

A Triple Anti-infective Regimen Including the Probiotic Strain *Lactobacillus rhamnosus casei* for the Prophylaxis of Neonatal Intensive Care Complications in Moderate and Late Preterm Infants

Bernhard Resch¹ , Julia Laubenbacher², Berndt Urlsberger¹ 

¹Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria

²Research Unit for Neonatal Infectious Diseases and Epidemiology, Medical University of Graz, Austria

Between 2005 and 2015, we performed a retrospective observational cohort study and identified 824 infants who were admitted on the first day of life and stayed at the NICU for at least 7 days with a gestational age ranging from 33 (+0) to 36 (+6) weeks. Exclusion criteria were admission to the NICU beyond the first day of life, stay at the NICU for less than 7 days, admission to and stay at the surgical department, death before day 7, or missing or unavailable data regarding the outcome. All infants had prospectively received the probiotic strain *Lactobacillus casei rhamnosus* (LCR)—Antibiophilus® 0.75 g [contains $\geq 0.75 \times 10^8$ colony forming units—CFU] per day divided in 2 doses if the birth weight was below 2 kg and 1.5 g per day divided in 2 doses with a weight above 2 kg from the first day throughout the stay at the NICU. The triple anti-infective treatment additionally included enteral gentamycin (Refobacin® 40 mg Amp. 15 mg/kg/day divided into 2 doses) and enteral nystatin (Mycostatin® 1mL = 100 000 IU/kg per day divided into 4 doses). A standardized enteral feeding regimen was applied to all preterm infants at the NICU and remained unchanged through the study time. The ethic committee of the Medical University of Graz approved the study (number 28-332 ex 15/16 in March 2016).

Twenty-six infants (3.2%) had at least one complication; their perinatal data are given in Table 1. Infants with complications had longer stays at the NICU and longer duration of mechanical ventilation. None of the study infants had necrotizing enterocolitis (NEC) stage \geq IIa or antibiotic-associated diarrhea (AAD), 1.9% had late-onset sepsis (LOS), 1.1% ventilator-associated pneumonia (VAP), and 0.6% multi-organ dysfunction syndrome (MODS).

The overall complication rate of 14.8% in very low birth weight (VLBW) infants was significantly higher compared to moderate/late preterm infants of the current study ($P < .0001$).¹ In detail, 0.9% of VLBW infants had a diagnosis of NEC, 12.1% exhibited at least one episode of LOS, 2.7% had a diagnosis of VAP, 3.8% MODS, and none AAD. In term infants needing intensive care we found a lower rate of VAP compared to moderate/late preterm (0% vs. 1.1%, $P = .0024$), low rates of MODS (0% vs. 0.6%, differences not significant) and higher rates of LOS (4.0% vs. 1.9%, $P = .018$) using our triple anti-infective regimen.² Near-term and late preterm newborns are well-known to have more perinatal and neonatal complications than full-term infants.^{3,4} Our multi-modal three-component regimen for NEC prevention has already been successfully implemented in other countries.⁵

Using the triple anti-infective regimen in moderate and late preterm infants proved to be safe and well tolerated and complications rates were low. Interestingly, we recently demonstrated that probiotics as part of the triple anti-infective regimen led to the early establishment of an abundant and rich gut microbiome and enteral gentamycin had no negative effects on the gut microbiome.⁶

Corresponding author:

Bernhard Resch

✉Bernhard.resch@medunigraz.at

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Table 1. Perinatal Data of the Study Cohort of 824 Moderate and Late Preterm Infants (33–36 Weeks of Gestational Age) Divided into Two Groups: Infants with and without Complications* of Neonatal Intensive Care Between 2005 and 2015

Parameters	Infants With Complications	Infants Without Complications	P
Patients	26 (3.2)	798 (96.8)	
Gestational age (weeks)	34.1 ± 0.9; 34 (33–36)	34.2 ± 1.0; 34 (33–36)	.306
Birth weight (g)	2237 ± 447; 2248 (1406–3220)	2198 ± 459; 2160 (1070–3990)	.334
Small for gestational age	3 (12)	202 (25)	.055
Male gender	16 (62)	457 (57)	.330
Human milk: formula: both	12 (46): 3 (12): 11 (42)	272 (34): 104 (13): 422 (53)	.104
Length of stay (days)	44 ± 55; 21 (9–245)	19 ± 11; 17 (7–128)	<.001
Respiratory support	26 (100)	387 (49)	<.001
Days on mechanical ventilation	43 (1–264)	5 (0–134)	<.001
Surfactant therapy	3 (12)	202 (25)	<.001
Antibiotics (days)	8 (5–156)	3 (0–77)	<.001
Early-onset sepsis	5 (19)	96 (12)	.136

Data are given as n (%) or mean ± SD; median (range).

*Complications included one or more of the following entities per infant: necrotizing enterocolitis, ventilator-associated pneumonia, multi-organ dysfunction syndrome, late-onset sepsis, or antibiotic-associated diarrhea.

In conclusion, moderate/late preterm infants were prone to a small amount of complications of neonatal intensive care that might have been mitigated by a triple anti-infective regimen.

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Informed Consent: Not applicable, due to the design of this study.

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