Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Infectious Causes of Necrotizing Enterocolitis

Sarah A. Coggins, BAa, James L. Wynn, MDb, Jörn-Hendrik Weitkamp, MDb,*

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common surgical emergency in premature infants, affecting approximately 7% of infants with less than 1500 g birth weights.1 Universally described risk factors include prematurity, aberrant microbial colonization, and lack of human milk feeding.2 NEC’s clinical presentation is nonspecific and can range from signs limited to the gastrointestinal (GI) tract (eg, feeding intolerance, ileus, abdominal distention, hematochezia) to catastrophic illness with multiorgan failure (eg, lethargy, apnea, metabolic acidosis, shock, disseminated intravascular coagulopathy) and death.3 Since its first mention in the medical

Disclosures: J.L. Wynn is supported by funding from the National Institutes of Health/National Institute of General Medical Sciences (NIH/NIGMS) GM106143. J.H. Weitkamp has been supported by award number K08HD061607 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NIH/NICHD), the Vanderbilt University Medical Center’s Digestive Disease Research Center sponsored by NIH grant P30DK058404 and CTSA award No. UL1TR000445 from the National Center for Advancing Translational Sciences (NCATS).

a Vanderbilt University School of Medicine, 2215 Garland Avenue, Nashville, TN 37232, USA; b Department of Pediatrics, Monroe Carell Jr. Children’s Hospital at Vanderbilt, Vanderbilt University, 2215 B Garland Avenue, 1125 MRB IV/Light Hall, Nashville, TN 37232, USA

* Corresponding author.

E-mail address: hendrik.weitkamp@vanderbilt.edu

Clin Perinatol 42 (2015) 133–154

http://dx.doi.org/10.1016/j.clp.2014.10.012 perinatology.theclinics.com

0095-5108/15/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
literature more than 150 years ago, NEC has stimulated intensive research in its
cause; despite seminal discoveries of epidemiologic and molecular risk factors
and pathways, the pathogenesis remains unclear.4 One reason for the lack in pro-
gress is inclusion of diseases closely resembling classic NEC as a complication of
preterm birth, such as spontaneous intestinal perforation (SIP), NEC in term infants,
cow-milk intolerance, and viral enteritis.5

The role of bacteria as significant contributors to NEC has been identified since the
first systematic descriptions of this disease.6,7 Pneumatosis intestinalis and portal
venous gas are pathognomonic radiographic signs of NEC8 and thought to be
caused by anaerobic bacteria, specifically clostridia.9 Gram-negative bacteria
have been most frequently associated with NEC, and the epithelial receptor and
innate immune sensor Toll-like receptor (TLR) 4 is elevated in the premature intestine
and required for the development of experimental NEC.10,11 NEC can occur in clus-
ters, and seasonal outbreaks of virus-associated NEC cases have been re-
ported.12–16 Here the authors attempted to summarize the main published data on
the role of microbes in NEC.

BACTERIA

Bacteria are clearly involved in the pathogenesis of NEC (Table 1); despite the paucity
of randomized control trials to determine the optimal antimicrobial regimen in prema-
ture infants, treatment with intravenous broad-spectrum antibiotics remains a main-
stay of the clinical management.17,18 However, many open questions remain,
including the role of specific bacterial overgrowth as the cause or the consequence
of NEC, timing of bacterial colonization during fetal/neonatal development, and
type of molecular interactions between different microbes and their host.19 Despite
the abundance of bacteria in the premature intestine early in life20 and the clinical
appearance of gram-negative sepsis, a positive blood culture is uncommon in infants
with NEC.21,22 This finding is surprising given the frequent growth of bacteria in peri-
toneal fluid.23 In 80 cases of NEC with intestinal perforation, Enterobacteriaceae were
present in the peritoneal fluid in 75% of cases, coagulase-negative Staphylococci

| Bacterial                  | Viral                      | Fungal                      |
|----------------------------|----------------------------|-----------------------------|
| *Clostridium* spp          | *Astrovirus*15,184,185      | *Candida* spp194,197–199    |
| *Butyricum*83–89           | *Cytomegalovirus*163–165   |                             |
| *Difficile*6,79,80         | *Coronavirus*167,168       |                             |
| *Perfringens*61–68         | *Coxackievirus* B2176,177  |                             |
| *Cronobacter (Enterobacter)* | *Echovirus*180            |                             |
| *sakazakii*91,101–103,105  | *Human immunodeficiency virus* (maternal exposure) 186–188 |
| *Enterococcus* (VRE)205    | *Norovirus*16,147,149,150  |                             |
| *Escherichia* coli22,114,116–119 | *Rotavirus*14,133–135      |                             |
| *Klebsiella* spp22,112–116 | *Torovirus*170,171         |                             |
| *Pseudomonas* aeruginosa123–125 |                        |                             |
| *Salmonella*206,207        |                             |                             |
| *Staphylococcus* aureus (MRSA)208 |                        |                             |
| *Staphylococcus* epidermidis118,212 |                        |                             |
| *Ureaplasma* urealyticum23,128,129 |                        |                             |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
(CoNS) in 14%, and anaerobes in 6%.\(^{23}\) Despite similar age at the time of intestinal perforation and similar mortality, the distribution of predominant organisms cultured from peritoneal fluid differed significantly between patients with NEC and SIP. *Candida* species (44%) and CoNS (50%) dominated samples from 36 patients with SIP.\(^{23}\) Specific bacteria have been suggested as important contributing factors in NEC,\(^{24,25}\) and NEC occurs typically after the first week post partum after the intestine has been colonized. In contrast, one study on human NEC samples using laser capture microdissection and subsequent sequencing combined with fluorescent in situ hybridization and bacterial rRNA-targeting oligonucleotide probes did not detect dominating potential pathogenic bacteria and suggested that NEC is a “non-infectious syndrome.”\(^9\)

Bacteria shape normal immune development including the development of T regulatory cells (Treg), which are critical for reducing inflammation-mediated injury.\(^{26–29}\) Another example is recruitment of intestinal intraepithelial lymphocytes (IEL) after microbial colonization of germ-free mice.\(^{30}\) IEL are reduced in human NEC suggesting that paucity of normal commensals in the newborn gut may alter intestinal immune development.\(^{31}\) Infectious complications of pregnancy, such as chorioamnionitis, increase the risk for NEC either by direct bacterial colonization or through the anatomic and immunologic changes following the inflammatory challenge of the developing intestine.\(^{25,32–36}\) Independent epidemiologic association between chorioamnionitis and NEC is difficult to prove, as chorioamnionitis is also the most important risk factor for prematurity and most severe NEC cases occur in extremely premature infants. However, after adjustment for antenatal steroid prophylaxis, gestational age, and surfactant treatment, the presence of intrauterine infection and the fetal inflammatory response syndrome (FIRS) remained independent predictors for NEC in several studies.\(^{32,33}\) Increased gastric neutrophil counts have been demonstrated in chorioamnionitis-exposed preterm infants, reflecting a proinflammatory state of the gut shortly after birth.\(^{37}\) Moreover, presence of microbes and inflammatory markers in the gut mirror that of the amniotic fluid when chorioamnionitis is present.\(^{38}\) Preterm labor and chorioamnionitis are also linked with abnormal intestinal development and fetal proliferation of activated T cells in the immature intestinal mucosa.\(^{35}\) At the same time, ileum Treg cell proportions are reduced in chorioamnionitis, whereas activated T effector cells are increased.\(^{39,40}\) Reduced Treg proportions in the small intestinal lamina propria characterize NEC in human disease and in animal models, suggesting the possibility of bacteria-induced fetal immune priming as a risk factor for NEC.\(^{41–43}\)

**Gram-Positive Bacteria**

The C-type lectin RegIII\(γ\) and its human counterpart, hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP), are antimicrobial proteins that bind peptidoglycan, a molecule that is exposed on the surface of gram-positive bacteria. RegIII\(γ\) expression is developmentally regulated and dependent on normal microbial ecology.\(^44\) Although the exact role and developmental regulation of HIP/PAP is unknown in human infants, lower levels, especially in preterm infants, could lead to aberrant intestinal colonization with gram-positive bacteria.

**Staphylococcus epidermidis**

Colonization of the maternal genital tract with *Staphylococcus* sp has been associated with a significantly increased risk for chorioamnionitis (odds ratio 18.4).\(^{33}\) The small intestine is colonized with staphylococci shortly after birth and in patients with or without NEC, specifically in infants delivered via cesarean section.\(^{20,45}\) CoNS were found to
preferentially translocate through the intestinal wall after ischemia-reperfusion injury in mice. Importantly, a lack of enteral nutrition and exposure to total parenteral nutrition alone reduce intestinal barrier function. CoNS are frequently cultured from postnatal stool samples and seem to increase the risk for NEC development.

**Clostridia species**

Clostridia are spore-forming anaerobic motile gram-positive rods. They can be found in soil and the human GI tract and can be considered part of the normal intestinal flora in newborns, especially premature infants exposed to the neonatal intensive care unit (NICU) environment and infants fed formula. Therefore, when isolated during disease, it is difficult to establish if they are pathogens or normal flora. However, patients with NEC with positive cultures for Clostridia spp have more extensive pneumatosis intestinalis, a higher incidence of portal venous gas, faster progression to more severe necrosis, and intestinal perforation with higher mortality. Clostridium spp were significantly more prevalent among samples from a preterm piglet model of NEC. Clostridia spp have been implicated in NEC for many years because the clinical presentation of diseases caused by these toxin-producing strains often resemble NEC. For example, pseudomembranous colitis as a result of overgrowth of *Clostridium difficile* in the colon can present with hematochezia and multiorgan failure. Enteritis necroticans, known as pigbel in Papua New Guinea, is a segmental necrotizing infection of the jejunum and ileum caused by *Clostridium perfringens*, type C.

**Clostridium perfringens**

*Clostridium perfringens* frequently colonizes the intestine of preterm infants within the first 2 weeks post partum. *Clostridium perfringens* types A to E form 12 different toxins: major toxins (eg, α-toxin = phospholipase C), collagenase, protease, hyaluronidase, deoxyribonuclease, enterotoxin, and neuraminidase. *Clostridium perfringens* α-toxin is produced by all 5 types of bacteria (A–E); increases capillary permeability; induces platelet aggregation, hemolysis, and myonecrosis; decreases cardiac contractility; and is lethal. *Clostridium perfringens* was identified as a causative agent of NEC in 22% of cases in one study. Compared with the control group (n = 32), the onset of disease was earlier in life, portal venous gas was more common (77%), the clinical course was more severe, and the mortality rate was more than twice as high (44%). Another study isolated *Clostridium perfringens* in patients with fatal outcomes and suggested it has the potential to trigger a fulminant and often lethal course. *Clostridium perfringens* has been declared as a possible risk factor for NEC as it was recognized by molecular techniques in the first 2 weeks post partum in 3 infants who later developed the disease. In one study, *Clostridium perfringens* was isolated from intestinal flora in 40% of infants with NEC compared with 13% of controls (P = .03) and has been associated with an NICU outbreak of NEC in another. *Clostridium perfringens* has also been associated with NEC in several animal models.

**Clostridium difficile**

*Clostridium difficile* is part of the commensal intestinal flora in humans but has recently attracted the attention of researchers because of its role as the most common cause of severe and refractory health care–associated diarrhea. After intestinal overgrowth following antimicrobial use, toxigenic strains can cause pseudomembranous colitis, ranging from mild diarrhea to fulminant colitis. *Clostridium difficile*’s 2 major toxins, *Clostridium difficile* toxin A (TcdA) and *Clostridium difficile* toxin B (TcdB), disrupt host cell function by inactivating small GTPases that regulate the actin cytoskeleton.
Both toxins can manifest disease on their own.\textsuperscript{71} During infancy, asymptomatic colonization with toxin-producing \textit{Clostridium difficile} is common and has been associated with changes in the intestinal microbiome composition.\textsuperscript{58,72–75} Delivery or exposure to human flora has no effect on colonization, and \textit{Clostridium difficile} originates from the NICU environment rather than maternal transmission.\textsuperscript{76,77} The involvement of \textit{Clostridium difficile} in NEC is controversial because toxin-producing \textit{Clostridium difficile} strains are not more frequently recovered in NEC.\textsuperscript{78} However, \textit{Clostridium difficile}–associated NEC cases have been described during a \textit{Clostridium difficile} outbreak.\textsuperscript{79,80}

\textit{Clostridium butyricum}
\textit{Clostridium butyricum} produces butyric acid through fermentation and a specific strain (MIYAIRI 588 strain of \textit{Clostridium butyricum}) is widely used as a probiotic in Asia.\textsuperscript{81} It can be isolated from soil, feces of healthy children and adults, as well as soured milk and cheeses. Type E can produce a neurotoxin and has been implicated in cases of botulism.\textsuperscript{82} Several reports state isolation of toxin-producing \textit{Clostridium butyricum} from peritoneal fluid, blood, and cerebrospinal fluid of patients with NEC.\textsuperscript{83} \textit{Clostridium butyricum} has been suggested as the primary cause of NEC in outbreak situations; but because of a lack of adequate controls, its primary role has been questioned.\textsuperscript{84,85} Isolation of \textit{Clostridium butyricum} in blood samples of infants with NEC may have resulted from mucosal breakdown and transmigration of these bacteria into the bloodstream.\textsuperscript{86} In a community analysis of bacteria found in tissue specimens from infants with NEC, the presence of \textit{Clostridium butyricum} and \textit{Clostridium parputrificum} highly correlated with histologic pneumatosis intestinalis.\textsuperscript{21} \textit{Clostridium butyricum} strains isolated from NEC cases can cause cecal lesions in animals with gas cysts, hemorrhagic ulceration, and necrosis.\textsuperscript{87–89} Lactose fermentation and production of butyric acid seem to be a prerequisite, and colonization with bifidobacterium was protective.\textsuperscript{67,90} Attachment of \textit{Clostridium butyricum} to the ileal mucosa has been associated with NEC in preterm, cesarean-derived, and formula-fed piglets.\textsuperscript{54}

\textbf{Gram-Negative Bacteria}

\textit{Cronobacter sakazakii}
With a reported incidence of one infection per 10,660 very low birth weight (VLBW, <1500 g) infants,\textsuperscript{91} \textit{Cronobacter sakazakii} (formerly \textit{Enterobacter sakazakii})\textsuperscript{92,93} infection is rare. \textit{Cronobacter sakazakii} has been isolated from powdered infant formula worldwide,\textsuperscript{94,95} and NICU outbreaks of invasive disease have been reported.\textsuperscript{96–100} Meningitis is the most prominent clinical manifestation,\textsuperscript{101} but outbreaks of NEC occurred in NICUs with isolation of \textit{Cronobacter sakazakii} from multiple patients’ body fluids and cans with powdered infant formula.\textsuperscript{102,103} \textit{Cronobacter sakazakii} is commonly found in soil, food items, and other environmental sources.\textsuperscript{104} Therefore, inappropriate hygiene practices including storage, temperature control, and hand, nipple, and bottle cleaning after powdered formula reconstitution may contribute to infection. Powdered formula is not a sterile product, and the World Health Organization recommends formula reconstitution with hot water (>70°C) (http://www.who.int/foodsafety/publications/micro/pif2007/en/).

\textit{Cronobacter sakazakii} binds to villi in the distal small intestine and can induce NEC from a direct toxic effect to gut epithelium in the rat pup model.\textsuperscript{105} \textit{Cronobacter sakazakii}’s best-characterized virulence factor, outer membrane protein A (\textit{ompA}), binds and invades human epithelial cells\textsuperscript{103} and brain endothelial cells,\textsuperscript{106–108} whereas its enterotoxin functions similarly to lipopolysaccharide (LPS) and modulates the activation of TLR 4.\textsuperscript{109} \textit{OmpA} also mediates recruitment of dendritic cells at the expense of
neutrophils and macrophages leading to epithelial injury through transforming growth factor-β production and iNOS activation.\textsuperscript{110,111}

**Klebsiella species**

*Klebsiella* sp have been described in NEC outbreaks with nosocomial origin.\textsuperscript{112,113} It is also one of the most common organisms responsible for bacteremia in NEC.\textsuperscript{22,114,115} A 1998 outbreak in Johannesburg was significant for isolation of a single clone of an extended-spectrum beta-lactamase–producing *Klebsiella* in blood cultures of patients with NEC, notable for sudden decompensation leading to shock and severe thrombocytopenia in all cases and for the absence of diarrhea or hematochezia.\textsuperscript{112}

**Escherichia coli**

*E. coli* is a similarly common organism found in normal gut flora; among infants with NEC, it has been isolated in blood in up to one-third of cases.\textsuperscript{22,114} Both *E. coli* and *Klebsiella* were isolated in feces at markedly higher rates in infants with NEC than those without.\textsuperscript{116} Several outbreaks of NEC associated with *E. coli* have been described.\textsuperscript{117,118} In one report, 15 of 16 infants with suspected or confirmed NEC had either enterotoxigenic *E. coli* or its heat-labile enterotoxin recovered in stool.\textsuperscript{118} A report of NEC associated with *E. coli* O157:H7 in a term infant resulted in death secondary to widespread intestinal necrosis.\textsuperscript{119}

**Pseudomonas**

*Pseudomonas* is well known for its role in nosocomial and immunocompromised infections. It forms biofilms and can colonize hard surfaces and respiratory equipment, with mechanical ventilation as a risk factor for infection. However, *Pseudomonas* also colonizes the GI tracts of 10% to 42% of newborns\textsuperscript{120,121} and 25% to 35% of normal adults.\textsuperscript{122} Among VLBW infants, it is primarily responsible for late-onset disease (sepsis, pneumonia, NEC). There are several reports of *Pseudomonas*-associated NEC. A Taiwanese study reports 45 infants with *Pseudomonas* in the stool, of whom one had NEC, 4 had colonic perforations, and 2 infants died of sepsis.\textsuperscript{123} Other studies noted an increased rate of NEC in infants with *Pseudomonas* bacteremia compared with nonbacteremic infants (36% vs 7%, respectively) and with it a much higher mortality rate (up to 50%), especially when signs of septic shock were present.\textsuperscript{124,125}

**Atypical Bacteria**

Unique in their lack of a cell wall, *Ureaplasma* are obligate intracellular mycoplasma that colonize human adult genital tracts. They may be vertically transmitted intrapartum, with nasopharyngeal colonization reported among 22% of NICU patients.\textsuperscript{126} Colonization is associated with chorioamnionitis,\textsuperscript{127} a known risk factor for NEC. However, the existence of a direct relationship between colonization with *Ureaplasma* and development of NEC is controversial. One study found a 2-fold increase in incidence of stage 2 or greater NEC associated with elevated interleukin (IL)-6 and IL-1 beta among infants colonized with *Ureaplasma* (12.3% vs 5.5%).\textsuperscript{25} Two other groups disagreed and found no increased incidence of NEC associated with *Ureaplasma* colonization.\textsuperscript{128,129}

**VIRUSES**

**Rotavirus**

A double-stranded DNA member of the Reovirus family, rotavirus causes GI disease by invading enterocytes and disrupting their absorptive and digestive activities.\textsuperscript{130} Fecal excretion of rotavirus can be found in up to half of infants in the newborn
Although most infants shed the virus asymptomatically, 8% to 30% of infants present with vomiting and diarrhea. Rotavirus infection tends to peak in the late winter/early spring, though introduction of a vaccine in young children has interrupted this seasonality. Several outbreaks of NEC have been associated with rotavirus infection with virus isolated from stool or serologic diagnosis and concomitant evidence of infection among a significant portion of NICU staff members. Risk factors for the development of serious GI disease included low birth weight and younger age. Notably, rotavirus-associated NEC has been found to cause less severe disease compared with NEC without rotavirus. Anatomic distinctions were also noted: left-sided, more distal colonic pneumatosis intestinalis in rotavirus NEC compared with right-sided, ileal pneumatosis in nonrotavirus NEC.

Norovirus (Norwalk virus), a nonenveloped positive-sense single-stranded RNA virus, is the most important cause of foodborne outbreaks of gastroenteritis and the second leading cause (after rotavirus) of gastroenteritis in young children. Both individual infections and outbreaks most commonly occur during winter. Seventeen percent of 75 premature infants less than 32 weeks’ gestation shed the virus in their stool over the first 4 weeks after admission in a NICU in Sydney. Norovirus prevalence was 1.9%, representing roughly half of all infants in that cohort who shed the virus. Controversy exists regarding the best methods for viral identification, with one report noting several norovirus-positive cases by enzyme-linked immunosorbent assay that were not corroborated by reverse transcription polymerase chain reaction or electron microscopy. The specificity of each aforementioned method is reportedly greater than 90%, and positivity in 2 of the 3 tests confirms norovirus infection. Norovirus has been thought to primarily affect the small intestine based on pathologic findings of villus blunting, crypt hypertrophy, and edema among adults infected with norovirus and mononuclear infiltrate and apoptosis in the jejunum and ileum of pediatric small bowel transplant recipients. However, a recent report described 3 premature infants with norovirus infections with radiographic evidence of extensive colonic pneumatosis and pathologic insult (fibrosis and hyperplastic vessels) limited to the colon. Apnea was noted as the primary presentation of norovirus infection in a preterm infant who subsequently developed watery diarrhea and positive stool cultures. Several small outbreaks associated with NEC have been described. The largest involved 8 cases of NEC with a 25% mortality rate and noted that, in comparison with nonoutbreak NEC cases, those associated with norovirus had significantly lower levels of neutrophil band forms. An outbreak of 8 cases of norovirus among premature infants was marked by abdominal distention, apnea, and increased gastric residuals. Vomiting and acute diarrhea were not predominant clinical features (27% and 0%, respectively), but one infant with proven norovirus developed NEC. A case-control study noted an increased prevalence of norovirus in stools of infants with NEC compared with non-NEC controls (40% vs 9%, respectively) and suggested an etiologic role of norovirus in the pathogenesis of NEC.

Cytomegalovirus (CMV), a double-stranded DNA herpesvirus, is well known to cause serious neonatal disease in its congenital form but has also been implicated in NEC. CMV transmission may occur via transplacental, intrapartum, or postpartum routes.
Rates of perinatal CMV infection in premature infants have been reported to be as high as 15% to 20%.\textsuperscript{151,152} Given their immunocompromised status, premature infants are at particular risk for postnatal infection from breast milk (transmission rates 5%–37%)\textsuperscript{153–155} or via transfused blood products.\textsuperscript{156–159} Among immunocompromised patients, CMV enteritis is common and marked by diarrhea, hematochezia, and toxic megacolon.\textsuperscript{160} In infants, however, CMV enteritis is unusual; the virus is a disputed player in the development of NEC. Patients may present with diarrhea or with disease resembling NEC but without distinguishing features, such as intestinal pneumatosis.\textsuperscript{161} However, several case reports linking confirmed cases of NEC to CMV infections have been reported, with clinical manifestations including abdominal compartment syndrome,\textsuperscript{162} viremia and sepsis,\textsuperscript{163} and colonic strictures.\textsuperscript{164} In one particularly severe case, fulminant NEC leading to death was associated with stool culture positive for CMV but with a notable reduction in diversity of bacterial flora, prompting speculation that intestinal CMV infection may predispose infants to NEC by altering intestinal immune responses and promoting secondary bacterial infection.\textsuperscript{165}

**Coronavirus (Torovirus)**

Coronaviruses are enveloped viruses with positive-sense RNA genomes that are known to cause respiratory\textsuperscript{166} and serious GI disease among infants.\textsuperscript{167,168} A coronavirus outbreak was associated with hemorrhagic NEC, and viral particles were visualized both in intestinal and fecal specimens.\textsuperscript{168} In another outbreak of NEC, coronavirus was detected in stool in 23 of 32 (72%) infants. Sixty percent of bedside nurses also shed the virus in stool, prompting speculation of nosocomial transmission.\textsuperscript{167} As members of the coronavirus family, toroviruses are a known agent of diarrhea in cattle and horses and have been associated with GI disease in children. Torovirus infections are known to occur year-round, with a substantial portion thought to be acquired nosocomially.\textsuperscript{169} Its association in neonatal disease was first described in 1982, when “virus-like particles” similar to coronavirus were detected in the stool of 80% of infants in an outbreak of bloody diarrhea, bilious gastric aspirates, and abdominal distention.\textsuperscript{170} Transmission was thought to be vertical because all but one mother had flulike or GI symptoms within 2 weeks of delivery, and viral particles were detected in meconium of several infants.\textsuperscript{170} One study reported the detection of torovirus in the stools of 48% of its patients with NEC and in 60% of those with stage III disease, although the presence or absence of torovirus did not affect mortality.\textsuperscript{171}

**Enteroviruses**

Enteroviruses are positive-sense, single-stranded RNA viruses encompassing multiple serotypes, including 2 specific viruses that have been associated with NEC: coxsackievirus and echovirus. These infections are seasonal, with most cases occurring during summer and fall.\textsuperscript{172–175} Among 27 infants with enterovirus, 3 had NEC marked by fevers, abdominal distention, and bloody diarrhea and one had coxsackievirus B and died following exploratory surgery revealing dusky jejunum.\textsuperscript{176} Another fatal case of NEC associated with widespread coxsackievirus B infection demonstrated ischemic ileum with subserosal hemorrhage; the child’s parents were both febrile at the time of birth.\textsuperscript{177} The clinical presentation of echovirus infection among premature infants ranges from asymptomatic to diarrheal illness\textsuperscript{178} to upper and lower respiratory tract infections.\textsuperscript{179} An outbreak of echovirus type 22 in a NICU resulted in a diarrheal illness among 12 premature infants, 6 (50%) of whom developed stage I NEC and one had pneumatosis intestinalis, but all survived.
Identification of echovirus was via stool culture in most infants, though a few only had increased serum antibody titers.\textsuperscript{180}

**Astrovirus**

As single-stranded RNA viruses, astroviruses were first described in infants during an outbreak of gastroenteritis in a newborn nursery.\textsuperscript{181} Few reports on the pathology of human astrovirus infection are available, but one study in a child following bone marrow transplant revealed villous blunting and inflammatory cell infiltrate in the duodenum and jejunum (not consistent with graft-versus-host disease).\textsuperscript{182} Alternatively, intestinal astrovirus infection in a turkey model leads to rearrangement of the actin cytoskeleton on ultrastructural examination and evidence of sodium malabsorption secondary to redistribution of sodium-hydrogen exchangers.\textsuperscript{183} There are multiple reports associating astrovirus with NEC.\textsuperscript{15,184,185} One report detected astrovirus in the stools of 6\% of infants with either gastroenteritis or NEC. Infants with astrovirus more frequently acquired NEC (9 of 14) than those with norovirus (1 of 8) or rotavirus (2 of 12).\textsuperscript{184} Compared with uninfected infants, those with astrovirus had increased hematochezia (54\% vs 15\%) and Bell stage II and III NEC (21\% vs 4\%).\textsuperscript{185}

**Human Immunodeficiency Virus**

One case-control study suggests that maternal human immunodeficiency virus (HIV) infection places premature infants at higher risk for the development of NEC (at a rate of 8.8\% vs 1.2\% in children of HIV-positive and HIV-negative mothers, respectively).\textsuperscript{186} Additional case reports describe development of NEC in 2 infants born to HIV-positive mothers; one infant also had trisomy 21.\textsuperscript{187,188} All HIV-positive mothers received antiretroviral drugs during pregnancy and/or labor, and all infants received antiretrovirals after birth; no infant was HIV positive. The investigators speculate that the reduced production of IL-12 and/or use of zidovudine may have predisposed infants of HIV-positive mothers to NEC.\textsuperscript{186}

**Fungi**

**Candida**

*Candida* is a classically dimorphic organism that produces both yeast and hyphal forms, though certain species differ slightly (*Candida glabrata* does not form hyphae, and *Candida parapsilosis* forms pseudohyphae). In VLBW infants, fungal colonization occurs in the first week of life at an estimated rate of 27\%, with *Candida* spp making up most of the organisms.\textsuperscript{189} *Candida albicans* is isolated in more than 60\% of cases of candidemia.\textsuperscript{190} Among the NICU population, the risk factors for both colonization and invasive disease include the use of central venous lines, intravenous lipids, and histamine H\textsubscript{2} receptor antagonists.\textsuperscript{191–193} It is unclear whether intestinal colonization with *Candida* spp is protective or a risk factor for NEC. In one study, none of 7 infants with NEC had viable fungal organisms detected in stool.\textsuperscript{194} Further complicating the picture is the frequent association of *Candida* with S.I.P.\textsuperscript{195,196} When *Candida* is linked to NEC, however, the results can be severe.\textsuperscript{197} 27\% of fatal cases of surgically treated NEC were associated with *Candida* sepsis, an outcome complicated by late diagnosis occurring either within 48 hours of death or at autopsy.\textsuperscript{198} On pathologic examination of 84 patients with NEC, yeast and pseudohyphae were detected in both the intestinal lumen and wall.\textsuperscript{199} Antifungal prophylaxis has been shown in a randomized controlled trial\textsuperscript{200} to have benefit in reducing both colonization and invasive disease\textsuperscript{201,202} but not NEC\textsuperscript{201} or overall mortality.\textsuperscript{203}
SUMMARY

NEC is a common and devastating problem for premature infants. Bacterial colonization seems to be a necessary but not sufficient contributor to NEC. Although intestinal pathogens may cause NEC-like illness in animal models or occasional clinical outbreaks, they are not detected in most cases of classic NEC. NEC outbreaks have been associated with clusters of viral GI infections, but the clinical presentation may vary and often affect the large intestine. Future studies are needed to determine the impact of host-specific GI tract microbial communities on the development of NEC.

Best practices

What is the current practice?

NEC

The guidelines of the Surgical Infection Society and the Infectious Diseases Society of America recommend fluid resuscitation, bowel decompression, antimicrobial therapy, and surgical intervention (laparotomy or drainage) if needed. Recommended antibiotics for complicated intra-abdominal infections in infants include combinations of ampicillin, gentamicin, and cefotaxime with or without anaerobic coverage with metronidazole, piperacillin-tazobactam, or meropenem. In spite of their frequent use, the safety and efficacy of various antimicrobial combination treatment strategies for NEC has not been established in randomized controlled trials. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee advises probiotics to decrease the incidence of NEC, and human milk should be used when possible. They conclude that there is a lack of evidence-based data to support definitive recommendations for the type of surgical treatment or length of antimicrobial therapy.

What changes in current practice are likely to improve outcomes?

Prevention of NEC is the most effective strategy because once the disease becomes clinically evident, a mucosal and systemic inflammatory cascade has already been activated and multiorgan injury is likely. For the same reasons, earlier diagnosis of NEC before clinical onset is an important goal.

Major recommendations

Medical management consists of bowel decompression, discontinuation of enteral feedings and medications, maintaining intravascular volume and electrolyte balance, and initiating broad-spectrum antibiotics based on known sensitivities of prevalent pathogens in the individual NICU. Typical regimens include ampicillin plus gentamicin to cover for common intestinal bacteria. Often the addition of a third antibiotic that provides more targeted anaerobic coverage (eg, clindamycin or metronidazole) is indicated when there is evidence of pneumatosis or bowel perforation. As an alternative, piperacillin-tazobactam may offer the advantage of broad-spectrum antimicrobial coverage including typical anaerobes of the intestinal flora. However, downsides are variable penetration into the cerebrospinal fluid and concerns for the emergence of drug resistance. Second-line therapy for severely ill infants can include meropenem and vancomycin in cases of positive cultures with resistant organisms, possible central nervous system infection, perforated bowel, and/or failed first-line or alternative therapy. Almost all of the drugs mentioned do not have a Food and Drug Administration label for use in this population because safety and efficacy data are lacking. Supportive management may require respiratory and blood pressure support and correcting anemia and thrombocytopenia and/or other coagulation defects. Serial abdominal radiographs are often recommended to monitor for intestinal pneumatosis, portal venous gas, and pneumoperitoneum. Early consultation with a pediatric surgeon is advised. Intestinal perforation or evidence of bowel necrosis is a common indication for operative management.

As a preventive measure, a more consistent practice style including the implementation of early...
breast milk feedings, standardized feeding regimens, and reduction of unnecessary antibiotics is recommended.

Clinical algorithms

The management of patients with NEC (medical and/or surgical) can be guided by Bell staging criteria as reported recently by Sharma and Hudak⁵¹¹ (Fig. 1).

Rating for the strength of the evidence

C (Recommendation based on consensus, usual practice, expert opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening)

Summary statement

NEC is a multifactorial disease, but bacteria and other microorganisms have been uniformly implicated somewhere along the pathogenic process. Because no specific microorganism can be considered causative in most cases of NEC, broad-spectrum antimicrobial therapy remains a mainstay in NEC treatment. More research is needed to determine the optimum therapy and to develop effective strategies for NEC prevention.

Data from Refs. ¹⁷, ¹⁸, ²⁰⁹–²¹¹

---

**Fig. 1.** Clinical decision algorithms. CBC, complete blood cell count; CRP, C-reactive protein; NPO, nil per os (nothing by mouth). (Adapted from Sharma R, Hudak ML. A clinical perspective of necrotizing enterocolitis: past, present, and future. Clin Perinatol 2013;40(1):27–51.)
REFERENCES

1. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001;107(1):E1.

2. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med 2011;364(3):255–64.

3. Kanto WP Jr, Hunter JE, Stoll BJ. Recognition and medical management of necrotizing enterocolitis. Clin Perinatol 1994;21(2):335–46.

4. Obladen M. Necrotizing enterocolitis—150 years of fruitless search for the cause. Neonatology 2009;96(4):203–10.

5. Gordon PV, Swanson JR, Attridge JT, et al. Emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell’s criteria? J Perinatol 2007;27(11):661–71.

6. Berdon WE, Grossman H, Baker DH, et al. Necrotizing enterocolitis in the premature infant. Radiology 1964;83:879–87.

7. Willi H. Über eine bösartige Enteritis bei Säuglingen des ersten Trimenons. Ann Pediatr 1944;162:87–112.

8. Buonomo C. The radiology of necrotizing enterocolitis. Radiol Clin North Am 1999;37(6):1187–98, vii.

9. Smith B, Bode S, Petersen BL, et al. Community analysis of bacteria colonizing intestinal tissue of neonates with necrotizing enterocolitis. BMC Microbiol 2011;11:73.

10. Leaphart CL, Cavallo J, Gribar SC, et al. A critical role for TLR4 in the pathogenesis of necrotizing enterocolitis by modulating intestinal injury and repair. J Immunol 2007;179(7):4808–20.

11. Neal MD, Sodhi CP, Dyer M, et al. A critical role for TLR4 induction of autophagy in the regulation of enterocyte migration and the pathogenesis of necrotizing enterocolitis. J Immunol 2013;190(7):3541–51.

12. Snyder CL, Hall M, Sharma V, et al. Seasonal variation in the incidence of necrotizing enterocolitis. Pediatr Surg Int 2010;26(9):895–8.

13. Meinzen-Derr J, Morrow AL, Hornung RW, et al. Epidemiology of necrotizing enterocolitis temporal clustering in two neonatology practices. J Pediatr 2009;154(5):656–61.

14. Sharma R, Garrison RD, Tepas JJ 3rd, et al. Rotavirus-associated necrotizing enterocolitis: an insight into a potentially preventable disease? J Pediatr Surg 2004;39(3):453–7.

15. Bagci S, Eis-Hubinger AM, Franz AR, et al. Detection of astrovirus in premature infants with necrotizing enterocolitis. Pediatr Infect Dis J 2008;27(4):347–50.

16. Stuart RL, Tan K, Mahar JE, et al. An outbreak of necrotizing enterocolitis associated with norovirus genotype GII.3. Pediatr Infect Dis J 2010;29(7):644–7.

17. Bell MJ, Ternberg JL, Bower RJ. The microbial flora and antimicrobial therapy of neonatal peritonitis. J Pediatr Surg 1980;15(4):569–73.

18. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50(2):133–64.

19. Cliebong MS, Boye M, Sangild PT. Bacterial colonization and gut development in preterm neonates. Early Hum Dev 2012;88(Suppl 1):S41–9.

20. Romano-Keeler J, Moore DJ, Wang C, et al. Early life establishment of sitespecific microbial communities in the gut. Gut Microbes 2014;5(2):192–201.
21. Clark RH, Gordon P, Walker WM, et al. Characteristics of patients who die of necrotizing enterocolitis. J Perinatol 2012;32(3):199–204.

22. Bizzarro MJ, Ehrenkranz RA, Gallagher PG. Concurrent bloodstream infections in infants with necrotizing enterocolitis. J Pediatr 2014;164(1):61–6.

23. Mollett DL, Tepas JJ 3rd, Talbert JL. The microbiology of neonatal peritonitis. Arch Surg 1988;123(2):176–9.

24. Mollett DL, Tepas JJ, Talbert JL. The role of coagulase-negative Staphylococcus in neonatal necrotizing enterocolitis. J Pediatr Surg 1988;23(1 Pt 2):60–3.

25. Okogbule-Wonodi AC, Gross GW, Sun CC, et al. Necrotizing enterocolitis is associated with ureaplasma colonization in preterm infants. Pediatr Res 2011;69(5 Pt 1):442–7.

26. Matsumoto S, Setoyama H, Umesaki Y. Differential induction of major histocompatibility complex molecules on mouse intestine by bacterial colonization. Gastroenterology 1992;103(6):1777–82.

27. Mazmanian SK, Liu CH, Tzianabos AO, et al. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 2005;122(1):107–18.

28. Hooper LV, Litman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012;336(6086):1268–73.

29. O’Mahony C, Scully P, O’Mahony D, et al. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-kappaB activation. PLoS Pathog 2008;4(8):e1000112.

30. Imaoka A, Matsumoto S, Setoyama H, et al. Proliferative recruitment of intestinal intraepithelial lymphocytes after microbial colonization of germ-free mice. Eur J Immunol 1996;26(4):945–8.

31. Weitkamp JH, Rosen MJ, Zhao Z, et al. Small intestinal intraepithelial TCRgamma-delta T lymphocytes are present in the premature intestine but selectively reduced in surgical necrotizing enterocolitis. PLoS One 2014;9(6):e99042.

32. Lau J, Magee F, Qiu Z, et al. Chorioamnionitis with a fetal inflammatory response is associated with higher neonatal mortality, morbidity, and resource use than chorioamnionitis displaying a maternal inflammatory response only. Am J Obstet Gynecol 2005;193(3 Pt 1):708–13.

33. Seliga-Siwecka JP, Kornacka MK. Neonatal outcome of preterm infants born to mothers with abnormal genital tract colonisation and chorioamnionitis: a cohort study. Early Hum Dev 2013;89(5):271–5.

34. Been JV, Lievense S, Zimmermann LJ, et al. Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. J Pediatr 2013;162(2):236–42.e2.

35. Wolfs TG, Buurman WA, Zoer B, et al. Endotoxin induced chorioamnionitis prevents intestinal development during gestation in fetal sheep. PLoS One 2009;4(6):e5837.

36. Wolfs TG, Kallapur SG, Knox CL, et al. Antenatal ureaplasma infection impairs development of the fetal ovine gut in an IL-1-dependent manner. Mucosal Immunol 2013;6(3):547–56.

37. Arnon S, Grigg J, Silverman M. Association between pulmonary and gastric inflammatory cells on the first day of life in preterm infants. Pediatr Pulmonol 1993;16(1):59–61.

38. Miralles R, Hodge R, McParland PC, et al. Relationship between antenatal inflammation and antenatal infection identified by detection of microbial genes by polymerase chain reaction. Pediatr Res 2005;57(4):570–7.

39. Luciano AA, Yu H, Jackson LW, et al. Preterm labor and chorioamnionitis are associated with neonatal T cell activation. PLoS One 2011;6(2):e16698.

Infectious Causes of Necrotizing Enterocolitis 145
40. Wolfs TG, Kallapur SG, Polglase GR, et al. IL-1alpha mediated chorioamnionitis induces depletion of FoxP3+ cells and ileal inflammation in the ovine fetal gut. PLoS One 2011;6(3):e18355.

41. Weitkamp JH, Rudzinski E, Koyama T, et al. Ontogeny of FOXP3(+) regulatory T cells in the postnatal human small intestinal and large intestinal lamina propria. Pediatr Dev Pathol 2009;12(6):443–9.

42. Weitkamp JH, Koyama T, Rock MT, et al. Necrotising enterocolitis is characterised by disrupted immune regulation and diminished mucosal regulatory (FOXP3)/effector (CD4, CD8) T cell ratios. Gut 2013;62(1):73–82.

43. Dingle BM, Liu Y, Fatheree NY, et al. FoxP3(+) regulatory T cells attenuate experimental necrotizing enterocolitis. PLoS One 2013;8(12):e82963.

44. Cash HL, Whitham CV, Behrendt CL, et al. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. Science 2006;313(5790):1126–30.

45. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107(26):11971–5.

46. Luo CC, Shih HH, Chiu CH, et al. Translocation of coagulase-negative bacterial staphylococci in rats following intestinal ischemia-reperfusion injury. Biol Neonate 2004;85(3):151–4.

47. Kansagra K, Stoll B, Rognerud C, et al. Total parenteral nutrition adversely affects gut barrier function in neonatal piglets. Am J Physiol Gastrointest Liver Physiol 2003;285(6):G1162–70.

48. Stewart CJ, Marrs EC, Magorrian S, et al. The preterm gut microbiota: changes associated with necrotizing enterocolitis and infection. Acta Paediatr 2012;101(11):1121–7.

49. Ferraris L, Butel MJ, Campeotto F, et al. Clostridia in premature neonates’ gut: incidence, antibiotic susceptibility, and perinatal determinants influencing colonization. PLoS One 2012;7(1):e30594.

50. Stark PL, Lee A. Clostridia isolated from the feces of infants during the first year of life. J Pediatr 1982;100(3):362–5.

51. Alfa MJ, Robson D, Davi M, et al. An outbreak of necrotizing enterocolitis associated with a novel clostridium species in a neonatal intensive care unit. Clin Infect Dis 2002;35(Suppl 1):S101–5.

52. Kosloske AM, Ulrich JA. A bacteriologic basis for the clinical presentations of necrotizing enterocolitis. J Pediatr Surg 1980;15(4):558–64.

53. Kosloske AM, Ulrich JA, Hoffman H. Fulminant necrotising enterocolitis associated with Clostridia. Lancet 1978;2(8098):1014–6.

54. Azcarate-Peril MA, Foster DM, Cadenas MB, et al. Acute necrotizing enterocolitis of preterm piglets is characterized by dysbiosis of ileal mucosa-associated bacteria. Gut Microbes 2011;2(4):234–43.

55. Singer DB, Cashore WJ, Widness JA, et al. Pseudomembranous colitis in a preterm neonate. J Pediatr Gastroenterol Nutr 1986;5(2):318–20.

56. Lallouette P, Bizzini B, Maro B, et al. Studies on the immunostimulating and anti-tumour activity of a fraction isolated from Corynebacterium granulosum. Dev Biol Stand 1977;38:111–3.

57. Petrillo TM, Beck-Sague CM, Songer JG, et al. Enteritis necroticans (pigbel) in a diabetic child. N Engl J Med 2000;342(17):1250–3.

58. Blakey JL, Lubitz L, Barnes GL, et al. Development of gut colonisation in preterm neonates. J Med Microbiol 1982;15(4):519–29.

59. McDonel JL. Clostridium perfringens toxins (type A, B, C, D, E). Pharmacol Ther 1980;10(3):617–55.
60. Flores-Diaz M, Alape-Giron A. Role of Clostridium perfringens phospholipase C in the pathogenesis of gas gangrene. Toxicon 2003;42(8):979–86.

61. Dittmar E, Beyer P, Fischer D, et al. Necrotizing enterocolitis of the neonate with Clostridium perfringens: diagnosis, clinical course, and role of alpha toxin. Eur J Pediatr 2003;167(8):891–5.

62. Schlapbach LJ, Ahrens O, Klimek P, et al. Clostridium perfringens and necrotizing enterocolitis. J Pediatr 2010;157(1):175.

63. de la Cochetiere MF, Piloquet H, des Robert C, et al. Early intestinal bacterial colonization and necrotizing enterocolitis in premature infants: the putative role of Clostridium. Pediatr Res 2004;56(3):366–70.

64. Blakey JL, Lubitz L, Campbell NT, et al. Enteric colonization in sporadic neonatal necrotizing enterocolitis. J Pediatr Gastroenterol Nutr 1985;4(4):591–5.

65. Kotsanas D, Carson JA, Awad MM, et al. Novel use of tryptose sulfite cycloserine egg yolk agar for isolation of Clostridium perfringens during an outbreak of necrotizing enterocolitis in a neonatal unit. J Clin Microbiol 2010;48(11):4263–5.

66. Miyakawa ME, Saputo J, Leger JS, et al. Necrotizing enterocolitis and death in a goat kid associated with enterotoxin (CPE)-producing Clostridium perfringens type A. Can Vet J 2007;48(12):1266–9.

67. Waligora-Dupriet AJ, Dugay A, Auzeil N, et al. Evidence for clostridial implication in necrotizing enterocolitis through bacterial fermentation in a gnotobiotic quail model. Pediatr Res 2005;58(4):629–35.

68. Cilieborg MS, Boye M, Molbak L, et al. Preterm birth and necrotizing enterocolitis alter gut colonization in pigs. Pediatr Res 2011;69(1):10–6.

69. Dubberke ER, Butler AM, Yokoe DS, et al. Multicenter study of Clostridium difficile infection rates from 2000 to 2006. Infect Control Hosp Epidemiol 2010;31(10):1030–7.

70. Pruitt RN, Lacy DB. Toward a structural understanding of Clostridium difficile toxins A and B. Front Cell Infect Microbiol 2012;2:28.

71. Kuehne SA, Cartman ST, Heap JT, et al. The role of toxin A and toxin B in Clostridium difficile infection. Nature 2010;467(7316):711–3.

72. Jacquot A, Neveu D, Aujoulat F, et al. Dynamics and clinical evolution of bacterial gut microflora in extremely premature patients. J Pediatr 2011;158(3):390–6.

73. Chang JY, Shin SM, Chun J, et al. Pyrosequencing-based molecular monitoring of the intestinal bacterial colonization in preterm infants. J Pediatr Gastroenterol Nutr 2011;53(5):512–9.

74. Rousseau C, Levenez F, Fouqueray C, et al. Clostridium difficile colonization in early infancy is accompanied by changes in intestinal microbiota composition. J Clin Microbiol 2011;49(3):858–65.

75. Donta ST, Myers MG. Clostridium difficile toxin in asymptomatic neonates. J Pediatr 1982;100(3):431–4.

76. Al-Jumaili IJ, Shibley M, Lishman AH, et al. Incidence and origin of Clostridium difficile in neonates. J Clin Microbiol 1984;19(1):77–8.

77. el-Mohandes AE, Keiser JF, Refat M, et al. Prevalence and toxigenicity of Clostridium difficile isolates in fecal microflora of preterm infants in the intensive care nursery. Biol Neonate 1993;63(4):225–9.

78. Lishman AH, Al Jumaili IJ, Elshibly E, et al. Clostridium difficile isolation in neonates in a special care unit. Lack of correlation with necrotizing enterocolitis. Scand J Gastroenterol 1984;19(3):441–4.

79. Han VK, Sayed H, Chance GW, et al. An outbreak of Clostridium difficile necrotizing enterocolitis: a case for oral vancomycin therapy? Pediatrics 1983;71(6):935–41.
80. Mathew OP, Bhatia JS, Richardson CJ. An outbreak of Clostridium difficile necrotizing enterocolitis. Pediatrics 1984;73(2):265–6.

81. Seki H, Shiohara M, Matsumura T, et al. Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI. Pediatr Int 2003;45(1):86–90.

82. McCroskey LM, Hatheway CL, Fenicia L, et al. Characterization of an organism that produces type E botulinal toxin but which resembles Clostridium butyricum from the feces of an infant with type E botulism. J Clin Microbiol 1986;23(1):201–2.

83. Sturm R, Staneck JL, Stauffer LR, et al. Neonatal necrotizing enterocolitis associated with penicillin-resistant, toxigenic Clostridium butyricum. Pediatrics 1980;66(6):928–31.

84. Howard FM, Flynn DM, Bradley JM, et al. Outbreak of necrotising enterocolitis caused by Clostridium butyricum. Lancet 1977;2(8048):1099–102.

85. Gotheffors L, Blenkharn I. Clostridium butyricum and necrotising enterocolitis. Lancet 1978;1(8054):52–3.

86. Mitchell RG, Etches PC, Day DG. Non-toxigenic clostridia in babies. J Clin Pathol 1981;34(2):217–20.

87. Popoff MR, Ravispe P. Lesions produced by Clostridium butyricum strain CB 1002 in ligated intestinal loops in guinea pigs. J Med Microbiol 1985;19(3):351–7.

88. Popoff MR, Szylit O, Ravispe P, et al. Experimental cecitis in gnotoxicen chickens monoassociated with Clostridium butyricum strains isolated from patients with neonatal necrotizing enterocolitis. Infect Immun 1985;47(3):697–703.

89. Bousseboua H, Le Coz Y, Dabard J, et al. Experimental cecitis in gnotobiotic quails monoassociated with Clostridium butyricum strains isolated from patients with neonatal necrotizing enterocolitis and from healthy newborns. Infect Immun 1989;57(3):932–6.

90. Butel MJ, Roland N, Hibert A, et al. Clostridial pathogenicity in experimental necrotising enterocolitis in gnotobiotic quails and protective role of bifidobacteria. J Med Microbiol 1998;47(5):391–9.

91. Stoll BJ, Hansen N, Fanaroff AA, et al. Enterobacter sakazakii is a rare cause of neonatal septicemia or meningitis in VLBW infants. J Pediatr 2004;144(6):821–3.

92. Machens HG, Ringe B, Ziemer G, et al. A new procedure for abdominal wound closure after pediatric liver transplantation: the “sandwich” technique. Surgery 1994;115(2):255–6.

93. Kucerova E, Clifton SW, Xia XQ, et al. Genome sequence of Cronobacter sakazakii BAA-894 and comparative genomic hybridization analysis with other Cronobacter species. PLoS One 2010;5(3):e9556.

94. Muytjens HL, Roelofs-Willemse H, Jaspar GH. Quality of powdered substitutes for breast milk with regard to members of the family Enterobacteriaceae. J Clin Microbiol 1988;26(4):743–6.

95. Chap J, Jackson P, Siqueira R, et al. International survey of Cronobacter sakazakii and other Cronobacter spp. in follow up formulas and infant foods. Int J Food Microbiol 2009;136(2):185–8.

96. Hoque A, Ahmed T, Shahidullah M, et al. Isolation and molecular identification of Cronobacter spp. from powdered infant formula (PIF) in Bangladesh. Int J Food Microbiol 2010;142(3):375–8.

97. Weir E. Powdered infant formula and fatal infection with Enterobacter sakazakii. CMAJ 2002;166(12):1570.

98. Ahmed SM, Lopman BA, Levy K. A systematic review and meta-analysis of the global seasonality of norovirus. PLoS One 2013;8(10):e75922.
99. Bar-Oz B, Preminger A, Peleg O, et al. Enterobacter sakazakii infection in the newborn. Acta Paediatr 2001;90(3):356–8.
100. Clark NC, Hill BC, O’Hara CM, et al. Epidemiologic typing of Enterobacter sakazakii in two neonatal nosocomial outbreaks. Diagn Microbiol Infect Dis 1990;13(6):467–72.
101. Urmenyi AM, Franklin AW. Neonatal death from pigmented coliform infection. Lancet 1961;1(7172):313–5.
102. van Acker J, de Smet F, Muyldermans G, et al. Outbreak of necrotizing enterocolitis associated with Enterobacter sakazakii in powdered milk formula. J Clin Microbiol 2001;39(1):293–7.
103. Townsend S, Hurrell E, Forsythe S. Virulence studies of Enterobacter sakazakii isolates associated with a neonatal intensive care unit outbreak. BMC Microbiol 2008;8:64.
104. Hunter CJ, Bean JF. Cronobacter: an emerging opportunistic pathogen associated with neonatal meningitis, sepsis and necrotizing enterocolitis. J Perinatol 2013;33(8):581–5.
105. Hunter CJ, Singamsetty VK, Chokshi NK, et al. Enterobacter sakazakii enhances epithelial cell injury by inducing apoptosis in a rat model of necrotizing enterocolitis. J Infect Dis 2008;198(4):586–93.
106. Singamsetty VK, Wang Y, Shimada H, et al. Outer membrane protein A expression in Enterobacter sakazakii is required to induce microtubule condensation in human brain microvascular endothelial cells for invasion. Microb Pathog 2008;45(3):181–91.
107. Nair MK, Venkitanarayanan K, Silbart LK, et al. Outer membrane protein A (OmpA) of Cronobacter sakazakii binds fibronectin and contributes to invasion of human brain microvascular endothelial cells. Foodborne Pathog Dis 2009;6(4):495–501.
108. Bensasson M, Perez-Busquier M, Dorfmann H, et al. Special radiographic features of the hand in patients with articular chondrocalcinosis. A controlled study. Ann Radiol (Paris) 1975;18(7):701–10.
109. Pagotto FJ, Nazarowec-White M, Bidawid S, et al. Enterobacter sakazakii: infectivity and enterotoxin production in vitro and in vivo. J Food Prot 2003;66(3):370–5.
110. Emami CN, Mittal R, Wang L, et al. Recruitment of dendritic cells is responsible for intestinal epithelial damage in the pathogenesis of necrotizing enterocolitis by Cronobacter sakazakii. J Immunol 2011;186(12):7067–79.
111. Emami CN, Mittal R, Wang L, et al. Role of neutrophils and macrophages in the pathogenesis of necrotizing enterocolitis caused by Cronobacter sakazakii. J Surg Res 2012;172(1):18–28.
112. Gregersen N, Van Nierop W, Von Gottberg A, et al. Klebsiella pneumoniae with extended spectrum beta-lactamase activity associated with a necrotizing enterocolitis outbreak. Pediatr Infect Dis J 1999;18(11):963–7.
113. Hill HR, Hunt CE, Matsen JM. Nosocomial colonization with Klebsiella, type 26, in a neonatal intensive-care unit associated with an outbreak of sepsis, meningitis, and necrotizing enterocolitis. J Pediatr 1974;85(3):415–9.
114. Boccia D, Stolfi I, Lana S, et al. Nosocomial necrotising enterocolitis outbreaks: epidemiology and control measures. Eur J Pediatr 2001;160(6):385–91.
115. Stone HH, Kolb LD, Geheber CE. Bacteriologic considerations in perforated necrotizing enterocolitis. South Med J 1979;72(12):1540–4.
116. Bell MJ, Feigin RD, Ternberg JL, et al. Evaluation of gastrointestinal microflora in necrotizing enterocolitis. J Pediatr 1978;92(4):589–92.
117. Speer ME, Taber LH, Yow MD, et al. Fulminant neonatal sepsis and necrotizing enterocolitis associated with a “nonenteropathogenic” strain of Escherichia coli. J Pediatr 1976;89(1):91–5.
118. Cushing AH. Necrotizing enterocolitis with Escherichia coli heat-labile enterotoxin. Pediatrics 1983;71(4):626–30.
119. Guner YS, Malhotra A, Ford HR, et al. Association of Escherichia coli O157:H7 with necrotizing enterocolitis in a full-term infant. Pediatr Surg Int 2009;25(5):459–63.
120. Borderon E, Thieffry JC, Jamet O, et al. Observations on the intestinal colonization by Pseudomonas aeruginosa in newborns. Biol Neonate 1990;57(2):88–97.
121. Jefferies JM, Cooper T, Yam T, et al. Pseudomonas aeruginosa outbreaks in the neonatal intensive care unit—a systematic review of risk factors and environmental sources. J Med Microbiol 2012;61(Pt 8):1052–61.
122. Olson B, Weinstein RA, Nathan C, et al. Epidemiology of endemic Pseudomonas aeruginosa: why infection control efforts have failed. J Infect Dis 1984;150(6):808–16.
123. Cheng YL, Lee HC, Yeung CY, et al. Clinical significance in previously healthy children of Pseudomonas aeruginosa in the stool. Pediatr Neonatol 2009;50(1):13–7.
124. Henderson A, Maclaurin J, Scott JM. Pseudomonas in a Glasgow baby unit. Lancet 1969;2(7615):316–7.
125. Leigh L, Stoll BJ, Rahman M, et al. Pseudomonas aeruginosa infection in very low birth weight infants: a case-control study. Pediatr Infect Dis J 1995;14(5):367–71.
126. Rudd PT, Carrington D. A prospective study of chlamydial, mycoplasmal, and viral infections in a neonatal intensive care unit. Arch Dis Child 1984;59(2):120–5.
127. Shurin PA, Alpert S, Bernard Rosner BA, et al. Chorioamnionitis and colonization of the newborn infant with genital mycoplasmas. N Engl J Med 1975;293(1):5–8.
128. Ozdemir R, Erdeve O, Yurttutan S, et al. Letter to the editor Re: Okogbule-Wonodi et al. Pediatr Res 69:442–447. Pediatr Res 2011;70(4):423–4 [author reply: 424].
129. Perzigian RW, Adams JT, Weiner GM, et al. Ureaplasma urealyticum and chronic lung disease in very low birth weight infants during the exogenous surfactant era. Pediatr Infect Dis J 1998;17(7):620–5.
130. Cox E, Christenson JC. Rotavirus. Pediatr Rev 2012;33(10):439–45 [quiz: 446–7].
131. Murphy AM, Albrey MB, Crewe EB. Rotavirus infections of neonates. Lancet 1977;2(8049):1149–50.
132. Chrystie IL, Totterdell BM, Banatvala JE. Asymptomatic endemic rotavirus infections in the newborn. Lancet 1978;1(8075):1176–8.
133. Rotbart HA, Nelson WL, Glode MP, et al. Neonatal rotavirus-associated necrotizing enterocolitis: case control study and prospective surveillance during an outbreak. J Pediatr 1988;112(1):87–93.
134. Rotbart HA, Levin MJ, Yolken RH, et al. An outbreak of rotavirus-associated neonatal necrotizing enterocolitis. J Pediatr 1983;103(3):454–9.
135. Keller KM, Schmidt H, Wirth S, et al. Differences in the clinical and radiologic patterns of rotavirus and non-rotavirus necrotizing enterocolitis. Pediatr Infect Dis J 1991;10(10):734–8.
136. Jiang X, Wang M, Wang K, et al. Sequence and genomic organization of Norwalk virus. Virology 1993;195(1):51–61.
137. Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis 2011;17(1):7–15.
138. Widdowson MA, Sulk A, Bulens SN, et al. Norovirus and foodborne disease, United States, 1991–2000. Emerg Infect Dis 2005;11(1):95–102.
139. Patel MM, Widdowson MA, Glass RI, et al. Systematic literature review of role of noroviruses in sporadic gastroenteritis. Emerg Infect Dis 2008;14(8):1224–31.
140. Naing Z, Rayner B, Killikullangara A, et al. Prevalence of viruses in stool of premature neonates at a neonatal intensive care unit. J Paediatr Child Health 2013;49(3):E221–6.
141. Wiechers C, Bissinger AL, Hamprecht K, et al. Apparently non-specific results found using a norovirus antigen immunoassay for fecal specimens from neonates. J Perinatol 2008;28(1):79–81.
142. Rabenau HF, Sturmer M, Buxbaum S, et al. Laboratory diagnosis of norovirus: which method is the best? Intervirology 2003;46(4):232–8.
143. Agus SG, Dolin R, Wyatt RG, et al. Acute infectious nonbacterial gastroenteritis: intestinal histopathology. Histologic and enzymatic alterations during illness produced by the Norwalk agent in man. Ann Intern Med 1973;79(1):18–25.
144. Schreiber DS, Blacklow NR, Trier JS. The mucosal lesion of the proximal small intestine in acute infectious nonbacterial gastroenteritis. N Engl J Med 1973;288(25):1318–23.
145. Dolin R, Levy AG, Wyatt RG, et al. Viral gastroenteritis induced by the Hawaii agent. Jejunal histopathology and serologic response. Am J Med 1975;59(6):761–8.
146. Morotti RA, Kaufman SS, Fishbein TM, et al. Calicivirus infection in pediatric small intestine transplant recipients: pathological considerations. Hum Pathol 2004;35(10):1236–40.
147. Pelizzo G, Nakib G, Goruppi I, et al. Isolated colon ischemia with norovirus infection in preterm babies: a case series. J Med Case Rep 2013;7(1):108.
148. Kamaluddeen M, Lodha A, Akierman A. Non-Rotavirus infection causing apnea in a neonate. Indian J Pediatr 2009;76(10):1051–2.
149. Turcios-Ruiz RM, Axelrod P, St John K, et al. Outbreak of necrotizing enterocolitis caused by norovirus in a neonatal intensive care unit. J Pediatr 2008;153(3):339–44.
150. Armbrust S, Kramer A, Olbertz D, et al. Norovirus infections in preterm infants: wide variety of clinical courses. BMC Res Notes 2009;2:96.
151. Mussi-Pinhata MM, Yamamoto Ay, do Carmo Rego MA, et al. Perinatal or early-postnatal cytomegalovirus infection in preterm infants under 34 weeks gestation born to CMV-seropositive mothers within a high-seroprevalence population. J Pediatr 2004;145(5):685–8.
152. De Cates CR, Gray J, Roberton NR, et al. Acquisition of cytomegalovirus infection by premature neonates. J Infect 1994;28(1):25–30.
153. Miron D, Brosilow S, Felszer K, et al. Incidence and clinical manifestations of breast milk-acquired Cytomegalovirus infection in low birth weight infants. J Perinatol 2005;25(5):299–303.
154. Lanzieri TM, Dollard SC, Josephson CD, et al. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. Pediatrics 2013;131(6):e1937–45.
155. Hamprecht K, Maschmann J, Vochem M, et al. Epidemiology of transmission of cytomegalovirus from mother to preterm infant by breastfeeding. Lancet 2001;357(9255):513–8.
156. Adler SP, Chandrika T, Lawrence L, et al. Cytomegalovirus infections in neonates acquired by blood transfusions. Pediatr Infect Dis 1983;2(2):114–8.
157. Yeager AS, Grumet FC, Hafleigh EB, et al. Prevention of transfusion-acquired cytomegalovirus infections in newborn infants. J Pediatr 1981;98(2):281–7.

158. Preiksaitis JK, Brown L, McKenzie M. Transfusion-acquired cytomegalovirus infection in neonates. A prospective study. Transfusion 1988;28(3):205–9.

159. Kim AR, Lee YK, Kim KA, et al. Transfusion-related cytomegalovirus infection among very low birth weight infants in an endemic area. J Korean Med Sci 2006;21(1):5–10.

160. Reyes C, Pereira S, Warden MJ, et al. Cytomegalovirus enteritis in a premature infant. J Pediatr Surg 1997;32(11):1545–7.

161. Cheong JL, Cowan FM, Modi N. Gastrointestinal manifestations of postnatal cytomegalovirus infection in infants admitted to a neonatal intensive care unit over a five year period. Arch Dis Child Fetal Neonatal Ed 2004;89(4):F367–9.

162. Lee SL, Johnsen H, Applebaum H. Cytomegalovirus enterocolitis presenting as abdominal compartment syndrome in a premature neonate. World J Pediatr 2012;8(1):80–2.

163. Tengsupakul S, Birge ND, Bendel CM, et al. Asymptomatic DNAemia heralds CMV-associated NEC: case report, review, and rationale for preemption. Pediatrics 2013;132(5):e1428–34.

164. Gessler P, Bischoff GA, Wiegand D, et al. Cytomegalovirus-associated necrotizing enterocolitis in a preterm twin after breastfeeding. J Perinatol 2004;24(2):124–6.

165. Tran L, Ferris M, Norori J, et al. Necrotizing enterocolitis and cytomegalovirus infection in a premature infant. Pediatrics 2013;131(1):e318–22.

166. Gagneur A, Sizun J, Vallet S, et al. Coronavirus-related nosocomial viral respiratory infections in a neonatal and paediatric intensive care unit: a prospective study. J Hosp Infect 2002;51(1):59–64.

167. Chany C, Moscovici O, Lebon P, et al. Association of coronavirus infection with neonatal necrotizing enterocolitis. Pediatrics 1982;69(2):209–14.

168. Moscovici O, Chany C, Lebon P, et al. Association of coronavirus infection with hemorrhagic enterocolitis in newborn infants. C R Seances Acad Sci D 1980;290(13):869–72.

169. Jamieson FB, Wang EE, Bain C, et al. Human torovirus: a new nosocomial gastrointestinal pathogen. J Infect Dis 1998;178(5):1263–9.

170. Vaucher YE, Ray CG, Minnich LL, et al. Pleomorphic, enveloped, virus-like particles associated with gastrointestinal illness in neonates. J Infect Dis 1982;145(1):27–36.

171. Lodha A, de Silva N, Petric M, et al. Human torovirus: a new virus associated with neonatal necrotizing enterocolitis. Acta Paediatr 2005;94(8):1085–8.

172. Pruekprasert P, Stout C, Patamasucon P. Neonatal enterovirus infection. J Assoc Acad Minors Phys 1995;6(4):134–8.

173. Ehrnst A, Eriksson M. Epidemiological features of type 22 echovirus infection. Scand J Infect Dis 1993;25(3):275–81.

174. Moore M, Kaplan MH, McPhee J, et al. Epidemiologic, clinical, and laboratory features of Coxsackie B1-B5 infections in the United States, 1970–79. Public Health Rep 1984;99(5):515–22.

175. Jenista JA, Powell KR, Menegus MA. Epidemiology of neonatal enterovirus infection. J Pediatr 1984;104(5):685–90.

176. Lake AM, Lauer BA, Clark JC, et al. Enterovirus infections in neonates. J Pediatr 1976;89(5):787–91.

177. Johnson FE, Cronic DM, Simmons MA, et al. Association of fatal Coxsackie B2 viral infection and necrotizing enterocolitis. Arch Dis Child 1977;52(10):802–4.
178. Nakao T, Miura R, Sato M. ECHO virus type 22 infection in a premature infant. Tohoku J Exp Med 1970;102(1):61–8.

179. Berkovich S, Pangan J. Recoveries of virus from premature infants during outbreaks of respiratory disease: the relation of ECHO virus type 22 to disease of the upper and lower respiratory tract in the premature infant. Bull N Y Acad Med 1968;44(4):377–87.

180. Birenbaum E, Handsher R, Kuint J, et al. Echovirus type 22 outbreak associated with gastro-intestinal disease in a neonatal intensive care unit. Am J Perinatol 1997;14(8):469–73.

181. Madeley CR, Cosgrove BP. Letter: viruses in infantile gastroenteritis. Lancet 1975;2(7925):124.

182. Sebire NJ, Malone M, Shah N, et al. Pathology of astrovirus associated diarrhoea in a paediatric bone marrow transplant recipient. J Clin Pathol 2004;57(9):1001–3.

183. Nighot PK, Moeser A, Ali RA, et al. Astrovirus infection induces sodium malabsorption and redistributes sodium hydrogen exchanger expression. Virology 2010;401(2):146–54.

184. Bagci S, Eis-Hubinger AM, Yassin AF, et al. Clinical characteristics of viral intestinal infection in preterm and term neonates. Eur J Clin Microbiol Infect Dis 2010;29(9):1079–84.

185. Chappe C, Minjolle S, Dabadie A, et al. Astrovirus and digestive disorders in neonatal units. Acta Paediatr 2012;101(5):e208–12.

186. Desfrere L, de Oliveira I, Goffinet F, et al. Increased incidence of necrotizing enterocolitis in premature infants born to HIV-positive mothers. AIDS 2005;19(14):1487–93.

187. Schmitz T, Weizsaeccker K, Feiterna-Sperling C, et al. Exposure to HIV and antiretroviral medication as a potential cause of necrotizing enterocolitis in term neonates. AIDS 2006;20(7):1082–3.

188. van der Meulen EF, Bergman KA, Kamps AW. Necrotising enterocolitis in a term neonate with trisomy 21 exposed to maternal HIV and antiretroviral medication. Eur J Pediatr 2009;168(1):113–4.

189. Baley JE, Kliegman RM, Boxerbaum B, et al. Fungal colonization in the very low birth weight infant. Pediatrics 1986;78(2):225–32.

190. Fridkin SK, Kaufman D, Edwards JR, et al. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995–2004. Pediatrics 2006;117(5):1680–7.

191. Saiman L, Ludington E, Dawson JD, et al. Risk factors for Candida species colonization of neonatal intensive care unit patients. Pediatr Infect Dis J 2001;20(12):1119–24.

192. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. The National Epidemiology of Mycosis Survey study group. Pediatr Infect Dis J 2000;19(4):319–24.

193. Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics 2010;126(4):e865–73.

194. Stewart CJ, Nelson A, Scribbins D, et al. Bacterial and fungal viability in the preterm gut: NEC and sepsis. Arch Dis Child Fetal Neonatal Ed 2013;98(4):F298–303.

195. Coates EW, Karlowicz MG, Croitoru DP, et al. Distinctive distribution of pathogens associated with peritonitis in neonates with focal intestinal perforation compared with necrotizing enterocolitis. Pediatrics 2005;116(2):e241–6.

196. Mintz AC, Applebaum H. Focal gastrointestinal perforations not associated with necrotizing enterocolitis in very low birth weight neonates. J Pediatr Surg 1993;28(6):857–60.
197. Parra-Herran CE, Pelaez L, Sola JE, et al. Intestinal candidiasis: an uncommon cause of necrotizing enterocolitis (NEC) in neonates. Fetal Pediatr Pathol 2010;29(3):172–80.

198. Smith SD, Tagge EP, Miller J, et al. The hidden mortality in surgically treated necrotizing enterocolitis: fungal sepsis. J Pediatr Surg 1990;25(10):1030–3.

199. Ballance WA, Dahms BB, Shenker N, et al. Pathology of neonatal necrotizing enterocolitis: a ten-year experience. J Pediatr 1990;117(1 Pt 2):S6–13.

200. Kaufman D, Boyle R, Hazen KC, et al. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med 2001;345(23):1660–6.

201. Kaufman DA, Morris A, Gurka MJ, et al. Fluconazole prophylaxis in preterm infants: a multicenter case-controlled analysis of efficacy and safety. Early Hum Dev 2014;90(Suppl 1):S87–90.

202. Healy CM, Campbell JR, Zaccaria E, et al. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant Candida species. Pediatrics 2008;121(4):703–10.

203. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA 2014;311(17):1742–9.

204. Ullrich T, Tang YW, Correa H, et al. Absence of gastrointestinal pathogens in ileum tissue resected for necrotizing enterocolitis. Pediatr Infect Dis J 2012;31(4):413–4.

205. Raskind CH, Dembry LM, Gallagher PG. Vancomycin-resistant enterococcal bacteremia and necrotizing enterocolitis in a preterm neonate. Pediatr Infect Dis J 2005;24(10):943–4.

206. Pumberger W, Novak W. Fatal neonatal Salmonella enteritidis sepsis. J Perinatol 2000;20(1):54–6.

207. Stein H, Beck J, Solomon A, et al. Gastroenteritis with necrotizing enterocolitis in premature babies. Br Med J 1972;2(5814):616–9.

208. Overturf GD, Sherman MP, Scheifele DW, et al. Neonatal necrotizing enterocolitis associated with delta toxin-producing methicillin-resistant Staphylococcus aureus. Pediatr Infect Dis J 1990;9(2):88–91.

209. Downard CD, Renaud E, St Peter SD, et al. American Pediatric Surgical Association Outcomes Clinical Trials Committee. Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg 2012;47(11):2111–22.

210. Weitkamp JH. More than a gut feeling: predicting surgical necrotising enterocolitis. Gut 2014;63(8):1205–6.

211. Sharma R, Hudak ML. A clinical perspective of necrotizing enterocolitis: past, present, and future. Clin Perinatol 2013;40(1):27–51.

212. Ng PC, Lewindon PJ, Siu YK, et al. Bacterial contaminated breast milk and necrotizing enterocolitis in preterm twins. J Hosp Infect 1995;31(2):105–10.