

**What is the efficacy and safety of methylxanthines (caffeine, theophylline — in intravenous form named aminophylline) for the prevention and treatment of apnea of prematurity?**

**Table 1: Caffeine vs placebo**

N	Author Year	Setting	Interventions	Sample size	Participants	Main Outcome	Risk Ratio (95%CI)
1	Murat 1981	HIC France	Caffeine for treatment of AOP	n=18	29 to 35 weeks gestation	0/9 vs 6/9 failed apnea reduction 2-7 days of therapy.	0.08 (0, 1.19)
2	Levitt 1988	HIC UK	Caffeine for prevention of AOP	n=54	Infants	12/27 vs 14/27 failed apnea reduction 2-10 days of therapy.	0.87 (0.52, 1.45)
3	Erenberg 2000	HIC USA	Caffeine for treatment of AOP	n=82	28-32 weeks gestation	14/45 vs 20/37 failed apnea reduction 7-10 days of therapy.  2/45 vs 1/37 death before discharge	0.58 (0.34, 0.97)  1.64 (0.16, 17.43)
4	Schmidt (Caffeine for Apnea of Prematurity Trial Group, CAP) 2006	HIC Multi-country	Caffeine for prevention of AOP	n=2006	Birth weight 500 to 1250 g	293/867 vs 329/858 cognitive delay at 18 to 21 months  52/1006 vs 55/1000 death before discharge	0.81(0.66, 0.99)  0.96 (0.64, 1.44)
5	Schmidt (CAP) 2007	HIC Multi-country	Caffeine for prevention of AOP	n=2006	Birth weight 500 to 1250 g	40/909 vs 66/901 cerebral palsy at 18 to 21 months  377/937 vs 431/932 died or survived with a neurodisability at 18 to 21 months	0.58 (0.39, 0.87)  0.77 (0.64, 0.93)

**HIC- high income country****Table 2: Aminophylline (theophylline) vs control**

<b>N</b>	<b>Author Year</b>	<b>Setting</b>	<b>Interventions</b>	<b>Sample size</b>	<b>Participants</b>	<b>Main Outcome</b>	<b>Risk Ratio (95%CI)</b>
1	Gupta 1981	HIC Australia	Theophylline	n=29	Infants	5/15 vs 14/14 failed apnea reduction 2-7 days of therapy.  1/15 vs 3/14 death before discharge	0.36 (0.18, 0.7)  0.31 (0.04, 2.65)
2	Sims 1985	HIC USA	Theophylline	n=43	Infants	9/21 vs 17/22 failed apnea reduction 2-7 days of therapy.  Death before discharge	0.55 (0.32, 0.95)  0.21 (0.01, 4.11)
3	Pellowski 1990	HIC Canada	Theophylline 2/10	n=10	Infants	2/10 vs 8/10 failed Apnea Reduction 2-7 days of therapy.	0.25 (0.07, 0.9)

**HIC- high income country****Table 3: Caffeine vs Aminophylline (theophylline)**

<b>N</b>	<b>Author Year</b>	<b>Setting</b>	<b>Interventions</b>	<b>Sample size</b>	<b>Participants</b>	<b>Main Outcome</b>	<b>Risk Ratio (95%CI)</b>
1	Brouard 1985	HIC France	Caffeine vs theophylline for treatment of AOP	n=16	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.01 (-0.19, 0.21)
2	Bairam 1987	HIC France		n=20	Infants	3/10 vs 2/10 failed apnea reduction 2-7 days of therapy.	1.35 (0.41, 4.52)

						Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.29 (-0.06, 0.64)
3	Fuglsang 1989	HIC Denmark	Caffeine vs Theophylline	n=18	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.04 (-0.14,0.22)
4	Scanlon 1992	HIC UK	Caffeine (higher vs standard dose) vs Theophylline for treatment of AOP	n=44	<31 weeks gestation	5/16 vs 1/14 vs 0/14 failed apnea reduction by 48 hours of therapy.	1.35 (0.41, 4.52)
5	Kumar 1992	HIC USA	Caffeine vs Aminophylline	n=24	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.09 (-0.28, 0.46)
6	Larsen 1995	HIC Denmark	Caffeine vs Aminophylline 2.5	n = 180	≤33 weeks gestation	No of apnea in 10 days.	No difference
7	Skouroliaou 2009	HIC Greece	Caffeine 4 (day 1-3) 0 (day 4-7) vs Aminophylline 5 (day 1-3) 0 (day 4-7)	n=70	<33 weeks gestation	Mean apnea events per day	No difference
8	Shivakumar 2016	LMIC (India)	Caffeine vs aminophylline	n=240	≤34 weeks gestation	Median Apnea rates at day 8-14	No difference
9	Khurana 2017	LMIC (India)	Caffeine (n=43) Cognitive 105.37 ± 13.75 Language 100.39 ± 15.05 Motor 102.72 ± 12.79 vs Aminophylline	n=240	Infants	Composite scores of BSID III components at 18–24 months of corrected age	No difference

			(n=36) Cognitive 99.97 ± 19.09 Language 101.63 ± 19.1 Motor 104.02 ± 20.0				
10	Afzal 2018	LMIC (Pakistan)	Caffeine 1.9±0.18 (1-3) 1.4±1.8 (4-7) 0.98±0.15 (15-21) vs Aminophylline 0.4±0.24 (1-3) 0.3±1.6 (4-7) 0.69±0.15 (15-21)	n=100	<34 weeks gestation	Mean apnea per day	Aminophylline significantly better in the following interval days 1-3, 4-7 and 15-21.
11	Zulqarnain 2019	LMIC (Pakistan)	Caffeine 2 (day 1-3) 2 (day 4-7) vs Theophylline 1 (day 1-3) 2 (day 4-7)	n=100	<33 weeks gestation	Mean apnea per day	Caffeine significantly better in the following interval days 1-3 and 4-7 p<0.05

HIC- high income country LMIC- low- and middle-income country