forms, is often

insufficient in premature infants. This enzymatic insufficiency can lead to maldigestion and the accumulation of undigested food in the intestinal lumen, creating an environment that favors bacterial overgrowth and the production of toxic metabolites. Furthermore, the absorptive surface area of the premature intestine may be reduced, and the transport mechanisms responsible for nutrient uptake may be inefficient, compromising the infant's ability to adequately absorb nutrients. Impaired intestinal motility is another significant factor. The coordinated contractions of the intestinal muscles, known as peristalsis, are responsible for propelling food along the digestive tract. In premature infants, these peristaltic movements can be weak, uncoordinated, or infrequent, leading to stasis of intestinal contents. This stasis can promote bacterial overgrowth, increase the contact time between bacteria and the intestinal mucosa, and impair the clearance of harmful substances. The underdeveloped mucosal barrier is a crucial vulnerability. The intestinal mucosa is a complex structure that acts as a selective barrier, allowing the absorption of nutrients while preventing the entry of harmful substances such as bacteria and toxins. In premature infants, this barrier is often immature, with thinner layers of cells, reduced production of mucus, and less effective tight junctions between cells. This "leaky gut" allows for increased permeability, facilitating the translocation of bacteria and their products from the intestinal lumen into the bloodstream and the intestinal wall, triggering an inflammatory cascade. Finally, the naive immune system of the premature infant contributes to the increased susceptibility to NEC. The immune system in the gut, known as the gut-associated lymphoid tissue (GALT), is responsible for mounting an appropriate immune response to pathogens while maintaining tolerance to commensal bacteria and dietary antigens. In premature infants, the GALT is immature, with reduced numbers and activity of immune cells, impaired production of antibodies, and dysregulation of cytokine responses. This immaturity can result in an exaggerated and uncontrolled inflammatory response to bacterial invasion, leading to the tissue damage characteristic of NEC.[11-13]

In this case, the infant developed RDS shortly after birth, requiring CPAP support. RDS is a common respiratory disorder in premature infants, primarily caused by a deficiency of surfactant. Surfactant is a complex mixture of lipids and proteins that reduces surface tension in the alveoli, preventing their collapse during expiration. The immature lungs of premature infants often produce insufficient surfactant, leading to alveolar collapse, impaired gas exchange, and respiratory distress. The occurrence of RDS in this infant is particularly relevant to the development of NEC due to the potential pathophysiological link between these two conditions. While seemingly disparate, the respiratory compromise in RDS can initiate a cascade of events that compromise intestinal integrity and increase the risk of NEC. A key mechanism by which RDS contributes to NEC involves the physiological stress response to hypoxia. Hypoxia, or reduced oxygen levels, is a common consequence of RDS due to impaired gas exchange in the lungs. In response to hypoxia, the body initiates a compensatory mechanism known as the "diving reflex." This reflex prioritizes oxygen delivery to vital organs such as the brain and heart by shunting blood away from less essential organs, including the intestines. This redistribution of blood flow results in intestinal hypoperfusion, meaning a reduction in the blood supply to the intestines. The intestinal mucosa is highly sensitive to ischemia, or lack of blood flow, and even a brief period of hypoperfusion can lead to significant damage. The reduced oxygen and nutrient delivery to the intestinal cells impairs their normal function, weakens the mucosal barrier, and makes the gut more susceptible to injury. Furthermore, the subsequent reperfusion of the intestines, when blood flow is restored after a period of ischemia, can paradoxically exacerbate the damage. This phenomenon, known as ischemia-reperfusion injury, involves the generation of reactive oxygen species and other inflammatory mediators that contribute to further tissue damage. In this case, the initial RDS

episode and the associated hypoxemia likely triggered the diving reflex and resulted in a period of intestinal hypoperfusion. This initial insult may have "primed" the gut, making it more vulnerable to the subsequent inflammatory processes that led to NEC.[14-16]

The diagnosis of NEC can be challenging, particularly in the early stages, as the initial symptoms can be non-specific and overlap with other common neonatal conditions. A high index of suspicion is crucial, especially in premature and low-birth-weight infants with risk factors such as RDS. In this case, the diagnosis of NEC was based on a combination of clinical signs and radiological findings. The initial symptoms that raised suspicion for NEC included abdominal distension, feeding intolerance, and irritability. Abdominal distension is a common finding in NEC, resulting from the accumulation of gas and fluid in the dilated loops of bowel. Feeding intolerance, manifested as bilious or brownish gastric residuals, vomiting, or refusal to feed, indicates impaired intestinal function. Irritability can be a non-specific sign of discomfort or pain due to the intestinal inflammation. As the disease progressed, the infant exhibited worsening abdominal distension, abdominal wall erythema, tenderness, and decreased bowel sounds. Abdominal wall erythema is a sign of inflammation extending to the abdominal wall. Tenderness on palpation indicates underlying intestinal inflammation and potential peritonitis. Decreased or absent bowel sounds suggest reduced intestinal motility or even ileus, a complete cessation of bowel movement. Systemic signs, such as lethargy and thrombocytopenia, also supported the diagnosis of NEC. Lethargy reflects the systemic effects of the inflammatory process and potential sepsis. Thrombocytopenia, a low platelet count, can be a sign of sepsis or disseminated intravascular coagulation (DIC), a serious complication of NEC. Radiographic evaluation plays a crucial role in confirming the diagnosis of NEC and assessing its severity. In this case, the initial Babygram showed bowel wall thickening, a significant finding suggestive of NEC. The subsequent abdominal X-ray confirmed this finding and revealed a ground-glass appearance, which can indicate inflammation and edema in the intestinal wall, and possible minimal free fluid. It is important to note that while pneumatosis intestinalis, the presence of gas within the bowel wall, is considered a hallmark radiographic finding of NEC, it was not explicitly reported in the imaging findings. However, the absence of pneumatosis does not rule out NEC, especially in the early stages. Bowel wall thickening is a significant and reliable sign of NEC, and when considered in conjunction with the clinical presentation, it can strongly support the diagnosis. Based on the modified Bell's staging criteria, the clinical and radiological findings in this case were most consistent with Stage II NEC. Bell's staging criteria provide a standardized system for classifying the severity of NEC, guiding management decisions and predicting outcomes. Stage II NEC is characterized by definite NEC, with both gastrointestinal and systemic signs, and radiographic evidence of bowel wall thickening. The absence of pneumoperitoneum, or free air in the abdominal cavity, indicates that intestinal perforation, a serious complication of NEC, had not occurred.[17-20]

4. Conclusion

This case report illustrates the complex interplay between prematurity, RDS, and NEC in a vulnerable neonate. The infant's premature birth and low birth weight were significant predisposing factors for both RDS and NEC. The development of RDS and the subsequent physiological response, including the diving reflex and intestinal hypoperfusion, likely contributed to the pathogenesis of NEC. The diagnosis of NEC was established through careful clinical observation and radiological findings, highlighting the importance of a high index of suspicion in at-risk infants. The identification of Klebsiella pneumoniae bacteremia and its antibiotic resistance pattern underscored the necessity of timely microbial surveillance and targeted antibiotic therapy. The successful conservative management of NEC in this case demonstrates that, in the absence of perforation,

a carefully structured approach involving bowel rest, parenteral nutrition, and appropriate antibiotic therapy can lead to favorable outcomes. This report contributes to the growing body of evidence supporting the feasibility of conservative treatment strategies in NEC, emphasizing the importance of individualized patient care and vigilant monitoring.

5. References

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