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Prevalence of Gram-negative bloodstream infections among colonized neonates: a systematic review and meta-analysis

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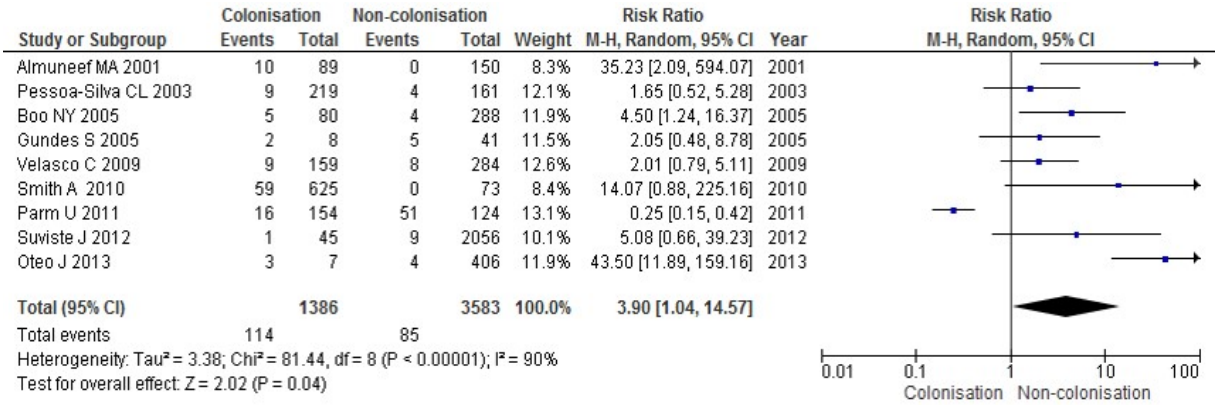
Background: Babies admitted to Neonatal Intensive Care Unit (NICU) are at high risk of developing bloodstream infections (BSI) due to both intrinsic and extrinsic risk factors. Among them, Gram-negative bacteria (GNB) are responsible for around 15-30% of all infections, with significant morbidity and mortality. GNB can cause both colonisation and infections. Under certain conditions, colonising strains can cause infections by gaining access to body sites that are usually sterile like bladder, lungs, or bloodstream. The actual mechanisms leading from colonisation to infection are still debated. By conducting a systematic literature review, we aimed to clarify the correlation between GNB colonisation and subsequent concordant infection in neonates.

Material/methods: Cohort studies published after 2000 up to June 2016 reporting data on the total number of neonates (0-28 days) colonised with GNB assessed by rectal/skin swab culture and the total number of GN-colonised babies infected by GNs (same bacteria) were included. The primary outcome was to assess if babies colonised by GNB were more likely to develop a GN-BSI. A meta-analysis with random effect model was performed for those studies reporting also the number of not-colonised infected neonates. Heterogeneity was assessed with the I^2 measure of inconsistency.

Results: 15 studies fulfilled inclusion criteria. 3 out of them were carried out during outbreaks. A total of 8,421 babies were screened. Among them, 1,984 (23.6%) were found to be colonised by GNB. Overall, the number of colonised infected babies was 157 (7.9%). 9 studies were included in the meta-analysis. The low number of studies did not allow the assessment of publication bias. The percentage of BSI among colonised and non-colonised babies was 8.2 *vs* 2.4% (p=0.04). Colonised neonates were significantly more at risk of developing BSI, with a Risk Ratio of 3.9 (95% CI 1.04-14.57). A high heterogeneity was found in these studies (I^2=90%; p<0.00001), mainly due to different study design and sampling issues.

Conclusions: The low number of included studies and the high heterogeneity highlighted among them do not allow any firm conclusions on the correlation between GNB colonisation and BSI in neonates. The analysis of prospective large cohorts of colonised neonates with clinical outcomes are still needed to clarify risk factors and the major determinants responsible for causing invasive infections in previously colonised neonates. Demonstrating the actual correlation between GNB colonisation and development of GNB infection may help to define the best strategies for Infection Prevention and Control (cohorting babies during hospital outbreaks – unit level) and the appropriate empiric antibiotic treatment (individual patient level).



Study or Subgroup	Colonisation Events	Colonisation Total	Non-colonisation Events	Non-colonisation Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Almuneef MA 2001	10	89	0	150	8.3%	35.23 [2.09, 594.07]	2001
Pessoa-Silva CL 2003	9	219	4	161	12.1%	1.65 [0.52, 5.28]	2003
Boo NY 2005	5	80	4	288	11.9%	4.50 [1.24, 16.37]	2005
Gundes S 2005	2	8	5	41	11.5%	2.05 [0.48, 8.78]	2005
Velasco C 2009	9	159	8	284	12.6%	2.01 [0.79, 5.11]	2009
Smith A 2010	59	625	0	73	8.4%	14.07 [0.88, 225.16]	2010
Parm U 2011	16	154	51	124	13.1%	0.25 [0.15, 0.42]	2011
Suviste J 2012	1	45	9	2056	10.1%	5.08 [0.66, 39.23]	2012
Oteo J 2013	3	7	4	406	11.9%	43.50 [11.89, 159.16]	2013
Total (95% CI)		**1386**		**3583**	**100.0%**	**3.90 [1.04, 14.57]**	
Total events	114		85				

Heterogeneity: Tau² = 3.38; Chi² = 81.44, df = 8 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.02 (P = 0.04)