World Nutrition Journal | eISSN 2580-7013

ARTICLE REVIEW

Antibiotic Treatment in Infants: Effect on the Gastro-intestinal Microbiome and Long Term Consequences

Linde Peeters[1], Siel Daelemans[1], Yvan Vandenplas[1]

1. *KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium*

Received May 21st, 2018
Accepted August 2nd, 2018

Link to DOI:
10.25220/WNJ.V02.i1.0003

Journal Website:
www.worldnutrijournal.org

Abstract

Introduction: The gastrointestinal microbiome is crucial for the development of a balanced immune system. Antibiotics are frequently administered to infants and cause intestinal dysbiosis. This narrative review highlights the long term health consequences of antibiotic administration to infants and young children. The necessity of administration of antibiotics should be well considered, since an association with short term consequences such as antibiotic associated diarrhoea and long term adverse effects such as overweight, inflammatory bowel syndrome, allergic disease have been reported.

Conclusion: The pros and cons of antibiotic administration to infants and young children should be considered.

Keywords antibiotic, immune system, microbiome

Introduction

The human gut microbiota has been estimated to be equal or probably even 10 to 100 times more important in number than the cells composing the human body.[1] Microbial colonization of the human gut begins in utero since bacteria have been detected in the umbilical cord, placenta, amniotic fluid and also in meconium.[2] After birth, the gastrointestinal tract is colonized by a rapidly diversifying microbiota, and it is during the first years of life that the establishment of a stable gut microbiome occurs that will persist during later childhood and adulthood. Microbial colonization of the infant gastrointestinal tract begins immediately after birth, and is determined by many factors such as the maternal microbiota, delivery mode, feeding and medication such as antibiotics and proton pump inhibitors.[1] Early colonization is crucial for a balanced development of the acquired immune system. In other words: early colonization is a major factor influencing for later health. It has been well established that antibiotics not only kill bacterial pathogens, but they will also profoundly disturb the equilibrium of the gastro-intestinal microbiome and are a well-known cause of dysbiosis. The use of antibiotics increased globally with 36% in a decade.[3] The long-term consequences of gastro-intestinal dysbiosis during early life are the focus of this narrative review. There is a strong association between the microbiota composition and factors such as age, nutrition, stress, and many diseases and conditions such as allergy, diabetes, irritable bowel syndrome, overweight and inflammatory bowel disease. While much of the emerging literature has focused on the potential benefits of probiotic treatment, antibiotics used to treat pathogenic bacterial infections are known to disrupt the diversity and number of microbial organisms in the intestine.

Corresponding author:
Prof. Y. Vandenplas
Kidz Health Castle, UZ Brussel, Vrije Unversiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
Tel: + 3224775794; Fax: +3224775783
e-mail: yvan.vandenplas@uzbrussel.be

Antibiotic associated diarrhea

The most frequent and best studied consequence of intestinal dysbiosis as a consequence of antibiotic intake is antibiotic associated diarrhea (AAD). AAD is an immediate or short-term adverse effect of antibiotic treatment, occurs in +/- 20 % of all antibiotic courses and depends on the class of antibiotic, the presence of risk factors in patients (host factors, hospitalization, nosocomial outbreaks). AAD is defined as a change in stool frequency with at least three liquid stools/day occurring during two consecutive days (early onset) or two to six weeks after antibiotic treatment (late onset), and if no other cause can be identified (intercurrent viral or bacterial infection, laxative use, other cause).[4] The class of antibiotics (broad spectrum), the duration of administration and the age of the patient are risk factors to develop AAD. The administration of some probiotic strains such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii* CNCM I-745 reduce the incidence and severity of AAD.[5]

Antibiotics early in life

Antibiotics may have a much broader impact, especially if given perinatal or to young infants. The administration of antibiotics intrapartum both during caesarean and vaginal delivery are associated with infant gut microbiota dysbiosis.[6] Maternal intrapartum antibiotic treatment is a key regulator of the initial neonatal oral microbiome.[7] Maternal intrapartum antibiotic prophylaxis will have a significant impact on the infant faecal microbial population, particularly in that of breastfed infants.[8] Intrapartum antibiotic administration results in a significant reduction in Bifidobacterium spp. strains.[9] The reduced abundance of these beneficial microorganisms, together with the increased amount of potentially pathogenic bacteria, may suggest these infants are more exposed to gastrointestinal or generally health disorders later in age. Dysbiosis acquired perinatal or during early life will induce long term consequences. Maternal antibiotic treatment, administered during pregnancy and lactation results in profound alterations in the composition of the microbiota in mothers and infants.[10] Prenatal antibiotics are associated with a larger body mass index (BMI) at the age of two years.[11] Children experiencing a higher number of respiratory tract infections in the first year of life already demonstrate an aberrant microbial developmental trajectory from the first month of life on.[12] Independent drivers of these aberrant developmental trajectories of respiratory microbiota members were mode of delivery, infant feeding, crowding, and recent antibiotic use .[12] Perinatal administration of antibiotics is often lifesaving and thus a medical need. However, special attention should be given to a balanced development of the gastrointestinal microbiome of infants born in these circumstances.

Antibiotics and weight

Subtherapeutic doses of antibiotics have been used as growth promoters in animal farming since the 1950s .[13] The effect is more pronounced for broad-spectrum antibiotics, and it is attenuated when animals are raised in sanitary conditions. Burgeoning empirical evidence suggests that antibiotics also affect human growth. As early as 1955, a randomized controlled trial in Navy recruits showed that a 7-week course of antibiotics led to significantly greater weight gain in the treated group compared with placebo.[13]

Antibiotic exposure before 6 months of age or repeatedly during infancy, was associated with increased BMI in healthy children.[14] Repeated exposure to antibiotics early in life, especially β-lactam agents, was shown to be associated with increased weight.[15] These adverse effects of antibiotics may play a role in the worldwide childhood obesity epidemic and highlight the importance of judicious use of antibiotics during infancy, favoring narrow-spectrum antibiotics.[14] Administration of three or more courses of antibiotics before children reach an age of two years is associated with an increased risk of early childhood obesity.[16] In a cohort study, 6.4 % children were obese at four years of age and exposure to antibiotics was associated with an increased risk of obesity at four years.[16] The more antibiotic courses, the stronger the risk.[16] Children

receiving antibiotics in the first year of life are more likely to be overweight at 12 years of age compared with those who were unexposed (32.4 *vs* 18.2%, P=0.002).[17] Repeated exposure to broad-spectrum antibiotics at ages 0 to 23 months is associated with early childhood obesity.[15] Sixty-nine percent of children were exposed to a mean of 2.3 antibiotic courses before the age of 24 months.[18] Exposure to antibiotics during the first 12 months of life was associated with a small increase in BMI in boys, but not in girls, aged 5-8 years in a large international cross-sectional survey .[19] The intestinal microbiota of infants is predictive of later BMI and may serve as an early indicator of obesity risk. Bifidobacteria and streptococci, which are indicators of microbiota maturation in infants, are likely candidates for metabolic programming of infants, and their influence on BMI appears to depend on antibiotic use.[20] If causality of obesity can be established in future studies, this will further highlight the need for restrictive antibiotic use.[15]

Because common childhood infections were the most frequent diagnoses co-occurring with broad-spectrum antibiotic prescription, narrowing antibiotic selection is potentially a modifiable risk factor for childhood obesity.[18] Administration early in life, cumulative exposure and broad spectrum antibiotics were additional risk factors associated with later obesity. In comparison to broad-spectrum antibiotics, narrow-spectrum antibiotics were not at any age or frequency associated with a risk for increased weight.[18] However, some studies do report contradictory results. Exposure to antibiotics within the first 6 months of life compared with no exposure was also shown to be not associated with a statistically significant difference in weight gain through age seven years.[21]

In summary, although literature is contradictory and thus the evidence is weak, there are many indicators that administration of broad spectrum antibiotics may be associated with a higher BMI during infancy and childhood.

Antibiotics and immunity and allergy

Synbiotic host and microbe interactions are critical for host metabolic and immune development. Early microbiota colonization may influence the occurrence of metabolic and immune diseases.[1]

Maternal use of antibiotics before and during pregnancy was associated with an increased risk of cow's milk allergy in the offspring, and persisted after adjusting for putative confounders.[22] A clear association was found between three or more courses of antibiotics during early life and cow's milk allergy, non-milk food allergy and other allergies in a longitudinal data analysis of 30,060 children.[22] The associations became stronger for younger age and differed by antibiotic class.[22] The risk of cow's milk allergy increased with increasing number of child's antibiotics used from birth to diagnosis of the allergy (test for trend $P < 0.001$).[23]

Antibiotics and the respiratory tract

Early introduction of solid foods such as fish and environmental factors such as living on a farm are protective factors for the development of later allergic disease. But administration of antibiotics during early life are a risk factor for allergic rhinitis and wheezing. Antibiotics during the first year of life are associated with an increased risk for wheezing and asthma up to the age of three and six years, independent of lower respiratory tract infections during the first year of life.[24-28] The strength of the association differs with the class of antibiotics, correlating with their effect on the gastrointestinal microbiome.[24] A dose-response effect was observed: when five or more antibiotic courses were administered, the risk to develop asthma increased significantly ($p<001$). There is no association between antibiotic use and late-onset asthma.[26] The adverse effect of antibiotics was particularly strong in children without a family history of asthma ($P(\text{interaction})=0.03$).[25] Retrospective studies had the highest pooled risk estimate for asthma compared with database and prospective studies. Respiratory infections, later asthma onset (asthma at or after two years) and exposure to antibiotics during pregnancy are all independent risk factor.

Antibiotics and Irritable Bowel Syndrome (IBS)

A statistically significant link between early life infections and IBS in adults aside from bronchitis could not be demonstrated.[29] These data confirm an early report concluding that antibiotic treatment

does not seem to be a major risk factor for recurrent abdominal pain at 12 years of age.[30] However, antibiotic use during the neonatale period was reported to be associated with infantile colic.[31]

Antibiotics and Inflammatory Bowel Disease (IBD)

Exposure to antibiotics throughout childhood is associated with IBD, and this relationship decreased with increasing age of exposure to antibiotics. Exposure before one year of age had the highest risk, decreasing at five and 15 years, although even antibiotics at the age of 15 still indicated a significant risk factor to develop IBD.[32] Each antibiotic course increased the risk to develop IBD with 6% (4%–8%).[32] Antibiotic use is common in childhood and its potential as an environmental risk factor for IBD warrants scrutiny.[33] Antibiotic exposure was significantly associated with Crohn's disease, being stronger in children, but was not significant for ulcerative colitis.[34] However, the antibiotic courses may also be the consequence of unrecognized and undiagnosed symptoms of IBD. Therefore, causality cannot be confirmed since antibiotics may be prescribed to children with intestinal symptoms of as yet undiagnosed IBD.[33]

Antibiotics and diabetes

Exposure to a single antibiotic prescription was not associated with higher adjusted diabetes risk, whereas treatment with two to five antibiotic courses was associated with an increase in diabetic risk for penicillin, cephalosporins, macrolides and quinolones.[35,36] The risk increased with the number of antibiotic courses. There was no association between exposure to anti-virals and anti-fungals and diabetes risk.[35] Exposure to antibiotics is likely to increase type 2 diabetes risk, but not for type 1 diabetes.[36,37] However, the findings may also represent an increased demand for antibiotics from an increased rate of infections in patients with yet undiagnosed diabetes.[36]

Conclusion

The most prevalent childhood bacterial infections in primary healthcare are respiratory, gastrointestinal and urogenital infections. Antibiotics are often unavoidable and sometimes life-saving. In many developing countries, antibiotic dispensing and its use in medicine, cattle breeding and agriculture are inadequately regulated, or existing laws are not being appropriately implemented. In addition, human travel contributes to antimicrobial drug resistance around the world. All of these factors have led to a very high level of bacterial resistance. However, antibiotics also cause intestinal dysbiosis, which on its turn is associated with an increased risk for adverse outcomes such as AAD, IBS, IBD, allergy, overweight, etc. Prudent use of antibiotics is paramount not only to reduce the propagation of antibiotic-resistant organisms but also to minimize the potentially detrimental long-term metabolic consequences of early antibiotic exposure. The long term adverse effects of broad spectrum antibiotics should be considered before these drugs are administered to young infants. The administration of some specific probiotics strains such as *Saccharomyces boulardii* have been shown to reduce the risk of short term adverse effects of antibiotics such as the risk to develop AAD. Whether probiotics may also reduce the risk to develop long term adverse effects of intestinal dysbiosis associated with repetitive antibiotic administration has not been validated and should be a focus of future research.

Future studies should investigate the effects of multiple exposures to broad-spectrum antibiotics during the second year of life. However, future studies should focus on the possible benefit of a rapid restoration of the dysbiosis caused by broad spectrum antibiotics.

Table 1. Antibiotics during early life and health effect.

Reference	Topic	OR	95 % CI
Metsälä [41]	CMPA (AB mother before pregnany)	1.26	1.20-1.33
	CMPA (AB mother during pregnancy)	1.21	1.14-1.28
Scott [16]	Obesity at 4 years	1.21	1.07-1.38
	Obesity at 4 years (< 3 AB courses)	1.07	0.91-1.23
	Obesity at 4 years (3-5 AB courses)	1.41	1.20-1.65
	Obesity at 4 years (> 6 AB courses)	1.47	1.19-1.82
Azad [17]	Obesity risk in boys	5.35	1.94-14.72
	Obesity risk in girls	1.13	0.46-2.81
	Obesity risk in boys (9 years)	2.19	1.06-4.54
	Obesity risk in girls (9 years)	1.20	0.53-2.70
	Obesity risk in boys (12 years)	2.85	1.24-6.51
	Obesity risk in girls (12 years)	1.59	0.68-3.68
Bailey [18]	Obesity (≥ 4 AB courses)	1.11	1.02-1.21
	Obesity (broad spectrum AB)	1.16	1.06-1.29
	Obesity (AB between 0-5 months)	1.11	1.03-1.19
	Obesity (AB between 6-11 months)	1.09	1.04-1.14
Hirsch [22]	Milk allergy	1.78	1.28-2.48
	Non-milk food allergy	1.65	1.27-2.14
	Other allergies	3.07	2.72-3.46
Risnes [25]	Asthma (>6 years)	1.52	1.07, 2.16
	Asthma (>3 years)	1.66	0.99, 2.79
	Asthma (no LRTI < 1 year)	1.66	1.12, 3.46
	Asthma (neg fam history)	1.89	1.00, 3.58
	Pos allergy test	1.59	1.10, 2.28
Ong [26]	Transient wheezing	2.0	1.9-2.2
	Asthma	1.6	1.5-1.7
	Asthma (>5 AB courses)	1.9.	1.5-2.6.
Alm [39]	Allergic rhnitis	1.75	1.03, 2.97
Metsälä [40]	Asthma (AB mother)	1.31	1.21-1.42
	Asthma (AB infant)	1.60	1.48-1.73
Murk [42]	Asthma (review, all studies)	1.52	1.30-1.77
	Asthma (retrospective studies)	2.04	1.83-2.27
	Asthma (database, prospective studies)	1.25	1.08-1.45
	Asthma (adjusted for resp inf)	1.16	1.08-1.25
	Asthma (onset> 2 years)	1.16	1.06-1.25
	Asthma (AB during pregnancy)	1.24	1.02-1.50
Pedersen [43]	Otitis media (AB during pregnancy)	1.30	1.04-1.63
	Otitis media (n° of AB courses)	1.20	1.04-1.40
	Ventilation tubes (AB third trimester)	1.60	1.08-2.36
Kronman [32]	IBD (AB < 1 year)	5.51	1.66-18.28
	IBD (AB < 5 years)	2.62	1.61-4.25
	IBD (AB < 15 years)	1.57	1.35-1.84
	IBD (1 or 2 AB courses)	3.33	1.69-6.58
	IBD (> 2 AB courses)	4.77	2.13-10.68
Hviid [33]	IBD	1.84	1.08 to 3.15
	Crohn's disease	3.41	1.45-8.02
	IBD (> 7 AB courses)	7.32	2.14-24.99
Ungaro [34]	Crohn's disease	1.74	1.35-2.23
	Ulcerative colitis	1.08	0.91-1.27
	Chrohn's disease (in children)	2.75	1.72-4.38
	Crohn's disease (metronidazole)	5.01	1.65-15.25
	Crohn's disease (fluoroquinolones	1.79	1.03-3.12
Boursi [35]	Diabetes (> 1 AB course, penicillin)	1.08	1.05-1.11
	Diabetes (> 1 AB course, quinolones)	1.15	1.08-1.23
	Diabetes (> 5 AB course, quinolones)	1.37	1.19-1.58

AB: antibiotic; IBD: inflammatory bowel disease; n°: number; pos: positive; resp inf: respiratory infection

Conflict of Interest

Authors declared no conflict of interest regarding this study

Open Access

References

1. Slykerman RF, Thompson J, Waldie KE, Murphy R, Wall C, Mitchell EA (2017) Antibiotics in the first year of life and subsequent neurocognitive outcomes. Acta Paediatr 106:87-94
2. Collado MC, Cernada M, Bauerl C, Vento M, Perez-Martinez G (2012) Microbial ecology and host-microbiota interactions during early life stages. Gut Microbes 3:352–365
3. Yasmin F, Tun HM, Konya TB, Guttman DS, Chari RS, Field CJ, Becker AB, Mandhane PJ, Turvey SE, Subbarao P, Sears MR; CHILD Study Investigators, Scott JA, Dinu I, Kozyrskyj AL (2017) Cesarean section, formula feeding, and infant antibiotic exposure: separate and combined impacts on gut microbial changes in later infancy. Front Pediatr 5:200
4. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC (2015) Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 12:CD004827
5. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z; ESPGHAN Working Group for Probiotics & Prebiotics (2016) Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. J Pediatr Gastroenterol Nutr 62:495-506
6. Azad MB, Konya T, Persaud RR, Guttman DS, Chari RS, Field CJ, Sears MR, Mandhane PJ, Turvey SE, Subbarao P, Becker AB, Scott JA, Kozyrskyj AL; CHILD Study Investigators (2016) Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG 123:983-993
7. Gomez-Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Dekker Nitert M (2017) Antibiotic treatment at delivery shapes the initial oral microbiome in neonates. Sci Rep 7:43481
8. Mazzola G, Murphy K, Ross RP, Di Gioia D, Biavati B, Corvaglia LT, Faldella G, Stanton C (2016) Early gut microbiota perturbations following intrapartum antibiotic prophylaxis to prevent Group B Streptococcal disease. PLoS One 11:e0157527
9. Aloisio I, Quagliariello A, De Fanti S, Luiselli D, De Filippo C, Albanese D, Corvaglia LT, Faldella G, Di Gioia D (2016) Evaluation of the effects of intrapartum antibiotic prophylaxis on newborn intestinal microbiota using a sequencing approach targeted to multi hypervariable 16S rDNA regions. Appl Microbiol Biotechnol 100:5537-5546
10. Gonzalez-Perez G, Hicks AL, Tekieli TM, Radens CM, Williams BL, Lamousé-Smith ES (2016) Maternal antibiotic treatment impacts development of the neonatal intestinal microbiome and antiviral immunity. J Immunol 196:3768-3779
11. Cassidy-Bushrow AE, Burmeister C, Havstad S, Levin AM, Lynch SV, Ownby DR, Rundle AG, Woodcroft KJ, Zoratti EM, Johnson CC, Wegienka G (2017) Prenatal antimicrobial use and early-childhood body mass index. Int J Obes (Lond) Epub ahead of print
12. Bosch AATM, Piters WAAS, van Houten MA, Chu MLJN, Biesbroek G, Kool J, Pernet P, de Groot PC, Eijkemans MJC, Keijser BJF, Sanders EAM, Bogaert D (2017) Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences. A Prospective Cohort Study. Am J Respir Crit Care Med 196:1582-1590
13. Forrest CB, Block JP, Bailey LC (2017) Antibiotics, infections, and childhood obesity. Lancet Diabetes Endocrinol 5:2-3
14. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H (2015) Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics 135:617-626
15. Mbakwa CA, Scheres L, Penders J, Mommers M, Thijs C, Arts IC (2016) Early life antibiotic exposure and weight development in children. J Pediatr 176:105-113.e2.
16. Scott F, Horton DB, Mamtani R, Haynes K, Goldberg DS, Lee DY, Lewis JD (2016) Administration of antibiotics to children before age 2 years increases risk for childhood obesity. Gastroenterology 151:120-129.e5
17. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL (2014) Infant antibiotic exposure and the development of childhood overweight and central adiposity.Int J Obes (Lond) 38:1290-1298
18. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA (2014) Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr 168:1063-1069
19. Murphy R, Stewart AW, Braithwaite I, Beasley R, Hancox RJ, Mitchell EA; ISAAC Phase Three Study Group (2014) Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study. Int J Obes (Lond) 38:1115-1119
20. Korpela K, Zijlmans MA, Kuitunen M, Kukkonen K, Savilahti E, Salonen A, de Weerth C, de Vos WM (2017)

Childhood BMI in relation to microbiota in infancy and lifetime antibiotic use. Microbiome 3;5:26
21. Gerber JS, Bryan M, Ross RK, Daymont C, Parks EP, Localio AR, Grundmeier RW, Stallings VA, Zaoutis TE (2016) Antibiotic exposure during the first 6 months of life and weight gain during childhood. JAMA 315:1258-1265
22. Hirsch AG, Pollak J, Glass TA, Poulsen MN, Bailey-Davis L, Mowery J, Schwartz BS (2017) Early-life antibiotic use and subsequent diagnosis of food allergy and allergic diseases. Clin Exp Allergy 47:236-244
23. Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM (2013) Mother's and offspring's use of antibiotics and infant allergy to cow's milk. Epidemiology 24:303-309
24. Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM (2015) Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. Clin Exp Allergy 45:137-145
25. Risnes KR, Belanger K, Murk W, Bracken MB (2011) Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. Am J Epidemiol 173:310-318
26. Ong MS, Umetsu DT, Mandl KD (2014) Consequences of antibiotics and infections in infancy: bugs, drugs, and wheezing. Ann Allergy Asthma Immunol 112:441-445.e1.
27. Pitter G, Ludvigsson JF, Romor P, Zanier L, Zanotti R, Simonato L, Canova C (2016) Antibiotic exposure in the first year of life and later treated asthma, a population based birth cohort study of 143,000 children. Eur J Epidemiol 31:85-94
28. Murk W, Risnes KR, Bracken MB (2011) Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics 127:1125-38
29. Krajicek EJ, Almazar AE, Larson JJ, Atkinson EJ, Talley NJ, Saito YA (2017) Early Infections and the risk of irritable bowel syndrome: A Case-Control Study. J Clin Gastroenterol [Epub ahead of print]
30. Uusijärvi A, Bergström A, Simrén M, Ludvigsson JF, Kull I, Wickman M, Alm J, Olén O (2014) Use of antibiotics in infancy and childhood and risk of recurrent abdominal pain--a Swedish birth cohort study. Neurogastroenterol Motil 26:841-850
31. Oosterloo BC, van Elburg RM, Rutten NB, Bunkers CM, Crijns CE, Meijssen CB, Oudshoorn JH, Rijkers GT, van der Ent CK, Vlieger AM (2018) Wheezing and infantile colic are associated with neonatal antibiotic treatment. Pediatr Allergy Immunol (in press)
32. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE (2012). Antibiotic exposure and IBD development among children: a population-based cohort study. Pediatrics 130:e794-803
33. Hviid A, Svanström H, Frisch M (2011) Antibiotic use and inflammatory bowel diseases in childhood. Gut 60:49-54
34. Ungaro R, Bernstein CN, Gearry R, Hviid A, Kolho KL, Kronman MP, Shaw S, Van Kruiningen H, Colombel JF, Atreja A (2014) Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol 109:1728-1738
35. Boursi B, Mamtani R, Haynes K, Yang YX (2015) The effect of past antibiotic exposure on diabetes risk. Eur J Endocrinol 172:639-648
36. Mikkelsen KH, Knop FK, Frost M, Hallas J, Pottegård A (2015) Use of antibiotics and risk of type 2 diabetes: a population-based case-control study. J Clin Endocrinol Metab 100:3633-3640
37. Mikkelsen KH, Knop FK, Vilsbøll T, Frost M, Hallas J, Pottegård A (2017) Use of antibiotics in childhood and risk of Type 1 diabetes: a population-based case-control study. Diabet Med 34:272-277
38. Ilić K, Jakovljević E, Skodrić-Trifunović V (2012) Social-economic factors and irrational antibiotic use as reasons for antibiotic resistance of bacteria causing common childhood infections in primary healthcare. Eur J Pediatr 171:767-777
39. Alm B, Erdes L, Möllborg P, Pettersson R, Norvenius SG, Aberg N, Wennergren G (2008) Neonatal antibiotic treatment is a risk factor for early wheezing. Pediatrics 121:697-702
40. Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM (2015) Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. Clin Exp Allergy 45:137-145
41. Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM [2013] Mother's and offspring's use of antibiotics and infant allergy to cow's milk. Epidemiology 24:303-309
42. Murk W, Risnes KR, Bracken MB [2011] Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics 127:1125-1138
43. Pedersen TM, Stokholm J, Thorsen J, Mora-Jensen AC, Bisgaard H (2017) Antibiotics in pregnancy increase children's risk of otitis media and ventilation tubes. J Pediatr 183:153-158.e1