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High-Dose Oral Erythromycin Decreased the Incidence of Parenteral Nutrition-Associated Cholestasis in Preterm Infants

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Background & Aims: Feeding intolerance because of functional gastrointestinal dysmotility and parenteral nutrition-associated cholestasis (PNAC) are common problems in preterm, very-low-birth-weight (VLBW) infants. This double-blind, randomized, placebo-controlled study aimed to assess the effectiveness of “high-dose” oral erythromycin as a prokinetic agent in decreasing the incidence of PNAC. Two secondary end points, including the time to achieve full enteral feeding and the duration of parenteral nutrition, were also evaluated. **Methods:** Infants consecutively admitted to the neonatal unit were randomized to receive erythromycin (12.5 mg/kg/dose every 6 hours for 14 days) or an equivalent volume of normal saline (placebo) if they attained less than half the total daily fluid intake (<75 mL/kg/day) as milk feeds on day 14 of life. **Results:** Of 182 VLBW infants enrolled, 91 received erythromycin. The incidence of PNAC was significantly lower in erythromycin-treated infants (18/91) compared with placebo infants (37/91; $P = .003$). Treated infants achieved full enteral nutrition significantly earlier (mean, 10.1; SE, 1.7 days; $P < .001$), and the duration of parenteral nutrition was also significantly decreased by 10 days ($P < .001$). Importantly, fewer infants receiving erythromycin had 2 or more episodes of septicemia ($n = 4$) compared with placebo patients ($n = 13$, $P = .03$). No serious adverse effect was associated with erythromycin treatment. **Conclusions:** High-dose oral erythromycin can be considered as a rescue measure for VLBW infants who fail to establish adequate enteral nutrition and in whom anatomically obstructive pathologies of the gastrointestinal tract have been excluded.

Milk intolerance associated with nonanatomically obstructive (ie, functional) gastrointestinal dysmotility is a common feeding problem in preterm, very-low-birth-weight (VLBW; <1500 g) infants.^{1,2} This clinical entity is believed to be the consequence of ineffective, infrequent, and uncoordinated bowel activity secondary to immaturity of the gastrointestinal tract.^{1,2} The difficulty of accurate interpretation of clinical signs and symptoms related to feed intolerance and the constant

fear of necrotizing enterocolitis (NEC)^{3,4} and gastrointestinal perforation associated with commonly used drugs such as corticosteroids and prostaglandin inhibitors^{5–7} often result in unnecessary and prolonged usage of parenteral nutrition. Because long-term hyperalimentation has been associated with increased risks of morbidity and life-threatening complications such as parenteral nutrition-associated cholestasis (PNAC),^{1,2} recurrent septicemia,^{8,9} biochemical rickets, nutritional deficiency and pain, as well as anesthetic risk because of repeated intravenous and long line insertion,¹⁰ prokinetic agents that can enhance gastrointestinal motility may be beneficial to these infants by promoting enteral feeding and reducing the duration of parenteral nutrition and associated adverse effects.

In 1997, we reported on a series of 7 preterm infants successfully treated with oral erythromycin for refractory gastrointestinal dysmotility.¹⁰ This affirmative experience led us to perform a preliminary randomized controlled trial (RCT) that demonstrated that oral erythromycin introduced at day 15 of life was effective in facilitating enteral feeding in VLBW infants with moderately severe gastrointestinal dysmotility.¹¹ More importantly, there was a nonsignificant trend suggesting that more infants with prolonged feed intolerance developed PNAC in the placebo group than in the oral erythromycin group.¹¹ However, there has been much controversy concerning the use of oral/intravenous erythromycin in promoting enteral feeding in preterm infants. To date, only a limited number of relatively small RCTs have been performed.^{11–18} Additionally, we considered that shortening of duration for achieving full enteral feeding alone was not a sufficient reason to recommend the use of prokinetic treatment in VLBW infants. Without definitive improvement in associated clinical outcomes such as PNAC, sepsis, and complications secondary to prolonged use of parenteral nutrition, treatment with erythromycin is

Abbreviations used in this paper: HIDA, hepatobiliary iminodiacetic acid; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PNAC, parenteral nutrition-associated cholestasis; VLBW, very low birth weight.

probably not clinically justified. Thus far, none of the published reports,¹²⁻¹⁸ including our own preliminary trial,¹¹ has adequate statistical power to address these critical issues. We, therefore, extended our original study to evaluate the impact of erythromycin on important clinical outcomes. The primary objective of this RCT is to evaluate whether the use of "high" (antimicrobial) dose oral erythromycin as a "rescue" treatment for gastrointestinal dysmotility is able to decrease the incidence of PNAC in VLBW infants. Furthermore, there are 2 secondary objectives: (1) first, to estimate more precisely the benefit of oral erythromycin as a prokinetic agent in promoting enteral feeding and (2), second, to determine whether the use of oral erythromycin can shorten the duration for requirement of parenteral nutrition. Acquiring such information will enable neonatal clinicians to define better the usefulness of oral erythromycin as a prokinetic agent in vulnerable infants. A reduction in the incidence of PNAC and the number of days on parenteral nutrition would greatly improve the well-being of preterm infants and could also translate into substantial savings on hyperalimentation and the need for investigation of prolonged cholestatic jaundice.

Materials and Methods

Patients

VLBW infants consecutively admitted to the neonatal intensive care unit (NICU) at the Prince of Wales Hospital, Hong Kong, during the 2 time periods—(1) November 1998 to May 2000 (phase 1) and (2) August 2002 to September 2006 (phase 2)—and satisfying the inclusion and exclusion criteria were eligible for recruitment into the study. The phase 1 study represented the period in which patients were recruited for the preliminary RCT,¹¹ and the phase 2 study comprised the period of subsequent recruitment for the extended trial. The gap period of nonrecruitment was the time taken to plan the phase 2 study and to apply for external funding to continue with the research project. The inclusion and exclusion criteria for the 2 recruitment periods were identical. In brief, the inclusion criteria were preterm infants (1) with birth weight <1500 g, (2) who received less than half of the total daily fluid intake or <75 mL/kg/day of milk feeds by the oral route on day 14 of postnatal age, and (3) with parental consent for entering into the study.¹¹ Infants were excluded if they had the following: (1) lethal congenital abnormalities or chromosomal disorders; (2) congenital cyanotic heart disease; (3) anatomic obstructive gastrointestinal pathologies, such as intestinal malrotation with or without volvulus, stenosis, or atresia, gastroschisis, exomphalos and Hirschsprung's disease; (4) NEC; or (5) undergone major gastrointestinal surgery within the first 14 days of life.¹¹ The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong for both phase 1

and phase 2 studies, and written parental consent was obtained before randomization and enrolment for each case.

Sample Size

After the phase 1 study, we retrospectively reviewed the incidence of PNAC in VLBW infants in the NICU. Cholestatic jaundice is conventionally defined as serum conjugated bilirubin concentration >34 mmol/L (ie, >2 mg/dL) in newborns.^{2,19-21} Although the cut-off value is considered arbitrary and does not necessarily correlate with any specific hepatic pathology, it has been extensively used in neonatal studies.^{2,19-21} The incidence of PNAC in VLBW infants who failed to attain half the expected volume of enteral feeding on day 14 for the past 3 consecutive years was found to vary between 35% and 43%. We made the assumption of decreasing the incidence from 40% to 20% after introducing oral erythromycin, and it was determined that 91 infants would be required in each arm (ie, a total of 182 infants) of an RCT to detect a significant difference at the 5% level and with a power of 80%. Because our experience in the phase 1 study indicated that we could recruit 56 infants with gastrointestinal dysmotility within a period of 19 months, we expected to complete the recruitment of the extra 126 infants within a 43-month period. We managed to enroll the full quota of patients in 50 months (phase 2 study). The delay was most likely due to the substantial drop in admissions to the NICU at the Prince of Wales Hospital during the severe acute respiratory syndrome (SARS) outbreak in March 2003 in Hong Kong because we admitted 2 of the sickest preterm infants born to mothers with SARS-associated coronavirus infection.²² The NICU statistics suggested that the general public took at least 6 to 9 months to regain confidence to give birth at the Prince of Wales Hospital and, hence, could explain the slight delay of the recruitment process.

Randomization

VLBW infants satisfying the entry criteria were randomly assigned by a computer minimization program on day 14 to receive either oral erythromycin or the placebo solution (normal saline). A research assistant not involved in the clinical care of infants performed the randomization by minimizing 3 predetermined clinical parameters that could potentially influence enteral feeding: gestational age, birth weight, and age at introduction of enteral feeding.¹¹ The attending clinical team looking after the infants was completely unaware of the randomization assignments because each recruited infant was labeled with a trial code number.

Medications

The enteral route of drug administration was purposefully chosen because life-threatening or fatal cardiac dysrhythmias associated with erythromycin were mainly

observed in patients with parenteral route of drug delivery.^{23,24} The peak serum erythromycin concentration after an intravenous infusion is typically 4- to 10-fold higher than the circulating level achieved by the same medication when it is given orally.²⁵⁻²⁷ Because the safe dosage of intravenous erythromycin has not been determined in VLBW infants,²⁸ administration of this drug by the intravenous route is, therefore, best avoided.

Oral erythromycin was commenced on day 15 of life because of the following reasons. A recent, large, population-based study has indicated that, although early exposure to erythromycin (ie, 3-13 days of life) was associated with an 8-fold increased risk of developing infantile hypertrophic pyloric stenosis, there was no evidence to suggest any increase in risk exposing to the same medication after 13 days of postnatal age.²⁹ Second, the timing and dosage of drug administration between the first and the second phase of the study should be the same. Third, we considered starting prokinetic treatment on day 15 of life to be optimal because oral erythromycin was used in this study as a "rescue" treatment. Thus, adequate time should be allowed for assessing the severity of gastrointestinal dysmotility and to exclude anatomic bowel obstruction, NEC, and other ominous gastrointestinal pathologies.

We opted to use a high (antimicrobial) dose of erythromycin (12.5 mg/kg/dose) in preference to a low-dose regime (1.5-5 mg/kg/dose)¹⁴⁻¹⁶ because of the following: (1) our previous clinical experience in the case series study¹⁰ and our preliminary RCT¹¹ both suggested that the high-dose regime was effective in promoting milk feeding and significantly reduced the time to achieve full enteral nutrition in VLBW infants, (2) higher doses of erythromycin have been shown to shorten the whole gut transit time and facilitate gastric emptying by stimulating postprandial antroduodenal motor activity,³⁰⁻³² (3) previous studies using the low-dose regime often required large intravenous loading doses of erythromycin (15-30 mg/kg/day) for the first few days of treatment,^{33,34} and (4) the oral route of drug administration is likely to be associated with a lower serum concentration than that achieved by the intravenous route.²⁵⁻²⁷

Patients randomized to receive the active treatment were prescribed erythromycin (Ery-Ped, erythromycin ethylsuccinate diluted to 12.5 mg/mL with sterile water; Abbott Laboratories, Abbott Park, IL) 12.5 mg/kg given every 6 hours, whereas infants allocated to receive the placebo solution were given an equivalent volume of normal saline. Because the Ery-Ped is a white liquid suspension, both the active drug and placebo solution were mixed thoroughly into milk feeds to mask their appearance from the attending neonatal team. This task was performed by 2 designated research staff members who were not involved in the daily clinical care of these infants. Furthermore, the drug preparation was identified only by a trial code number to ensure effective blinding.

The drug treatment was started on day 15 of postnatal age immediately after randomization, and all infants received a 14-day course of treatment. If oral feeding had to be discontinued after starting the study, all oral medications, including erythromycin and placebo solution, were suspended. Administration of the study solutions was resumed only after the infants were restarted on enteral nutrition. During both phases of the study, the use of other prokinetic agents such as cisapride, domperidone, and metoclopramide was strictly prohibited. Electrocardiography was performed immediately before and in the second week of drug treatment to assess the QTc intervals.

Enteral and Parenteral Nutrition

All VLBW infants were routinely started on parenteral nutrition (6% TrophAmine; McGaw Inc, Irvine, CA, and 20% Intralipid; Kabi Pharmacia AB, Stockholm, Sweden) on day 3 of life according to the unit guidelines. Oral milk feeds were usually started within the first week of life (usually between day 3 and day 6) at the discretion of the attending clinical team and were given as intermittent boluses under gravity through the orogastric tube starting at 1 mL/h. The attending nurse aspirated the stomach once every 4 hours to measure the gastric residuals. Oral intake was then increased cautiously at a rate of 0.5-1 mL/h/day as tolerated. Infants were fed mother's milk whenever possible, but preterm commercial formulas were also used with mothers' permission if breast milk was not available. All infants were examined at least twice a day and closely monitored for the occurrence of regurgitation/vomiting, diarrhea, abdominal distention, and volume of gastric residuals. A strict protocol was implemented for discontinuing and restarting of enteral feeding. The attending clinician would consider discontinuing enteral feeding when (1) vomiting or significant regurgitation more than 2 times in 24 hours, (2) volume of gastric residuals exceeded half of the oral intake in the previous 4 hours on 2 occasions within the same day, (3) clinical signs and symptoms were suggestive of NEC or other sinister intraabdominal pathologies, and (4) repeated regurgitation resulting in aspiration pneumonia. Oral feeding together with the study drug was resumed as soon as the above signs and symptoms subsided. The end points of half, three-quarters, and full enteral feedings were defined as achieving 75, 115, and 150 mL/kg/day, respectively, of milk feeds.

Investigation of PNAC

All infants receiving parenteral nutrition had liver function monitored weekly until discharged from the NICU or when the parameters reverted back to the normal range. Because each of the enrolled infants were assigned a trial code number, both groups of patients were monitored identically. Infants suspected of PNAC and who had deranged hepatic function for more than 4

weeks or did not show any improvement after discontinuation of parenteral nutrition were subjected to further investigations. Paired serologic titers for hepatitis A, B, and C; toxoplasmosis, rubella, cytomegalovirus, and herpes virus type 2 (TORCH); and syphilis were performed. Urine samples were collected for cytomegalovirus shell vial culture. These infants also had ultrasound assessment of the liver and biliary structures after priming with phenobarbitone, and those with suspicious or abnormal scans were further subjected to the ^{99m}Tc hepatobiliary iminodiacetic acid (HIDA) scan. If biliary atresia could not be ruled out by radiologic tests, liver biopsy and/or operative cholangiography were recommended. This algorithm for investigation of neonatal liver disease and prolonged conjugated hyperbilirubinemia was the guideline of the NICU and strictly enforced during the study period.

Microbiologic Studies

Stool samples for microbiologic culture were collected from the studied infants immediately before treatment, after 10 days of medication, and 4 weeks after the treatment had been terminated. All specimens were cultured on a wide range of selective culture media as previously described.³ In brief, these culture media included the following: (1) deoxycholate citrate agar, thiosulphate citrate bile sucrose agar, MacConkey agar and selenite-F enrichment broth (further subcultured onto deoxycholate citrate agar after incubation), incubated aerobically at 37°C for 18–24 hours; (2) blood agar supplemented with vitamin K1 and cycloserine cefoxitin fructose agar incubated anaerobically at 37°C for 48 hours; (3) Skirrow agar incubated under microaerophilic conditions at 42°C for 48 hours; and (4) Sabouraud dextrose agar incubated aerobically at 30°C for 48 hours. Stool pathogens, including *Salmonella* species, *Shigella* species, thermophilic *Campylobacter* species, and *Vibrio* species, were identified using standard biochemical test, the API systems (bioMerieux, Marcy-l'Étoile, France), and serologic tests where appropriate. Predominant or pure growth of aerobes, anaerobes, and fungi were recorded. The microbiologists who performed the stool culture were unaware of the randomization assignments. These microbiologic tests were, however, discontinued after the outbreak of SARS in March 2003 because of the heavy workload in the laboratory and restructuring of the service. Thus, only the initial 41% of infants (37 and 38 infants in the erythromycin and placebo group, respectively) had the microbiology tests performed to look for any change in the pattern of bacterial colonization in the bowel.

Data Collection

The demographic data and clinical characteristics of infants are summarized in Table 1. Details of enteral feeding, including the time after randomization achiev-

ing half, three-quarters, and full enteral feeding; types of milk feeds; and duration of parenteral nutrition and potential adverse effects, and complications associated with the drug treatment and prolonged hyperalimentation, such as the incidence of infantile hypertrophic pyloric stenosis, cardiac dysrhythmias, electrocardiographic QTc intervals before and during oral erythromycin treatment, and changes in stool microbial flora, were monitored. Important clinical outcomes in addition to PNAC, including sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, NEC, duration of hospitalization, and mortality were also documented.

Statistical Analysis

The Fisher exact test and Mann-Whitney *U* test were used to compare proportions and continuous variables between groups when appropriate. The mixed-effects models³⁵ were used to assess the longitudinal data on feeding after adjustment for individual random factors. All tests were performed by the Windows version of S-Plus 2000 (MathSoft, Inc., Seattle, WA). The mixed-effects models were fitted using the function *lme* in S-Plus. All comparisons were 2-tailed, and the level of significance was set at 5%. The results were analyzed on an intention-to-treat basis.

Results

Ninety-five and 243 VLBW infants were admitted to the NICU during phase 1 and phase 2, respectively, of the study over a total period of 69 months, and of whom 56 and 126 infants with moderately severe gastrointestinal dysmotility were enrolled, respectively. The schematic flow chart revealed details of the recruitment process (Figure 1). Ninety-one infants received oral erythromycin, and an equal number received the placebo solution. The clinical characteristics of the groups are summarized in Table 1. All clinical features except the oxygenation index at 12 hours of life were comparable between the 2 groups. Erythromycin-treated infants had significantly higher oxygenation index than placebo infants in the immediate perinatal period ($P = .04$; Table 1).

The clinical outcomes are summarized in Table 2. The incidence of PNAC was significantly higher in the placebo (37/91 infants) than in the oral erythromycin group (18/91 infants, $P = .003$). Investigations for cholestatic jaundice indicated that 1 infant in the placebo group was infected with cytomegalovirus, and the infant had positive urinary excretion of the virus, and another infant in the oral erythromycin group failed the ^{99m}Tc HIDA scan and was suspected to have biliary atresia. The parents of the latter infant refused operative cholangiography and liver biopsy, but the patient recovered uneventfully after achieving full enteral feeding and discontinuation of parenteral nutrition. The inclusion or exclusion of these 2 cases did not significantly alter the overall outcome of PNAC. Although the overall maximum serum total bili-

Table 1. The Clinical Characteristics of the Oral Erythromycin and Placebo Groups

Clinical characteristics	Oral erythromycin group (n = 91)	Placebo group (n = 91)	P values
Gestational age (wk)	28.6 (27.3–30.5)	28.9 (26.6–30.6)	.96
Birth weight (g)	1095 (868–1285)	1090 (890–1375)	.91
Sex:			
Female:male, n	46 (51%):45 (49%)	47 (52%):44 (48%)	1.00
Inborn infants, n	90 (99%)	89 (98%)	1.00
Mode of delivery:			
Cesarean section:vaginal, n	49 (54%):42 (46%)	47 (52%):44 (48%)	.88
Antenatal dexamethasone:			
Mothers received antenatal dexamethasone, n	74 (81%)	76 (84%)	.85
Dosage (mg)	20 (6–24)	20 (6–24)	.77
Time intervals between last dose of dexamethasone and delivery (h)	26.5 (5.25–72.0)	23.5 (6.0–72.0)	.93
Apgar scores:			
1 Min	7 (5–8)	7 (6–8)	.46
5 Min	9 (7–10)	8 (8–9)	.35
Arterial cord blood			
pH	7.29 (7.25–7.32)	7.30 (7.22–7.34)	.88
Base excess (mmol/L)	–4.0 (–5.3 to –2.5)	–4.1 (–7.0 to –2.0)	.45
First venous hematocrit after delivery	0.49 (0.44–0.54)	0.49 (0.45–0.55)	.48
Temperature on admission (°C)	36.2 (35.8–36.5)	36.0 (35.8–36.5)	.32
Infants requiring exchange transfusion, n	3 (3%)	2 (2%)	1.0
CRIB score	2 (1–4)	2 (1–3)	.70
Oxygenation index (at 12 h)	5.8 (3.3–13.2)	4.3 (2.7–8.0)	.04 ^a
Patent ductus arteriosus, n	38 (42%)	31 (34%)	.36
Umbilical arterial catheter:			
Number of infants, n	59 (65%)	53 (58%)	.45
Duration (days)	8 (0–17)	6 (0–15)	.38
Umbilical venous catheter:			
Number of infants	79 (87%)	78 (86%)	1.00
Duration (days)	15 (8–23)	14 (6–21)	.38
Type of milk feeds:			
Breast milk:formula milk:mixed, n	19 (21%):22 (24%):50 (55%)	13 (14%):21 (23%):57 (63%)	.45
Postnatal drugs			
Fentanyl:			
Number of infants	77 (85%)	80 (88%)	.67
Duration (days)	5 (1–8)	3 (2–14)	.91
Vecuronium:			
Number of infants	11 (12%)	16 (18%)	.40
Duration (days)	0 (0–0)	0 (0–0)	.37
Indomethacin:			
Number of infants	68 (75%)	62 (68%)	.41

NOTE. Results are expressed as median (interquartile range) and number (%).

CRIB, Clinical risk index for babies.

^a $P < .05$.

rubin and conjugated bilirubin concentrations did not differ significantly between groups, the maximum serum alanine aminotransferase concentration was significantly higher in infants receiving the placebo solution ($P = .04$; Table 2). Significantly more placebo infants (23/91 infants) had abnormally elevated serum alanine aminotransferase concentration (normal range, <53 IU/L) compared with erythromycin-treated patients (11/91 infants; $P = .036$).

The mixed-effects models³⁵ were used to analyze the longitudinal data on feeding after adjustment for the first day of milk introduction. The results indicated that VLBW infants were able to achieve half, three-quarters, and full enteral nutrition (mean [SE]) 18.1 [0.8], 25.8

[1.0], and 33.7 [1.4] days, respectively, after introduction of milk feeding, but this process could be advanced by 5.1 [0.8], 7.6 [1.3], and 10.1 [1.7] days to 13.0 [0.5], 18.3 [0.7], and 23.6 [1.0] days, respectively, if oral erythromycin was used simultaneously ($P < .001$ in all comparisons). Furthermore, infants were able to achieve half, three-quarters, and full enteral feeding 9.5 [0.8], 17.2 [1.0], and 25.0 [1.4] days, respectively, after starting the placebo solution, and this duration could be shortened significantly to 4.1 [0.4], 9.3 [0.6], and 14.4 [0.9] days (ie, shortened by 5.3 [0.8], 8.0 [1.2], and 10.6 [1.6] days), respectively, by oral erythromycin treatment ($P < .001$ in all comparisons). Additionally, the median times of parenteral nutrition and lipid infusion in erythromycin-treated infants

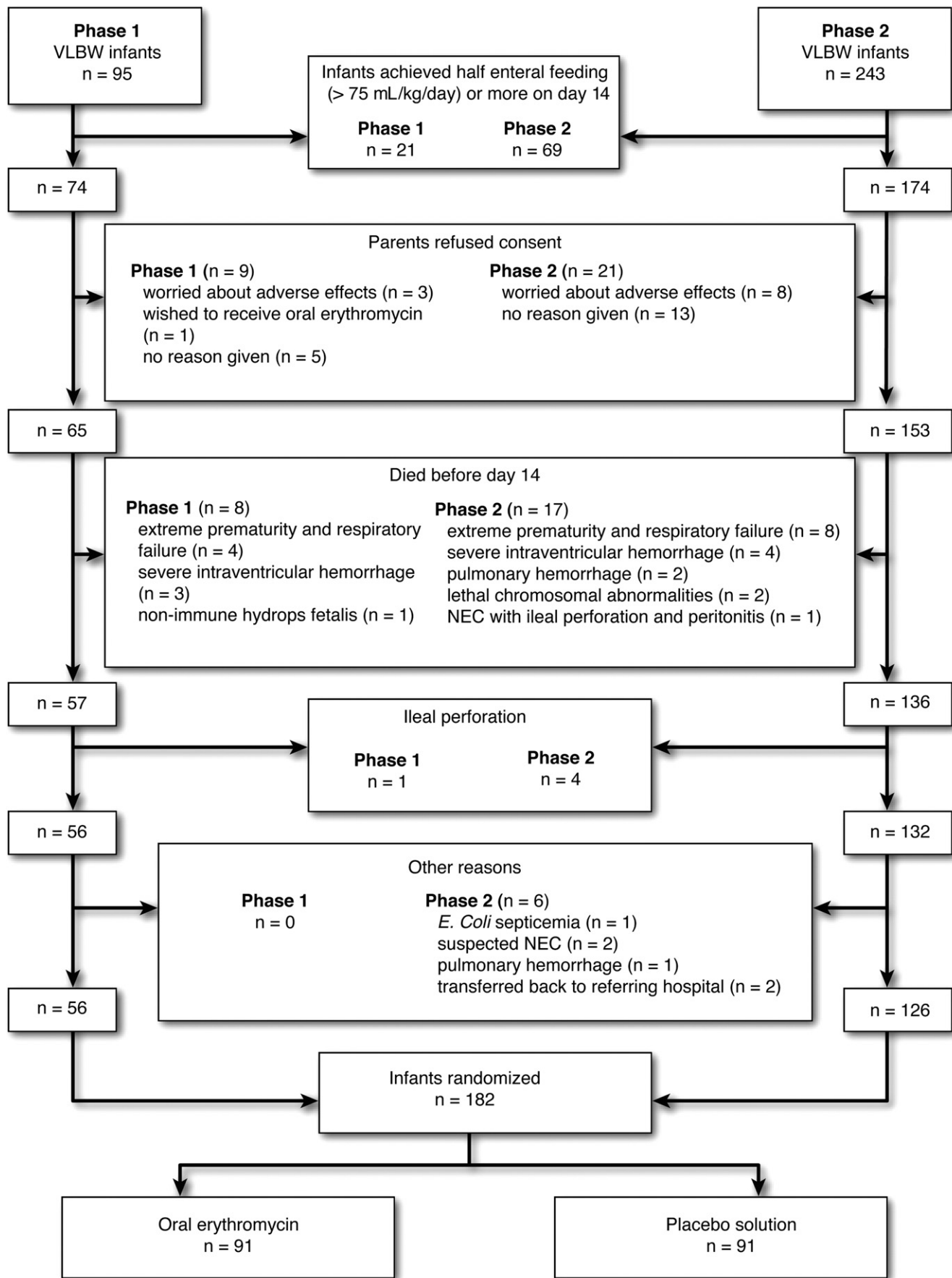


Figure 1. A schematic flow chart revealing details of the recruitment process in both phase 1 and phase 2 of the study.

Table 2. Comparison of Clinical Outcomes Between Study Groups

Clinical outcomes	Oral erythromycin group (n = 91)	Placebo groups (n = 91)	P values
Gastrointestinal outcomes			
Age commenced on enteral feeding (days)	6 (4–8)	6 (4–8)	.65
Age commenced on trial medications (days)	15 (14–16)	15 (14–15)	.12
Time after birth achieved half enteral feeding (75 mL/kg/day) (days)	18 (17–21)	21 (18–28)	<.001 ^a
Time after birth achieved three-quarters enteral feeding (115 mL/kg/day) (days)	22 (20–28)	29 (23–38)	<.001 ^a
Time after birth achieved full enteral feeding (150 mL/kg/day) (days)	26 (23–32)	38 (30–50)	<.001 ^a
Duration of parenteral nutrition (days)	23 (19–30)	33 (22–47)	<.001 ^a
Duration of lipid infusion (days)	20 (16–26)	30 (20–44)	<.001 ^a
Necrotizing enterocolitis (after day 14), n	0 (0%)	1 (1%)	1.00
Infantile hypertrophic pyloric stenosis, n	0 (0%)	0 (0%)	1.00
Hepatic outcomes			
PNAC (conjugated hyperbilirubinemia >34 mmol/L), n	18 (20%)	37 (41%)	.003 ^b
Maximum serum total bilirubin concentration (mmol/L)	169 (148–192)	165 (151–188)	.88
Maximum serum conjugated bilirubin concentration (mmol/L)	23 (15–31)	27 (13–61)	.08
Maximum serum alanine aminotransferase concentration (IU/L)	19 (13–30)	27 (13–50)	.04 ^b
Infants with abnormal liver enzyme (serum alanine aminotransferase concentration >53 IU/L), n	11	23	.04 ^b
Cardiorespiratory outcomes			
Duration of IPPV/HFOV (days)	6 (4–14)	5 (3–18)	.48
Duration of mechanical ventilation (days)	24 (11–47)	24 (7–44)	.34
Maximum mean airway pressure (cm H ₂ O)	10.5 (8.0–13.0)	9.8 (7.8–12.5)	.31
Maximum O ₂ concentration	0.40 (0.30–0.59)	0.35 (0.25–0.50)	.15
Duration of O ₂ dependence (days)	15 (3–33)	10 (1–30)	.21
O ₂ requirement >28 days, n	31 (35%)	26 (29%)	.42
O ₂ supplementation at 36 weeks postconceptional age, n	10 (11%)	5 (5%)	.14
O ₂ supplementation at 36 weeks postconceptional age plus death cases, n	11 (12%)	8 (9%)	.48
QTc interval before medication (ms)	0.38 (0.36–0.41)	0.38 (0.35–0.40)	.66
QTc interval after medication (ms)	0.39 (0.36–0.41)	0.38 (0.36–0.41)	.78
Ventricular ectopics, n	1	2	1.00
Microbiologic outcomes			
Number of infants with septicemia, n ^c			
0 Episode	65 (71%)	64 (70%)	
1 Episode	22 (24%)	14 (15%)	
2 Episodes	2 (2.5%)	11 (12.5%)	
3 Episodes	2 (2.5%)	2 (2.5%)	.03 ^b
Stool culture (gram-positive organism:gram-negative organism:fungus), n ^d			
Immediately before drug treatment	13:7:2	14:10:1	.73
During drug treatment	14:8:3	13:14:2	.48
4 Weeks after termination of drug treatment	8:8:1	8:11:2	.89
Others			
Intraventricular hemorrhage, n			
Grade 0–2	85 (93%)	82 (90%)	
Grade 3 or 4	6 (7%)	9 (10%)	.59
Duration of hospitalization (days)	80 (66–104)	88 (66–125)	.20
Died, n	2 (2%)	4 (4%)	.95

NOTE. Results were median (interquartile range) and number (%).

HFOV, high frequency oscillatory ventilation; IPPV, intermittent positive pressure ventilation; PNAC, parenteral nutrition-associated cholestasis.

^a*P* < .001.

^b*P* < .05.

^cThe Fisher exact test was used to compare the number of episodes of septicemia between the erythromycin and placebo groups. There was a significant overall difference between groups (*P* = .032). Furthermore, if the number of episodes of septicemia was categorized into 0 or 1 episodes vs 2 or 3 episodes, the results remained significantly different between erythromycin-treated and nontreated infants (*P* = .039).

^dOnly the first 75 infants had samples sent for stool culture, of whom 37 infants received oral erythromycin and 38 infants received the placebo solution.

were both significantly decreased by 10 days (*P* < .001; Table 2).

The number of infants with culture proven septicemia were similar between the oral erythromycin (n = 26) and the placebo group (n = 27; Table 3). Nine (10%) and 11

(12%) infants in the erythromycin and placebo group developed septicemia during the treatment period, respectively. However, significantly fewer infants receiving oral erythromycin had 2 or more episodes of septicemia (n = 4) compared with their placebo counterparts (n =

Table 3. Organisms Causing Septicemia

Organisms	Oral erythromycin group	Placebo group
Number of septicemic episodes, n	32	42
Gram-positive organisms:		
Coagulase-negative staphylococci	21	28
<i>Enterococcus</i> species	1	1
<i>Staphylococcus aureus</i>	2	–
Methicillin-resistant <i>Staphylococcus aureus</i>	1	1
Gram-positive <i>Bacillus</i> species	1	4
<i>Micrococcus</i> species	–	1
Gram-negative organisms:		
<i>Serratia</i> species	1	3
<i>Escherichia coli</i>	1	1
<i>Klebsiella</i> species	1	–
<i>Acinetobacter</i> species	1	–
<i>Pseudomonas</i> species	–	1
Fungi:		
<i>Candida albicans</i>	1	2
<i>Candida parasilosis</i>	1	–

13; $P = .039$). Furthermore, an overall analysis on the timing of septicemic episodes indicated that sepsis occurred significantly later in life in placebo infants (median, 24.5; interquartile range, 17.3–42.5 vs median, 34.0; interquartile range, 24.3–52.0 days for the erythromycin and placebo groups, respectively; $P = .035$). The organisms causing septicemia are listed in Table 3, and the predominant growth of organisms from stool cultures immediately before, during, and 4 weeks after the drug treatment are summarized in Table 4. There was no

evidence to suggest any outbreak of infection or emergence of multidrug-resistant organisms during the study period. Other important outcomes, including bronchopulmonary dysplasia defined as oxygen requirement >28 days or at 36 weeks postconceptional age (with or without including death cases), NEC, periventricular hemorrhage, duration of hospitalization, and number of death cases did not differ significantly between groups. There was also no significant increase in potential adverse effects associated with oral erythromycin treatment such as prolongation of QTc intervals, cardiac dysrhythmia, or emergence of a specific group of resistant organisms in the bowel flora. No cases of infantile hypertrophic pyloric stenosis were observed in either group.

Discussion

This is the first RCT of erythromycin to address the issue of clinical outcomes in VLBW infants. Our findings suggested that the use of high-dose oral erythromycin as a rescue measure for gastrointestinal dysmotility in preterm VLBW infants could significantly reduce the incidence of PNAC. The time to reach full enteral feeding, the need for hyperalimentation, and the incidence of recurrent septicemia were also significantly decreased.

PNAC, defined as serum conjugated bilirubin concentration >34 mmol/L,^{2,19–21} is a common problem and is estimated to occur between 35% and 43% of VLBW infants with gastrointestinal dysmotility in our NICU. The prevalence in the current study was 41% and is within the range of our estimation. Our results suggested that the incidence of PNAC in the placebo group was doubled

Table 4. Predominant Growth of Organisms From Stool Cultures Immediately Before, During, and 4 Weeks After Oral Erythromycin and Placebo Treatment

Organisms	Oral erythromycin group (n = 37)			Placebo group (n = 38)		
	Immediately before treatment	During treatment	4 Weeks after treatment	Immediately before treatment	During treatment	4 Weeks after treatment
Number of positive stool cultures, n	22	25	17	25	29	21
Gram-positive organisms:						
Coagulase-negative staphylococci	9	8	6	10	8	3
Nonhemolytic streptococci	1	1	–	–	–	–
<i>Staphylococcus aureus</i>	2	–	–	1	–	–
Methicillin-resistant <i>Staphylococcus aureus</i>	–	–	–	–	1	–
<i>Enterococcus</i> species	1	4	2	2	3	5
<i>Bacteroides fragilis</i>	–	1	–	1	1	–
Gram-negative organisms:						
<i>Pseudomonas</i> species	1	1	1	1	–	–
<i>Acinetobacter</i> species	1	1	–	1	1	–
<i>Stenotrophomonas</i> species	2	1	–	1	–	–
<i>Klebsiella</i> species	2	2	2	1	4	7
<i>Enterobacter</i> species	1	2	2	5	4	1
<i>Proteus</i> species	–	–	1	1	3	2
<i>Serratia</i> species	–	1	2	–	–	1
<i>Citrobacter</i> species	–	–	–	–	2	–
Fungi:						
<i>Candida</i> species	2	3	1	1	2	2

compared with infants treated with erythromycin. Thus, the number of VLBW infants with gastrointestinal dysmotility needed to be treated to prevent 1 case of PNAC is estimated to be 5 (95% CI: 2–8). This result represents a robust treatment effect. In contrast to PNAC caused by surgical-induced short gut syndrome or intestinal failure in which the infants usually have prolonged parenteral nutrition resulting in hepatic failure and death, advanced liver injury associated with gastrointestinal dysmotility of prematurity is infrequent.^{1,2} This observation could be confirmed by the mild to modest increase in serum alanine aminotransferase and the marginal significant increase in conjugated bilirubin concentrations. However, it is important to note that significantly more infants in the placebo group had abnormally raised alanine aminotransferase levels indicating a degree of hepatic damage (Table 2). Furthermore, clinical signs and biochemical parameters may sometimes be deceiving because these indicators do not necessarily correlate closely with disease severity at the late stage of deterioration,¹ and rapid decompensation of hepatic function can occur unexpectedly after a relatively short course of parenteral nutrition.^{1,36} One infant in the placebo group developed life-threatening hepatic failure with markedly deranged clotting profile, portal hypertension, esophageal varices, and frank hematemesis. This infant also had multiple pathologic fractures secondary to osteopenia and substrate deficiency rickets, yet he survived after tolerating full enteral feeding and cessation of hyperalimentation. To date, there is no definitive treatment for PNAC apart from stopping parenteral nutrition, and the only solution to arrest the progression of liver disease is to achieve full enteral nutrition as soon as it is practicable.¹ Predictably, the hepatic function in all affected infants was reversible and recovered within 2–4 months after stopping parenteral nutrition.

The results also suggested that the use of oral erythromycin would significantly shorten the requirement of hyperalimentation by 10 days. This finding could be translated into substantial savings both in human resources and cost for preparation of parenteral nutrition and, more importantly, infant exposure to complications of intravascular lines such as the repeated trauma of line insertion¹⁰ and recurrent sepsis.^{8,9} The principal organisms responsible for septicemia in the current and previous studies in preterm infants were coagulase-negative staphylococci (Table 3).³⁷ Because colonization of indwelling lines with these microorganisms is common after repeated infusions and bactericidal activities of phagocytosis and intracellular killing of coagulase-negative staphylococci in neutrophils are defective during long-term parenteral nutrition,³⁸ shortening the need for hyperalimentation and elimination of intravascular lines could have been responsible for the significant decrease in incidence of recurrent septicemia in erythromycin-treated infants. Recurrent sepsis in the presence of PNAC

could result in more rapid deterioration of hepatic function and damage of liver parenchyma by inhibiting hepatocellular bile acid transport and activation of hepatic macrophages via locally produced procholestatic cytokines such as tumor necrosis factor α .^{39–41} Thus, decreasing recurrent sepsis could have the additional benefit of interrupting the vicious cycle for causing further intrahepatic cholestasis and destruction of liver tissue.¹

In accordance with our previous findings,^{10,11} VLBW infants with functional gastrointestinal dysmotility achieved half, three-quarters, and full enteral feeding significantly earlier after treatment with high-dose oral erythromycin compared with the placebo. Nonetheless, there are controversies concerning the effectiveness of erythromycin in promoting enteral feeding.^{11–18} To date, of the 8 RCTs reported in the English literature, 3 used erythromycin as a prophylactic prokinetic agent and 5 as rescue treatment.^{11–18} Of the prophylactic studies, 2 of the 3 RCTs did not reveal any benefit,^{17,18} but the third study by Oei and Lui demonstrated that erythromycin-treated infants had significantly fewer episodes of large residual gastric aspirates and were able to attain full oral feeding more quickly.¹³ Prophylactic studies of such nature, however, do not necessarily reflect the efficacy of erythromycin as a prokinetic agent because infants with protracted feed intolerance are not specifically targeted for treatment. Five RCTs used erythromycin as rescue treatment in preterm newborns with feed intolerance.^{11,12,14–16} Two of the 5 trials, including our preliminary RCT,¹¹ found erythromycin to be beneficial.^{11,12} Our previous study using the same high-dose (12.5 mg/kg every 6 hours for 14 days) as the current trial revealed that oral erythromycin could shorten the time for achieving full enteral nutrition and that there was a nonsignificant trend of an increased risk for developing PNAC in placebo infants.¹¹ A recent study by Nuntnarumit et al also suggested that the use of an intermediate dose of oral erythromycin (10 mg/kg every 6 hours for 2 days, followed by 4 mg/kg every 6 hours for the next 5 days) could significantly reduce the number of withheld feeds and the time to full feeding.¹² In contrast, low-dose rescue treatment (3 mg/kg administered every 6 hours intravenously,¹⁶ and 6–15 mg/kg/day given orally^{14,15}) was not useful in facilitating enteral feeding. Two of the latter trials were small, involving no more than 15 patients in each group, and, therefore, might not have adequate statistical power to detect subtle differences in feeding.^{14,15} In the third RCT, the infants did not have protracted feed intolerance because the mean time to attain full enteral feeding ranged between 13.6 and 16.4 days in the erythromycin and placebo groups, respectively.¹⁶ These investigators concluded that a larger RCT would be warranted to address this important issue. Another plausible explanation for the discrepancy of results between studies could have been related to the different dosages used. It is possible that a higher dosage (ie, an intermediate or

a high dose) is required for effective stimulation of the gastrointestinal tract.^{12,42}

Other prokinetic agents such as cisapride and metoclopramide have been used to promote gastrointestinal motility and/or treatment of gastroesophageal reflux in infancy. However, only a small number of RCTs were performed on cisapride in preterm infants, and the number of participants involved in each study was relative small.^{43–48} Although 2 studies suggested that cisapride might improve feeding tolerance,^{43,44} others were unable to confirm such benefits.^{45–48} Furthermore, the latter trials demonstrated no significant advantage in reducing the daily total gastric aspirate,^{45,46} time to establish full enteral feeding,⁴⁸ or no change and even delay in gastric emptying time^{45,47} or whole gut transit time.⁴⁷ Additionally, serious adverse effects, including QT prolongation, life-threatening arrhythmia, and increase in thickness of the pylorus muscle, were observed.^{43,46,49} Even fewer data were available on metoclopramide in young infants. One case series suggested that metoclopramide might be potentially useful in infants with regurgitation or gastroparesis following abdominal surgery but not in those with gastroparesis associated with prematurity.⁵⁰

Although the exact mechanism in which erythromycin facilitates advancement of enteral feeding is not fully understood, there is substantial evidence to suggest that the prokinetic action is mediated via the motilin pathway principally at the levels of the stomach and proximal small bowel.^{51–53} Stimulation of this pathway results in increase in the proximal gastric tone,⁵⁴ greater amplitude and more frequent antral contractions,^{55–58} suppression of pyloric contractions and consequently reducing outlet resistance,⁵² and increase in the frequency of duodenal contractions.⁵⁹ Recent studies have indicated the presence of 2 main types of motilin receptors.⁶⁰ The neural motilin receptors on cholinergic neurons respond to low-dose (1–3 mg/kg) erythromycin and predominantly enhances the phase III migrating motor complexes, whereas the smooth muscle motilin receptors respond to higher doses of erythromycin and are mainly responsible for producing sustained antral contractions and facilitating antroduodenal coordination.^{30,32,53,58} Despite reports suggesting that gut immaturity could have been a crucial factor for the lack of response to erythromycin in infants <32 weeks gestation,⁵¹ the current evidence from clinical trials suggests that this could not fully explain the bedside findings.^{10–13} There is now evidence to suggest that the development of the gastrointestinal neuroendocrine network is mostly complete by 25 weeks gestation and that the distribution of motilin in the gastrointestinal tract at 20 weeks gestation closely resembles the pattern of distribution in adults.^{61,62} Thus, preterm infants at very early gestations are already equipped with the essential anatomic and physiologic apparatus necessary for proper functioning of the bowel. In addition, exposure of the immature bowel to milk or exogenous motilin can

result in earlier detection of phase III motor activity than would normally be expected for the gestational age.^{63–65} In human studies, a case series performed in preterm infants at 23–30 weeks gestations demonstrated that the use of intravenous erythromycin (0.75 mg/kg) could significantly increase antral clusters of contractions. The antral motility index was increased 4-fold and, thus, suggested the presence of functioning motilin receptors at very early gestations.⁶⁶ In another study, the same group of investigators studied different doses (10 mg vs 3 mg) of erythromycin administered orally and showed that 10 mg but not 3 mg significantly increased gastric emptying.³¹ It was proposed that a decrease in the pyloric tone coupled with an increase in tone of the proximal stomach could have been responsible for the prokinetic effect.³¹ A recent crossover study further indicated that oral erythromycin (10 mg/kg every 8 hours) enhanced antral contractility and increased whole gut transit time measured by ultrasonography and the carmine red dye method, respectively.³² In contrast, Jadcherla and Berseth using low-dose oral erythromycin (0.75–3 mg/kg) failed to initiate phase III motor migrating complexes in patients <31 weeks gestation but could induce them in a dose-dependent manner in infants ≥32 weeks.⁶⁷ ElHennawy et al also reported in a RCT that low-dose oral erythromycin (1.5 mg/kg) was unable to induce stronger or more frequent antroduodenal contractions compared with untreated patients and that the transit time from duodenum to anus was similar between the 2 groups.¹⁵ Thus, the cumulating evidence suggests that the action of erythromycin for promoting enteral feeding is probably dose as well as age dependent. Because there are clinical data to support that an intermediate or a high oral dose of erythromycin^{10–12} is more effective than lower doses^{14,15} for rescue treatment, we speculate that the lower intragastric doses are probably insufficient in providing adequate drug concentrations either locally or systemically for exerting the desired prokinetic effects. The time of introduction of milk feeding 9 days (median) prior to commencement of erythromycin and the use of this prokinetic agent as rescue rather than prophylactic treatment could have the advantage of accelerating and allowing time for bowel maturation such that the gut may become more susceptible to prokinetic drug stimulation.^{63–65}

No major adverse effect was encountered with oral erythromycin. In particular, none of the studied infants had infantile hypertrophic pyloric stenosis within the study period. The relatively low incidence of pyloric stenosis in Chinese babies⁶⁸ coupled with erythromycin administration not earlier than day 13 of life²⁹ have probably minimized the risk of developing this complication. Thus far, none of the other RCTs encountered this problem.^{11–18} Because the incidence of infantile hypertrophic pyloric stenosis is estimated to be 1–3 cases per 1000 live births,⁶⁹ an 8-fold increase in risk because of erythromy-

cin²⁹ would substantially increase the incidence to 8–24 cases per 1000 livebirths (ie, 1 case in 41- to 125-treated infants). This prevalence should have been detected by this or the combination of clinical trials.^{11–18} Therefore, the effect of erythromycin on infantile hypertrophic pyloric stenosis is likely to be small, and the benefits probably outweigh its risks. Three infants developed transient ventricular ectopics (Table 2). The infant in the erythromycin group developed the dysrhythmia on day 5 and before administration of prokinetic treatment, whereas the other 2 infants developed ventricular ectopics before and during placebo treatment. All patients recovered spontaneously within 12 hours of onset. No definitive cause was found. The QTc intervals before and during drug administration were similar between the 2 groups. The use of erythromycin was also not associated with an increase risk of NEC. The prevalence of NEC in the NICU has been significantly improved after introduction of new hand hygiene measures⁷⁰ and remained at a very low level during the study period. Importantly, the stool culture surveillance showed that the pattern of microorganisms did not change significantly between erythromycin-treated and placebo infants. One culture revealed methicillin-resistant *Staphylococcus aureus* in a placebo infant, and the emergence of *Stenotrophomonas* species was associated with the use of carbapenem antibiotics in these patients (Table 4). There was no outbreak of infection and NEC or emergence of multidrug-resistant organisms within the 69-month study period.

There are limitations in this study. First, the RCT was performed in a single center, and the results may not be generalizable to other NICUs. However, the strong treatment effect suggests that the data are robust, and attending neonatologists should be able to observe similar beneficial effects in their own population. One could also argue that the majority of PNAC cases were mild and question whether an antimicrobial agent in therapeutic dose should be initiated for treatment of such a benign condition. However, a life-threatening case with hepatic failure was observed during the study period. In addition, the duration for requirement of parenteral nutrition and the incidence of recurrent septicemia were significantly decreased. The absence of any major adverse effects such as infantile hypertrophic pyloric stenosis and life-threatening cardiac arrhythmias should justify the use of oral erythromycin as a “rescue” measure for infants with moderately severe gastrointestinal dysmotility. Undoubtedly, the future development of a new generation of macrolide analogues devoid of antibiotic activity but retaining motilinomimetic properties would be a distinct advantage.^{71,72} Second, much effort had been focused on identifying multidrug-resistant organisms in both blood and stool cultures because the study was performed in an intensive care setting. However, these conventional microbiologic culture techniques might not be sensitive enough to detect subtle changes of microflora in the

gastrointestinal tract. Recent studies suggested that the use of broad-spectrum antimicrobial agents in the early perinatal period could disturb normal developmental gene expression, impair maturation of the bowel protective barrier, interfere with the proper formation of the mucus gel layer overlying the gut epithelium, and change the pattern of microbial colonization in the gastrointestinal tract.^{73,74} Such modulating effects on the critical suckling-weaning transitional period could have long-lasting consequences because changes in the microbiota and gut mucosal barrier might potentially be associated with increased susceptibility to infection or developing inflammatory or atopic diseases in later life.⁷⁴ In this aspect, microbial genomic analysis or DNA microarray analysis would be of value in future studies to identify any alteration of the bowel microbiota and long-term effects of antibiotics on the gut microenvironment.

In summary, this is the largest RCT of oral erythromycin for assessing its prokinetic effect in preterm infants and is also the first study to assess clinical outcomes systematically. Our findings suggest that the use of a rescue high-dose oral erythromycin could effectively reduce the incidence of PNAC by 50% in VLBW infants with moderately severe gastrointestinal dysmotility. In addition, the treatment is also associated with an earlier time (10.1 days) to achieve full enteral feeding, decreasing the requirement for parenteral nutrition, and reducing the number of recurrent septicemia. No major adverse effects or life-threatening complications were encountered. The findings also demonstrate the importance of using the medication appropriately in a sufficiently “high-dose” and as a “rescue” therapy. These favorable data should strengthen the confidence of neonatal clinicians in using oral erythromycin as a prokinetic agent in moderate to severe cases. Although the current evidence suggests that the use of oral erythromycin at the antimicrobial dose is probably safe and does not readily promote the emergence of multidrug-resistant organisms, the sample size may still be inadequate to detect subtle adverse effects or outcomes in the long-term. Thus, oral erythromycin in a sufficient dosage can be considered after day 14 of life as a rescue treatment in preterm infants who fail to establish adequate enteral nutrition and in whom anatomically obstructive pathologies of the gastrointestinal tract have been excluded. We, however, caution against prophylactic or routine use of erythromycin as a prokinetic agent because the data from prophylactic RCTs have not been convincing and its safety profile, especially its influence on bowel microbiota and gut protective barrier, needs to be further addressed.

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