

Male Sex Predisposes the Newborn Surgical Patient to Parenteral Nutrition–Associated Cholestasis and to Sepsis

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Hypothesis: Sepsis is an epiphenomenon of parenteral nutrition–associated cholestasis (PNAC) and not a causative factor, and the incidence of sepsis is not affected by the presence or absence of PNAC.

Design: Observational cohort study.

Setting: Pediatric surgery department in a tertiary referral children’s hospital.

Patients: Newborns receiving PN for at least 7 days following intestinal surgery.

Main Outcome Measures: The criteria for PNAC were as follows: PN for at least 14 consecutive days, conjugated bilirubin level greater than 1.5 mg/dL ($>26 \mu\text{mol/L}$), conjugated bilirubin fraction greater than 50%, and absence of another identifiable cause of cholestasis. The identification of septic events was based on Centers for Disease Control and Prevention criteria.

Results: The patients (26 with PNAC and 72 without PNAC) were well comparable for underlying disease, gestational age, birth weight, and age at the start of PN. Time receiving PN and length of hospital stay were significantly ($P<.001$) longer in patients with PNAC. Parenteral nutrition–associated cholestasis was associated with male sex ($P=.03$; odds ratio, 2.8; 95% confidence interval, 1.1-7.1). The overall sepsis incidence was low (9 per 1000 hospital days). The sepsis incidence tended to be higher in patients with PNAC than in patients without PNAC (11.8 vs 7.1 per 1000 days; $P=.08$), but was significantly higher in male than in female patients (12.2 vs 5.6 per 1000 days; $P=.01$). Most septic events were caused by coagulase-negative staphylococci.

Conclusions: Sepsis is an epiphenomenon of PNAC rather than a causative factor. Moreover, male sex predisposes the newborn surgical patient to PNAC and to sepsis.

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PARENTERAL nutrition–associated cholestasis (PNAC) is a potentially life-threatening complication of PN seen in 7.4% to 84% of parenterally fed infants.¹ Its etiology is multifactorial; underlying disease, gestational age, birth weight, interval between birth and start of PN, PN duration, sepsis, remaining small bowel length, and number of operative procedures all influence PNAC incidence.²⁻¹⁶ The identification of risk factors has been hampered by their interaction and the small size and heterogeneity of the populations described in most studies. The role of sepsis has remained especially controversial. Although several researchers^{5,8,12,17,18} suggest every attempt should be made to prevent sepsis because they believe it to be an important causative factor for PNAC, others^{2,8,19,20} have argued that the role of sepsis has been overemphasized or even that sepsis is an epiphenomenon of PNAC.

To assess the relation between sepsis and PNAC, we studied a homogeneous cohort of newborn surgical patients with a congenital or an acquired intestinal anomaly. We hypothesized that sepsis is an epiphenomenon of PNAC and that the incidence of sepsis would not be affected by the presence or absence of PNAC.

RESULTS

In the 6-year study period, 123 newborns were given PN for 7 or more days following surgery. Twenty-five newborns were excluded because they did not have an intrinsic intestinal anomaly (congenital diaphragmatic hernia [$n=13$], isolated gastroschisis [$n=6$], omphalocele [$n=2$], bladder exstrophy [$n=2$], Ondine curse [$n=1$], and intracranial hemorrhage [$n=1$]). Parenteral nutrition–associated cholestasis did not occur in any of the excluded patients.

Parenteral nutrition–associated cholestasis was diagnosed in 26 of the 98 new-

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PATIENTS AND METHODS

CLINICAL SETTING

The Department of Pediatric Surgery forms part of a university tertiary referral children's hospital serving a population of approximately 4.5 million. The pediatric surgical inpatient clinic consists of a 35-bed medium-care unit and a 14-bed intensive care and high-care unit, annually admitting between 1600 and 1800 patients. Most are newborns and infants admitted because of congenital or neonatally acquired anomalies. The study period was from January 1, 1991, through December 31, 1996. During the study period, the PN regimen and the antibiotic policy did not change. When PN was administered for more than a few days, as in our study population, a central venous catheter (Broviac catheter) was surgically introduced under general anesthesia.

PARENTERAL NUTRITION

Parenteral nutrition was provided according to hospital guidelines. Total PN provided 2.5 g/kg per day of amino acids (Aminovenös N Paediatric; Fresenius AG, Bad Homburg, Germany) to newborns and 2.0 g/kg per day of amino acids to older infants. Carbohydrates (Dextrose; Fresenius AG) provided approximately 65% and fat (Intralipid 20%; Pharmacia AB, Stockholm, Sweden) approximately 35% of nonprotein calories. Enteral nutrition was introduced and advanced, and PN tapered as quickly as possible, based on stool output and weight gain. During tapering, the relative volumes of amino acids, lipids, and carbohydrates in PN were kept within narrow limits.

CLINICAL DATA

The hospital information system and the pharmacy's PN registry were used to identify all newborns who required a

surgical procedure and were receiving PN for 7 or more days following surgery. The medical records were reviewed for patient characteristics and to identify cholestasis and septic events. Patient characteristics included gestational age, sex, primary diagnosis, length of the hospital stay, age at the start of PN, days receiving PN, and outcome (alive or dead). Patients were included in our study if the primary reason for PN was an intrinsic intestinal anomaly. The diagnosis of PNAC was based on widely accepted clinical criteria^{2,4-8,14,21}: PN for at least 14 consecutive days, conjugated bilirubin level greater than 1.5 mg/dL (>26 µmol/L), conjugated bilirubin fraction greater than 50%, and absence of another identifiable cause of cholestasis.

SEPTIC EVENTS

The Centers for Disease Control and Prevention criteria for nosocomial infections were used to identify septic events.²² For septic events to be considered, positive blood culture results were mandatory. Primary and secondary bloodstream infections were grouped together as "sepsis." If more than 1 microorganism was identified in 1 or more separate blood cultures taken on the same day, this was thought to reflect 1 septic event. Blood cultures taken on consecutive days and yielding different microorganisms were thought to reflect separate infections.

STATISTICAL ANALYSES

Statistical analyses were performed on a personal computer (Macintosh; Apple Computer, Inc, Cupertino, Calif) using a statistical software package (StatView, version 4.5; SAS Institute Inc, Cary, NC). Continuous data were analyzed using the *t* or Mann-Whitney statistic, and are reported as mean ± 1 SD or median (range). Nominal data were analyzed using the Fisher exact statistic, unless otherwise noted. *P* < .05 was considered statistically significant.

Table 1. Characteristics of Patients With PNAC vs Patients Without PNAC*

Characteristic	Patients With PNAC (n = 26)	Patients Without PNAC (n = 72)	P Value
Male-female ratio	17:9	29:43	.03
Gestational age, mean ± SD, wk	33.9 ± 4.0	34.7 ± 4.1	.41
Birth weight, mean ± SD, g	1979 ± 852	2085 ± 889	.60
Age at the start of PN, d	3.5 (0-27)	5.0 (1-24)	.19
Time receiving PN, d	46.5 (17-324)	24.5 (7-81)	<.001
Length of the hospital stay, d	66.5 (30-394)	41.0 (9-125)	<.001

*Data are given as median (range) unless otherwise indicated. PNAC indicates parenteral nutrition-associated cholestasis.

borns included in our study. It resolved before hospital discharge in 9 patients, was still present at discharge in 16, and progressed to fatal liver failure in 1. Patients with and without PNAC were similar for gestational age, birth weight, and age at the start of PN. Patients with PNAC were given PN significantly longer and stayed in the hospital significantly longer than patients without PNAC

(**Table 1**). Parenteral nutrition-associated cholestasis was associated with male sex (*P* = .03; **Table 1** and **Table 2**); the odds ratio of PNAC occurring in male vs female newborns was 2.8 (95% confidence interval, 1.1-7.1). These odds were not attributable to known differences between male and female patients. Indeed, gestational age, birth weight, age at the start of PN, time receiving PN, and length of hospital stay were all similar in male and female newborns (**Table 2**).

Patient characteristics are summarized in **Tables 1** and **2**, and primary diagnoses are summarized in **Table 3**. Of 26 patients with PNAC, 2 died; of 72 without PNAC, 10 died (*P* = .51). In 2 patients without PNAC, death was closely related to a septic event.

Overall, 51 septic events were identified in 35 patients. Sepsis was seen in 13 (50%) of the 26 patients who developed PNAC and in 22 (31%) of the 72 without PNAC (*P* = .10). In 8 (31%) of the 26 patients with PNAC, sepsis had occurred before PNAC was diagnosed.

In view of the association between PNAC and male sex, we calculated sepsis incidences for male and female patients with and without PNAC separately (**Table 4**). An overall χ^2 analysis yielded a *P* value of .03. Subse-

Table 2. Characteristics of Male vs Female Patients*

Characteristic	Male Patients (n = 46)	Female Patients (n = 52)	P Value
Ratio of patients with PNAC—patients without PNAC	17:29	9:43	.03
Gestational age, mean ± SD, wk	34.4 ± 3.9	34.5 ± 4.2	.91
Birth weight, mean ± SD, g	2059 ± 810	2056 ± 939	.99
Age at the start of PN, d	4.0 (0-21)	6.0 (1-27)	.11
Time receiving PN, d	31.5 (9-324)	29.5 (7-89)	.43
Length of the hospital stay, d	50.0 (12-394)	44.0 (9-125)	.62

*Data are given as median (range) unless otherwise indicated. PNAC indicates parenteral nutrition–associated cholestasis.

quently, all male patients were compared with all female patients, and all patients with PNAC were compared with all patients without PNAC. The incidence of sepsis was significantly higher in male than in female patients ($P = .01$) and tended to be higher in patients with PNAC than in patients without PNAC ($P = .08$) (P values not corrected for multiple comparisons).

Most of the 56 microorganisms cultured during the 51 septic events were coagulase-negative staphylococci (19 of 30 isolates in patients with PNAC and 18 of 26 isolates in patients without PNAC [$P = .78$]). Other microorganisms isolated were as follows: Enterobacteriaceae ($n = 7$), enterococci ($n = 7$), coliforms ($n = 3$), and yeasts ($n = 2$). On 5 occasions, 2 different microorganisms were identified on the same day and, therefore, held jointly responsible for one septic event. In one male patient with PNAC, 2 consecutive septic events were only 2 days apart; otherwise, the interval between 2 septic events in a patient was at least 1 week.

COMMENT

In a homogeneous group of surgical newborns with an intrinsic intestinal anomaly, we found male sex to be a predisposing factor for PNAC and for sepsis.

To our knowledge, the association between male sex and PNAC has not been noted before. This may be because of the study designs, small patient numbers, and the heterogeneity of the populations studied. Several studies^{2,3,5,7,9-15} aiming to identify PNAC risk factors were descriptive rather than comparative, did not discuss the sex distribution, or described a small or mixed medical-surgical population. Ginn-Pease et al⁴ compared 16 surgical newborns with PNAC with 30 without PNAC and concluded that sex did not seem significant in the development of PNAC. Bos et al⁸ did not find a significantly different sex distribution between 15 surgical newborns with PNAC and 79 without PNAC.

Gestational age, birth weight, age when PN is started, and underlying disease affect PNAC incidence.^{2,4,5,12} In our study, these factors were similar in both groups. In keeping with previous studies,^{2,4,12,17} patients who developed PNAC were given PN longer than patients without PNAC and stayed in the hospital longer. Days receiving PN and length of hospital stay are often considered proxies for the severity of the underlying disease. The observed sex dis-

Table 3. Primary Diagnoses*

Diagnosis	Patients With PNAC	Patients Without PNAC	Total
Necrotizing enterocolitis	15	39	54
Duodenal obstruction	3	17	20
Meconium ileus and/or meconium peritonitis	5	4	9
Atresia			
Small intestine	2	6	8
Esophageal	1	5	6
Anorectal malformation	0	1	1
Total	26	72	98

*PNAC indicates parenteral nutrition–associated cholestasis.

Table 4. Sepsis Incidence*

	Male Patients	Female Patients	Total
With PNAC	24/1679 (14.3)	3/613 (4.9)	27/2292 (11.8)†
Without PNAC	12/1278 (9.4)	12/2079 (5.8)	24/3357 (7.1)†
Total	36/2957 (12.2)‡	15/2692 (5.6)‡	51/5649 (9.0)

*Data are given as number of septic events/number of hospital days (sepsis incidence per 1000 hospital days). PNAC indicates parenteral nutrition–associated cholestasis.

†The incidence of sepsis was higher ($P = .08$) in patients with PNAC vs patients without PNAC.

‡The incidence of sepsis was significantly higher ($P = .01$) in male vs female patients.

tribution might then ensue if the underlying disease would generally be more severe in male than in female patients. We are not aware of any such differences. Also, days receiving PN and length of hospital stay do not solely reflect the severity of disease but are the composite result of the severity of the underlying disease,^{14,23,24} the adverse effect of PNAC on intestinal function,²⁵ and the adverse effects of disease-related and iatrogenic complications like septic events. Moreover, days receiving PN and length of hospital stay were similar in male compared with female patients and, therefore, do not explain the observed association between male sex and PNAC.

An association between male sex and sepsis has recently also been demonstrated in adult surgical intensive care unit (ICU) patients. Wichmann et al²⁶ found a significantly higher incidence of severe sepsis in men when compared with women. Similarly, male sex has been identified as a risk factor for nosocomial pneumonia in adult ICU patients.²⁷ Furthermore, Hubacek et al²⁸ recently demonstrated an association between sepsis and common polymorphisms in the gene for lipopolysaccharide-binding protein, a protein secreted into the bloodstream by hepatocytes that plays a crucial role in the modulation of lipopolysaccharide-induced cell responses in male, but not in female, ICU patients. We are not aware of similar data in pediatric surgical ICU patients. Animal experiments²⁹⁻³¹ suggest the underlying mechanism is a detrimental immunological effect of the male sex steroid testosterone or of low levels of female sex steroids. Interestingly, these immunological effects of sex steroids are reversed in older animals.^{32,33}

The relation between sepsis and PNAC is controversial. It has long been known that a severe bacterial infection may cause cholestatic jaundice in infants. It may be the only symptom of the infection, or precede it, and is completely reversible in those who survive.³⁴ Jaundice accompanying bacterial infections has been described in adults as well.³⁵ In the study by Wichmann et al,²⁶ male sex not only increased the risk of severe sepsis but also the incidence of septic liver failure. Interestingly, mortality was not influenced by sex,²⁶ suggesting that in adult ICU patients septic liver failure is reversible too.

Several,^{5,8,12,17,18} but not all,^{19,36} studies have shown that sepsis is seen in a larger proportion of patients with PNAC than patients without PNAC, and concluded that sepsis is a risk factor for PNAC. Most of these studies, however, did not account for differences in sex ratio or exposure time, ie, length of stay, even though greater length of stay had previously been associated with PNAC.^{2,4} In effect, these studies were sepsis prevalence studies. When male and female patients are taken together, the sepsis prevalence in our patients with PNAC was 50%, implying that PNAC occurred and progressed in 1 of 2 patients without the aid of a septic event. In only 1 of 3 did sepsis occur before PNAC was diagnosed. Sepsis incidence in patients with PNAC tended to be higher than in patients without PNAC, but remained low (11.8 per 1000 hospital days, ie, approximately 1 event in 3 months, vs 7.1 per 1000 hospital days). These incidences resemble those found by Sondheimer et al¹⁴ in 42 newborns receiving long-term PN after neonatal intestinal resection (approximately 10-12 per 1000 hospital days in patients with PNAC and 4 per 1000 hospital days in patients without PNAC). The overall sepsis incidence in our study (9 per 1000 hospital days) was comparable to those recently found in surgical newborns³⁷ and in surgical patients of all pediatric ages¹⁷ (7.3 per 1000 days in both studies). In the study by Sondheimer et al, the age at first infection was much lower in infants with PNAC than in infants without PNAC, and cholestasis developed relatively shortly after the first infection in 90% of the patients. Unfortunately, Sondheimer et al did not describe the sex distribution of their patients. Our data suggest that observed differences between patients with PNAC and patients without PNAC may depend on the number of male patients with PNAC.

Whereas many researchers find sepsis an important risk factor for the initiation or progression of PNAC, some have taken a different view^{2,19} or have argued that an increased sepsis incidence is a consequence rather than a cause of PNAC.^{8,20} In our study, sepsis incidence was not increased in female patients with PNAC and sepsis incidence was higher in male than in female patients, irrespective of the absence or presence of PNAC. Moreover, most septic events were caused by coagulase-negative staphylococci. These infections are thought to result from vascular access techniques and, to our knowledge, have never been linked to intestinal pathological features.³⁸ All these observations support the view that sepsis is an epiphenomenon of PNAC rather than a causative factor.

Our observation that male sex predisposes the surgical newborn to PNAC and to sepsis may explain the association between sepsis and cholestasis found in other

studies. If our findings are corroborated, they may have implications for our understanding of the mechanism of disease and for the design of studies aiming to prevent or treat PNAC.

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Surgical Anatomy

There are five types of choledochal cysts:
 Type I: Dilation of the common bile duct
 Type II: Diverticulum of the common bile duct
 Type III: Choledochocele
 Type IV: Multiple intrahepatic and extrahepatic choledochocysts
 Type V: Single or multiple intrahepatic cysts (Caroli's disease).

Source: Blackbourne LH, Fleischer KJ. *Advanced Surgical Recall.* Baltimore, Md: Williams & Wilkins; 1997:874.