Aspiration pneumonia: With special reference to pathological and epidemiological aspects, a review of the literature

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Summary Silent aspiration plays an important role in the pathogenesis of bacterial pneumonia in the elderly. Defense of the airway is impaired in the elderly by alteration in respiratory mechanics; decreased mucociliary clearance and immunosenescence. And, the number of microorganisms in the oral cavity of the elderly is usually larger than that of young adults because of gradual reduction in production of saliva. A relationship between poor oral health and respiratory disease has been suggested by a number of recent microbiologic and epidemiologic studies, especially in elder subjects; who requiring help with feeding, wearing denture/edentate, with periodontal disease, and so on. Several researchers have reported that using professional oral health care (POHC) can prevent pneumonia. Oral/respiratory mucosal tissues produced cytokine that stimulated by oral microorganisms and were altered expression of various cell adhesion molecules on their surface in response to cytokine stimulation. Then, aspiration pneumonia histopathologically characterized with inflammatory response including macrophage infiltration was caused by aspiration of oral microorganisms, acid and food particle. In conclusion, silent aspiration may be a key risk factor for the pathogenesis of pneumonia in the elderly patients with poor oral hygiene.

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1. Introduction

Pneumonia is the fourth leading cause of death in Japan, resulting in 110,000 deaths in 2007, which represents a mortality rate of 87.4 per 100,000 individuals [1]. The mortality rate due to pneumonia increases with age. Pneumonia is an inflammation of the lungs by viruses, fungi, parasites or bacterial infections, and the last one is usually classified as community-acquired pneumonia (CAP) or nosocomial (hospital-acquired) pneumonia. The differential diagnosis is important because the pathogens implicated and the preventive measures taken are different for the 2 types. The causative microorganisms of these 2 types differ. CAP is usually associated with infection by Streptococcus pneumoniae and Haemophilus influenzae and with other species such as Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila; a variety of anaerobic species can also be involved [2]. The spectrum of microorganisms responsible for nosocomial pneumonia is quite different, with Gram-negative bacteria and Staphylococcus aureus being the most prevalent [3].

Aspiration pneumonia (AP) is defined as lower respiratory tract infections mostly in elderly people who have aspirated oropharyngeal or gastric contents, and this condition is most often associated with dysphasia [4]. Though researchers have indicated that 5—15% of CAP is AP [5,6], AP likely occurs more frequently than reported, because the disease is not recognized in many cases. The reason the disease is not always recognized is that the causative microorganism of AP is common to CAP and nosocomial pneumonia and the spectrum of AP is even broader [3]. Bartlett et al. reported that anaerobic bacteria were detected in 93% of AP, and the mixed infection of anaerobic bacteria and aerobically growing bacteria were often observed [7]. Namely, the causative bacteria involved are indigenous oral flora or they are acquired in the hospital. But the frequency of infection with anaerobic microorganisms is uncertain because of the technical difficulty associated with anaerobic culture and the possibility of contamination by anaerobic oral flora during sampling. Anaerobic bacteria are not routinely cultured from bronchial secretions due to these difficulties [8], and this might be one of the reasons why little research exists concerning oral flora and aspiration pneumonia.

The term “aspiration” was mainly used as “apparent aspiration” for the pediatric accident of swallowing foreign bodies until around 1995 [9,10]. As for silent aspiration, it is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract and may cause infections such as AP or aspiration pneumonitis. The right lung of incident rate of AP is high. The foreign body drops easily to right bronchia because right bronchium is sharper bifurcated angle from the trachea than a left one [11]. Contraction of AP or aspiration pneumonitis was caused by silent aspiration in some dysphagic patients with neurological disorders [12]; Parkinson’s disease or alcoholism was suspected [8]. And children with neurologically based dysphagia were also thought to be at high risk [13]. Generally, abnormal oropharyngeal colonization as a result of medical complications is shown in dysphagic patients who have decreased immunity and/or impaired pulmonary clearance. Those subsequently develop pneumonia when potential respiratory pathogens are aspirated together with food and/or liquid [14].

Further, nondysphagic persons may occasionally experience microaspiration of pharyngeal secretions during sleep or at times of depressed consciousness [15—17]. Also, approximately half of all healthy adults also aspirate small amounts of oropharyngeal secretions during sleep [16,17]. In 1994, Kikuchi et al. examined the occurrence of silent aspiration during sleep in elderly patients with CAP by using indium-111. Silent aspiration in patients with CAP was more frequent than in age-matched control subjects (71% vs 10%) [18]. Therefore, it seems reasonable to conclude that silent aspiration has an important role in pneumonia that occurs in the elderly.

2. Silent aspiration and oral hygiene

2.1. Aging

Silent aspiration appears to play an important role in the pathogenesis of bacterial pneumonia and chronic pulmonary disease [19–22]. Elderly people frequently aspirate during sleep [16,17], and pneumonia develops when the defense mechanism of the healthy lung organization is overwhelmed [23] and/or weaken by aging. Defense of the airway is impaired in the elderly by alteration in respiratory mechanics, decreased mucociliary clearance, immunosenescence and, in some cases, concomitant illnesses that predispose to aspiration [24,25].

It is suggested that swallowing function and the cough reflex are important defenses to the aspiration [26]. Sekizawa et al. described that marked depression of the cough reflex was shown in elderly patients with pneumonia [27]. Petroiaianni et al. also reported that the increased incidence of AP with aging might be a consequence of impairment of swallowing and the cough reflex [28].

In contrast, the occurrence of aspiration in healthy elderly people is not different from that in younger persons in previous studies, though older people swallow more slowly [29]. The cough reflex also did not decrease with aging [30]. Therefore, it may be considered that aging alone is not causes of elderly AP. However, oropharyngeal deglutition is impaired with aging, because of increased neural processing time and diminished oral control [23]. Further, the incidence of cerebrovascular and degenerative neurologic disease increase with aging, and these impediments are strongly
associated with impaired swallow and cough reflex and increased risk of aspiration [30]. The number of microorganisms in the oral cavity of the elderly is usually larger than that of young adults because of a gradual reduction in basic oral function [31,32], such as diminished production of saliva as a result of medications and oral/dental disease [14]. It is thought that these oral environments of elder person become risks of AP.

Adaptive immune responses are required to defend the lung against pathogens. Microbes initiate both innate immune responses and specific adaptive immune response [33]. The aging of lungs is a diversified decline in pulmonary immune function, on the contrary. Alveolar defenses are divided into resident defense mechanisms, inflammatory responses, and specific immune responses. Aged T-lymphocytes are markedly impaired in their ability to activation and proliferation in response to an antigen [25,34]. In addition, the ability of the T-lymphocytes with secreting interleukin-2 declines with age, and the macrophages by senescent T cells were diminished [34].

These many interacting and compounding impairments may explain the increased susceptibility of the elderly to pulmonary infection.

2.2. Epidemiology

It was at the 1990s that the epidemiologic studies of the environment in the oral cavity, quality of life and pneumonia were started [35–39]. The history of the epidemiologic study concerning elderly AP is comparatively shallow. Because the mortality rate of pneumonia rises remarkably with aging [40], the elderly generation is a logical target of this research. And elder person often has complex factors; poor nutritional status and medication could confound the relationship between oral conditions and pneumonia. In the most recent studies [8,14,41], oral conditions emerged as potentially important risk factors of AP after adjustment for established medical risk factors. A relationship between poor oral health and respiratory disease has been suggested by a number of recent microbiologic and epidemiologic studies, especially in high-risk subjects.

Terpenning et al. [39] reported that requiring help with feeding was one of the most significant risk factor of AP in dentate patients. As for requiring help with feeding, it means serious oral health problems; including poor oral hygiene, high level of dental needs and low rates of dental care utilization [42,43]. For instance, Scannapieco et al. described a plaque index (OHI) was associated with chronic respiratory disease [44]. Significant positive correlation was found between salivary bacteria and visual evaluation of plaque index in dentate patients [45]. And, the number of patients developing pneumonia is larger in dentate patients with tongue plaque index (TPI)-based poor scores than those with good scores [45]. In addition, it is known that anaerobic lung infectious disease develops after saliva aspiration, especially in patients with periodontal disease [46]. Scannapieco et al. reviewed the association between periodontal disease and pneumonia, and mentioned that poor oral hygiene and periodontal diseases appeared to be related with pneumonia [47,48]. In conclusion, the periodontal disease and dental plaque may act as a reservoir of respiratory pathogens in dentate patients.

As for denture-wearing patients, denture hygiene is suggested to be a significant factor in pharyngeal bacterial colonization [49]. Eighteen species of microorganisms were detected in denture plaque. A variety of pathogens colonized on dentures of dependent elderly [50]. In addition, agreement rate of the race of the bacillus of the denture and the pharynx is reported to be 68.5% [49]. It is necessary to think about the denture as an important reservoir of microorganism. Tongue-coating is a risk indicator of AP also in edentate subjects [45]. It is not overemphasized even if it is describe that denture plaque controlling is necessary for the prevention of aspiration pneumonia. [51,52].

Plaque is a complex system that associates microorganisms embedded in an extracellular matrix. Bacteria constitute approximately 70—80% of the solid material, and 1 mm³ of plaque contains more than 10⁶ bacteria with 300 different aerobic and anaerobic species [53]. From the above-mentioned reports, plaque may serve as a reservoir for respiratory pathogens, especially in high-risk elderly patients with poor oral hygiene, periodontal disease, dentate and edentate by epidemiology [44—52,54,55].

2.3. Candida spp.

Pneumonia is an inflammation of the lungs by microorganism infection. One study reported a patient suspected of Candidal pneumonia, though the majority of AP is a bacterium [56]. Pulmonary fungal infection of community-acquired origins is becoming a serious problem. Candidal pneumonia has 2 forms. The most common form is a hematogenously disseminated pulmonary infection along with various other organs, often resulting in fungal emboli in the lungs. The other form is rare and occurs after aspiration of oral/oropharyngeal material, causing primary pneumonia [57].

For latter form, Candida infection usually occurs in at-risk patients. It is described that aspiration is important as the route of entry of intrabronchial and intralveolar fungi that is not vascular invasion [58]. Then, Yamamoto et al. performed amplified polymorphic DNA analysis and DNA sequence examination of Candida strains isolated from the oral cavity and autopsied lung. It was revealed the identity of both strains as Candida albicans. The DNA analyses therefore suggest that oral Candida was aspirated and multiplied in the lungs, and this result suggests the importance of oral hygiene for AP [59].

C. albicans is the most common Candida pathogen not only in systemic but also in Candidal pneumonia [60–63]. Candida glabrata accounts for up to 20% of Candidal pneumonia [63] occurs almost exclusively in immunocompromised patients [64]. However, some epidemiologic studies have described that C. glabrata is a pathogen of lower respiratory infections [61–63].

Report of C. albicans infection of denture plaque was published [65]. As for the etiology of the Candida growth environment, adherence of C. albicans to denture-based acrylic resin, in vitro, is related to the hydrophobicity of the organism [66]. That is, denture-based acrylic resin is easily colonized by oral endogenous bacteria and Candida spp., and eventually by extra-oral species such as Staphylococcus spp., Pseudomonadaceae or members of Enterobacteriaceae. This microbial reservoir may be responsible for AP, especially in geriatric patients [51]. Abe et al. reported that
POHC in elderly people decreased the cell numbers of *Candida* in the oral cavity [67].

### 2.4. Professional oral health care (POHC)

Dentists have the role of maintaining oral health to prevent AP. Sarin et al. [68] reviewed microorganisms that caused AP and provided oral health care guidelines. The common microorganisms of the oral cavity and respiratory system are *S. aureus, H. influenzae, Actinomyces species* and *Peptostreptococcus*. Previous epidemiological studies reported that elderly people who received POHC showed a lower prevalence for respiratory pathogens [69,70] such as *Staphylococcus* species [71,72], *Streptococci* [71], *Pseudomonas aeruginosa* [72] and *C. albicans* [72] than those who did not.

The relationship between potential respiratory pathogens that cause pneumonia and colonize the oral cavity of high-risk elderly people, for example, those in intensive care units [22,73,41], and nursing home residents [41,74,75] were reported. Significantly, results from 3 preliminary intervention trials demonstrate that attention to oral hygiene, either by the use of mechanical cleaning and/or oral antiseptic rinses, significantly reduces the rate of lower respiratory infection in institutionalized subjects [76–78]. Further, the ratio of fatal AP [72] and dying from pneumonia [79] in POHC patients was significantly lower than that in patients without POHC. In another report, cough reflex sensitivities in the intervention group were significantly higher than those of the control group (*p* < 0.05) [80]. Like the above-mentioned study, many review papers with positive results concerning the relationship between POHC and AP [8,14,48,81–83] have been reported (Table 1).

However, some researchers have reported that there is no relationship between oral health and AP. Multivariate analysis identified tube feeding, presence of a hyperextended neck, contractions, malnutrition, and the use of benzodiazepines and anticholinergics as risk factors for AP for long-term care patients, but the results were not sufficient for dental characteristics [84]. There is a report that mechanically ventilated intensive care is mainly a risk factor for bacterial pneumonia [85]. Although medical ICU patients tended to have more dental plaque than preventative dentistry’s outpatient, there was no significant difference noted between the presence of dental plaque and respiratory pathogen colonization [73].

Most data showed a high level of dental needs; untreated coronal and/or root decay among the majority of nursing home residents, accompanied by significantly reduced oral health-related quality of life [86]. Interventional epidemiological studies indicate that oral microorganisms might cause lung infection.

### 3. Etiology

#### 3.1. Pathological approach

Though interventional epidemiological research had been a main method in the research of AP, it is shifting to experi-
mental pathology research. For instance, it was reported that DNA of microorganism in the bronchial tube and oral cavity of pneumonia patients were consisted [87]. Therefore, pathological approach of the process the aspiration of the microorganism in the oral cavity to bronchial tube, proliferation, and progressing to AP is necessary.

An illustration of aspiration pneumonia is shown in Fig. 1. Aspiration of indigenous oral flora and colonization into the lung are the course of lung infection by the oral microorganism. In short, the oral flora are released into the saliva and aspirated into the lower airway.

The pathogenesis of pneumonia begins with the colonization of the oropharyngeal surfaces by potential respiratory pathogens. The adhesion of bacteria to these surfaces is usually mediated by specialized bacterial surface structures, which bind to specific receptors on the host surface. Oral bacteria are potent stimulators of cytokine production from oral epithelial cells [88], and those may also modulate the adhesion of respiratory pathogens to respiratory epithelial cells. Oral bacterial products or cytokines in oral/pharyngeal aspirates have 2 kinds of function; one is stimulating cytokine production from oral epithelial cells [88,89], and the other is modulating the adhesion of respiratory epithelial cells [89]. Then, epithelial cells also alter expression of various cell adhesion molecules on their surface in response to cytokine stimulation [90]. Variation in expression of such adhesion molecules may alter the interaction of bacterial pathogens on the mucosal surface [91]. Once aspirated into the lower airway, the bacteria adhere to the bronchial or alveolar epithelium, again via specific adhesion—receptor interactions, which include lectin as well as protein-protein interactions for glycoproteins and glucolipids [89]. Epithelial cell destruction by adhered bacteria may be due to the direct effect of bacterial products on membrane permeability. Wilson R et al. have demonstrated that bronchial secretions may also contain bacterial toxins, which can cause epithelial necrosis and disrupt ciliary ultrastructure [92]. One of the main functions of the airway epithelium is to inactivate and remove infectious particles from inhaled air and thereby prevent infection of the distal lung. Necrosis in airway epithelium might decrease removal capacity.

Studies of pulmonary infections have demonstrated that there is also a close relationship between bacterial load and neutrophil recruitment [93]. In acid aspiration-induced systemic organ injury, cytokines have been shown to increase neutrophil—endothelial adhesion [94]. Therefore, the neutrophils engulf and degenerate necrotic cells. Neutrophils may play important roles in the phagocytosis and pathogenesis of infective lung diseases, due to their ability to release a variety of oxidants and proteolytic enzymes capable of causing acute and chronic lung injury. As grounds for this hypothesis, neutrophils with a left shift were a common finding in dogs with AP [95].

AP is characterized histopathologically as granulomatous bronchopneumonia with prominent formation of macrophages/multi-nucleated giant cells. Migration of macrophages is caused by repeatable chronic aspiration of particulate food matter [96] and response of acid-induced lung injury [97]. However, phagocytic exposure of the macrophages was inhibited by in vitro exposure of the macrophages to acid [98]. In addition, a robust tumor necrosis factor-alpha (TNFalpha) response is seen following aspiration of food particles, while there is only a modest response to acid. TNFalpha might play a role in the pathogenesis of AP induced by food matter [99]. In conclusion, this accumulation of harmful bacteria and local inflammatory agents at the moment of aspiration may be the key risk factor in the pathogenesis of pneumonia associated with poor oral hygiene.

However, further research is necessary, because only recently research has focused on the mechanisms responsible for acid and base secretion into the airway surface liquid [100], and reports of the AP animal model with silent aspiration of food matter at the present stage are scarce.
<table>
<thead>
<tr>
<th>Author</th>
<th>Ref.</th>
<th>Year</th>
<th>Animal</th>
<th>Method</th>
<th>Control group</th>
<th>Experimental group</th>
<th>Instillation condition</th>
<th>Analytical item</th>
<th>Main result</th>
</tr>
</thead>
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<tr>
<td>Kudoh et al.</td>
<td>[106]</td>
<td>2001</td>
<td>Wister rat</td>
<td>Trans-oral endotracheal instillation</td>
<td>PBS (pH 7.4)</td>
<td>HCL (pH 1.0, 0.1 ml)</td>
<td>0.1 ml</td>
<td>Cultured alveolar macrophage</td>
<td>++ TNF-α nitric oxide</td>
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<tr>
<td>Mitsushima et al.</td>
<td>[103]</td>
<td>2002</td>
<td>Mouse</td>
<td>Intratracheal instillation</td>
<td>NS</td>
<td>HCL 10⁻¹ to 10⁻⁴ N</td>
<td>50 μl</td>
<td>Histopathological analysis</td>
<td>3 ++ Numerous neutrophils infiltrated in the lung tissue in HCL 10⁻¹ N with bacteria</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>SEM study</td>
<td>3 ++ Numerous bacteria were found on exfoliated epithelium</td>
</tr>
<tr>
<td>Raghavendran et al.</td>
<td>[108]</td>
<td>2005</td>
<td>WT and MCP-1 (--/-)</td>
<td>Intratracheal instillation</td>
<td>Normal saline (pH 5.3)</td>
<td>NS⁺ + HCL (pH 1.25)</td>
<td>3.6 ml/kg</td>
<td>Histopathological analysis</td>
<td>1,2,3 WT Granuloma formation</td>
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<td></td>
<td></td>
<td>BAL analysis</td>
<td>1,2,3 MCP-1 (--/-) Severe diffuse pneumonia Several inflammatory mediators</td>
</tr>
<tr>
<td>Rotta et al.</td>
<td>[107]</td>
<td>2004</td>
<td>Long Evans rat</td>
<td>Aspiration introduced in the trachea by direct puncture</td>
<td>NS⁺ (pH 5.3)</td>
<td>Gastric aspirate (pH 1.25) + NS⁺</td>
<td>1.2 ml/kg</td>
<td>Mortality rate</td>
<td>1,2,NS 3 0.0% 31.8%</td>
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<td>BAL analysis</td>
<td>3 &gt;12 Neutrophil counts MCP-1</td>
</tr>
<tr>
<td>Allen et al.</td>
<td>[101]</td>
<td>2007</td>
<td>C57BL/6 mice</td>
<td>Instilled from deep oropharynx</td>
<td>PBS (pH 7.4)</td>
<td>HCL (pH 1.8)</td>
<td>75 μl</td>
<td>Histopathological analysis BALF analysis</td>
<td>1 ++ Fibrinogen and fibrin accumulation Total cells Neutrophils Total lung fibrin levels</td>
</tr>
<tr>
<td>Appel et al.</td>
<td>[105]</td>
<td>2007</td>
<td>F344 rat</td>
<td>Aspiration through ventilator placed</td>
<td>NS⁺</td>
<td>Gastric fluid</td>
<td></td>
<td>Cytokine analysis</td>
<td>1 ++ Macrophage Tcell</td>
</tr>
<tr>
<td>Nader et al.</td>
<td>[98]</td>
<td>2007</td>
<td>Long Evans rat</td>
<td>Intratracheal instillation</td>
<td>NS⁺</td>
<td>Low pH saline</td>
<td></td>
<td>Cytokine analysis</td>
<td>2,3 &gt;1 Mononuclear cells</td>
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</table>
3.2. Animal experimental approach

Table 2 shows details of the research on aspiration pneumonia in animal models. Some research that used animal models of AP used artificial suction of acid. Acid aspiration in mice leads to substantial deterioration in lung function. Bronchoalveolar lavage fluid demonstrated a significant rise in total cells by 4 h and a significant increase in neutrophils relative to saline controls by 24 h, and both remained elevated to 48 h. Total fibrin lung levels increased progressively compared to the control group and showed significantly greater levels of fibrin and fibrinogen from 4 to 48 h by immunohistochemistry [101].

It was shown that suction of acid caused migration of inflammatory cells; mainly neutrophils and beginning of tissue restoration. Likewise, lung-lining fluid is a primary constituent of the pulmonary host defense system. The pathogenicity of microorganism in airways and alveoli might be increased when microorganism clearance in both regions were suppressed by low pH [102]. As a result, it is suggested that bacterial adherence to epithelium of the lungs would be enhanced [103].

The lung tissue of rats was histopathologically demonstrated to have bronchopneumonia with formation of multinucleated giant cells, on the contrary [104]. As for the relation between aspiration and macrophage infiltration, an inflammatory reaction that consists of T cells and macrophages was caused by repetitive aspiration [105,106]. Chronic inflammatory infiltrates including multinucleated giant cells were observed when treated with gastric fluid, neutralized gastric fluid, bile and food suspension [96]. In addition, bronchoalveolar lavage of rats that were firstly aspirated with rat gastric fluid adjusted to pH 1.2, and secondly aspirated with bacteria, had remarkably increased MCP-1 concentration [107]. WT mice had prominent granuloma formation in lung tissue after aspiration, though MCP-1(+/−) mice had little or no evidence of granuloma formation [108]. From this, acid aspiration-induced airway epithelial injury and enhanced bacterial adherence to the epithelium. And, macrophages/multinucleated giant cells play a key role in repeated aspiration. That is, these cells migrate to encapsulate aspirated foreign body and to stop the inflammation.

4. Conclusion

The research of AP has been advanced based on epidemiology analysis. Especially, several researchers have reported that intervention with POHC can help prevent pneumonia. Silent aspiration of oropharynx bacterial pathogen to the lower respiratory tract is an important risk factor for nosocomial pneumonia [109]. Knowledge within the profession will improve the environment in the oral cavity of elderly people who need intensive care. For instance, Chiba et al. described that around 90% of caregiver managers recognized the importance of oral care and were interested in oral care [110]. Caregiver oral care knowledge is important for preventing AP. Dentist should initiate POHC though a lot of professions of the nurse, the care person, and the helper, etc. are involved. Therefore, dentists should study AP more, and instruct other care providers. In addition, more research on AP is needed.
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