ARTICLE

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Patent ductus arteriosus and spontaneous intestinal perforation in a cohort of preterm infants

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OBJECTIVE: To assess whether either duration and magnitude of ductal shunt or medical treatment for patent ductus arteriosus (PDA) are related to spontaneous intestinal perforation (SIP).
STUDY DESIGN: Clinical charts of infants <29 weeks' gestation born from 2006 to 2018 were reviewed. Echocardiographic examinations were evaluated according to McNamara and Sehgal's staging system.
RESULTS: A higher percentage of patients with SIP had a hemodynamically significant PDA (HSPDA) and was treated with either NSAIDs or paracetamol (79% vs 53% and 81% vs 54%, respectively). Among non-treated patients, we found a 1.32 increase in the odds of SIP per day of persistence of HSPDA. In the cohort of patients treated despite the absence of HSPDA, we found a 2.35 increase in the odds of SIP per dose of drug administered.
CONCLUSION: Both treating a non-HSPDA and leaving a HSPDA to its natural history seem to be associated with SIP.

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INTRODUCTION

Spontaneous intestinal perforation (SIP) has been considered as a well-defined disease since the 80's [1]. Although both necrotizing enterocolitis (NEC)-related intestinal perforation and SIP affect the same organ and population, the two types of intestinal perforation are distinct clinical and pathological entities [2, 3]. SIP occurs in relatively younger and lower birth weight infants and usually happens within the first two weeks, in the absence of clinical and histological signs typical of NEC [4–6]. Clinical characteristics of SIP may include bluish discoloration of the abdomen and pneumoperitoneum or gasless abdomen on the X-ray, in the absence of pneumatosis intestinalis or portal venous air [7]. From a histopathologic point of view, SIP is characterized by a focal and isolated intestinal perforation with intact surrounding intestinal walls and with no evidence of intestinal inflammation and bowel ischemia typical of NEC [8]. In terms of outcomes, SIP appears to be related with poor development at 18–22 months similarly to surgical NEC [9, 10].

A persistent patent ductus arteriosus (PDA) is a frequent finding in preterm infants, affecting up to 60% of those born before 28 weeks' gestation [11]. It is often associated with other morbidities of prematurity, but its causative role is still uncertain [12]. Furthermore, the treatment of PDA remains controversial in terms of cost-effectiveness and its management has considerably changed over the past decade, shifting from early treatment, even prophylactical, to no treatment at all [13, 14]. It is still unclear if SIP is a consequence of the hemodynamic disturbance of the PDA on the mesenteric blood flow or, conversely, it is a side effect of cyclooxygenase inhibition determined by the drugs [15, 16]. Attempts to correlate SIP with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have led to contrasting observations. Prophylactic use of indomethacin has been associated with SIP in some studies [17], but not in the largest RCT on this topic [18], which did not make a clear distinction between SIP and NEC. Nevertheless, other studies seem to prove an increased risk related to indomethacin use alone [15, 19] or in association with postnatal steroids [20, 21]. In a 2004 randomized controlled trial by Gournay et al. ibuprofen also showed trends toward a higher risk of SIP [22]. More recently, Kelleher et al. observed a reduced incidence of SIP in infants exposed to prophylactic indomethacin and feeding as compared to controls [23]. Therefore, the contribution of NSAIDS to SIP remains controversial. In most recent years, the use of paracetamol has emerged as a possible alternative to NSAIDs in the treatment of PDA, given its high security profile (with fewer side effects, especially renal ones) and similar therapeutic efficacy [24, 25]. On the other hand, no data on the incidence of SIP among preterm infants receiving paracetamol are available to date [26].

PDA itself is believed to potentially damage the bowel integrity as a consequence of the diastolic blood steal from the mesenteric circulation. The lack of a standardized approach to define hemodynamically significant PDA (HSPDA) among different studies makes its clinical impact on neonatal morbidities difficult to determine [27]. In 2007 McNamara et al. proposed a staging system based on a set of echocardiographic parameters defining the magnitude of the ductal shunt [28]. We previously applied this scoring system to a cohort of preterm infants and tried to correlate the duration and the severity of ductal shunt to the risk of developing bronchopulmonary dysplasia [29].

Aim of present study is to evaluate the incidence of SIP in a cohort of preterm infants treated for PDA, and to assess whether

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the duration and magnitude of ductal shunt rather than the exposure to medical treatment are related to a higher risk of developing SIP.

METHODS

This observational, retrospective study was conducted at the Neonatal Intensive Care Unit of the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan on a consecutive cohort of preterm infants born between November 2006 and December 2018. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed and the study received the approval of the local ethical committee (Milano Area 2). All infants <29 weeks' gestational age were included in the study. Exclusion criteria were birth outside our institution, major malformations, critical congenital heart disease, and early death (in the first 72 h of life).

Electronic medical records of all included patients were retrospectively reviewed. The following demographic and clinical data were collected: gestational age (GA), sex, birth weight (BW), Apgar score, twin pregnancy and twin-to-twin transfusion (TTTS), intrauterine growth restriction (IUGR), use of antenatal steroids (ANS), premature rupture of membranes (PROM), clinical chorioamnionitis, early (in the first 72 h of life) or late (after 72 h of life) proven sepsis (with positive blood culture), need for inotropes, use of post-natal steroids and occurrence of SIP. SIP was defined as an intestinal perforation occurring in the first 15 days of life in the absence of clinical (e.g., bloody stools), radiographical (e.g., pneumatosis intestinalis, pneumobilia and portal venous gas) or histopathological (e.g., diffuse bowel ischemia) signs consistent with NEC. As to medications (e.g., inotropes and steroids), only those administrated within the first 15 days of life or before the diagnosis of SIP were taken into consideration.

A systematic review of all echocardiographic examinations was then carried out. We took into account only echocardiographic examinations performed before the onset of SIP (for patients who developed it) or during the first 15 days of life, assuming that a PDA cannot be considered a risk factor for intestinal perforation further on. The presence of PDA was evaluated and, for each day of ductal patency, the severity of the ductal shunt was estimated through the staging system proposed by McNamara and Sehgal [28]. This staging system provides four grades of severity of the ductal shunt, based on defined echocardiographic criteria: E1 (no evidence of ductal flow); E2 (small and non-significant PDA with transductal diameter <1.5 mm, restrictive continuous transductal flow, no signs of left heart pressure loading, no signs of left heart pressure loading, normal superior mesenteric arterial diastolic flow); E3 (moderate HSPDA with transductal diameter 1.5–3.0 mm, unrestrictive pulsatile transductal flow, LA:Ao ratio 1.5–2:1, mild-moderate left heart pressure loading, decreased or absent diastolic flow in superior mesenteric artery); and E4 (large HSPDA with transductal diameter >3.0 mm, unrestrictive pulsatile transductal flow, LA:Ao ratio > 2:1, mitral regurgitant jet >2.0 m/s, severe left heart pressure loading, reversal of end diastolic flow in the superior mesenteric artery).

A severity stage (E2, E3 or E4) was assigned to each day of ductal patency. In the event of missing daily assessments, in-between days were assigned partly (50%) to the stage detected on the first examination and partly (50%) to the stage detected on the second examination (e.g., if a stage 2 was detected on day of life 2 and no ultrasound was performed until day 5 when a stage 3 was detected, in-between days 3 and 4 were registered as stage 2 and 3, respectively). Thus, the duration of any ductal patency (E2 + E3 + E4) and the duration of HSPDA (E3 + E4) was calculated and expressed in days. Stages 3 and 4 of HSPDA were considered together due to the limited sample size of Stage 4. In our NICU all extremely preterm infants receive the first echo within 24 h from birth; subsequent examinations are scheduled according to the clinical and echocardiographic scenario.

Finally, if patients received a pharmacological treatment for PDA within the first 15 days of life or before perforation in case of SIP, the type of medication (ibuprofen, indomethacin or paracetamol), the timing of first dose and the number of doses given were recorded.

In our NICU the prevalent attitude towards PDA is a selective, early treatment approach but the final decision on whether, when and how to treat a PDA is discussed collegially. As a result, infants were preferably treated with ibuprofen but also indomethacin was used in some cases, while in recent years several patients were treated with paracetamol. In some cases, multiple courses of different drugs were attempted.

Clinical and demographic features of the two groups (SIP vs no SIP) were compared by using *t* test or Mann–Whitney *U* test for normally or non-normally distributed continuous variables, respectively, and by using Fisher's exact test for categorical variables. A $p < 0.05$ was considered statistically significant.

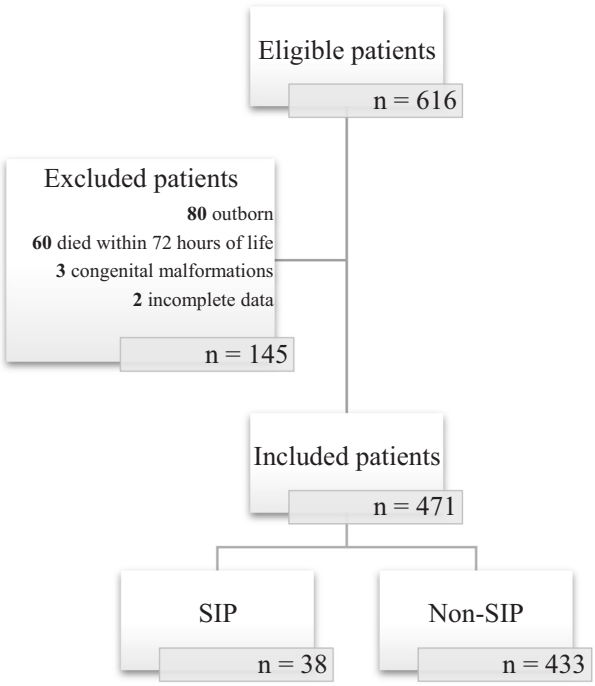
In order to study the association between PDA, NSAIDs and SIP, logistic regression was performed, adjusting for possible confounders and stratifying the sample by presence of HSDA or by need for medical treatment. Confounders were chosen among variables that are known risk factors for SIP and that showed a statistically significant difference between two groups in the initial univariate. For each variable, the odds ratio (OR) and the relative confidence interval (CI) were obtained. All statistical analyses were performed with SPSS Statistics 25 (IBM Corp., Armonk, New York).

RESULTS

Between November 2006 and December 2018, 616 infants were eligible for the study: 145 were excluded, mainly because they were outborn or deceased within the first 72 h of life, and 471 were included in the study (Fig. 1). Among these, 38 (8%) developed SIP. Approximately 95% of patients had a diagnosis of PDA, which was confirmed for at least 2 days in 356 infants (75.6%), and 265 patients (56.3%) received a treatment for PDA, either NSAIDs or paracetamol. SIP was diagnosed in 31 out of 265 treated patients (11.7%) and 7 out of 206 non-treated patients (3.4%). SIP occurred in 26 out of 241 patients (10.8%) who received NSAIDs only.

Newborns who developed SIP had lower GA and BW, a lower Apgar score at 1 and 5 min, an increased need for inotropes and post-natal steroids and an increased incidence of late-onset sepsis. No differences were detected in terms of sex, twin pregnancy, TTTS, IUGR, clinical chorioamnionitis, PROM, early-onset sepsis, minimal enteral feeding (MEF), and day of feeding (Table 1).

PDA (any grade > 2 days) was more common (97% vs 73%, $p <$ 0.001) and with longer exposure (7 days vs 4 days, p 0.012) in



SIP, spontaneous intestinal perforation

Fig. 1 Inclusion flow diagram. Flow chart shows number of eligibile patients, number of excluded patients and causes of exclusion, number of included patients and numerosity of SIP and non SIP groups.

infants who developed SIP. Focusing on HSPDA, patients with SIP presented with HSPDA more frequently (79% vs 53%, p 0.002) and for a longer period of time (2.5 days vs 1 day, p 0.003; Table 2).

Moreover, a higher percentage of patients with SIP underwent a medical treatment for PDA, especially considering any kind of treatment (e.g., NSAIDs or paracetamol, 81% vs 54%, p 0.001) compared to NSAIDs only (68% vs 50%, p 0.028; Table 2). Also 7 out of 206 non-treated patients developed SIP: they all had HSPDA but could not be treated due to contraindications. Medical treatment was administered at a median time of 48 h after birth in both groups, without significant differences.

Logistic regression was performed after correction for confounders (i.e., GA, Apgar score at 5 min after birth, use of postnatal steroids and need for inotropes) and after stratification of the sample for presence of HSPDA or medical treatment for PDA. Indeed, since interaction and effect modification between these two variables was assessed, resulting statistically significant (p 0.045), stratification of the sample was required in order to study the specific effect of one variable on the risk of developing SIP. Therefore, a first analysis stratifying the sample for the presence of a medical treatment for PDA was performed and two different cohorts were identified: non-treated patients ($n = 265$) and treated patients ($n = 206$). In the cohort of non-treated patients, we found an increased odds of 1.32 of developing SIP per day of persistence of HSPDA (OR 1.32, 95% CI 1.03–1.70), while no effect of HSPDA could be identified in the cohort of treated patients (OR 0.95, 95% CI 0.83–1.07).

A second analysis stratifying the sample for the presence of HSPDA was then performed and two different cohorts were identified: patients with HSPDA ($n = 262$) and patients without HSPDA ($n = 209$). In the cohort of patients with no evidence of HSPDA, we found a 2.35-fold increase in the odds of SIP per dose of NSAIDs or paracetamol administered (OR 2.35, 95% CI 1.42–4.54). In the cohort of patients affected by HSPDA, no effect of medical treatment on developing SIP could be recognized (OR 1.03, 95 IC % 0.96–1.09).

Table 1. Comparison of demographic and clinical data between groups.

	Non-SIP ($n = 433$)	SIP ($n = 38$)	p value
GA, weeks, mean (±SD)	26.3 (±1.6)	25.2 (±1.6)	<0.001*
Weight, grams, mean (±SD)	851.8 (±256.4)	755.4 (±190.3)	0.024*
APGAR 1′, median (IQR)	5 (4; 7)	4 (3; 6)	0.008^
APGAR 5′, median (IQR)	8 (7; 8)	7 (6.75; 8)	0.004^
IUGR, *n* (%)	76 (17%)	2 (0.5%)	0.065°
Male sex, *n* (%)	219 (50%)	21 (55%)	0.615°
Twins, *n* (%)	162 (37%)	14 (37%)	>0.999°
TTTS, *n* (%)	44 (10%)	4 (10%)	>0.999°
Clinical chorioamnionitis, *n* (%)	125 (29%)	15 (39%)	0.195°
PROM, *n* (%)	164 (38%)	19 (50%)	0.165°
Early-onset sepsis, *n* (%)	14 (3%)	1 (2%)	>0.999°
Late-onset sepsis, *n* (%)	41 (9%)	11 (29%)	0.001°
Postnatal corticosteroids, *n* (%)	135 (31%)	19 (50%)	0.029°
Inotropes, *n* (%)	204 (47%)	26 (68%)	0.012°
MEF, *n* (%)	402 (93%)	36 (95%)	>0.999°
Day of starting MEF, median (IQR)	2 (2; 3)	3 (2; 3)	0.060^

GA gestational age, *IUGR* intrauterine growth restriction, *IQR* interquartile range, *MEF* minimal enteral feeding, *PROM* premature rupture of membranes, *SD* standard deviation, *TTTS* twin-to-twin transfusion.
*Student's *t* test, ^Mann–Whitney *U* test, °Fisher's exact test.

DISCUSSION

During this 12-year study, the incidence of SIP was 8%, in line with the literature on the topic [8]. With regard to patients who received a medical treatment for PDA, the incidence of SIP was 11.7%, which declined to 10.8% considering a treatment with NSAIDs only. Previously, Rao et al. described a 8.8% occurrence of SIP in a cohort of preterm infants treated with ibuprofen for PDA [30].

The echocardiographic PDA staging system proposed by McNamara et al. allowed us to discriminate different stages of severity of PDA and to study its influence on clinical outcome in our population in terms of SIP. We observed that the treatment of a non-significant PDA is associated with a 2.35 increase in the odds of SIP for each additional administered dose of NSAIDs or paracetamol. On the other hand, we found a 1.32 increase in the odds of SIP for each day of exposure to a E3 or E4 PDA, in the absence of medical treatment.

This study leads to two distinct observations: treating a PDA that does not meet the criteria for hemodynamically significance increases the odds of SIP and leaving a HSPDA to its "natural history" also may increase the odds of SIP. Unfortunately, in the interception of the two systems, i.e., patients with a HSPDA and pharmacologically treated, the statistical analysis does not allow us to clarify what could be the relative contribution of either HSPDA clinical dimension or pharmacological treatment to the development of SIP.

As far as SIP prevention is concerned, the more convincing strategy seems to be an early targeted treatment, based on the

Table 2. Comparison of magnitude and duration of ductal shunt and pharmacological treatment between groups.

	Non-SIP ($n = 433$)	SIP ($n = 38$)	p value
PDA any grade >2 days, *n* (%)	319 (73%)	37 (97%)	<0.001°
PDA E3E4, *n* (%)	231 (53%)	30 (79%)	0.002°
PDA E4, *n* (%)	20 (5%)	2 (5%)	0.695°
Reverse flow SMA, *n* (%)	17 (4%)	2 (5%)	>0.999°
PDA E2E3E4, days, median (IQR)	4 (2; 9)	7 (5; 9)	0.012^
PDA E3E4, days, median (IQR)	1 (0; 3)	2.5 (1; 5)	0.003^
PDA E2, days, median (IQR)	3 (1;5)	3 (2; 4)	0.232^
PDA E2[†], days, median (IQR)	3 (1; 5)	3 (3; 6)	0.219^
Treatment with NSAIDs, *n* (%)	215 (50%)	26 (68%)	0.028°
Treatment with NSAIDs or paracetamol, *n* (%)	234 (54%)	31 (81%)	0.001°
Time to treatment, hours, median (IQR)	48 (24; 97)	48 (26; 96)	0.853^
NSAIDs total doses, median (IQR)	0 (0; 3)	3 (0; 3)	0.023^
NSAIDs or paracetamol total doses, median (IQR)	1 (0; 3)	3 (1.8; 5.5)	<0.001^

IQR interquartile range, *SD* standard deviation, *SMA* superior mesenteric artery.
*Student's *t* test, ^Mann–Whitney *U* test, °Fisher's exact test.
[†]Excluding patients with PDA classified at least once as E3 or E4.

prompt echocardiographic identification of a HSPDA before it becomes symptomatic. In these terms, the Neonatologist Performed Echocardiography (NPE) seems to be the more useful tool to select preterm infants who might benefit the most with pharmacological treatment [31, 32]. The definition of hemodynamical significance is still under debate. Therefore, a growing body of literature proposes a comprehensive evaluation of clinical, laboratory, such as NT-proBNP [33, 34], and instrumental data, such as Near-Infrared Spectroscopy (NIRS) [35, 36], other than echo. No single parameter can, in fact, predict the risk of non-spontaneous closure of the ductus arteriosus and the possible related co-morbidities [37]. Following the staging system used in this study [28], other staging strategies have been suggested in literature, combining risk factors for non-spontaneous closure, clinical criteria and echocardiographic criteria in the attempt of defining the outcome of a HSPDA [38–41]. However, none of these have been translated into clinical practice. It is mandatory to specify that data supporting the evidence of real efficacy and long-term beneficial effects of early targeted treatment are still lacking and the results of RCTs in progress at present time might give us a clearer picture [42].

From this perspective, our study may provide a further validation to McNamara's PDA staging system.

The association that we found between SIP and paracetamol could cause some concerns. Nevertheless, our data showed that SIP was more common in patients treated with the whole range of pharmacological options, i.e., including paracetamol, (81% vs 54%, *p* 0.001) rather than in those treated with NSAIDs only (68% vs 50%, *p* 0.028). Paracetamol has emerged in recent years as a valid alternative to cyclooxygenase inhibitors in the treatment of PDA, also showing an equal therapeutic efficacy in the latest meta-analysis [24, 25] and fewer side effects, in particular kidney-related, even though no data are available on the incidence of SIP in paracetamol treated preterm infants [24, 26]. Given that the pharmacological mechanisms of action of paracetamol are not so different from that of NSAIDs (possibly involving different sites of the same enzyme complex responsible for the synthesis of prostaglandin H2) [43], this conceivable association should be better investigated in future studies.

The timing of treatment with NSAIDs represents another largely debated issue, with focus on a possible association between early administration and a greater risk of SIP [15, 19]. Our study does not seem to confirm this association, since no differences have been found among SIP and non-SIP groups in terms of timing of treatment. On the other hand, we have observed a greater use of postnatal steroids in SIP patients (31% vs 50%, p 0.029) as previously observed in other studies [20, 21].

Last but not least, our data show an association among SIP and late onset sepsis (LOS) (29% vs 9%, p 0.001), which has already been outlined by other studies [44, 45]. Nevertheless, the association has been previously related to Candida albicans and Coagulase-Negative Staphylococci (CoNS) [44, 45] infections, while in our cohort of patients the majority of infections within the group of SIP cases were caused by Gram negative bacteria. It is our opinion that even if we focused on LOS which were diagnosed before or in concomitance with the event of perforation, it is difficult to determine if bacteremia was causative or consequence of SIP.

In conclusion, our data suggest that both treating a non-HSPDA and delaying treatment of a HSPDA are associated with SIP. Accordingly, neither a prophylactic treatment of PDA nor a wait-and-see approach may be supported, while a targeted treatment after a thorough analysis of echocardiographic findings may be the best option. Paracetamol should be used with caution since it does not seem to be risk-free in the pathogenesis of SIP. Further large population-based studies are still needed to clarify the role of HSPDA and its treatment in the pathogenesis of SIP.

REFERENCES

1. Aschner JL, Deluga KS, Metlay LA, Emmens RW, Hendricks-Munoz KD. Spontaneous focal gastrointestinal perforation in very low birth weight infants. J Pediatr. 1988;113:364–7.
2. Gordon PV. Understanding intestinal vulnerability to perforation in the extremely low birth weight infant. Pediatr Res. 2009;65:138–44.
3. Buchheit JQ, Stewart DL. Clinical comparison of localized intestinal perforation and necrotizing enterocolitis in neonates. Pediatrics. 1994;93:32–6.
4. Gordon PV, Attridge JT. Understanding clinical literature relevant to spontaneous intestinal perforations. Am J Perinatol. 2009;26:309–16.
5. Novack CM, Waffarn F, Sills JH, Pousti TJ, Warden MJ, Cunningham MD. Focal intestinal perforation in the extremely-low-birth-weight infant. J Perinatol. 1994;14:450–3.
6. Okuyama H, Kubota A, Oue T, Kuroda S, Ikegami R, Kamiyama M. A comparison of the clinical presentation and outcome of focal intestinal perforation and necrotizing enterocolitis in very-low-birth-weight neonates. Pediatr Surg Int. 2002;18:704–6.
7. Vongbhavit K, Underwood MA. Intestinal perforation in the premature infant. J Neonatal Perinat Med. 2017;10:281–9.
8. Pumberger W, Mayr M, Kohlhauser C, Weninger M. Spontaneous localized intestinal perforation in very-low-birth-weight infants: A distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg. 2002;195:796–803.
9. Wadhawan R, Oh W, Hintz SR, Blakely ML, Das A, Bell EF, et al. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. J Perinatol. 2014;34:64–70.
10. Wadhawan R, Oh W, Vohr BR, Saha S, Das A, Bell EF, et al. Spontaneous intestinal perforation in extremely low birth weight infants: association with indometacin therapy and effects on neurodevelopmental outcomes at 18-22 months corrected age. Arch Dis Child Fetal Neonatal Ed. 2013;98:F127–32.
11. Sehgal A, McNamara PJ. The ductus arteriosus: a refined approach! Semin Perinatol. 2012;36:105–13.
12. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis. J Perinatol. 2010;30:241–52.
13. El-Khuffash A, Weisz DE, McNamara PJ. Reflections of the changes in patent ductus arteriosus management during the last 10 years. Arch Dis Child Fetal Neonatal Ed. 2016;101:F474–8.
14. Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? Eur J Pediatr. 2009;168:907–14.
15. Attridge JT, Clark R, Walker MW, Gordon PV. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. J Perinatol. 2006;26:93–9.
16. Bloom B. Attridge et al. present an analysis of a complex data set, which offers important confirmation of the differences between the clinical presentation of spontaneous intestinal perforations (SIP) and surgical necrotizing enterocolitis (NEC). J Perinatol. 2006;26:384–6.
17. Fujii AM, Brown E, Mirochnick M, O'Brien S, Kaufman G. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol. 2002;22:535–40.
18. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis. N. Engl J Med. 2001;344:1966–72.
19. Sharma R, Hudak ML, Tepas JJ, Wludyka PS, Teng RJ, Hastings LK, et al. Prenatal or postnatal indomethacin exposure and neonatal gut injury associated with isolated intestinal perforation and necrotizing enterocolitis. J Perinatol. 2010;30:786–93.
20. Stark A, Carlo W, Tyson J, Papile L, Wright L, Shankaran S, et al. Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N. Engl J Med. 2001;344:95–101.
21. Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114:1649–57.
22. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:1939–44.
23. Kelleher J, Salas AA, Bhat R, Ambalavanan N, Saha S, Stoll BJ, et al. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics. 2014;134:e1369–77.
24. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants a systematic review and meta-analysis. JAMA. 2018;319:1221–38.

25. Marconi E, Bettiol A, Ambrosio G, Perduca V, Vannacci A, Troiani S, et al. Efficacy and safety of pharmacological treatments for patent ductus arteriosus closure: a systematic review and network meta-analysis of clinical trials and observational studies. Pharm Res. 2019;148:104418.
26. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low-birth-weight infants. Cochrane Database Syst Rev. 2018;4: CD010061. https://doi.org/10.1002/14651858.CD010061.pub3.
27. Shepherd JL, Noori S. What is a hemodynamically significant PDA in preterm infants? Congenit Heart Dis. 2019;14:21–6.
28. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed. 2007;92:424–7.
29. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr. 2015;166:1488–92.
30. Rao R, Bryowsky K, Mao J, Bunton D, McPherson C, Mathur A. Gastrointestinal complications associated with ibuprofen therapy for patent ductus arteriosus. J Perinatol. 2011;31:465–70.
31. van Laere D, van Overmeire B, Gupta S, El Khuffash A, Savoia M, McNamara PJ, et al. Application of NPE in the assessment of a patent ductus arteriosus. Pediatr Res. 2018;84:46–56.
32. O'Rourke DJ, El-Khuffash A, Moody C, Walsh K, Molloy EJ. Patent ductus arteriosus evaluation by serial echocardiography in preterm infants. Acta Paediatr. 2008;97:574–8.
33. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ. Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed. 2008;93:F407–12.
34. El-Khuffash AF, Amoruso M, Culliton M, Molloy EJ. N-terminal pro-B-type natriuretic peptide as a marker of ductal haemodynamic significance in preterm infants: a prospective observational study. Arch Dis Child Fetal Neonatal Ed. 2007;92:F421–2.
35. Chock VY, Rose LA, Mante JV, Punn R. Near-infrared spectroscopy for detection of a significant patent ductus arteriosus. Pediatr Res. 2016;80:675–80.
36. Arman D, Sancak S, Gürsoy T, Topcuoğlu S, Karatekin G, Ovalı F. The association between NIRS and Doppler ultrasonography in preterm infants with patent ductus arteriosus. J Matern Neonatal Med. 2020;33:1245–52.
37. Lee JA. Practice for preterm patent ductus arteriosus; focusing on the hemodynamic significance and the impact on the neonatal outcomes. Korean J Pediatr. 2019;62:245–51.
38. Gursoy T, Hayran M, Derin H, Ovali F. A clinical scoring system to predict the development of bronchopulmonary dysplasia. Am J Perinatol. 2014;32:659–65.
39. El-Khuffash AF, Slevin M, McNamara PJ, Molloy EJ. Troponin T, N-terminal pro natriuretic peptide and a patent ductus arteriosus scoring system predict death before discharge or neurodevelopmental outcome at 2 years in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2011;96:133–8.
40. El-Khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr. 2015;167:1354–61.
41. Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: role in predicting outcomes. Eur J Pediatr. 2013;172:179–84.
42. Wyllie JP, Gupta S. Prophylactic and early targeted treatment of patent ductus arteriosus. Semin Fetal Neonatal Med. 2018;23:250–4.
43. Jasani B, Weisz DE, McNamara PJ. Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants. Semin Perinatol. 2018;42:243–52.
44. Meyer CL, Payne NR, Roback SA. Spontaneous, isolated intestinal perforations in neonates with birth weight <1,000 g not associated with necrotizing enterocolitis. J Pediatr Surg. 1991;26:714–7.
45. Adderson EE, Pappin A, Pavia AT. Spontaneous intestinal perforation in premature infants: a distinct clinical entity associated with systemic candidiasis. J Pediatr Surg. 1998;33:1463–7.

AUTHOR CONTRIBUTIONS

AM, GF, NP, FS and FM contributed to the conception and the design of the manuscript. AM collected the data retrospectively. AM, NP and FS performed statistical analysis. AM and GF wrote the first draft of the manuscript. All authors contributed to manuscript critical revision, read and approved the submitted version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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