Original Article

Early Life Empirical Antibiotics Use and Subsequent Body Weight Development

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Objective: Antibiotics, especially ampicillin and gentamicin, are widely used for risk of early-onset sepsis in newborns. Murine colonic microbiome and adiposity are known to be altered by low dose penicillin exposure in early life. However, studies on the effect of early life empirical antibiotics with ampicillin and gentamicin on future infant body weight are rare. We aimed to investigate the impact of ampicillin and gentamicin exposure during the first month and body weight development in 1-month, 6-month, 1-year, and 2-year-old babies.

Methods: The medical records of term infants between January 2013 and December 2014 were retrospectively reviewed. Clinical characteristics, birth body weight and antibiotics data were recorded. Body weight at 1 month, 6 months, 1 year and 2 years of age were compared between infants exposed and unexposed to antibiotics.

Results: A total of 126 neonates, with 42 (33%) antibiotics exposed and 84 (67%) unexposed infants were enrolled in this study. The general characteristics of the two groups were similar. Antibiotics exposure during the first month of life was not associated with significantly increased body weight and weight gain ratio in 1-month, 6-month, 1-year, and 2-year-old babies. Among potential confounders, maternal pre-delivery body moss index (BMI) affected body weight (adjusted $p = 0.019$) and its gain (adjusted $p = 0.022$) at 2 years of age.

Conclusions: Exposure to antibiotics with ampicillin and gentamicin in early life did not affect body weight or its gain in infants up to 2 years of age. Thus, the combination of these two antibiotics is safe and not a risk factor for future childhood overweight and obesity.

Key words: ampicillin, antibiotics exposure, body weight gain, gentamicin, neonate

Introduction

Antibiotics are commonly used in neonates because of the high risk of invasive bacte-

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rial infections and the difficulty in accurately identifying newborn infants with septicemia. Most neonates are empirically treated using a combination of ampicillin and gentamicin as the most preferred antibiotics. Its benefits are prominent when such treatment is needed and it is effective.[1] However, there are many well-known untoward consequences of antibiotics exposure including the financial cost and development of microbial antibiotic resistance. Besides, several studies have demonstrated the potentially detrimental long-term impact of early antibiotic exposure on intestinal microbiota and body weight change in children.[2-6]

The human gut microbiota has an essential role in influencing metabolism, adipose tissue expansion, and further causing obesity in the human body.[7-9] The microbiota among neonates is simpler than adults and is gradually established after birth.[10] Many external factors such as age, environment, lifestyle, dietary changes, antibiotics use, new species invasion, mode of delivery, preterm birth, and host genetics can alter intestinal microbiota in neonates.[11,12] In animal studies, antibiotics exposure in early life, especially low dose penicillin, is shown to have a considerable impact on early gut microbiota development and maturation.[13-15] Although a few studies suggest that antibiotics exposure in early life significantly increased the risk of obesity later, other studies have failed to show such impact.[2-6] Furthermore, antibiotics other than penicillin were used in these studies. Hence, it is difficult to compare these clinical results with those of animal studies. Consequently, our study aims to investigate the association between early-life penicillin exposure and body weight change in infants at 1 month, 6 months, 1 year, and 2 years of age.

Methods

Study designs and subjects

This was a retrospective cohort study and data was collected from in-patient and out-patient medical records in E-Da Hospital, Taiwan. All term neonates (gestational age (GA) ≥ 37 weeks) with appropriate weight for their GA (birth body weight (BBW) ≥ 10th percentile and ≤ 90th percentile), and admitted to our neonatal care unit between January 2013 and December 2014 were enrolled in this study. Neonates who were preterm, post-term, small for GA (BBW < 10th percentile), large for GA (BBW > 90th percentile), with presence of major congenital anomalies, congenital disease, infants of diabetic mothers, and of pregnancy induced hypertensive mothers were excluded in this survey. The study was approved by E-Da Hospital's Institutional Review Board. All patient information was de-identified before analysis.

Exposed group comprised infants who were suspected of having infection or sepsis within 1-month after birth and treated with parenteral ampicillin and gentamicin. The regimen of empirical antibiotics was as follows: ampicillin, 50 mg/kg/dose intravenously every 12 hours and gentamicin, 4 mg/kg/dose intravenously every 24 hours. Non-exposed group was defined as healthy newborn infants who met the inclusion criteria. We grouped all participants according to their gestational age into early term, full term, and late term. To minimize the influence of confounding factors between the two groups, we matched the groups for gestational age (one antibiotic exposed infant matched to two unexposed ones) and compared the outcomes among them.

Other demographic characteristics (BBW, mode of delivery, Apgar score, maternal age, maternal body weight, maternal body height, maternal body mass index (BMI)) were also reviewed.

Assessment of body weight

All infants had a preventative health visit

for vaccination at 1 month, 6 months, 1 year, and 2 years of age according to Taiwan vaccination programs. Body weight and health status were measured at every visit. Infants with missing body weight data at either time point were excluded.

Statistical analysis

Data were analyzed using IBM SPSS statistical software 24.0 (IBM Corporation, Armonk, NY, USA). Proportions are presented for categorical variables and mean ± standard deviation are presented for continuous variables. The Chi-square test (for categorical variables) and Student's t-test (for continuous variables) were used for comparisons between the two groups. Correlation analysis was used to compare the significance between 2 continuous variables. Multivariate linear regression was performed to adjust the potential variables associated with outcomes including BBW, maternal pre-delivery BMI, mode of delivery and sex. Statistical significance was defined as p value < 0.05.

Results

There were 1551 neonates who met the inclusion criteria during this 2 years review. After excluding the infants with incomplete data, a total of 126 neonates were included in this study. There were 42 infants (33.3%) exposed to antibiotics in the first month of life. Among the 126 participants, 71 (56.3%) were male. Overall, the mean GA was 39.09 ± 1.05 weeks, and the mean BBW was 3.22 ± 0.28 kilograms. The demographic characteristics of the two groups are shown in Table 1. The infants in antibiotics exposed group had a significantly lower Apgar score at 1 minute (7.38 ± 1.31 vs. 8.00 ± 0.16, p = 0.004) and 5 minutes (8.62 ± 0.83 vs. 9.00 ± 0.16, p = 0.005). We found no significant differences between the two groups with respect to GA, BBW, mode of delivery, sex, maternal age, maternal pre-delivery BMI, maternal pre-delivery body weight, and term classification (Table 1).

Body weight, body weight gain, and body weight gain ratio at four-time window

Body weight, body weight gain (BWG), and BWG ratio at 1 month, 6 months, 1 year and 2 years of age were recorded in all 126 infants. We used Student's t test to evaluate the relationship of these parameters to the exposed antibiotics. There was no significant difference in body weight at any time point between the two groups (Fig. 1): 1 month (p = 0.47), 6 months (p = 0.784), 1 year (p = 0.719), and 2 years (p = 0.383). BWG and BWG ratio at birth and the four-time points were not significantly different between the groups either. After adjusting for potential confounders (BBW, sex, mode of delivery, maternal pre-delivery BMI) using linear regression, we found that antibiotics exposure in infants was independent of increased body weight (p = 0.796), BWG (p = 0.825) and BWG ratio (p = 0.772) at 2 years of age (Table 2).

Sex stratification between antibiotics exposed and unexposed group

Previous reports have shown greater effects of antibiotics exposure among boys versus girls.[17] Therefore, we examined associations in subsamples stratified by sex. Sex stratification revealed that antibiotic exposure in early life had no significant impact on body weight, BWG and BWG ratio at 2 years of age.

Among girls, the mean BBW was significantly higher in the antibiotics exposed group compared to unexposed group (3.27 ± 0.26 kg vs. 3.10 ± 0.22 kg, p = 0.022). However, the mean body weight, BWG and BWG ratio did not differ significantly between the two groups at the four time points studied. Similarly, mean body weight, BWG, and BWG ratio in boys also had no association to antibiotics exposure.

Table1. Demographic characteristics of antibiotics exposed and unexposed neonates

	Antibiotics exposed (n = 42)	Antibiotics unexposed (n = 84)	*p*
GA, mean ± SD (weeks)	39.20 ± 1.06	39.06 ± 1.05	0.472
Birth weight, mean ± SD (kg)	3.26 ± 0.29	3.19 ± 0.27	0.213
Mode of delivery			> 0.99
Vagina	32 (76.2 %)	64 (76.2 %)	
Cesarean	10 (23.8 %)	20 (23.8 %)	
Gender			0.099
Male	28 (66.7 %)	43 (51.2 %)	
Female	14 (33.3 %)	41 (48.8 %)	
Apgar score (1 min)	7.38 ± 1.31	8.00 ± 0.16	0.004
Apgar score (5 min)	8.62 ± 0.83	9.00 ± 0.16	0.005
Maternal age	29.52 ± 5.49	30.55 ± 4.94	0.293
Maternal pre-delivery body weight	70.80 ±11.00	69.00 ± 10.57	0.376
Maternal pre-delivery BMI	28.23 ± 4.44	26.86 ± 3.69	0.069
Term classification*			> 0.99
Early term	18 (42.8 %)	36 (42.8 %)	
Full term	23 (54.8 %)	46 (54.8 %)	
Late term	1 (2.4 %)	2 (2.4 %)	
Age at evaluation (days)			
1-month-old	34.98 ± 4.27	35.05 ± 4.69	0.934
6-month-old	190.43 ± 7.57	192.48 ± 14.83	0.402
1-year-old	375.26 ± 10.55	379.11 ± 28.73	0.404
2-year-old	809.21 ± 49.16	808.10 ± 56.22	0.913

*Term definition: Early term: between 37 weeks + 0 days to 38 weeks + 6 days; Full term: between 39 weeks + 0 days to 40 weeks + 6 days; Late term: between 41 weeks + 0 days to 41 weeks + 6 days; BMI= body mass index; GA= gestational age; SD= standard deviation

Table2. Body weight, body weight gain, and body weight ratio at each time point between antibiotics exposed and unexposed groups

	Antibiotics exposed (n = 42)	Antibiotics unexposed (n = 84)	*p* value	Adjusted* *p* value
Body weight (kg)				
1-month-old	4.55 ± 0.41	4.48 ± 0.53	0.471	0.891
6-month-old	8.11 ± 0.95	8.07 ± 0.86	0.784	0.768
1-year-old	9.43 ± 1.16	9.50 ± 0.91	0.719	0.337
2-year-old	12.55 ± 1.82	12.27 ± 1.23	0.383	0.796
Body weight gain (△)				
$\triangle_{1m - Birth}$	1.29 ± 0.33	1.29 ± 0.43	0.981	0.891
$\triangle_{6m - Birth}$	4.86 ± 0.94	4.88 ± 0.83	0.899	0.762
$\triangle_{1y - Birth}$	6.17 ± 1.13	6.30 ± 0.88	0.466	0.337
$\triangle_{2y - Birth}$	9.18 ± 1.73	9.11 ± 1.22	0.793	0.825
Body weight gain ratio (△ / BBW)				
$\triangle_{1m - Birth}$/BBW	0.40 ± 0.11	0.41 ± 0.14	0.814	0.964
$\triangle_{6m - Birth}$/BBW	1.51 ± 0.35	1.54 ± 0.30	0.574	0.791
$\triangle_{1y - Birth}$/BBW	1.91 ± 0.40	1.99 ± 0.34	0.232	0.325
$\triangle_{2y - Birth}$/BBW	2.84 ± 0.60	2.88 ± 0.49	0.675	0.772

*Co-variates included in the linear regression analysis: birth body weight, gender, mode of delivery, maternal pre-delivery body mass index; BBW= birth body weight

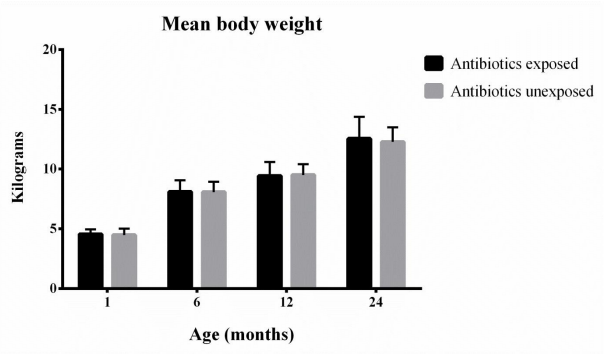

Fig. 1 Mean body weight between antibiotics exposed and unexposed group showed no significant differences at the four time points.

Linear regression analysis after adjusting confounding factors (birth body weight, mode of delivery, and maternal BMI) showed no significant differences in body weight, BWG, and BWG ratio at the four-time points (Table 3).

Factors associated to body weight and body weight difference at 2 years of age

Factors associated to body weight and BWG at 2 year were analyzed. After adjusting confounding factors (birth body weight, sex, mode of delivery, and maternal pre-delivery BMI), mode of delivery (95% CI, -1.23 to -0.05; p = 0.034) and maternal pre-delivery BMI (95% CI, 0.01 to 0.14, p = 0.019) remained two factors that affected body weight significantly at 2 years of age. The BWG between birth and 2 years revealed statistically significant differences in maternal pre-delivery BMI (p = 0.023) (Table 4).

Discussion

Our study provides evidence using a retrospective chart review on the effects of antibiotics exposure in the first month of life on the subsequent body weight of babies followed up to 2 years of age. Our results showed that antibiotics exposure early in life did not have any short-term associations with weight gain. The body weight and BWG in the antibiotics exposed group at 1 month, 6 months, 1 year, and 2 years of age did not differ from the antibiotics unexposed group. The ratio of BWG to BBW was also analyzed, and no significant result was found. There are many studies investigating the association of antibiotics exposure and body weight in childhood. Some of these studies found no correlation between antibiotics exposure in early life and the subsequent overweight or obesity,[2,3] which is consistent with our results. All participants in our study were Taiwanese and malnutrition is a rare issue in our country. A potential explanation for these results is that infants with acute severe malnutrition and small for gestational age were excluded in our study. Antibiotics are known to improve recovery and/or growth in such infants.[18]

To our knowledge, the effect of early life empirical antibiotics with ampicillin and gentamicin on future infant body weight has seldom been discussed. Because early life is a critical period for metabolic development, microbiota disruption during this window would lead to changes in body composition.[14] In humans, disruption of microbiota during early-life by antibiotics is probably associated with an increased risk of overweight status later in childhood.[19] Cox et al. showed that low-dose penicillin delivered to mice at birth would disrupt microbiota during maturation and alter host metabolism and adiposity.[14] Penicillin, cephalosporins, macrolides, or trimethoprim-sulfamethoxazole have been used in infants in previous studies to evaluate if they have similar direct effects on the human intestinal microbiota.[2,4,20] The results of these studies were inconsistent because the growth-promoting effects varied between different types of antibiotics. In our study, all infants in the antibiotic exposure group received parenteral ampicillin (a β-lactam antibiotic within the penicillin group), which is similar to Cox et al.'s animal study.[14] Our results were in contrast to the animal study, but were partially

Table3. Sex stratification between antibiotics exposed and unexposed groups

	Boys (n = 71)				Girls (n = 55)			
	Antibiotics exposed	Antibiotics unexposed	*p* value	Adjusted* *p* value	Antibiotics exposed	Antibiotics unexposed	*p* value	Adjusted* *p* value
Number	28 (39.4%)	43 (60.6%)			14 (25.5 %)	41 (74.5%)		
GA, mean ± SD (weeks)	39.02 ± 1.05	39.09 ± 1.10	0.784		39.58 ± 1.02	39.03 ± 1.02	0.086	
Birth weight, mean ± SD (kg)	3.25 ± 0.31	3.27 ± 0.29	0.737		3.27 ± 0.26	3.10 ± 0.22	0.022	
Body weight (kg)								
1-month-old	4.60 ± 0.37	4.59 ± 0.61	0.929	0.725	4.46 ± 0.48	4.37 ± 0.43	0.539	0.567
6-month-old	8.20 ± 1.02	8.30 ± 0.84	0.661	0.740	7.94 ± 0.82	7.83 ± 0.83	0.652	0.650
1-year-old	9.59 ± 1.12	9.73 ± 0.89	0.560	0.610	9.10 ± 1.20	9.25 ± 0.87	0.619	0.272
2-year-old	12.61 ± 1.89	12.56 ± 1.22	0.904	0.990	12.43 ± 1.74	11.98 ± 1.17	0.278	0.578
BW change (△)								
$\triangle_{1m - Birth}$	1.35 ± 0.27	1.31 ± 0.48	0.690	0.718	1.18 ± 0.40	1.27 ± 0.38	0.471	0.556
$\triangle_{6m - Birth}$	4.95 ± 1.02	5.02 ± 0.84	0.743	0.739	4.67 ± 0.76	4.72 ± 0.79	0.820	0.643
$\triangle_{1y - Birth}$	6.34 ± 1.08	6.46 ± 0.91	0.632	0.613	5.83 ± 1.17	6.14 ± 0.84	0.274	0.270
$\triangle_{2y - Birth}$	9.22 ± 1.76	9.33 ± 1.21	0.739	0.591	9.11 ± 1.72	8.88 ± 1.19	0.577	0.662
BW change ratio (△ /BBW)								
$\triangle_{1m - Birth}$/BBW	0.42 ± 0.10	0.40 ± 0.15	0.584	0.628	0.36 ± 0.12	0.41 ± 0.13	0.228	0.563
$\triangle_{6m - Birth}$/BBW	1.54 ± 0.38	1.55 ± 0.32	0.915	0.765	1.43 ± 0.25	1.53 ± 0.27	0.267	0.667
$\triangle_{1y - Birth}$/BBW	1.97 ± 0.40	1.99 ± 0.37	0.793	0.583	1.79 ± 0.38	1.99 ± 0.31	0.056	0.283
$\triangle_{2y - Birth}$/BBW	2.86 ± 0.62	2.88 ± 0.48	0.880	0.571	2.80 ± 0.56	2.88 ± 0.50	0.605	0.671

*Co-variates included in the linear regression analysis: birth body weight, mode of delivery, maternal pre-delivery body mass index

BBW= birth body weight; BW= body weight; GA= gestational age; SD= standard deviation

Table4. Factors associated with body weight and body weight change at 2 years of age

Factors	Body weight at 2 years of age			Body weight gain at 2 years of age		
	p value	Adjusted*		*p* value	Adjusted*	
		β (95% CI)	*p* value		β (95% CI)	*p* value
Antibiotics exposed	0.383	0.02 (-0.47 to 0.61)	0.796	0.793	-0.02 (-0.59 to 0.47)	0.825
Birth body weight	0.048	0.11 (-0.34 to 1.48)	0.218	0.628	-0.10 (-1.42 to 0.38)	0.254
Gender	0.062	0.14 (-0.12 to 0.91)	0.131	0.166	0.14 (-0.11 to 0.90)	0.120
Mode of delivery	0.085	-0.19 (-1.23 to -0.05)	0.034	0.327	-0.16 (-1.11 to 0.06)	0.080
Maternal pre-delivery BMI	0.026	0.21 (0.01 to 0.14)	0.019	0.046	0.21 (0.01 to 0.14)	0.022

*Co-variates included in the linear regression analysis: birth body weight, gender, mode of delivery, maternal pre-delivery body mass index
BMI= body mass index

in line with the results of Saari et al.[4] In a recent study, amoxicillin treatment did not alter human gut microbiota composition after 7 days of antibiotic treatment in obese men.[21]Both, ampicillin and gentamicin are largely eliminated by the kidneys and most likely have little direct contact with the colonic microbiota. This may explain why ampicillin and gentamicin had no pronounced weight gaining effect in children. Besides, these results also highlight the safety of using ampicillin and gentamicin in children suspected of neonatal infection or sepsis.

Human gut microbiota is gradually established after birth, and it could be altered by many external factors including antibiotics, environment, dietary changes, and others.[7,11,12] Previous studies have investigated the effect of antibiotics exposure within 6-12 months of life on children's growth.[2-4] Our study population was composed of newborn infants who were exposed to antibiotics within the first month of life. Food and environment were fairly uncomplicated in this age group compared to previous studies. Hence, we could minimize the effects of these factors which might alter growth. In addition, our study population was carefully screened for other potential factors that might affect growth. We matched the two groups by gestational age (early term, term and late term) because it can contribute to childhood obesity.[22] Besides, statistical adjustment was performed for BBW, mode of delivery, maternal pre-delivery BMI and sex.

Although antibiotics exposed in early life may not cause significant BW gains later, maternal pre-delivery BMI did show a significant correlation with BW and BWG at 2 years of age in this study. It is known that high pre-pregnancy BMI can cause many adverse pregnancy outcomes and is related to infant body weight and offspring overweight/obesity, but the effect of pre-delivery BMI is rarely studied.[17,23,24] Latinen et al. examined the association of maternal gestational weight gain during the first 20 weeks with overweight/obesity and abdominal obesity of offspring at the age of 16 years.[25] Their results showed that maternal pregravid obesity (BMI $\geq$ 30 kg/m^2) conferred more than a four-fold risk for adolescent offspring overweight or obesity compared to mothers of normal weight. If high pre-pregnancy BMI or body weight gain can cause adverse pregnancy outcomes and infant body weight in later life, then high pre-delivery BMI, a factor right before delivery, should more or less have a similar effect. Similarly, our results showed that higher the maternal pre-delivery BMI, the higher the infant body weight and BWG at 2 years, but its effect on childhood obesity was unknown. Further scientific explorations on this topic are needed in the future.

There are some limitations in our study. First, this study was designed to be retrospective but not prospective. However, this issue was minimized by matching the groups by gestational age and adjusting the related confounding factors in this study. Another limitation is the sample size and selection. Participants in this study were from a single hospital located in southern Taiwan, and a study on different races may lead to different results. We need more cases and patients living in other regions within Taiwan, and maybe from various races to create a large-scale study.

The use of empirical antibiotics including ampicillin and gentamicin for neonatal sepsis is widespread. Our study demonstrated that exposure to ampicillin and gentamicin during the first month of life had no significant influence on body weight and BWG at 2 years of age. There are many factors that associate with overweight and obesity through childhood; however, antibiotics exposure in infants during the first month of life may not be one of them.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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