Briefly Legal: Failure to Diagnose a Classic Case of Spontaneous Intestinal Perforation (SIP)

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"A 23 1/7 weeks' gestation, she presented to the hospital having developed vaginal bleeding and abdominal cramping after using cocaine the night before. The presumptive cause of the bleeding and cramping was placental abruption associated with cocaine use. Although there was unlikely sufficient time for obtaining a therapeutic benefit, soon after admission, the mother was given terbutaline, magnesium sulfate, and betamethasone."

At the time of her pregnancy, the patient was a 43-year-old G50P4 woman with two prior cesarean sections, whose prenatal course was complicated by active cocaine use, heavy smoking, and the consumption of several beers daily. She had a history of syphilis and chlamydia, both treated six years earlier. She was group B Streptococcus (GBS) negative. A 23 1/7 weeks' gestation, she presented to the hospital having developed vaginal bleeding and abdominal cramping after using cocaine the night before. The presumptive cause of the bleeding and cramping was placental abruption associated with cocaine use. Although there was unlikely sufficient time for obtaining a therapeutic benefit, soon after admission, the mother was given terbutaline, magnesium sulfate, and betamethasone. Shortly after that, however, she developed a fever of 101^{0}F and spontaneous rupture of membranes with the production of malodorous amniotic fluid. Because of the presumptive diagnoses of chorioamnionitis and placental abruption, and the four prior cesarean sections (uterine rupture could not be excluded), the decision was made to deliver the baby by repeat cesarean section.

At birth, the 570-g male infant received Apgar scores of 4^1,5^5,5^{10}. The arterial cord gas pH was 7.14, the pCO_2 was 56 mmHg, the pO_2 was 23 mmHg, and the base deficit (BD) was 10.7. Still in the delivery room, the baby was placed in a plastic bag to maintain his temperature and immediately intubated. He was given positive pressure ventilation and surfactant replacement therapy before being brought to the Newborn Intensive Care Unit (NICU). The placenta revealed a 25% abruption with histological evidence of chorioamnionitis.

In the NICU, his physical examination was normal, though immature. A CBC revealed a marked anemia with a hematocrit of 30%. The remainder of the CBC was unremarkable. The infant required moderately high ventilator settings and 100% inspired oxygen. Antibiotics were started, and several hours after admission, a second dose of surfactant replacement was administered for respiratory distress syndrome. Because of mildly low blood pressure, normal saline boluses were given, and dopamine was begun, followed by packed red blood cell transfusions. On DOL 1, a cranial ultrasound showed intraventricular hemorrhages, grade 3 on the right and grade 4 on the left. Over the next week and a half, the infant followed a stormy course with the development of a tension pneumothorax relieved by a chest tube, a patent ductus arteriosus treated with indomethacin, seizures controlled by phenobarbital, hyperglycemia controlled by insulin and posthemorrhagic ventriculomegaly. Because of the child's instability related to these conditions, feeding was withheld. He was fed parenterally via a percutaneous intravenous catheter with \increasing amounts of nutrients. On DOL 10, greenish fluid began draining from his orogastric tube. His abdominal girth had suddenly increased from 16 cm to 18.5 cm, despite a 15% weight loss from birth. On examination, the abdomen was tense and bluish.

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A single, flat-plate radiograph revealed a paucity of gas in the bowel but no intramural gas to suggest necrotizing enterocolitis. The blood culture taken after birth was negative, but the one repeated on DOL 14 showed ***coagulase-negative staphylococcus*** (CONS). The green output and abdominal findings on examination continued. Despite daily "abdominal radiographs," no cross-table lateral or left lateral decubitus radiographs were obtained to determine the presence of abdominal free air better. Indeed, some of the radiographs included only the chest. These radiographs were consistently interpreted as showing a paucity of intestinal gas, with no portal venous gas or free air. The differential diagnosis of the treating neonatologist included necrotizing enterocolitis and ileus from sepsis. It did not include intestinal perforation. Inexplicably, the neonatologist did not reorder the abdominal radiographs when the abdomen was not included in the radiograph, nor was a cross

Issue	SIP	NEC
Pathophysiology	-localized to the area of perforation characterized as isolated mucosal ulceration with submucosal thinning -focal intestinal perforation, generally in the watershed area of the terminal ileum, without gross findings elsewhere -ischemia, reperfusion, or thromboembolism -operative findings typically involve a single subcentimeter perforation, usually on the antimesenteric border of the small intestine, with minimal peritoneal contamination and healthy appearing surrounding intestine	-primarily driven by ischemia and initiation of enteral feeds resulting in full-thickness hemorrhagic necrosis of the intestinal mucosa. -characterized by inflammation, invasion of enteric gas-forming organisms, and dissection of gas into the muscularis and portal venous system -depending on the progression of the disease and the presence of underlying pathogenic factors, it may move into gangrenous necrosis and perforation -as the intestine heals, bowel wall thickening, fibrinous adhesions, and areas of stenosis may appear
Incidence and population affected	-mainly 25-27 weeks	-peaks at 29 -32 w -90% preterm -10% term with a strong association with congenital heart disease, gastroschisis, hypoxic-ischemic events
Gender	M>F	M=F
Timing	-preterm infant, usually within the first ten days	-typically presents after the first week and after the infant has begun to feed.
Presentation	-abdominal distension, classical bluish discoloration of the abdominal wall in the absence of abdominal wall erythema -if diagnosis missed, progression to instability	-a usually vague, nonspecific, slight change in vital signs, new onset or increase in apnea, feeding intolerance, increased gastric residuals, emesis -with the progression of disease; cardiovascular instability, lethargy, distension, tenderness, lack of bowel sounds
Radiologic Imaging	- gasless abdomen, absence of pneumatosis intestinalis and portal venous air. Cross-table lateral view or lateral decubitus with the left side down shows free air 2/3 time - 1/3 of the time, free air is not found because perforation is walled off or has been resorbed	-pneumatosis intestinalis, portal venous air, transient thickening of the intestinal wall, fixed dilated small bowel loops -free air if perforation occurs -significant bowel distension or fixed bowel loops
Associated infection	-concomitant sepsis with CONS	-30% cultures positive, probably reflecting a breakdown in the mucosal barrier leading to bacterial translocation
Laboratory	-may have: high or low white blood cell counts, thrombocytopenia, low hct	
Diagnosis	-operative findings of isolated bowel perforation in otherwise normal bowel	-pneumatosis intestinalis and/or portal venous gas

Management	-gastric decompression -withholding feedings -correction of acidosis, anemia, and thrombocytopenia. -blood pressure support -antibiotic coverage: 2 broad-spectrum agents that cover intestinal microorganisms, typically ampicillin, and an aminoglycoside or third-generation cephalosporin, although occasionally *Staphylococcal* species are heavy colonizers of the intestinal tract, Furthermore, nafcillin or vancomycin should be considered. In situations with suspected or proven intestinal perforation, aggressive anaerobic coverage with clindamycin is often added -surgical repair (bedside drain, especially in cases of instability)	
Differential Dx	NEC, malrotation, intestinal atresia, intussusception, aganglionosis, and volvulus	SIP, malrotation, intestinal atresia, intussusception, aganglionosis, and volvulus
Morbidity	-similar risk for neurodevelopmental impairment as surgical NEC	-strictures post NEC -depends on gestational age, BW, the extent of bowel involvement, & need for surgical intervention.
Mortality	Infants diagnosed with SIP had higher mortality than controls. In bivariate analyses, SIP had higher mortality than NEC in the overall population. That could be explained by SIP occurring more frequently in infants with younger GA and smaller BW. In fact, in infants with BW 1000–1499, the mortality from NEC was greater than SIP, and within the group of infants with BW <1000 g, mortality from SIP and NEC did not differ. After controlling for confounding variables in regression analysis, NEC had a higher adjusted odds ratio for mortality than SIP. Therefore, it is plausible to hypothesize that SIP is a sign of severe immaturity, making them more vulnerable to increased mortality and other complications.	

Discussion

Pathology

Spontaneous intestinal perforation (SIP), also called isolated intestinal perforation and focal intestinal perforation, is a disease entity first appreciated in the late 1980s as more immature infants survived. Over the years, there have been increasing reports of SIP in VLBW and ELBW neonates. SIP is localized to the perforation area generally in the watershed areas of the terminal ileum, without gross findings elsewhere, and is characterized as isolated mucosal ulceration with submucosal thinning. SIP usually occurs before the initiation of enteral feeds. In patients with SIP, operative findings typically include a single, small (<1 cm diameter) perforation, usually on the antimesenteric border of the small intestine, with minimal peritoneal contamination and a healthy appearance surrounding the intestine. The predominant pathophysiologic feature is circulatory, namely, ischemia, reperfusion, or thromboembolism.

Population affected

The median gestation age for SIP ranges from 25-27 weeks, and the median birth weight ranges from 670 to 973 grams. Some studies have found that SIP appears more frequently in male than female infants. Severe chorioamnionitis (as present in this case) is an antenatal risk factor for SIP.

Cocaine, Steroids, and Indomethacin

Indomethacin has been used antenatally for tocolysis and prophylactically in high-risk neonates to help close the ductus in premature fetuses. It is well known that cocaine use during pregnancy has adverse consequences for both the mother and fetus. Among 17,466 non-Asian singleton deliveries in 1988 from the University of Illinois Perinatal Network database in the metropolitan Chicago area, Handler et al. found elevated adjusted relative risks (RR) of SGA births (RR = 2.8, 95% (CI) 2.2-3.7), prematurity (RR = 2.4, 95% CI 1.9-3.1), abruptio placentae (RR = 4.5, 95% CI 2.4-8.5), and perinatal death (RR = 2.1, 95% CI 1.1-4.0) for "any" cocaine users (n = 408) compared with non-using women cocaine, other drugs or alcohol) Paradoxically, cocaine use decreases neonatal morbidity in patients with preterm premature rupture of membranes compared to those where rupture occurs without cocaine. After birth, prophylactic indomethacin is used by over a quarter of neonatologists because of its short-term benefits in closing the ductus arteriosus. While brief antenatal exposure to indomethacin (≤ 2 days) is not associated with SIP, randomized controlled trials (RCTs) have found that infants exposed to both indomethacin and corticosteroids after birth are at increased risk of SIP. Paradoxically, antenatal glucocorticoids may be somewhat protective, while neonatal steroids alone may increase the risk of SIP. Trials of prophylactic indomethacin alone have not been shown to predispose to SIP. Whether prophylactic neonatal indomethacin alone or combined with antenatal steroids increases the rate of SIP has led to contrary conclusions.

table or lateral view requested.

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On DOL 15, the surgical consult, finally obtained, requested a cross-table lateral view, revealing a pneumoperitoneum. The baby was transferred to a regional children's hospital for surgical care. A Penrose drain was inserted into the abdomen at the referral hospital, which drained stool and blood. Following this intervention, the infant's abdominal exam and clinical findings improved. He did develop a partial small bowel obstruction that responded to conservative care without surgery. Neurosurgical interventions included a reservoir placed and multiple taps until he was large enough to tolerate the placement of a ventricular-peritoneal (VP) shunt. The multiple taps prior to the VP shunt caused hyponatremia, requiring boluses of normal saline after the procedures. He was diagnosed with retinopathy of prematurity, for which he underwent laser treatment.

He was discharged from the hospital at three months of age. His discharge diagnoses included: BPD, posthemorrhagic obstructive hydrocephalus s/p VP shunt, retinopathy of prematurity s/p laser, and osteopenia. On-up examination, he had profound cognitive deficits, cerebral palsy, and visual impairment.

"Both the birthing hospital and the neonatologist were sued. In deposition testimony, the plaintiff neonatology expert was critical of the treating neonatologist for 1) Failing to consider SIP in the differential diagnoses. 2) Not ordering a left lateral decubitus or cross-table view to look for free air in the peritoneal space. 3) Not obtaining a surgical consult. 4) not reordering abdominal radiographs when they failed to include the abdomen. "

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The defense claimed that the problems with the baby were those related exclusively to the severe prematurity and the mother's use of cocaine. The birthing hospital and the defendant neonatologist settled the matter out of court.

When steroids are administered prenatally, the physiological surge in bioactivity in the fetus/newborn lasts approximately 72 h after the last betamethasone dose. Indeed, several studies have identified that the combination of recent (< 7 days, <3 days) antenatal glucocorticoids and prophylactic neonatal indomethacin was associated with SIP. In an intent to treat, a multi-epoch study of the role of prophylactic indomethacin (PINDO) on rates of death or bronchopulmonary dysplasia, grades 2 and 3 (death/BPD) in newborns <25 weeks, Clyman et al. found no significant differences in the incidence of death/BPD or of secondary outcomes (necrotizing enterocolitis/spontaneous perforations, or intraventricular hemorrhage (grades 3 or 4) in various comparisons between infants born in a PINDO epoch and those born in the Expectant Management epoch. They concluded that despite being at high risk for PDA-related morbidities, PINDO did not appear to alter the rates of intestinal perforation or any secondary outcomes in infants <25 weeks. They did find that PINDO treatment resulted in far more frequent closure of the ductus by 7-8 days (85% v. 24%).

"If early diagnosis is followed by timely resection, the morbidity and mortality statistics with SIP are better than those with surgically treated NEC. Thus, co-management or prompt consultation with a pediatric surgeon is vital to timely and appropriate care. "

Clinical features

The signs and symptoms of SIP usually develop suddenly without prior clinical evidence of intestinal inflammation. Since an intestinal perforation has occurred, affected infants often appear deceptively better than expected. The infants are initially fairly stable, then suddenly develop abdominal wall distension, which is classically blue. The most common organism associated with SIP is CONS. The differential diagnosis of abdominal distention includes ileus from sepsis and NEC. Less common causes include malrotation, intestinal atresia, intussusception, aganglionosis, and volvulus. Radiographic findings are nonspecific and often include a paucity of gas or "a gasless abdomen." Pneumoperitoneum is present about two-thirds of the time. When the perforation has been rapidly walled off or the free air resorbed, pneumoperitoneum may not be found. Careful abdominal examinations, close attention to the clinical course, and undertaking proper radiography are the keys to diagnosing SIP and providing timely intervention. If early diagnosis is followed by timely resection, the morbidity and mortality statistics with SIP are better than those with surgically treated NEC. Thus, co-management or prompt consultation with a pediatric surgeon is vital to timely and appropriate care. Many infants do very well with localized resection and primary

anastomosis, although some evidence focuses on peritoneal drainage as a definitive, non-surgical treatment.

Suggested Reading

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Disclosures: The authors have no disclosures

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