

This is a text version of a podcast from PedsCases.com on “**Necrotizing Enterocolitis**” These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedsCases.com/podcasts.

Necrotizing Enterocolitis

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Introduction

Hi all, my name is Arun Dhir, a fourth year medical student at the University of British Columbia. This podcast was developed with Dr. Mandeep Mahal of the UBC Faculty of Medicine, Department of Pediatrics. Today, we will be discussing necrotizing enterocolitis, or “NEC” for short.

Objectives

1. Review the presentation of NEC including key features on history and physical exam
2. List the investigations used to diagnose NEC
3. Outline the nonpharmacologic, pharmacologic, and surgical management of NEC
4. Discuss some of the long term complications of NEC
5. Delineate some of the primary prevention strategies for NEC

Clinical case

To bring some context to this talk, let’s begin with a brief vignette. You are a 4th year student on your pediatrics rotation. You are called to assess a premature male infant born 5 days ago at 34+4 weeks gestation by spontaneous vaginal delivery to a healthy mother with no sepsis risk factors. Initially, he was thought to be demonstrating apnea of prematurity, but has now developed worsening apnea, bradycardia, and temperature instability. In addition, he had nonbilious vomiting with his last nasogastric feed of expressed breast milk. On examination, his abdomen is somewhat distended and you find blood in his diaper. While there are a number of conditions on your differential, you are worried this premature infant is developing necrotizing enterocolitis.

Definition

Necrotizing enterocolitis, or “NEC” for short, is a serious gastrointestinal disease affecting neonates. As the name would suggest, NEC involves necrosis of the bowel wall and its

subsequent consequences. The condition affects up to 3 in every 1000 newborns, and between 1 to 8% of neonatal intensive care patients.¹

Epidemiology and Pathophysiology

Although we do not know what definitively causes NEC, two of the strongest risk factors are prematurity and receiving enteral feedings. The timeline for development of NEC is inversely related to gestational age - infants born closer to term may develop NEC within the first week of life, whereas NEC may be seen in severely premature neonates as late as 4 weeks of life.² Other known risk factors include formula use in premature infants, black race, prolonged postnatal exposure to antibiotics, gastroschisis and conditions that promote hypoxia - such as a patent ductus arteriosus or congenital heart disease, polycythemia, receiving exchange transfusions and the use of histamine H2 receptor blockers.³ The evidence for these additional risk factors, however, is not as strong.

The pathogenesis of NEC is thought to arise from the immaturity of the intestinal barrier and may be precipitated by exposure to infectious agents in the setting of altered gut motility, reduced IgA secretions, and impaired mucosal defenses.^{2,3}

Clinical Presentation, Diagnosis, and Staging

The initial signs of NEC may be subtle and nonspecific - these include apnea, bradycardia, lethargy, irritability, and temperature instability. Following this, GI-specific symptoms may develop, such as abdominal wall distension, tenderness, and discoloration. Infants may have difficulty feeding and present with increased gastric residuals and emesis. Diarrhea and hematochezia are also seen.^{2,3}

Unfortunately, there are no particularly sensitive or specific tests for NEC. The diagnosis of NEC is based on a combination of clinical, radiographic, and laboratory findings. Generally, the following investigations are ordered:

- CBC and differential may show an elevated white blood cell count
- An electrolyte panel may show abnormalities such as hyponatremia.
- A CRP, a nonspecific test suggesting inflammation, will likely be elevated.
- Arterial blood gases may show metabolic and respiratory acidosis.
- Blood cultures, as well as urine and stool cultures should be ordered to identify infectious sources and direct therapy if possible.
- Coagulation studies may show prolonged PT, PTT, and INR with a low fibrinogen, suggesting disseminated intravascular coagulation. This is known to occur with NEC in some cases.

¹ Marc Dante K, Kliegman RM. Nelson Essentials of Pediatrics E-Book. Elsevier Health Sciences; 2014.

² Rich BS, Dolgin SE. Necrotizing Enterocolitis. Pediatrics in Review. 2017 Dec 1;38(12):552–9.

³ Thompson A. First Consult - Necrotizing enterocolitis in newborns [Internet]. 2013 [cited 2018 Aug 12]. Available from: https://www-clinicalkey-com.ezproxy.library.ubc.ca/#!/content/medical_topic/21-s2.0-2001187

Sequential anteroposterior and lateral abdominal radiographs, initially every 6 to 12 hours, play an important role in the diagnosis and management of NEC. These may not be diagnostic early on. The classic, pathognomonic finding on x-ray is “pneumatosis” - visible air within the intestinal wall. This occurs due to bacteria in the intestinal lumen making their way into the walls and creating hydrogen gas, appearing as “soap bubble lucencies”. Other nonspecific radiographic findings seen in NEC include bowel wall thickening, centralized intestinal loops - a sign of ascites, and a fixed intestinal loop. In up to one-third of patients, pneumoperitoneum may be seen, suggesting intestinal perforation. This is an absolute indication for surgical management.^{2,3}

How do we grade the severity of NEC? In 1978, Dr. Martin Bell proposed three main stages of NEC. This staging has since been modified to incorporate new knowledge. The Modified Bell Staging Criteria ranges from stage I to stage III with subcategories of each. Stage IA describes suspected NEC with less specific symptoms, whereas stage IIIB describes advanced NEC that includes bowel perforation.^{4,5} The severity of NEC helps decide the level of management.

Differential Diagnosis

Earlier, I mentioned that the initial presenting symptoms of NEC may be nonspecific. Let’s briefly review a few major conditions on the differential.

- **Sepsis** presents similarly to early NEC
- **Infectious enteritis** may present similarly, and in fact may rarely show pneumatosis on x-ray. Pathogens may be bacterial or viral and may be distinguished by stool culture.
- **Neonatal appendicitis** is a rare disorder and can present similarly, the diagnosis is made through laparotomy.
- **Spontaneous intestinal perforation** is another cause of pneumoperitoneum in neonates. This condition tends to present in very low birth weight infants less than 1500 g and lacks the clinical findings of hypotension and abdominal distension in NEC. In addition, this typically presents earlier.
- **Hirschsprung disease**, which is caused by the failure of ganglion cells to migrate to the bowel, can create an aperistaltic segment of bowel. This functional constipation can lead to bacterial overgrowth, and ultimately toxic megacolon and sepsis. It is diagnosed by barium enema and intestinal biopsy.
- **Malrotation with volvulus** can cause compression of mesenteric vessels, leading to intestinal necrosis - this is a surgical emergency. This diagnosis is made by an upper GI contrast study.
- **Anal fissures** are generally benign lesions that cause bloody stools and can be identified on physical exam

⁴ Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg.* 1978 Jan;187(1):1–7.

⁵ Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. *Semin Neonatol.* 2003 Dec;8(6):449–59.

- Other rare causes include bleeding disorders, vascular malformations, rectal polyps, and intussusception.^{3,6} Always remember to consider your differential based on the clinical situation and re-evaluate your diagnosis in light of new findings.

Management

Let's split management into nonpharmacologic, pharmacologic, and surgical.

Starting with non-pharmacologic measures, strict bowel rest is necessary: stop all enteral feeds and insert a nasogastric or orogastric tube for decompression. Obtain central IV access, generally with a peripherally inserted central catheter. IV fluids and parenteral nutrition will also be needed.^{2,3}

The pharmacologic management begins with broad spectrum antibiotics for 7 to 14 days as up to 30% of neonates develop bacteremia.⁷ There is no standard agent, but patients should be covered for gram-negative, gram-positives, and anaerobic pathogens. For patients with positive fungal cultures, or those who are deteriorating, antifungals may be added.²

Electrolyte abnormalities and metabolic acidosis should be addressed. In addition, patients may require respiratory support and intubation as lung expansion may be limited by abdominal distension. Fluids and vasopressors should be used to support blood pressure. Blood products should be used to address anemia, low platelets, or disseminated intravascular coagulation.³

Up to 50% of patients will require surgical management. There is only one absolute indication for surgical management: intestinal perforation, suggested by pneumoperitoneum on x-ray or paracentesis showing leaked enteric contents. Generally, surgical management is pursued if a patient is not improving or is deteriorating on medical management alone.^{3,7} There are two main forms of surgical management.

1. Insertion of an intra-abdominal drain is a bedside procedure performed with local anesthesia and may be used in patients too sick for laparotomy. This serves to relieve abdominal pressure and evaluation of contaminated ascitic fluid. Peritoneal fluid is cultured and the abdominal cavity is irrigated.⁷
2. Exploratory laparotomy may be pursued in patients with confirmed perforations or deterioration on medical therapy. This allows for identification and resection of full-thickness necrosed bowel, or identification of an alternate diagnosis. In some cases, a second look procedure is performed in 1-2 days. If bowel is removed, a proximal enterostomy is created, as well as a distal mucous fistula. At a later procedure, often in 4-6 weeks, a reanastomosis procedure is performed. If only a small area of bowel is affected, a primary anastomosis is performed.

⁶ Kim J. Neonatal necrotizing enterocolitis: Clinical features and diagnosis. In: UptoDate [Internet]. Waltham, MA.: UptoDate; 2018 [cited 2018 Aug 12].

⁷ Kim J. Neonatal necrotizing enterocolitis: Management. In: UptoDate [Internet]. Waltham, MA.: UptoDate; 2018 [cited 2018 Aug 12].

A Cochrane systematic review in 2011 looked at two randomized controlled trials and found no significant mortality differences between procedures. Nearly half of the patients in the drain group went on to need surgery.⁸ In other words, some patients do well with a drain, whereas others will go on to require a laparotomy for definitive management. Given that there is a paucity of research in this area, it is difficult to make firm recommendations for a treatment approach.

Complications

Despite medical and surgical therapy - or in some cases, *because* of these therapies, there are a number of complications that may follow NEC. Short gut syndrome may be seen in neonates who received surgical resections of necrotic tissue, or from impaired physiology secondary to the disease. NEC is the most common cause of short gut syndrome in children. Essentially, the remaining functional bowel is unable to meet the body's needs. Patients who survive NEC with short gut syndrome may be dependent on total parenteral nutrition for up to 2 years. Likely due to the increased disease severity, surgically managed patients may also suffer neurodevelopmental consequences in addition to those associated with prematurity alone.⁹ As with any intra-abdominal surgery, stricture formation and subsequent intestinal obstruction may also occur.³

Prevention

Lastly, we will discuss the prevention of NEC. The most obvious way would be to avoid a preterm delivery. In addition, the use of antenatal corticosteroids - administered before 34 weeks in imminent premature delivery - has been shown to be helpful, likely due to the beneficial effects on lung function and oxygenation.¹⁰ The use of both maternal and donor breast milk over formula has been shown to have some benefit in reducing NEC incidence.¹¹ A growing area of interest is the use of probiotics as primary prevention of NEC. It is thought that inappropriate colonization of the intestine by pathogens may promote the development of NEC,

⁸ Rao SC, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database of Systematic Reviews [Internet]. 2011 [cited 2018 Aug 12];(6). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006182.pub2/abstract>

⁹ Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2007 May;92(3):F193–8.

¹⁰ Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth - Roberts, D - 2006 | Cochrane Library [Internet]. [cited 2018 Aug 12]. Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004454.pub2/full>

¹¹ Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database of Systematic Reviews [Internet]. 2014 [cited 2018 Aug 12];(4). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002971.pub3/abstract>
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thus providing beneficial bacterial strains may be helpful.¹² A 2010 Cochrane review found that amongst nine studies, supplementation significantly reduced the incidence of severe NEC.¹³ At this time, however, the specifics of which probiotic organisms and the duration of treatment are unclear.

Summary

In summary, NEC is an illness seen primarily in enterally fed premature newborns. The diagnosis is made based on clinical findings, supported by abnormal lab results and characteristic findings on radiography. Management includes strict bowel rest and up to two weeks of broad spectrum antibiotic treatment. Patients with pneumoperitoneum or who continue to deteriorate may receive surgical therapy in the form of peritoneal drainage or exploratory laparotomy, and potential bowel resection. Long term consequences include short-gut syndrome, neurodevelopmental delays, and intestinal strictures. Although there is no clear way to prevent the development of NEC, save for avoiding preterm delivery if possible, the use of breast milk and probiotics may be helpful.

Thank you for listening I hope you have enhanced your knowledge of NEC!

¹² Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, et al. Oral Probiotics Prevent Necrotizing Enterocolitis in Very Low Birth Weight Neonates. *The Journal of Pediatrics*. 2005 Aug 1;147(2):192–6.

¹³ AlFaleh KM, Bassler D. Cochrane review: Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Evidence-Based Child Health: A Cochrane Review Journal*. 2010 Mar 1;5(1):339–68.