Table 2: Overview of the included studies that examined antibiotic treatment's effect on the gut microbiota

Author, year	Study design	Gestational age/ Birth-weight	Population size	Antibiotic Exposure	Main result regarding gut microbiota
Bennet, 1987[140]	Prospective cohort	24 – 42 weeks	165	Yes/no	Decreased colonization with *Bacteriodes*, *Bifidobacterium*, and *Lactobacilli*
Blakey, 1982[154]	Prospective cohort	< 37 weeks/ ≤ 1500 g	28	Yes/no	Decreased levels of *Lactobacilli*, *E. coli*, *Bacteriodes*, and *C. difficile* day 0 – 20
Bonnemaison, 2003[142]	Prospective cohort	28 – 40 weeks/ 940 – 3950 g	30	Yes/no Broad- vs. narrow-spectrum	Decreased diversity and more Staphylococci and Candida after broad-spectrum treatment
Butel, 2007[143]	Prospective cohort	30 – 36 weeks/ 990 – 2750 g	52	Yes/no	Similar rate of previous antibiotic treatment in patients with and without Bifidobacteria
Ferraris, 2012[144]	Retrospective cohort	< 36 weeks	76	Yes/no Prolonged vs. short	Decrease in *C. difficile* (p=0.001) after ≥ 10 days of treatment
Fouhy, 2012[145]	Prospective cohort	≥ 37 weeks	18	Yes/no	Increased rate of *Proteobacteria*, decreased rate of *Bifidobacterium*, *Lactobacilli* & *Acitenobacter* 4 weeks after treatment
Gewolb, 1999[146]	Prospective cohort	< 1000 g	29	Prolonged vs. short	Inverse correlation between treatment duration and total bacterial count (r=-0.482) and number of species (r=0.491)
Greenwood, 2014[147]	Prospective cohort	≤ 32 weeks	74	Yes/no Prolonged vs. short	Infants with ≥ 5 days treatment had lower diversity (p=0.001) and more *Enterobacter* (p=0.016)
Jacquot, 2011[148]	Prospective cohort	≤ 30 weeks	28	Yes/no	Inverse correlation between days of treatment duration and diversity at 6 weeks (r=-0.52; p=0.0184)
Jenke, 2013[149]	Prospective cohort	< 27 weeks	68	Yes/no	Increased prevalence of *C. difficile* on day 7 of life after > 48 h treatment (OR 1.78; 95% CI 0.94 - 3.38)
La Rosa, 2014[150]	Prospective cohort	23 – 33 weeks ≤ 1500 g	58	Yes/no	Increased levels *Gammaproteobacteria* in patients with GA < 26 weeks, less *Clostridia* in patients with GA ≤ 28 weeks
Lindberg, 2011[151]	Prospective cohort	≥ 37 weeks	200	Yes/no	Decreased colonization with *S. aureus* (OR 0.03; p=0.01)
Metsvaht, 2010[111]	Randomized Controlled Trial		283	Broad- vs. narrow-spectrum	Less *Enterococci* and *S. aureus* and more CoNS with ampicillin & gentamicin than penicillin and gentamicin
Westerbeek, 2013[153]	Randomized controlled trial	< 32 weeks/ < 1500 g	113	Yes/no	Decreased total bacteria count (p<0.001)

OR; odds ratio, CI; confidence interval, GA; gestational age, *E. coli*; *Escherichia coli*, *S. aureus*; *Staphylococcus aureus*, CONS; *coagulase-negative Staphylococci*

Table 3: Overview of included studies that examined antibiotic treatment's effect on the risk of necrotizing enterocolitis

Author, year	Study design	Gestational age/ Birth-weight	Population size	Antibiotic exposure	Main results regarding NEC
Alexander, 2011[155]	Case-control		372	Yes/no Prolonged vs. short Broad- vs. narrow-spectrum	OR 1.10 (95% CI 1.02 – 1.19; p=0.015)* after treatment, OR 4.16 (95% CI 1.29 – 13.44) with clindamycin, decreased risk after treatment in patients with sepsis
Carter, 2012[156]	Retrospective cohort	23 – 30 weeks	549	Yes/no Prolonged vs. short	GA 23 – 26: OR 1.60 (1.20 – 2.14) per week of treatment GA 27 – 30: 2.27 (1.23 – 4.17) per week of treatment
Chong, 2013[157]	Retrospective cohort	≤ 1500 g	714	Broad- vs. narrow-spectrum	Lower rate after treatment with piperacillin-tazobactam than ampicillin & gentamicin (1.1% vs. 11.0%; p<0.0001)
Cotten, 2009[158]	Retrospective cohort	≤ 1000 g	4039	Prolonged vs. short	OR 1.07 (95% CI 1.04 – 1.10) per day OR 1.34 (95% CI 1.04 – 1.73) with ≥ 4 days of treatment
Greenwood, 2014[147]	Prospective cohort	≤ 32 weeks	74	Prolonged vs. short	Higher rate of prolonged treatment in patients with NEC, sepsis, or death (p=0.044)
Krediet, 2003[159]	Case-control	24.5 – 42 weeks/ 555 - 4460	208	Yes/no	OR 0.3 (95% CI 0.2 – 0.6; p<0.05)
Kuppala, 2011[132]	Retrospective cohort	≤ 32 weeks/ ≤ 1500 g	365	Yes/no Prolonged vs. short	OR 1.08 (95% CI 0.83 – 1.40) per day OR 1.28 (95% CI 0.42 – 3.93) with ≥ 5 days of treatment
Millar, 1992[160]	Randomized controlled trial	< 33 weeks	143	Broad- vs. narrow-spectrum	Lower NEC-rate after treatment with vancomycin & aztrenoam than vancomycin & gentamicin (0% vs 14.6%; p=0.028)
Shah, 2013[160]	Retrospective cohort	< 28 weeks	216	Prolonged vs. short	NEC/death OR 2.1 (95% CI 0.8 – 5.3; p=0.128)** after ≥ 4 days treatment
Tagare, 2010[162]	Randomized controlled trial	> 37 weeks	140	Yes/no	Similar NEC-rate after treatment (13% vs. 4.2%; p=0.062)
Torrazza, 2013[163]	Case-control	≤ 32 weeks	53	Prolonged vs. short	Similar duration of treatment in patients with or without NEC (p≥0.05)
Wang, 2009[164]	Case-control	25 - 32	20	Prolonged vs. short	Longer duration of treatment with NEC than without (mean days 13.7 vs. 3.7; p=0.005)

NEC; necrotizing enterocolitis, OR; odds ratio, CI; confidence interval, GA; gestational age, SD; standard deviation* Multivariate logistic regression; ** Adjusted for gestational age and intrauterine growth retardation

Table 4: Overview of included studies that examined antibiotic treatment's effect on the risk of fungemia

Author, year	Study design	Gestational age/ Birth-weight	Population size	Antibiotic exposure	Main results regarding fungemia
Ariff, 2010[165]	Case-control		81	Prolonged vs. short Broad- vs. narrow-spectrum	Fungemia patients had a higher mean duration of treatment with most antibiotics than controls, but shorter duration of ampicillin treatment
Benjamin, 2003[166]	Retrospective cohort	< 1250 g	21 233	Broad- vs. narrow-spectrum	OR 1.30 (95% CI 1.02 – 1.64; p=0.03) with vancomycin OR 1.98 (95% CI 1.56 – 2.46; p>0.001) with cephalosporin OR 1.77 (95% CI 1.33 – 2.29; p=0.001)* with cephalosporin/carbapenem
Cotten, 2006[137]	Retrospective cohort	≤ 1000 g	3702	Yes/no Prolonged vs. short	Candidemia OR 2.16 (95% CI 1.42 – 3.27; p<0.05)* with antibiotics, correlation between candidemia and cephalosporins (r=0.67; p=0.015)
Lee, 2013[178]	Retrospective cohort	> 1500 g	411 866	Yes/no	OR 1.6 (95% CI 1.1 – 2.4)* with third-generation cephalosporins, carbapenems, ticarcillin, or piperacillin
Linder, 2004[168]	Case-control		112	Yes/no; prolonged vs. short	Significant association between candidemia and use of gentamicin, cefotaxime, ceftazidime, vancomycin, meropenem, amikacin and metronidazole
Natarajan, 2009[169]	Case-control	≤ 1500 g	29	Prolonged vs. short	Patients with candidemia responsive to treatment received less antibiotics (mean 7.1 vs 14.5 days; p<0.05)
Pera, 2002[170]	Case-control	< 1250 g	65	Prolonged vs. short	OR 1.146 (95% CI 1.00 – 1.20; p<0.001) per day
Singh, 1999[171]	Prospective cohort	< 37 weeks	70	Yes/no	Significantly associated with rate of treatment (p<0.01)
Tewari, 2014[172]	Randomized controlled trial	≥ 28 weeks ≥ 1000 g	187	Broad- vs. narrow-spectrum	Only one case of fungemia
Warris, 2001[173]	Case-control	< 34 weeks	24	Prolonged vs. short	Candidemia patients received longer durations of treatment than controls (mean 19.3 vs. 3.2; p<0.001) and more types of antibiotics (mean 4.4 vs. 1.2; p<0.001)
Yu, 2013[174]	Case-control		135	Yes/no Prolonged vs. short Broad- vs. narrow-spectrum	OR 1.0 (1.0 – 1.1; p=0.4) with antibiotics OR 2.4 (95% CI 1.2 – 5.2; p<0.05) with imipenem OR 3.9 (95% CI 1.7 – 9.3; p<0.01) with vancomycin OR 5.3 (95% CI 2.4 – 11.7; p<0.01) with third-gen cephalosporin OR 4.6 (95% CI 1.5 – 14.0; p=0.04)* with third-gen cephalosporin

OR; odds ratio, CI; confidence interval
*Adjusted in a multivariate model