Distinctive Distribution of Pathogens Associated With Peritonitis in Neonates With Focal Intestinal Perforation Compared With Necrotizing Enterocolitis

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ABSTRACT. *Objective.* ***Candida* and coagulase-negative staphylococci are emerging pathogens associated with focal intestinal perforation (FIP) and necrotizing enterocolitis (NEC) in neonates. The objective of this study was to determine whether there are significant differences in the predominant pathogens in culture-positive cases of peritonitis associated with FIP compared with NEC in neonates.**

Methods. **A retrospective cross-sectional study was conducted of neonates with peritoneal culture-positive peritonitis associated with FIP or NEC over a 12-year study period (1989–2000). Cases with peritonitis were identified from a microbiology database. NEC was defined by radiologic evidence of pneumatosis intestinalis or portal venous gas or by pathology reports or surgical operative notes describing large areas of transmural bowel necrosis. FIP was defined as a <1-cm intestinal perforation surrounded by otherwise normal tissue in the absence of NEC.**

Results. **Thirty-six cases of FIP were compared with 80 cases of NEC. Birth weight and gestational age were significantly lower in infants with FIP compared with NEC. Age at intestinal perforation and case fatality rates were similar between FIP and NEC. There were striking differences in the distribution of predominant pathogens associated with peritonitis in NEC and FIP cases. Enterobacteriaceae were present in 60 (75%) of 80 NEC cases compared with 9 (25%) of 36 FIP cases. In contrast, *Candida* species were found in 16 (44%) of 36 FIP cases compared with 12 (15%) of 80 NEC cases, and coagulase-negative staphylococci were present in 18 (50%) of 36 FIP cases versus 11 (14%) of 80 NEC cases. There were no significant differences between FIP and NEC cases for the presence of *Enterococcus* species (28% vs 23%) or anaerobes (3% vs 6%). Stratified analysis for birth weight <1200 g found similar significant differences in the predominant pathogens for FIP ($n = 29$) and NEC ($n = 38$). Results from peritoneal fluid cultures resulted in changes in antimicrobial therapy in 46 (40%) of 116 cases.**

Conclusions. ***Candida* species and coagulase-negative staphylococci were the predominant pathogens in FIP peritonitis in contrast to Enterobacteriaceae in NEC peritonitis. A peritoneal fluid culture should be obtained in all neonates with intestinal perforation, regardless of cause, because it may help to direct the choice of the most effective antimicrobial.** *Pediatrics* **2005;116:e241–e246. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2537;** ***infant, necrotizing enterocolitis, focal intestinal perforation, peritonitis, microbiology.***

ABBREVIATIONS. FIP, focal intestinal perforation; NEC, necrotizing enterocolitis; CONS, coagulase-negative staphylococcal.

Recently, focal intestinal perforation (FIP) in neonates was reported as "distinctly different from necrotizing enterocolitis (NEC) in clinical correlates and outcomes."[1,2] Small case series have associated FIP with systemic candidiasis[3] and/or coagulase-negative staphylococci (CONS).[2,4] Likewise, CONS and *Candida* species were reported as common pathogens in 2 case series of peritonitis associated with NEC.[5,6] Uauy et al[7] looked at NEC and found that "Gram-positive organisms predominated in positive blood cultures for stage I and II necrotizing enterocolitis, whereas enteric bacteria were isolated more frequently in infants with stage III disease." Furthermore, Karlowicz[6] described a significantly increasing incidence of candidal peritonitis associated with NEC. Because clinical features and outcomes for FIP versus NEC seem to be different, perhaps there are also significant differences in the distribution of pathogens associated with peritonitis in neonates with FIP versus NEC.

Current recommendations for empirical antibiotic treatment of infants with NEC include ampicillin, gentamicin, and clindamycin, although some clinicians recommend substituting vancomycin for ampicillin.[8] Benjamin et al[9] suggested initiating empirical antifungal therapy in a specific subset of preterm neonates with late-onset sepsis, but we are unaware of any recommendations for empirical antifungal therapy in neonates with NEC despite an increasing prevalence of *Candida* peritonitis. Recommendations for empirical antibiotic treatment in cases of FIP may need to be different than for cases of NEC if there are significant differences in the distribution of associated pathogens, especially CONS and *Candida* species. Our objective was to determine whether significant differences exist in the distribution of pathogens associated with peritonitis caused by FIP compared with NEC.

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METHODS

Study Population

A retrospective cross-sectional study was conducted to compare neonates with FIP and NEC. The study included all patients who had a positive peritoneal culture associated with either FIP or NEC and were hospitalized in the NICU at Children's Hospital of the King's Daughters between January 1, 1989, and December 31, 2000. This hospital contains the regional referral nursery for southeastern Virginia and northeastern North Carolina. We excluded neonates who had bowel perforation associated with any other condition besides FIP or NEC.

Definitions

Peritonitis was defined by growth of any pathogen from an intraoperative peritoneal culture in a neonate with a bowel perforation. All cases had both an aerobic and an anaerobic culture obtained at the time of surgery, either open laparotomy or peritoneal drain placement. Associated bacteremia/fungemia was defined as a positive blood culture within 3 days of the positive peritoneal culture with isolation of the same organism. Case fatality in association with peritonitis was defined as death within 14 days of intestinal perforation.

Database Management

The neonatology division maintains several databases that prospectively abstract information from medical records of infants who are admitted to the NICU. Data are entered by research nurses and are monitored closely and reviewed periodically by the senior clinical investigator (M.G.K.) for quality improvement. Two separate databases were used as information sources: a neonatal database and a microbiology database. Study patients were identified as those having a positive peritoneal culture in the microbiology database and were patients in the NICU during the defined study period. The neonatal database then was used to describe basic demographic, morbidity, and outcomes data. The microbiology database identified the pathogens associated with each study patient's peritonitis. Data from the 2 databases then were entered into a single study database for analysis. The study was approved by the Institutional Review Board of Eastern Virginia Medical School.

Diagnosis

A careful review of each study patient was performed to identify whether the bowel perforation was a FIP or secondary to NEC. A stepwise approach to the diagnosis was performed with each study case. Review of all radiologic reports on the day of surgery and during the 3 days before identified NEC cases as those with pneumatosis intestinalis or portal venous gas. When radiographic evidence was inconclusive, a review of the operative report was used to estimate the size of perforation and the extent of bowel involvement and to note gross surgical evaluation of the surrounding bowel. When the operative report described >1 cm of necrotic bowel or multiple areas of necrosis, it was diagnosed as NEC. When the report described <1 cm of bowel involvement with otherwise normal surrounding tissue, it was diagnosed as FIP. When the case still was inconclusive, a review of the gross pathologic findings of the operatively resected bowel was performed. Similar to the operative reports, when the pathology report described >1 cm of necrotic bowel or multiple areas of necrosis, the diagnosis of NEC was made. When the pathology report described a <1-cm perforation with otherwise normal surrounding tissue, the diagnosis of FIP was made. Using this stepwise approach, each bowel perforation was classified as either a FIP or perforation secondary to NEC.

Statistical Methods

Comparisons between groups were made with the unpaired t test for parametric data or with the Mann-Whitney U test for nonparametric data. Categorical data were analyzed with the Fisher's exact test. Significance was declared at $P < .05$.

RESULTS

Study Group

A total of 143 neonates were identified as having peritonitis during the 12-year study period. Of these, 116 were associated with either FIP or NEC. The remaining 27 patients were excluded from the study because peritonitis/perforation was associated with other pathology (eg, gastroschisis, omphalocele, volvulus, intestinal atresia). Thirty-six had peritonitis associated with FIP, and 80 had perforation caused by NEC. Of the 116 cases of either FIP or NEC, 106 underwent open laparotomy and 10 had a peritoneal drain placed under sterile conditions. No distinctive trends in occurrence of either condition were observed throughout the 12-year study period (Fig 1). The birth weight of patients with FIP (median: 772 g; range: 482–4390) was significantly lower than in infants with NEC (median: 1273 g; range: 510–3210; $P < .0001$; Table 1). The gestational age of patients with FIP (median: 26 weeks; range: 23–40) was significantly less than that of infants with NEC (median: 29.5 weeks; range: 23–40; $P = .007$). There were no differences between infants with FIP compared with NEC with respect to the age at intestinal perforation or case fatality rate.

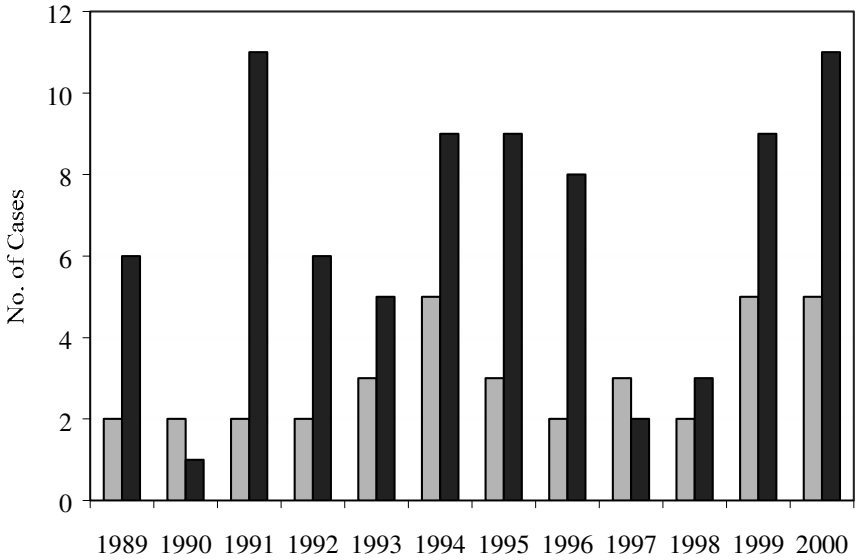

Fig 1. Yearly cases of FIP (□; $n = 36$) and NEC (■; $n = 80$).

TABLE 1. Clinical Characteristics of Neonates With Peritonitis Associated With FIP Versus NEC

	FIP (n = 36)	NEC (n = 80)
Birth weight, g, median (range)*	772 (482–4390)	1273 (510–3210)
Gestational age, wk, median (range)†	26 (23–40)	29.5 (23–40)
Age at perforation, d, median (range)	13.5 (3–56)	14 (3–38)
Male gender, n (%)	28 (78)	48 (60)
Black ethnicity, n (%)	20 (56)	57 (71)
Case fatality, n (%)	11 (31)	25 (31)

* $P < .0001$.
† $P = .007$.

Microbiology

Striking differences in the distribution of predominant pathogens associated with peritonitis in FIP and NEC cases were observed (Table 2, Fig 2). CONS were present in 18 (50%) of 36 FIP cases compared with 11 (14%) of 80 NEC cases ($P < .0001$). *Candida* species were found in 16 (44%) of 36 FIP cases compared with 12 (15%) of 80 NEC cases ($P = .0010$). In contrast, Enterobacteriaceae were present in 60 (75%) of 80 NEC case versus 9 (25%) of 36 FIP cases ($P < .0001$). There were no significant differences between FIP and NEC cases for the presence of *Enterococcus* species (28% vs 23%) or anaerobes (3% vs 6%). There was no difference in the prevalence of polymicrobial peritonitis between the 2 cohorts. Two or more organisms were isolated in the peritoneal fluid of 17 (47%) of 36 FIP cases and 31 (39%) of 80 NEC cases. These distributions remained the same when the 10 cases in which peritoneal drains were placed in lieu of an open laparotomy were either included or excluded.

Given the significant difference in the median birth weight between patients with FIP and NEC, we analyzed the lowest birth weight subpopulation of infants with birth weight <1200 g. Table 3 and Fig 3 show that in comparing 29 cases of FIP with 38 cases of NEC in neonates who weighed <1200 g, the same significant differences in the distribution of pathogens were seen. A total of 55% of FIP cases compared with 21% of NEC cases grew CONS from the peritoneal fluid ($P = .005$). *Candida* species were present in the peritoneal fluid in 48% of FIP cases compared with 21% of NEC cases ($P = .03$). Enterobacteriaceae were the most common isolates associated with NEC (55% vs 17% of FIP cases; $P = .002$).

TABLE 2. Peritoneal Isolates Recovered From Neonates With FIP Versus NEC

	FIP, % (n) (N = 36)	NEC, % (n) (N = 80)
Gram-positive		
CONS*	50 (18)	14 (11)
S aureus	0 (0)	1 (1)
Enterococcus species	28 (10)	23 (18)
Streptococcus species	3 (1)	0 (0)
Diphtheroids	3 (1)	3 (2)
Gram-negative		
Enterobacteriaceae†	25 (9)	75 (60)
E Coli	3 (1)	28 (22)
Klebsiella species	8 (3)	28 (22)
Enterobacter species	11 (4)	25 (20)
Citrobacter species	0 (0)	4 (3)
Serratia species	0 (0)	1 (1)
Proteus species	3 (1)	0 (0)
Pseudomonas species	8 (3)	1 (1)
Acinetobacter species	3 (1)	0 (0)
Anaerobes	3 (1)	6 (5)
Bacteroides species	3 (1)	5 (4)
Clostridium species	0 (0)	1 (1)
Candida species‡	44 (16)	15 (12)

* $P < .0001$.
† $P < .0001$.
‡ $P = .001$.

An associated bacteremia/fungemia was present in 14 (39%) of 36 FIP cases, compared with only 16 (20%) of 80 cases of NEC ($P = .04$). Candidemia was present in 9 cases of FIP and 5 cases of NEC. Enterobacteriaceae bacteremia was present in 3 cases of FIP and 10 cases of NEC. CONS bacteremia was present in 2 cases of FIP and 3 cases of NEC. Polymicrobial sepsis was present in 4 cases of FIP and 2 cases of NEC peritonitis. Candidemia was associated with candidal peritonitis in 14 (50%) of 28 cases compared with bacteremia in 22 (21%) of 106 cases of bacterial peritonitis ($P = .004$).

The results of peritoneal fluid cultures changed antibiotic selection in 46 (40%) of 116 cases. These changes were attributable to the growth of candida or CONS in all but 1 case, in which methicillin-resistant *Staphylococcus aureus* was identified.

DISCUSSION

This is the largest reported case series to compare peritonitis associated with FIP and NEC, 2 conditions that vary in demographics, pathology, and clinical course.[1] We now demonstrate that they are distinctly different in associated microbiology. FIP occurs in neonates with smaller gestational ages and lower birth weights than NEC. NEC is more likely to be associated with Enterobacteriaceae peritonitis, whereas FIP is most frequently associated with coagulase-negative staphylococcal and *Candida* species peritonitis. These microbiologic associations remain constant when controlling for lower birth weight (<1200 g). The application of these data occurs at 2 levels. First, the distinctive distribution of pathogens when comparing FIP and NEC supports the need to obtain peritoneal fluid cultures in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient. Second, it sheds light on which organisms should be targeted by antimicrobials when empirically treating neonates with documented FIP or NEC.

Previous authors have suggested an association between FIP and both CONS and *Candida* species. Adderson et al[3] compared 12 cases of FIP with 55 cases of NEC, noting that one third of their infants with FIP had systemic candidiasis at the time of perforation. Mintz et al[2] described a series of 9 neonates with FIP and concluded that the perforations seemed to be associated with *Candida* species and/or CONS. Another report of 7 patients with FIP found CONS infections associated with 6 of its cases and *Candida* species associated with 2.[4] Ours is the first large data set to compare the presence of these or-

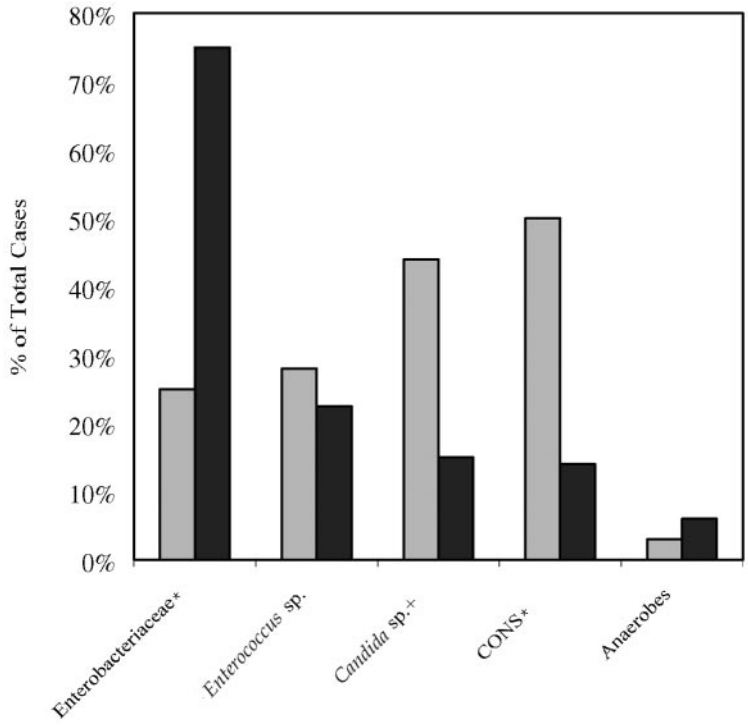

Fig 2. Distribution of pathogens, FIP (□; $n = 36$) versus NEC (■; $n = 80$). * $P < .0001$; † $P = .001$.

TABLE 3. Peritoneal Isolates Recovered From Neonates With Birth Weight <1200 g and FIP Versus NEC

	FIP, % (*n*) ($N = 29$)	NEC, % (*n*) ($N = 38$)
Gram-positive		
CONS*	55 (16)	21 (8)
S aureus	0 (0)	3 (1)
Enterococcus species	31 (9)	26 (10)
Streptococcus species	3 (1)	0 (0)
Diphtheroids	3 (1)	5 (2)
Gram-negative		
Enterobacteriaceae†	17 (5)	55 (21)
E Coli	3 (1)	8 (3)
Klebsiella species	3 (1)	26 (10)
Enterobacter species	10 (3)	24 (9)
Citrobacter species	0 (0)	5 (2)
Serratia species	0 (0)	3 (1)
Proteus species	0 (0)	0 (0)
Pseudomonas species	7 (2)	0 (0)
Acinetobacter species	3 (1)	0 (0)
Anaerobes	3 (1)	3 (1)
Bacteroides species	3 (1)	3 (1)
Clostridium species	0 (0)	0 (0)
Candida species‡	48 (14)	21 (8)

* $P = .005$.
† $P = .002$.
‡ $P = .03$.

ganisms between FIP and NEC. It underscores the importance of evaluating and treating FIP and NEC as distinctly separate disease processes.

The standard of care for patients with documented NEC or FIP continues to include broad-spectrum antimicrobial coverage; however, the agents of choice vary between centers. Lee and Polin[8] recommended ampicillin, gentamicin, and clindamycin, with the possible substitution of vancomycin for ampicillin as a result of the increasing prevalence of CONS. Others have proposed ticarcillin and an aminoglycoside, usually gentamicin.[10] Foglia[11] endorsed amikacin and Flagyl in place of gentamicin and clindamycin. Neu[12] advocated starting ampicillin and gentamicin after a blood culture is obtained, substituting vancomycin for ampicillin when CONS is suspected and then adding either clindamycin or metronidazole, for anaerobic coverage, when perforation is suspected or has occurred. This lack of agreement within the medical literature confirms that peritoneal fluid cultures should be obtained in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial therapy for each individual patient.

In neonates with culture-positive peritonitis, 44% of patients with FIP and 15% with NEC showed evidence of *Candida* species peritonitis, emphasizing the need to address the use of antifungal agents in cases of bowel perforation in the NICU. We identified associated candidemia in only 14 (50%) of the 28 cases of culture-proven candidal peritonitis; therefore, it is imperative that the clinician be aware of patients who are at risk for fungal disease. Bond et al[13] described 3 cases of fatal candidal enteritis seen on pathologic evaluation and therefore recommended "review of pathologic specimens for invasive fungal enteritis with institution of aggressive combination therapy in confirmed cases." In a previous publication, Karlowicz[6] proposed that amphotericin B be considered in neonates who weigh <1000 g and have stage IIIB NEC, "especially in those with a history of prolonged umbilical vessel catheterization, prolonged antibiotic therapy, and prolonged intubation." In a report on neonates with NEC, Smith et al[14] recommend amphotericin B for patients who remain symptomatic despite negative bacterial cul-

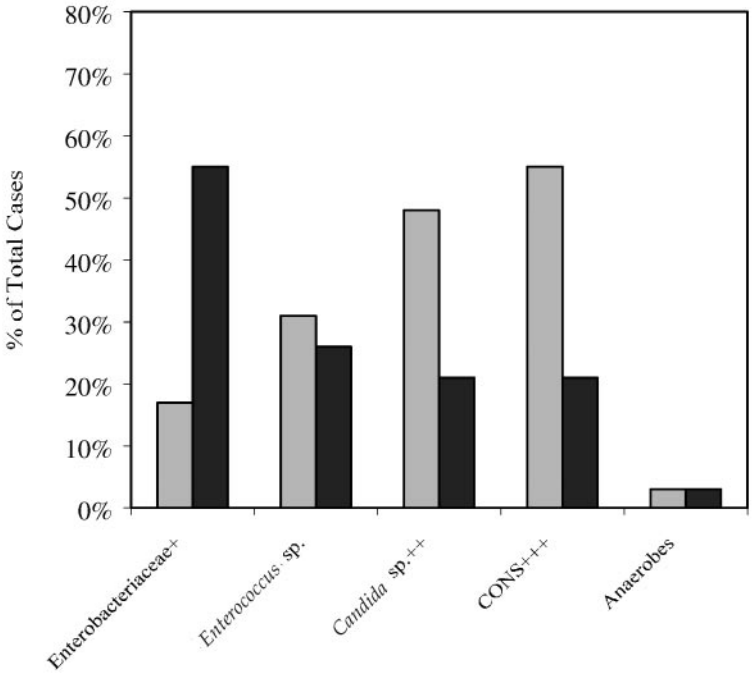

Fig 3. Distribution of pathogens, FIP (□; $n = 29$) versus NEC (■; $n = 38$; <1200 g). * $P = .002$; † $P = .03$; ‡$P = .005$.

tures. The most current recommendations from Benjamin et al,[9] based on a study of neonates with birth weight <1250 g, encourage consideration of empiric antifungal therapy pending culture results on the basis of noted risk factors: <25 weeks' estimated gestational age, thrombocytopenia at the time of blood culture, or 25 to 27 weeks without thrombocytopenia but with a history of third-generation cephalosporin or carbapenem exposure in the preceding 7 days. It has been suggested that earlier institution of antifungal therapy may alter outcome in infants with *Candida* peritonitis.[6,15] We conclude that a peritoneal culture obtained at the time of surgical intervention is reasonable, as it may allow more rapid identification of fungal peritonitis and allow initiation of antifungal therapy as promptly as possible.

CONS is a common blood culture isolate when blood cultures are performed during evaluation for late-onset sepsis in NICUs. The majority of neonatologists who were polled by Rubin et al[16] reported their preference for use of vancomycin as a first-line agent for suspected late-onset sepsis in certain clinical scenarios. This contradicts the findings by multiple authors[17,18] that the mortality as a result of CONS late-onset sepsis is no different when using vancomycin empirically versus using vancomycin in a restricted protocol. In addition, the routine use of empiric vancomycin has been shown to increase the risk for vancomycin-resistant *Enterococcus*,[8] and we noted enterococcal growth in 26 (22%) of 116 total cases. We recommend a protocol that does not use vancomycin empirically for FIP or NEC but reserves its use for culture-proven CONS disease or in the rare case of methicillin-resistant *S aureus*. The mean time to detection of CONS in a blood culture is 21.7 hours.[19] We therefore endorse the change from ampicillin or oxacillin to vancomycin only when growth of Gram-positive cocci in clusters is noted on a culture. The clinician, however, should have a particularly heightened awareness for CONS in cases of FIP.

When empirically treating neonates with FIP and NEC with antimicrobials is considered, the clinician should be aware of the microbiologic associations with each disease. Our data confirm that the distribution of pathogens associated with FIP is distinctively different from that associated with NEC. CONS and *Candida* species are the predominant organisms associated with FIP, whereas Enterobacteriaceae are most likely associated with NEC. Controversy exists as to the appropriate empirical antimicrobial treatment for neonates with NEC and FIP. Although we have demonstrated differences in the distribution of pathogens associated with NEC and FIP, there is significant overlap between the 2 groups in the specific organisms themselves. We are not endorsing changes in the empirical coverage, just providing awareness of the distribution of pathogens. In addition, we do not encourage the empirical use of vancomycin but rather reserve its use for the presence of CONS growth on cultures. Antifungal therapy should be considered in neonates with FIP and those who continue to deteriorate clinically despite conventional antimicrobial treatment. A Gram stain and KOH prep of the peritoneal fluid may provide additional information for early detection of candidal and CONS peritonitis. This was not systematically performed at our institution, however, and would warrant additional investigation. By following the growth of intraoperative peritoneal cultures, our initial empirical antimicrobial choice was altered in 40% of cases, hallmarking the critical importance that a peritoneal fluid culture be obtained in all neonates with intestinal perforation regardless of cause, because it may help to direct the choice of the most effective antimicrobial.

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