

Oral Care, Inflammatory Cytokines, and Aspiration Pneumonia in Elderly Persons

Yasuyuki Taooka^{1,2}, Takeshi Isobe², Yukari Tsubata², Megumi Hamaguchi², Shunichi Hamaguchi², Junya Inata¹, Hiroyuki Ito¹, Yuki Fukushiro¹

1 Department of Respiratory Medicine, Medical Corporation JR Hiroshima Hospital, Hiroshima, Japan;

2 Department of Internal Medicine, Division of Medical Oncology and Respiratory Medicine, Shimane University Faculty of Medicine, Izumo, Japan.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Yasuyuki Taooka, MD, Ph D, FCCP, FACP, FRSM, Chief, Department of Respiratory Medicine, Medical Corporation JR Hiroshima Hospital, Hiroshima, Japan.

Email: taooka-alg@umin.ac.jp

Received: December 12, 2020

Revised: January 2, 2020

Accepted: January 5, 2020

Published online: January 29, 2021

ABSTRACT

Aspiration pneumonia is one of the major causes of death for elderly persons. In nursing home-associated pneumonia (NHCAP), micro-aspiration, higher mortality, and antibiotic-resistant bacterial infections are well-known problems. In NHCAP cases, several factors on the host side are related to high mortality. The importance of daily oral care in elderly patients with dysphagia is also well recognized. Silent aspiration of bacteria-containing saliva and salivary pro-inflammatory cytokines produced by interdental plaque and periodontitis might stimulate lower respiratory inflammation and lead to aspiration pneumonia. However, the relationship between micro-aspiration and inflammatory cytokines produced in the lower

respiratory tract remains uncertain. In this context, oral care, dental care, and the inhibitory effects of dental care on recurrent aspiration pneumonia in elderly persons will be discussed.

Key words: Oral care; Pneumonia; Inflammatory cytokines; Micro-aspiration; Geriatric

© 2021 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Taooka Y, Isobe T, Tsubata Y, Hamaguchi M, Hamaguchi S, Inata J, Ito H, Fukushiro Y. Oral Care, Inflammatory Cytokines, and Aspiration Pneumonia in Elderly Persons. *Journal of Respiratory Research* 2021; 7(1): 152-154 Available from: URL: <http://www.ghrnet.org/index.php/jrr/article/view/3085>

List of abbreviations

NHCAP: nursing home associated pneumonia; HCAP: healthcare-associated pneumonia; POHC: professional oral health care; CVD: cerebral vascular disease; IL: interleukin; COPD: chronic obstructive lung disease

PNEUMONIA, MICRO-ASPIRATION, AND ORAL CARE IN ELDERLY PERSONS

Aspiration pneumonia is well known as a cause of pneumonia in elderly persons. We previously reported the involvement of interleukin (IL)-17A in extravasation of neutrophils in cases of aspiration pneumonia^[1]. In elderly patients with aspiration pneumonia, cerebral vascular disease (CVD) and diabetes mellitus were found to be related to a poor prognosis^[2]. Improvement of mortality and inhibiting recurrent pneumonia are major problems in elderly patients with pneumonia. The importance of oral care in elderly patients with swallowing disorders is also well recognized, and many papers have already been published^[3-5]. Periodontitis is a polymicrobial infection and multifactorial disease, and it is characterized by chronic inflammation of the periodontium^[3]. Oral health is closely related to systemic diseases, including CVD, and pneumonia. Inadequate oral care might result in accumulation of bacterial plaque biofilm^[4,5].

Generally, oral care is divided into two categories. One is oral

health self-care (basic daily oral care), and the other is professional oral health care (dentist care or dental hygienist care). Basic daily oral care includes brushing teeth and dentures and swabbing the buccal mucosa and tongue. On the other hand, professional oral health care includes brushing teeth, swabbing the buccal mucosa and tongue, cleaning dentures, mouth-rinse, and dental visit. So far, differences between and the efficiency of the two categories have not been well examined. Furthermore, the relationship between micro-aspiration of bacteria-containing plaque and cytokine stimulation in the lower respiratory tract remains uncertain. In this manuscript, professional oral health care and its inhibitory effect on recurrent aspiration pneumonia in elderly persons are discussed. In addition, oral care and lower respiratory inflammation are also discussed from the viewpoint of cytokines.

BASIC ORAL HEALTH CARE

The purpose of basic daily self-oral care is cleaning the oral cavity, improving eating function training, and prevention of dry mouth. After daily oral hygiene care, including oral moisture retention and cleaning of the tongue and palate, pathogen colonization could be minimized^[4,5]. Mechanical stimulation of the oral mucosa leads to brain stimulation and improvements in dysphagia, latency time of the swallowing response, and the cough reflex. Oral health care can help prevent aspiration pneumonia associated with dysphagia. Improving eating function reduces the occurrence rate of massive aspiration. One merit of conventional oral care is that nursing staff and non-specialists, including the patient's family, can be involved in the patient's care. Recently, Takahashi *et al* reported^[6] that aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributed to the aggravation of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2.

PROFESSIONAL ORAL HEALTH CARE (POHC) AND DENTAL CARE

POHC is expected to prevent recurrence of aspiration pneumonia in elderly persons. However, there are only a few lines of evidence showing that POHC intervention after illness improves severe aspiration pneumonia^[7]. Since POHC requires seeing a dentist or dental hygienist, not all patients can receive such care. One major merit of POHC is plaque removal and treatment of periodontitis^[8,9], which might lead to mechanical removal of oral pathogens. One systematic review by Liu *et al* reported^[10] that it was not possible to establish the effects of POHC on the incidence rate of healthcare-associated pneumonia (HCAP) compared with usual oral care over an 18-month period of observation. Furthermore, they reported that POHC reduced pneumonia-associated death by 60% in comparison with usual oral care over a 24-month follow-up period. In addition, another paper reported^[11] that POHC suppresses mortality due to pneumonia and prevents morbidity with influenza.

INDUCED-SPUTUM AND SALIVARY CYTOKINES AS BIOMARKERS

In an animal model experiment^[12], heat-inactivated periodontopathic bacteria induced the production of inflammatory cytokines including IL-6 and IL-8 by pharyngeal, bronchial, and alveolar epithelial cells, where these bacteria induced cytokine production more than *S. pneumoniae*. When the periodontopathic bacterium *F. nucleatum* is injected into the murine trachea, protein levels of IL-6 and

keratinocyte-derived chemokine were markedly increased in the lower respiratory tissues and serum, indicating that the bacterium could induce pro-inflammatory cytokine production *in vivo*. This micro-aspiration stimulates inflammation of the lower respiratory tract and produces pro-inflammatory cytokines^[13]. Salivary cytokines stimulated by periodontitis and interdental plaque might release lower respiratory tract cytokines. So far, several other reports^[14-16] about periodontitis and salivary inflammatory cytokines have been published. Escalona *et al* reported^[17] that the gingival fluid levels of IL-1 α , IL-1 β , tumor necrosis factor- α , IL-6, and IL8 in chronic periodontitis cases were higher and associated with the severity of periodontitis. Members of the IL-1 family are thought to act as the key mediators of the host response to microbial invasion, inflammation, and tissue injury^[14,18]. We also reported the involvement of IL-3 γ one of the IL-1 family members, in acute lung injury^[19]. Do induced-sputum inflammatory cytokines act as biomarkers of micro-aspiration? Do salivary cytokines act as biomarkers of pneumonia risk? As far as we could determine, there have been no reports of the inhibitory effects of salivary and or induced-sputum inflammatory cytokine changes after POHC. However, in chronic obstructive lung disease (COPD), there have been many reports about induced-sputum cytokine levels and sputum microbiota. For example, Tangedal *et al* reported^[20] the changes in microbial composition between stable COPD and exacerbations. Pro-inflammatory cytokine levels were significantly different between the groups, and changes in the sputum microbiota with COPD states were accompanied by changes in cytokines. Other research also reported^[21] that IL-1 β was associated with acute exacerbation of COPD and reaffirmed the association between IL-1 β pathway activation and airway bacterial infection in COPD. Therefore, induced-sputum cytokines and salivary cytokines could become non-invasive biomarkers of aspiration pneumonia. Comparing with induced sputum, saliva can be easily, repeatedly, and noninvasively obtained and stored without the use of specialized equipment. From the point of view of POHC, removal of interdental plaque and treatment of periodontitis would suppress salivary cytokine production. Furthermore, aspiration of salivary cytokines stimulates inflammation of the lower respiratory tract and increases sputum-induced cytokines^[17,18].

FUTURE DIRECTION

Taken together, POHC is recommended for elderly persons with swallowing disorders and those with aspiration pneumonia. POHC might have the possibility of reducing pneumonia-associated death compared with daily self-oral care. Salivary cytokines and/or sputum-induced cytokines might act as biomarkers for the risk of aspiration pneumonia. However, more scientific evidence from the laboratory is needed before this knowledge can be translated into practice. Finally, we should pay attention to the future of the field of oral care-related research.

ACKNOWLEDGMENT

A grant for English proofreading of this manuscript was given by *Taiyo Life Welfare Foundation* (Tokyo, Japan) (to Yasuyuki Taooka).

REFERENCES

1. Taooka Y, Ohe M, Chen L, Sutani A, Higashi Y, Isobe T. Increased expression levels of integrin α 9 β 1 and CD11b on circulating neutrophils and elevated serum IL-17A in elderly aspiration pneumonia. *Respiration* 2013; 86: 367-375. [PMID: 23257917];

- [DOI: 10.1159/000345390]
2. Taooka Y, Takezawa G, Ohe M, Sutani A, Isobe T. QTC interval prolongation as a prognostic factor of elderly pneumonia. *Multidisciplinary Respiratory Medicine*. 2014; 59: 1-6. <http://www.mrmjournal.com/content/9/1/59>. [PMID: 25705382]; [DOI: 10.1186/2049-6958-9-59]
 3. Saito M, Shimazaki Y, Nonoyama T, Tadokoro Y. Association of oral health factors related to oral function with mortality in older Japanese. *Gerodontology*. 2020 Nov 12. [PMID: 33184952]; [DOI: 10.1111/ger.12508]
 4. Tada A, Miura H. Prevention of aspiration pneumonia (AP) with oral care. *Arch Gerontol Geriatr*. 2012;55:16-21. [PMID:21764148]; [DOI: 10.1016/j.archger.2011.06.029]
 5. Takeuchi K, Izumi M, Furuta M, Takeshita T, Shibata Y, Kageyama S, Okabe Y, Akifusa S, Ganaha S, Yamashita Y. Denture wearing moderates the association between aspiration risk and incident pneumonia in older nursing home residents: a prospective cohort study. *Int J Environ Res Public Health*. 2019;16:554. [PMID: 30769876]; [DOI: 10.3390/ijerph16040554]
 6. Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. *J Oral Sci*. 2020 Nov 12. [PMID: 33177276]; [DOI: 10.2334/josnusd.20-0388]
 7. Adachi M, Ishihara K, Abe S, Okuda K, Ishikawa T. Effect of professional oral health care on the elderly living in nursing homes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002;94(2):191-5. [PMID: 12221387]; [DOI: 10.1067/moe.2002.123493]
 8. Raghavendran K, Mylotte JM, Scannapieco FA. Nursing home-associated pneumonia, hospital-acquired pneumonia and ventilator-associated pneumonia: the contribution of dental biofilms and periodontal inflammation. *Periodontol* 2000. 2007;44:164-77. [PMID: 17474932]; [DOI: 10.1111/j.1600-0757.2006.00206.x]
 9. Gomes-Filho IS, Cruz SSD, Trindade SC, Passos-Soares JS, Carvalho-Filho PC, Figueiredo ACMG, Lyrio AO, Hintz AM, Pereira MG, Scannapieco F. Periodontitis and respiratory diseases: A systematic review with meta-analysis. *Oral Dis*. 2020; 26:439-446. [PMID: 31715080]; [DOI: 10.1111/odi.13228]
 10. Liu C, Cao Y, Lin J, Ng L, Needleman I, Walsh T, Li C. Oral care measures for preventing nursing home-acquired pneumonia. *Cochrane Database Syst Rev*. 2018;9(9):CD012416. [PMID: 30264525]; [DOI: 10.1002/14651858.CD012416.pub2]
 11. Nawata W, Umezaki Y, Yamaguchi M, Nakajima M, Makino M, Yoneda M, Hirofujii T, Yamano T, Ooboshi H, Morita H. Continuous professional oral health care intervention improves severe aspiration pneumonia. *Case Rep Dent*. 2019; 4945921. [PMID: 31934463]; [DOI: 10.1155/2019/4945921]
 12. Johnson, L. Periodontal bacteria influence inflammasome activation and cytokine secretion during oral infection. UC Merced. 2016; ProQuest ID: Johnson_ucmerced_1660D_10213. Merritt ID: ark:/13030/m5p6095m. Retrieved from <https://escholarship.org/uc/item/70h4v8t7>
 13. Belstrøm D, Damgaard C, Könönen E, Gürsoy M, Holmstrup P, Gürsoy UK. Salivary cytokine levels in early gingival inflammation. *J Oral Microbiol*. 2017; 9:1364101. [PMID: 28839521]; [DOI: 10.1080/20002297.2017.1364101]
 14. Taylor JJ. Protein biomarkers of periodontitis in saliva. *ISRN Inflamm*. 2014; 593151. [PMID: 24944840]; [DOI: 10.1155/2014/593151]
 15. Jaedicke, Katrin M, Preshaw, Philip M, Taylor, John J. Perio 2000 Salivary analysis of cytokines in periodontal disease. *Periodontology*. 2000; 70. 164-183. [ISSN 09066713]
 16. Sakalauskiene J, Giedrimiene D, Gleiznys D, Gleiznys A, Gleizniene R, Vitkauskiene A. Peripheral blood leukocytes interleukin-1 beta (IL-1 β) cytokine hyper-reactivity in chronic periodontitis. *Med Sci Monit*. 2016;22:4323-4329. [PMID: 27847385]; [DOI: 10.12659/MSM.898422]
 17. Escalona LA, Mastromatteo-Alberga P, Correnti M. Cytokine and metalloproteinases in gingival fluid from patients with chronic periodontitis. *Invest Clin*. 2016;57:131-142. [PMID: 28429894]
 18. Ren C, McGrath C, Jin L, Zhang C, Yang Y. The effectiveness of low-level laser therapy as an adjunct to non-surgical periodontal treatment: a meta-analysis. *J Periodontal Res*. 2017;52:8-20. [PMID: 26932392]; [DOI: 10.1111/jre.12361]
 19. Taooka Y, Hotta T, Isobe T: Editorial; IL-36 γ and infectious lung diseases. *Journal of Respiratory Research*. 4: 137-139, 2018. [doi:10.17554/j.issn.2412-2424.2018.04.40]
 20. Tangedal S, Nielsen R, Aanerud M, Persson LJ, Wiker HG, Bakke PS, Hiemstra PS, Eagan TM. Sputum microbiota and inflammation at stable state and during exacerbations in a cohort of chronic obstructive pulmonary disease (COPD) patients. *PLoS One*. 2019;14:e0222449. [PMID: 31527888]; [DOI: 10.1371/journal.pone.0222449]
 21. Damera G, Pham TH, Zhang J, Ward CK, Newbold P, Ranade K, Sethi S. A sputum proteomic signature that associates with increased IL-1 β levels and bacterial exacerbations of COPD. *Lung*. 2016;194:363-9. [PMID: 27083436]; [DOI: 10.1007/s00408-016-9877-0]