

Original Article

Factors associated with oral *Candida* colonization in neonates at intensive care unit

I Putu Wijana, MD; Hendra Santoso, MD; I Made Swastika, MD

ABSTRACT

Background Oral candidiasis still has high prevalence and frequently causes problems in the neonatal period.

Objective To evaluate some factors associated with the occurrence of oral *Candida* colonization in neonates.

Methods A cross sectional study was performed at the Intensive Care Unit, Neonatology Division, Department of Child Health, Medical School, Udayana University/Sanglah Hospital Denpasar, from November 2002 to April 2003. Eighty neonates were enrolled. Oral mucous swabs were obtained and examined for *Candida* colonization using potassium hydroxide (KOH). Data were analyzed by prevalence ratio and logistic regression; a p value of <0.05 was considered significant.

Results The prevalence of oral *Candida* colonization was 55% (44/80). The colonization was significantly associated with age of >1 week, male sex, gestational age of <37 weeks, Apgar score of <7, birth weight of <1500 grams, oral mucous pH of <7, systemic antibiotic use, and steroid use by mother. Breastfeeding was a protective factor. Correlation between variables using Spearman test revealed correlation coefficient of <0.5. By logistic regression, birth weight of <1500 grams (p=0.04) and systemic antibiotic use (p=0.01) were significant associated factors of oral *Candida* colonization, while breastfeeding was a significant protective factor (p=0.03).

Conclusion Birth weight of <1500 grams and systemic antibiotic use were significant associated factors of oral *Candida* colonization and breastfeeding was a significant protective factor of oral *Candida* colonization in neonates [Paediatr Indones 2004;44:188-192].

Keywords: neonatal, preterm, oral *Candida* colonization, KOH examination

Oral candidiasis is a common opportunistic infection of the oral cavity caused by overgrowth of *Candida albicans*.¹⁻⁵ The risk factors are prematurity, prolonged systemic antibiotic, corticosteroid, or aminophylline treatment, and formula feeding.^{2,6,7} A neonate,

especially a preterm, has an immature and uninitiated immune response that can lead to enhanced susceptibility to infection of *Candida*. Neutrophils, macrophages, and lymphocytes have a major role in protecting the host against *Candida* infection.^{2,8-11} Acute pseudomembrane is the most common sign of oral candidiasis. Pseudomembranous candidiasis is characterized by extensive white pseudomembrane consisting of desquamated epithelial cells, fibrin, and fungal hyphae. These white patches occur on the surface of the labial and buccal mucous membrane, tongue, and oropharynx. The patches can usually be scraped off with a swab to expose an underlying erythematous mucosa.^{2,12-14}

The incidence of oral candidiasis varies depending on age and certain predisposing factors. Reported peak incidence was around the second week of life. The incidence of oral candidiasis was equal in males and females. Akpan¹⁵ reported that the incidence of *Candida albicans* isolated from the oral cavity of neonates was 45%. In the USA,¹⁴ as many as 37% of newborns may develop oral candidiasis

From the Departments of Child Health (IPW, HS); Dermato-Venereology (IMS), Medical School, Udayana University, Sanglah Hospital, Denpasar, Indonesia

Reprint requests to: I Putu Wijana, MD, Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar, Jalan Nias, Denpasar, Indonesia. Tel. 62-361-227911-15 Ext. 128; Fax. 62-361-244038, email: ikaunud@centrin.net.id.

during the first months of life. Rippon² reported that oral candidiasis in neonates was about 23%. In Cipto Mangunkusumo Hospital, Jakarta, Aisah¹⁶ found that 76% of diaper rash cases in neonates are caused by *Candida albicans*. The purpose of this study was to evaluate some associated factors of the occurrence of oral *Candida* colonization in neonates.

Methods

This was a cross-sectional study, conducted from November 2002 until April 2003. The inclusion criteria were newborns hospitalized in the intensive care unit, Sanglah Hospital whose parents agreed to follow the procedure of this study. Infants with incomplete medical records are excluded.

The sample size was calculated based on an assumption that the incidence rate of oral *Candida* colonization in neonates was approximately 37%. A minimal sample of 80 was required ($p < 0.05$, power 80%).

Subjects were recruited consecutively. Demographic data (birth weight, sex, gestational age, mode of delivery) were retrieved from medical records. Clinical data (clinical manifestation and oral mucous pH) were collected through the examination of the patients.

Statistical analysis was done using SPSS 10.0 for Windows computer program. Comparison between the study groups for nominal variables was performed with the chi-square test. Associated factors of oral *Candida* colonization (age of >1 week, gestational age of <37 weeks, male sex, Apgar score of <7 , birth weight of <1500 grams, oral mucous pH of <7 , systemic antibiotic treatment, steroid use by mother, mode of delivery, and breastfeeding) were evaluated by prevalence ratio (PR) and 95% confidence interval (95%CI). Correlation between factors and oral *Candida* colonization were evaluated with Spearman test. Variables with p value of <0.05 by univariate analysis were calculated into multiple regression analysis. A p value of <0.05 was considered significant.¹⁷⁻¹⁹

Results

Subjects' characteristics

During November 2002 to April 2003, 80 infants were enrolled in this study. No infant received steroid or

aminophylline treatment. Forty-three of 80 (54%) were girls and 37 (46%) were boys. The mean gestational age was 34.5 weeks (SD 2.9) and the mean chronological age was 7.7 days (SD 2.9).

Prevalence ratio

The total frequency of oral *Candida* colonization was 44 of 80 subjects (55%). Some factors had significant prevalence ratio (PR >1) and p value of <0.05 for oral *Candida* colonization (Table 1). Factor insignificantly associated with oral candidiasis was mode of delivery, while breastfeeding was proven as a significant protective factor. Systemic antibiotic usage had the highest prevalence ratio (PR = 2.77), followed by age of >1 week (PR = 2.38), and oral mucous pH (PR = 2.21).

TABLE 1. PREVALENCE RATIO OF ASSOCIATED FACTORS OF ORAL *CANDIDA* COLONIZATION IN NEONATES

Associated factors	KOH positive	KOH negative	PR	95%CI	p
Age					
≥ 1 week	34	13	2.38	1.38;4.12	0.00
<1 week	10	23			
Sex					
Male	25	12	1.52	1.02;2.28	0.03
Female	19	24			
Gestational age					
<37 weeks	33	17	1.80	1.08;2.95	0.01
≥ 37 weeks	11	19			
Apgar score					
<7	31	12	2.05	1.27;3.30	0.001
≥ 7	13	24			
Birth weight					
<1500 grams	23	9	1.64	1.11;2.42	0.01
≥ 1500 grams	21	27			
Oral mucous pH					
<7	33	13	2.21	1.32;3.72	0.001
≥ 7	11	23			
Systemic antibiotic					
Yes	39	20	2.77	1.26;6.09	0.001
No	5	16			
Steroid use by mother					
Yes	23	10	1.56	1.05;2.30	0.02
No	21	26			
Mode of delivery					
Vaginam	34	27	1.05	0.65;1.71	0.81
Non Vaginam	10	9			
Breastfeeding					
Yes	10	25	0.37	0.21;0.65	0.00
No	34	11			

PR: prevalence ratio; CI: confidence interval

Correlation

According to Spearman test, there was a weak positive correlation between age of <1 week and oral *Candida* colonization, while breastfeeding had a weak negative

TABLE 2. CORRELATION MATRIX BETWEEN ASSOCIATED FACTORS AND ORAL *CANDIDA* COLONIZATION IN NEONATES

		Age	Sex	BW	GA	AS	pH	AB	Steroid	Breastfeeding
Candidiasis	r	0.416	0.234	0.277	0.285	0.370	0.374	0.391	0.248	-0.469
	p	0.00	0.036	0.013	0.01	0.010	0.001	0.00	0.027	0.00

r: correlation coefficient, KOH: potassium hydroxyde, BW: birth weight; GA: gestational age; AS: Apgar score. AB: systemic antibiotic

correlation with oral candidiasis ($r=-0.469$, $p<0.0001$). The complete values of coefficient correlation and p values can be seen in Table 2.

Logistic regression analysis

Table 3 shows that independent variables significantly associated with oral *Candida* colonization were systemic antibiotic use (OR=5.53, $p=0.01$), birth weight of <1500 grams (OR= 4.85, $p=0.04$), and breastfeeding (OR=0.31, $p=0.03$). On the other hand, age of >1 week, gender, gestational age, Apgar score, oral mucous pH, and steroid use by mother had no significant association with oral *Candida* colonization.

Discussion

The prevalence of oral *Candida* colonization in this study was 55% (44/80). Similar results were reported by Akpan (40-45%),¹⁵ Gupta *et al* (32%),²⁰ and Mudra (37%).¹⁴ We found that the prevalence of oral *Candida* colonization was significantly higher in neonates with age of ≥ 1 week compared to that in neonates of <1 week ($p<0.0001$, PR=2.38, 95%CI 1.38;4.12). Baley *et al*²¹ found that 66% of *Candida albicans* colonization in VLBW occur in the second week of life, which is similar to that reported by Gupta *et al*²⁰.

The colonization of oral *Candida* occurred more frequently in males compared to females ($p=0.03$, PR=1.59, 95%CI 1.02;2.28). Gupta *et al*²⁰ reported that oral candidiasis is significantly more frequent in males. Colonization of oral candida also occurred more frequently in neonates with gestational age of <37 weeks compared to those of ≥ 37 weeks ($p=0.01$, PR=1.8, 95%CI 1.08; 2.99). Baley *et al*²² reported that 26% of *Candida* colonization occur in preterm neonates, while Kaufman *et al*²³ found this proportion to be 50%.

In this study, the colonization of oral *Candida* more frequently occurred in neonates with asphyxia during delivery compared to those without, with a p value of <0.0001 and PR=2.05 (95%CI 1.27;3.3). Similar result was also reported by Gupta *et al*²⁰. The colonization of oral *Candida* in neonates with birth weight of <1500 grams was higher compared to that of ≥ 1500 grams ($p=0.01$, PR=1.64, 95%CI 1.11;2.42). Baley *et al*²¹ found that the prevalence of *Candida* colonization in VLBW neonates was 46%. In this study, the colonization of oral *Candida* was significantly more frequent in neonates with oral mucous pH of <7 compared to that of ≥ 7 ($p<0.001$, PR=2.21 95%CI 1.32;3.72).

The increasing use of antibiotics, particularly the broad-spectrum ones, has resulted in increasing incidence of *Candida* colonization. In this study, the prevalence of oral *Candida* colonization was higher in neo-

TABLE 3. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

Variables	B	SE	p	OR	95%CI
1. Age	0.50	0.73	0.48	1.66	0.39;6.97
2. Sex	0.52	0.68	0.44	1.69	0.44;6.52
3. Birth weight of <1500 g	1.57	0.77	0.04	4.85	1.06;22.06
4. Gestational age	0.82	0.70	0.53	1.54	0.38;6.15
5. Apgar score	0.86	0.84	0.32	2.28	0.43;12.05
6. Oral mucous pH	0.86	0.68	0.20	2.37	0.62;9.10
7. Systemic antibiotic use	1.71	0.70	0.01	5.53	1.38;22.16
8. Steroid use by mother	-0.52	0.97	0.59	0.59	0.08;4.03
9. Breastfeeding	-1.40	0.65	0.03	0.31	0.69;0.88

SE: standard error, OR: odds ratio

nates with systemic antibiotic use compared to those of without ($p < 0.0001$, $PR = 2.77$, $95\%CI$ 1.26;6.09). Similar result was reported by Gupta et al.²⁰

The use of corticosteroids, which may change flora as well as function of immune modulators, is also a risk factor for oral candidiasis.⁶ Neonates delivered from mothers using corticosteroids had higher prevalence of oral candidiasis compared to those who were not ($p = 0.02$, $PR = 1.56$, $95\%CI$ 1.05;2.30). Botas²⁴ reported that the administration of intravenous corticosteroid significantly increases the risk of *Candida* infection in preterm infants. Hope²⁵ found that 60% of immunocompetent infants have signs of oropharyngeal thrush.

Oral colonization of *Candida* in breastfed neonates was lower compared to that in formula fed neonates ($p < 0.0001$, $PR = 0.37$, $95\%CI$ 0.21;0.65). Breastfeeding is a protective factor against oral candidiasis because breast milk contains SIgA, IgM, IgG, lactoferrin, lactoperoxidase, lysozym, macrophages, and neutrophils.^{2,26} Oral colonization of *Candida* was not significantly different between vaginally and non-vaginally delivered neonates ($p = 0.81$, $PR = 1.05$, $95\%CI$ 0.65;1.7). These results differ from those of Baley²¹ who stated that *Candida* colonization was significantly more frequent in neonates with vaginal delivery.

By Spearman test, two factors had weak correlations with oral candidiasis i.e., age of >1 week and breastfeeding, while other factors did not have significant statistical correlation. By multivariate analysis, three factors had significant association with oral *Candida* colonization in neonates i.e., birth weight < 1500 grams ($p = 0.04$; $OR = 4.85$; $95\%CI$ 1.06;6.52), systemic antibiotic use ($p = 0.01$, $OR = 5.53$; $95\%CI$ 1.38;22.16), and breastfeeding ($p = 0.31$; $OR = 0.31$; $95\%CI$ 0.69;0.88).

In conclusion, there are three independent factors associated with oral *Candida* colonization in neonates i.e., birth weight of < 1500 grams, systemic antibiotic use, and breastfeeding which is a protective factor.

References

1. Miller MJ. Fungal infection. In: Klein JO, Remington JS, editors. Infectious diseases of the fetus & newborn infant. 4th ed. Philadelphia: Saunders; 1995. p.703-43.
2. Rippon JW. Medical mycology. 2nd ed. Philadelphia: Saunders; 1982. p. 484-501.
3. Lay KM, Russel C. *Candida* species and yeasts in mouths of infants from a special care unit of a maternity hospital. Arch Dis Child 1987;52:794-6.
4. Melnick JL. Medical mycology. In: Jawetz E, editor. Review of medical microbiology. 15thed. California: Lange Medical Publication; 1982. p. 297-9.
5. Hughes PA, Martha L, Harry H. Neonatal candidiasis. In: Bodey GP, editor. Pathogenesis, diagnosis, and treatment. 2nded. New York: Raven Press; 1993. p. 261-77.
6. Shahe V, Smith CB. Pathogenesis, host resistance, and predisposing factors. In: Bodey GP, editor. Pathogenesis, diagnosis, and treatment. 2nded. New York: Raven Press; 1993. p. 59-75.
7. Wade JC. Epidemiology of *Candida* infection. In: Bodey GP, editor. Pathogenesis, diagnosis, and treatment. 2nd ed. New York: Raven Press; 1993. p. 85-107.
8. Suharno S, Tantien, Evita, Kusmarinah. Mekanisme pertahanan pejamu pada infeksi Kandida. MDVI 2000;27:187-93.
9. Kirkpatrick CH. Immune responses to fungi. In: Rich R, Thomas AF, editors. Clinical immunology principle and practice. Philadelphia: Mosby; 1999. p. 571-7.
10. Roitt I, Brostoff J, Male D. Immunology. 5thed. Philadelphia: Mosby; 1998. p. 43-54.
11. Thrush or Candidiasis. Available from: URL: <http://www.child.org/dental/thrush.asp.html>
12. Neonatal candidiasis. Availabe from: URL: http://www.doctorfungus.org/fungi_action/human/candida/neonatal.htm.
13. Koch H, Graber MA. Pediatrics: neonatal infections. Available from: URL: <http://www.vh.org/pediatric/provider/pediatrics/familypracticehanbook/neonatalinfections.html>.
14. Mudra K. Oral thrush. Available from: URL: <http://www.emedicine.com/ped/topic25.html>.
15. Akpan A, Morgan R. Oral candidiasis. Postgrad Med J 2002;78:455-9.
16. Aisah SB, Lestari TS. Pengobatan kombinasi mikonazol nitrat 0,25% dan seng oksida 15% pada penderita dermatitis popok. Presented at PIT IDAI; 2001 June 25; Palembang, Indonesia.
17. Ghazali MV, Sastromiharjo, Soejarwo R. Studi cross sectional. In: Sastroasmoro S, Ismael S, editors. Dasar-dasar metodologi penelitian klinis. 1st ed. Jakarta: Binarupa Aksara; 1995. p. 66-77.
18. Madiyono B, Moeslichan MZ, Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. Dasar-dasar metodologi penelitian klinis. 1st ed. Jakarta: Binarupa Aksara; 1995. p. 187-212

19. Sastroasmoro S. Memahami nilai p dan interval kepercayaan dalam studi analitik. Sari Pediatri 1994;1:169-78.
20. Gupta P. Clinical profile and risk factors for oral candidiasis in sick newborns. Indian Pediatr 1996;33:299-303.
21. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infant: therapeutic toxicity. Pediatrics 1984;73:153-7.
22. Baley J, Kliegman RM, Boxerbaum, Fanaroff. Fungal colonization in the very low birth weight infant. Pediatrics 1986;78:225-32.
23. Kaufman D, Boyle R, Hazen K, Robinson M. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med 2001;345:1660-6.
24. Botas CM, Kurlat L, Young S. Disseminated *Candida* infection and intravenous hydrocortisone in preterm infants. Pediatrics 1995;95:883-7.
25. Hoppe JE. Treatment of oropharyngeal candidiasis in immunocompetent infants: a randomized multicenter study of miconazole gel vs nystatin suspension. The anti fungals study group. Pediatr Infect Dis J 1997;16:288-93.
26. Suradi R. Spesifisitas air susu ibu. Presented at The National Scientific Meeting of The Indonesian Society of Pediatricians; 2001 June 25; Palembang, Indonesia.