

*Invited Review*

## **Preventive Strategies for Aspiration Pneumonia in Elderly Disabled Persons**

TAKASHI OHRUI

*Department of Geriatric and Respiratory Medicine,  
Tohoku University Graduate School of Medicine, Sendai, Japan*

OHRUI, T. *Preventive Strategies for Aspiration Pneumonia in Elderly Disabled Persons*. Tohoku J. Exp. Med., 2005, **207** (1), 3-12 — Pneumonia is the fourth leading cause of death despite the availability of potent new antimicrobials in Japan. Aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is one of the most important risk factors for pneumonia. Impairments in swallowing and cough reflexes among disabled older persons, e.g., related to cerebrovascular disease, increase the risk of pneumonia. Thus, strategies to reduce the volumes and pathogenicity of aspirated material should be pursued. Since both swallowing and cough reflexes are mediated by endogenous substance P contained in the vagal and glossopharyngeal nerves, pharmacologic therapy using angiotensin-converting enzyme inhibitors, which decrease substance P catabolism, can improve both reflexes and result in the lowering of the risk of pneumonia. Similarly, since the production of substance P is regulated by dopaminergic neurons in the cerebral basal ganglia, treatment with dopamine analogs or potentiating drugs such as amantadine can reduce the incidence of pneumonia. Furthermore, since mortality from infections correlates with cutaneous anergy, interventions that reverse these age-associated changes in the immune system are also effective. The main theme of this review is to discuss how pneumonia develops in disabled older people and to suggest preventive strategies that may reduce the incidence of pneumonia among these subjects. ——— pneumonia; disabled older persons; silent aspiration; dopamine; substance P

© 2005 Tohoku University Medical Press

Pneumonia is a common cause of death among older people despite the availability of potent novel antimicrobials. Both the increased incidence of pneumonia and high mortality among older people are a consequence of a number of age-related factors including coexisting illnesses, therapeutic interventions, and decreased host de-

fense mechanisms. In those, aspiration is possibly the most important risk factor for pneumonia in the elderly (Yamaya et al. 2001a). Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract. Several pulmonary syndromes may occur after aspiration, depending on the amount and na-

---

Received June 16, 2005; revision accepted for publication June 20, 2005.

Correspondence: Takashi Ohrui, M.D., Ph.D., Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

e-mail: [ohrui@geriat.med.tohoku.ac.jp](mailto:ohrui@geriat.med.tohoku.ac.jp)

Dr. T. Ohrui is a recipient of the 2004 Gold Prize, Tohoku University School of Medicine.

ture of the aspirated material, the frequency of aspiration, and the host's response to the aspirated material (Marik 2001). In those, aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions that are colonized by pathogenic bacteria, whereas aspiration pneumonitis (Mendelson's syndrome) is a chemical injury caused by the inhalation of sterile gastric contents (Marik 2001). Although there is some overlap between these syndromes, they are distinct clinical entities. This article focuses on the pathophysiology and the management of aspiration pneumonia.

### *Mechanisms for development of aspiration pneumonia*

Pneumonia in the elderly is often caused by an inapparent swallowing disorder (Yamaya et al. 2001a, 2002; Ohru et al. 2003; Kubo et al. 2005). Such silent aspiration frequently occurs and is a more important cause of pneumonia than the acute aspiration of gastric content in older people (Berk et al. 1983). Silent aspiration of oropharyngeal bacterial pathogens to the lower respiratory tract is an important risk factor for community-acquired pneumonia (Kikuchi et al. 1994) as well as nosocomial pneumonia in the elderly (Johanson et al. 1972). Normal hosts are less likely to develop pneumonia because they either aspirate smaller volumes or are able to clear bacteria rapidly (Toews et al. 1990). However, an extremely small volume (0.01 ml) of saliva contains pathogenic numbers of bacteria (Toews et al. 1990). Elderly patients with a predisposition to aspiration frequently aspirate oropharyngeal secretions and the development of pneumonia occurs when normal pulmonary defense mechanisms are overwhelmed (Nakagawa et al. 1997).

Adequate protective reflexes in the airway are important and the suppression or absence of these reflexes has been suggested as leading to pneumonia (Nakagawa et al. 1997). For example, Nakajoh et al. (2000) reported that the incidence of pneumonia was higher in patients having both a latency of swallowing response longer than 5 seconds following stimulation and a cough threshold for inhalation of citric acid aerosol higher than

a concentration of  $1.35 \text{ (log mg mL}^{-1}\text{)}$ . Thus, the progressive loss of protective reflexes (i.e., swallowing and cough reflexes) with age is thought to be one of the mechanisms for aspiration pneumonia, which is often seen in older people (Pontoppidan and Beecher 1960). In fact, impaired swallowing and cough reflexes have been shown in patients suffering from aspiration pneumonia (Sekizawa et al. 1990; Nakazawa et al. 1993). However, re-evaluation of age-related changes in protective reflexes in individuals who lead active daily lives has shown that both reflexes do not decrease with the advance of age (Katsumata et al. 1995; Kobayashi et al. 1997), indicating that involuntional and degenerative changes associated with aging often result in marginally compensated protective reflexes (Sheth and Diner 1988).

Disorders of the central nervous system are more likely to develop in the elderly, and pneumonia has been estimated to occur in about one third of patients with stroke (Walker et al. 1981; Kobayashi et al. 1994). The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration (Horner et al. 1988). Nakagawa et al. (1997) have shown that the risk of pneumonia was significantly higher in patients with basal ganglia infarcts than in patients with or without cerebral hemispheric strokes in other locations. They found that multiple episodes of pneumonia occurred only in patients with bilateral basal ganglia infarcts and that there was a higher mortality rate associated with pneumonia in these patients. Delayed triggering of the swallowing reflex occurs in patients with infarcts in the basal ganglia (Sheth and Diner 1988). These results strongly suggest that disruption of basal ganglia functions is critically important in the development of aspiration pneumonia.

The pharyngeal, laryngeal and tracheal epithelia, the sites most important for initiation of swallowing and cough reflexes, have an extensive plexus of nerves which contains substance P (Pernow 1983; Baluk et al. 1992). Capsaicin desensitization, which abolishes substance P from the airway and upper digestive tract, or a neuroki-

nin (NK)-1 receptor antagonist markedly attenuated the cough response to tussive stimuli (Ujiie et al. 1993; Sekizawa et al. 1995; Ebihara et al. 1996) and distilled water-induced swallowing reflex in guinea pigs (Jin et al. 1994), suggesting an important role of substance P-containing nerves in the initiation of these protective reflexes. Thus, irritation of laryngeal and pharyngeal mucosa by stimuli may activate capsaicin-sensitive sensory nerves, releasing substance P, with the result that protective reflexes are initiated by stimulation of the glossopharyngeal and vagal sensory nerves (Sekizawa et al. 1996).

Dopamine agonist treatments in the rat bring about a heightened striosomal expression of substance P and both dopamine D<sub>1</sub> and D<sub>2</sub> antagonists decrease substance P (Graybiel 1990). Mice lacking the dopamine D<sub>1</sub> receptor (Xu et al. 1994), and those treated with dopamine D<sub>1</sub> receptor antagonist (Jia et al. 1998), showed abnormal motor activities and feeding and swallowing problems. An impairment of dopamine metabolism in the basal ganglia is observed in patients with infarcts in the basal ganglia (Itoh et al. 1993, 1994). Patients with basal ganglion infarcts may suffer from reduced dopamine metabolism, which decreases substance P in the glossopharyngeal and vagal sensory nerves. Suppression of substance P concentration in these nerves impairs both swallowing and cough reflexes, which increases the frequency of silent aspiration. Because the act of swallowing and coughing is a fundamental defense mechanism against aspiration of oropharyngeal contents into the respiratory tract, impairment of both reflexes is one of the major reasons for the development of aspiration pneumonia.

In patients with aspiration pneumonia, unlike those with aspiration pneumonitis, the episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient at risk for aspiration has radiographic evidence of an infiltrate in a characteristic bronchopulmonary segment. Elderly persons frequently receive poor oral care, resulting in oropharyngeal colonization by potential respiratory tract pathogens, including *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. These pathogens are

aspirated and may cause pneumonia (Marik 2001).

#### *Treatments for aspiration pneumonia*

Antibiotic therapy is unequivocally indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurs as well as the patient's general health. However, antibiotic agents with activity against gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones, and piperacillin, are usually required (Marik 2001). Kanda et al. (2004) evaluated an additive effect of angiotensin-converting-enzyme inhibitor and amantadine to the conventional antibiotic therapy for pneumonia and found that the combinatorial usage of these drugs can shorten the duration of hospitalization and antibiotic usage, inhibit MRSA infection and lower the medical costs for treatment of pneumonia.

#### *Strategies for the prevention of aspiration pneumonia (Fig. 1)*

##### *Pharmacologic therapy*

**Capsaicin.** Because substance P is a neurotransmitter of the swallowing reflex and substance P is depleted in patients with aspiration pneumonia (Nakagawa et al. 1995), capsaicin, a pungent substance in red peppers that stimulates sensory nerves, may improve the swallowing reflex in these patients (Yamaya et al. 2001a). Ebihara et al. (1993) measured the swallowing reflex with a bolus injection of 1 ml of solution into the pharynx through a nasal catheter and suggested that the addition of a low dose of capsaicin to liquid or food may stimulate the swallowing reflex and help to prevent aspiration pneumonia in the elderly.

**Angiotensin-converting-enzyme (ACE) inhibitors.** A well-known adverse effect of angiotensin converting enzyme (ACE) inhibitor is a dry cough (Israili and Hall 1992). Substance P is degraded by ACE (Skidgel and Erdos 1987), and its action is potentiated by ACE inhibitors (Cascieri et al. 1984; Shore et al. 1988). Using ACE inhibitors, substance P might accumulate in the upper respiratory tract because of inhibited ACE activity

### Strategies for the prevention of aspiration pneumonia

- 1) Pharmacologic therapy
  - a) Capsaicin
  - b) Angiotensin-converting-enzyme inhibitors
  - c) Dopamine and amantadine
  - d) Cilostazol
  - e) Folic acid
- 2) Oral hygiene
- 3) Sitting position
- 4) Avoidance of neuroleptics
- 5) Handwashing
- 6) Vaccines
  - a) Influenza vaccines
  - b) 23-valent pneumococcal vaccines
  - c) Bacillus Calmette-Guerin (BCG) vaccines

Fig. 1

and cause an increase in the sensitivity of the cough reflex (Ebihara et al. 1996; Sekizawa et al. 1996; Yamaya et al. 2001a). In a similar way to the cough reflex, ACE inhibitors improve the swallowing reflex in older patients with aspiration pneumonia (Nakayama et al. 1998). Sekizawa et al. (1998) compared the rate of pneumonia in stroke patients treated with ACE inhibitors with that in patients treated with other antihypertensive drugs and found that the risk of pneumonia is reduced by about a third if ACE inhibitors are used for hypertension, compared with the use of other antihypertensive drugs. ACE inhibitors, therefore, may have beneficial effects on the prevention of pneumonia in these patients. Arai et al. (1998) reported that the rate of pneumonia was significantly lower in elderly hypertensive patients given ACE inhibitors than in those treated with calcium channel blockers. However, Teramoto and Ouchi (1999) denied the advantage of ACE inhibitors over calcium channel blockers in preventing pneumonia in adult and elderly hypertensives. In elderly individuals, the severity of the underlying cerebrovascular disease greatly affects the susceptibility to pneumonia. ACE inhibitors could be useful in the prevention of aspira-

tion pneumonia in elderly patients with stroke but not in those without hypertension.

*Dopamine and amantadine.* Delayed triggering of the swallowing reflex occurs in patients with basal ganglia infarctions (Nakazawa et al. 1993; Yamaya et al. 2001a) and an impairment of dopamine metabolism in the basal ganglia is observed in these patients (Itoh et al. 1993, 1994). Kobayashi et al. (1996) investigated whether levodopa improves the swallowing reflex in patients with basal ganglia infarctions who had a history of aspiration pneumonia. The subjects were given an intravenous drip infusion of levodopa (50 mg in 20 ml saline) for 30 min. They found that the administration of levodopa improves the impaired swallowing reflex in these patients. Since dopamine supplementation improves the swallowing reflex in patients with cerebral infarctions, Nakagawa et al. (1999) investigated whether amantadine, a drug that acts as a dopamine releaser from dopaminergic nerve terminals, lowers the incidence of pneumonia in patients with cerebral infarctions. Patients were randomly assigned amantadine 100 mg per day or no active treatment and were investigated for 3 years. During follow-up, a relative risk of developing pneumonia in pa-

tients on no active treatment compared with those on amantadine was 5.92. Their findings suggest that the risk of pneumonia is lowered by approximately 80% if amantadine is used in patients with previous stroke (Nakagawa et al. 1999). Amantadine may, therefore, have beneficial effects on the prevention of pneumonia in these patients. Of course, other recognized effects of amantadine might also have impacted the incidence of pneumonia in these studies. For example, amantadine improves the conscious state in patients with brain injury (Zafonte et al. 1998), and more alert stroke patients may be less likely to aspirate. In addition, dopaminergic receptors have been identified in the lower esophageal sphincter, and amantadine might reduce gastroesophageal reflux (Wakabayashi et al. 1989), and thereby lower the risk of aspiration pneumonia. Finally, antiviral effects and prevention of influenza infection might also lower the incidence of pneumonia over a three year period (Zimmerman et al. 1997). Thus, the mechanisms by which amantadine might positively affect the incidence of pneumonia remain to be proven (Sekizawa et al. 1999).

*Cilostazol.* Disorders of the central nervous system including dementia and atherosclerotic cerebrovascular disease are more often associated with aspiration than other specific neuromuscular disorders (Feinberg et al. 1990; Yamaya et al. 2001b). The mechanisms by which brain injury affects the risk of aspiration are beginning to be delineated. For example, in healthy people, the frequency of swallowing during sleep is slightly less than when awaking (Miller 1982), but severe delay of the swallowing response in the night compared with that in the day was observed in patients with multiple lacunar infarctions (Pinto et al. 1994). Cough reflex and spontaneous cough are also suppressed during sleep in patients with evidence of cerebrovascular injury (Zheng et al. 1997; Wang et al. 1998). Thus, patients with cerebrovascular diseases are particularly susceptible to development of aspiration pneumonia during sleep.

Other evidence of the importance of cerebrovascular diseases comes from studies of patients

with silent cerebral infarction, i.e., patient with radiographic evidence of infarction without frank signs of neurological impairment. Silent cerebral infarction is quite common among the elderly. Silent cerebral infarction was observed in 23% of elderly people in the United States (Longstreth et al. 1998), in 42% of older adults in one Japanese study (Hougaiku et al. 1992), and in 51% in another Japanese study (Imai et al. 1996). Not only is silent stroke a risk factor for clinical stroke (Kobayashi et al. 1997) which obviously increases the risk of aspiration pneumonia, but Nakagawa et al. (2000) reported that patients with silent cerebral infarction were more likely to develop pneumonia (20%) than were controls (5%) without silent cerebral infarction over a two year period. In this study, deep silent infarcts were more closely associated with the incidence of pneumonia (29%) than superficial infarcts (7%). Thus, silent cerebral infarction should be considered as a potential risk for the development of aspiration pneumonia. Taken together, it is reasonable to propose that treatment aimed at reducing the incidence and severity of cerebral vascular disease, e.g., anti-hypertensive therapy, or anticoagulation and anti-platelet therapy in selected populations, may not only prevent future stroke but also reduce the incidence of aspiration pneumonia. In a comparison between a group receiving cilostazol, an anti-platelet agent, for three years and a cilostazol non-receiving group, the incidence of cerebral infarction decreased to 50% in the cilostazol group (Yamaya et al. 2001b). Furthermore, the incidence of pneumonia also reduced by approximately half (Yamaya et al. 2001b).

*Folic acid.* Folate plays a pivotal role in the synthesis of dopamine and its deficiency is common in older people, especially in institutionalized subjects. Folate deficiency may be an independent marker for increased risk of aspiration pneumonia in older people (Sato et al. 2001). Folic acid supplementation may prevent the incidence of pneumonia by improving the swallowing function in these susceptible subjects (Sato et al. 2001). Therefore, for older people, in order to prevent pneumonia, nutrition has to be taken into consideration as well.

### *Oral hygiene*

The microbiologic etiology of aspiration pneumonia is usually traced to organisms that inhabit the oropharynx, and aspiration of pharyngeal contents has been suggested as the mechanism by which these bacteria reach the lower respiratory tract (Pierce and Sanford 1974; Yamaya et al. 2001a). Johanson and Harris (1980) speculated that the pulmonary infections caused by bacteria following the introduction of pathogenic organisms by aspiration of oropharyngeal contents is one of the major reasons for pneumonia in the elderly. Since aspiration of bacteria in oropharyngeal secretions is an important risk factor for nosocomial pneumonia in the elderly (Johanson et al. 1972), poor oral health may also contribute to the development of pneumonia (Fukayo et al. 2003). Yoneyama et al. (1999) assessed the rate of pneumonia in elderly people receiving oral care and in those who did not. During 2 years of follow-up, pneumonia was diagnosed in 19% of participants who did not receive oral care and 11% of those who received. The relative risk of developing pneumonia on no active oral care compared with oral care was 1.67 (Yoneyama et al. 1999). Thus, monitoring the attention given to the oral hygiene of dependent patients can probably lower the incidence of aspiration pneumonia. Furthermore, in a previous study, Yoshino et al. (2001) stimulated the gum-ridge with a brush with no toothpaste immediately after a meal. No matter where in their mouth they stimulated, the swallowing reflex improved after the stimulation on the gum-ridge. This result tells us that stimulation of the mouth is transmitted to the brain, and certainly improves the swallowing reflex, which is one of the most important defensive mechanisms against aspiration of micro-organisms which colonize in the human body. Brushing in the mouth is not only good for the prevention of dental caries and gum-boils but also very good for improving swallowing reflex. Stimulation of the mouth requires less time and effort than the arms and legs. All we need is a little bit of stimulus.

### *Sitting position*

Gastroesophageal reflux is very common in

general and more common in elderly subjects. It has been estimated that more than one third of older people have intermittent symptoms of gastroesophageal reflux. In addition, the supine position, possibly by increasing the aspiration of gastric contents into the lung, may lead to pneumonia in patients on mechanical ventilation (Yamaya et al. 2001a). Finally, nasogastric tubes promote aspiration of gastric contents by impairing swallowing, causing stagnation of oropharyngeal secretions and reducing the tone of the lower esophageal sphincter (Yamaya et al. 2001a). Simple approach to all of these problems may involve elevating the head of the bed. Meguro et al. (1992) showed that elevating the bed after each meal for 2 hours decreased the febrile days presumptively by avoiding aspiration of gastric contents. Matsui et al. (2002) also emphasized the importance of patients' sitting position after meal for the prevention of respiratory tract infections.

### *Avoidance of neuroleptics*

The cough reflex can be suppressed by use of sedative drugs. Irwin et al. (1998) reported a consensus panel report of the American College of Chest Physicians, "Managing Cough as a Defense Mechanism and as a Symptom" and did not identify any age-related changes in cough reflex. However suppression of cough reflex by anesthesia, sedative hypnotics, or analgesic narcotics should be considered to be a major risk for aspiration pneumonia in older patients, especially during sleep (Huxley et al. 1978). Attracting attention to minimizing the use of agents which suppress the cough reflex is crucial for caring for elderly patients. When older people take benzodiazepines, their swallowing reflex will not go down significantly. However, when they take neuroleptics, which mostly act as a dopamine receptor antagonist, their swallowing reflex does go down clearly, which makes things even more troublesome leading to pneumonia (Wada et al. 2001).

### *Handwashing*

Gram-negative bacilli and *Staphylococcus aureus* commonly colonize the hands of health

care providers (Maki 1978). Although usually transient, hand colonization may persist, particularly in workers with dermatitis. Handwashing before and after contact with patients is an effective method for removing transient bacteria (Craven et al. 1991), but this is often a neglected behavior by medical personnel. The use of gloves and gowns can significantly reduce nosocomial infection and pneumonia (Leclair et al. 1987). Hospitals with effective surveillance and infection control programs have rates of pneumonia 20% lower than hospitals without such programs (Haley et al. 1985). Adherence to infection control practices such as handwashing is fundamental for the prevention of nosocomial pneumonia. Unfortunately, such barrier methods will not be effective in preventing infection with organisms that are part of the critically ill patient's endogenous flora; thus, most gram-negative pneumonias cannot be avoided by isolation methods (American Thoracic Society 1995). Improved handwashing practices and appropriate handling of mechanical feeding, suction, and respiratory devices should reduce the spread of infectious agents in institutional settings.

### *Vaccines*

*Influenza vaccines.* Influenza vaccination is effective in older adults not only in preventing primary influenza pneumonia but also secondary bacterial pneumonia (Muder 1998). Although an increased risk of pneumonia mortality is found in patients with limitations in activities of daily living (Nichol et al. 1998; Fukushima et al. 1999a; Ohruai et al. 2000), even bedridden elderly patients can be effectively immunized against influenza (Fukushima et al. 1999b) and the duration of febrile days and all respiratory conditions associated with influenza can be reduced (Fukushima et al. 1999c).

*23-valent pneumococcal vaccines.* The efficacy of pneumococcal vaccine among high risk patients has been the subject of some controversy. Some investigators estimate an approximately 60% to 95% prevention rate of pneumonia by 23-valent pneumococcal vaccine in immunocompetent elderly and other high-risk patients (Sims

et al. 1988). It is currently recommended in the United States that all adults 65 years or older and those at risk because of underlying illnesses receive both of these vaccines (U.S. Department of Health and Human Services 1997). Chiba et al. (2004) demonstrated that pneumococcal vaccination significantly shortened the overall febrile days and significantly reduced the rate of hospitalization for pneumonia even in bed-ridden patients. Pneumococcal vaccination is of benefit and recommended for elderly disabled patients at high-risk for pneumonia.

*Bacillus Calmette-Guérin (BCG) vaccines.* The tuberculin skin test is an easy way to check the cell-mediated immunity in elderly people (Fukushima et al. 1999a; Nakayama et al. 2000). Almost all Japanese over 65 years old may have a positive tuberculin skin test. If a person shows negative, it means that his or her cell-mediated immunity is depressed. We undertook a trial to vaccinate bedridden elderly people with BCG vaccine. During follow-up, new pneumonia was diagnosed in 42% of the elderly disabled patients with negative tuberculin responses, in 15% of the tuberculin converted patients by BCG and in 13% of the patients with positive tuberculin responses. BCG inoculation might reactivate the depressed T helper-1 mediated cellular immunity and prevent pneumonia in immobile elderly patients (Nakayama et al. 2002).

### **CONCLUSION**

Silent aspiration, which is frequently observed in patients with basal ganglia infarctions, might be an important risk factor for elderly pneumonia. Measurement of a swallowing latency is useful to identify a subject susceptible to pneumonia. The swallowing function might be partly regulated by dopaminergic neurons and substance P containing sensory nerves. Disruption of the basal ganglia leads to an impairment of the swallowing function and may predispose stroke patients to pneumonia. ACE inhibitors and amantadine may have beneficial effects on the prevention of pneumonia. Similarly, oral care improves swallowing reflexes and lowers the risk of pneumonia. Vaccines are also effective even in dis-

abled elderly patients in a bedridden condition. Since elderly pneumonia frequently recurs and is often lethal, it is important to identify high-risk patients and give some protection to these patients.

### Acknowledgments

I would like to thank Prof. H. Sasaki and Prof. K. Sekizawa for useful discussions. This study was supported in part by grants from the Japanese Foundation for Aging and Health (No.1122001).

### References

- American Thoracic Society (1995) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies. *Am. J. Respir. Crit. Care Med.*, **153**, 1711-1725.
- Arai, T., Yasuda, Y., Toshima, S., Yoshimi, N. & Kashiki, Y. (1998) ACE inhibitors and pneumonia in elderly people. *Lancet*, **352**, 1937-1938.
- Baluk, P., Nadel, J.A. & McDonald, D.M. (1992) Substance P-immunoreactive sensory axons in the rat respiratory tract: A quantitative study of their distribution and role in neurogenic inflammation. *J. Comp. Neurol.*, **319**, 586-598.
- Berk, S.L., Verghese, A., Holtscaw, S.A. & Smith, J.K. (1983) Enterococcal pneumonia. Occurrence in patients receiving broad-spectrum antibiotic regimens and enteral feeding. *Am. J. Med.*, **74**, 153-154.
- Cascieri, M.A., Bull, H.G., Mumford, R.A., Patchett, A.A., Thornberry, N.A. & Liang, T. (1984) Carboxyl-terminal tripeptidyl hydrolysis of substance P by purified rabbit lung angiotensin-converting enzyme and the potentiation of substance P activity in vivo by captopril and MK-4222. *Mol. Pharmacol.*, **25**, 287-293.
- Chiba, H., Ohrui, T., Matsui, T., Fukushima, T. & Sasaki, H. (2004) Benefits of pneumococcal vaccination for bedridden patients. *J. Am. Geriatr. Soc.*, **52**, 1410.
- Craven, D.E., Steger, K.A. & Barber, T.W. (1991) Preventing nosocomial pneumonia: state of the art and perspectives for the 1990s. *Am. J. Med.*, **91**, 44S-53S.
- Ebihara, T., Sekizawa, K., Nakazawa, H. & Sasaki, H. (1993) Capsaicin and swallowing reflex. *Lancet*, **341**, 432.
- Ebihara, T., Sekizawa, K., Ohrui, T., Nakazawa, H. & Sasaki, H. (1996) Angiotensin-converting enzyme inhibitor and dantrolene increase sensitivity of cough reflex in female guinea pigs. *Am. J. Respir. Crit. Care Med.*, **153**, 812-819.
- Feinberg, M.J., Knebl, J., Tully, J. & Segall, L. (1990) Aspiration and the elderly. *Dysphagia*, **5**, 61-71.
- Fukayo, S., Nonaka, K., Shimizu, T. & Yano, E. (2003) Oral health of patients with Parkinson's disease: factors related to their better dental status. *Tohoku J. Exp. Med.*, **201**, 171-179.
- Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. & Sasaki, H. (1999a) Depression of T helper-1 and tuberculin responses in older bed-bound patients. *J. Am. Geriatr. Soc.*, **47**, 259-260.
- Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. & Sasaki, H. (1999b) Influenza vaccination in bedridden patients. *Arch. Intern. Med.*, **159**, 316-317.
- Fukushima, T., Nakayama, K., Monma, M., Sekizawa, K. & Sasaki, H. (1999c) Benefits of influenza vaccination for bedridden patients. *Arch. Intern. Med.*, **159**, 1258.
- Graybiel, A.M. (1990) Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci.*, **13**, 244-254.
- Haley, R.W., Culver, D.H., White, J.W., Morgan, W.M. & Emori, T.G. (1985) The nationwide nosocomial infection rate: a new need for vital statistics. *Am. J. Epidemiol.*, **121**, 159-167.
- Horner, J., Massey, E.W., Riski, J.E., Lathrop, D.L. & Chase, K.N. (1988) Aspiration following stroke: clinical correlates and outcome. *Neurology*, **38**, 1359-1362.
- Hougaku, H., Matsumoto, M., Kitagawa, K., Harada, K., Oku, N., Itoh, T., Maeda, H., Handa, N. & Kamada, T. (1992) Silent cerebral infarction as a form of hypertensive target organ damage in the brain. *Hypertension*, **20**, 816-820.
- Huxley, E.J., Viroslav, J., Gray, W.R. & Pierce, A.K. (1978) Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am. J. Med.*, **64**, 564-568.
- Imai, Y., Tsuji, I., Nagai, K., Watanabe, N., Ohkubo, T., Sakuma, M., Hashimoto, J., Itoh, O., Satoh, H., Hisamichi, S. & Abe, K. (1996) Circadian blood pressure variation related to morbidity and mortality from cerebrovascular and cardiovascular disease. *Ann. NY Acad. Sci.*, **783**, 172-185.
- Irwin, R.S., Boulet, L.P., Cloutier, M.M., Fuller, R., Gold, P.M., Hoffstein, V., Ing, A.J., McCool, F.D., O'Byrne, P., Poe, R.H., Prakash, U.B.S., Pratter, M.R. & Rubin, B.K. (1998) Managing cough as a defense mechanism and as a symptom. *Chest*, **114**, 133S-181S.
- Israili, Z.H. & Hall, W.D. (1992) Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann. Intern. Med.*, **117**, 234-242.
- Itoh, M., Ido, T., Sasaki, H. & Meguro, K. (1993) First signs of Alzheimer's? *Science*, **259**, 898.
- Itoh, M., Meguro, K., Fujiwara, T., Hatazawa, J., Iwata, R., Ishiwata, K., Takahashi, T., Ido, T. & Sasaki, H. (1994) Assessment of dopamine metabolism in brain of patients with dementia by means of <sup>18</sup>F-fluorodopa and PET. *Ann. Nucl. Med.*, **8**, 245-251.
- Jia, Y.X., Sekizawa, K., Ohrui, T., Nakayama, K. & Sasaki, H. (1998) Dopamine D<sub>1</sub> receptor antagonist inhibits swallowing reflex in guinea pigs. *Am. J. Physiol.*, **274**, R76-R80.
- Jin, Y., Sekizawa, K., Fukushima, T., Morikawa, M., Nakazawa, H. & Sasaki, H. (1994) Capsaicin desensitization inhibits swallowing reflex in guinea pigs. *Am. J. Respir. Crit. Care Med.*, **149**, 261-263.
- Johanson, W.G., Pierce, A.K., Sanford, J.P., Thomas, G.D. & Pierce, A.K. (1972) Nosocomial respiratory infections with gram-negative bacilli: the significance of colonization of the respiratory tract. *Ann. Intern. Med.*, **77**, 701-706.
- Johanson, W.G. & Harris, G.D. (1980) Aspiration pneumonia, anaerobic infection and lung abscess. *Med. Clin. North Am.*, **64**, 385-394.
- Kanda, A., Ebihara, S., Yasuda, H., Ohrui, T., Sasaki, T. & Sasaki, H. (2004) A combinatorial therapy for pneumonia in elderly people. *J. Am. Geriatr. Soc.*, **52**, 846-847.
- Katsumata, U., Sekizawa, K., Ebihara, T. & Sasaki, H. (1995) Aging effects on cough reflex. *Chest*, **107**, 290-291.
- Kikuchi, R., Watanabe, N., Konno, T., Mishina, N., Sekizawa, K. & Sasaki, H. (1994) High incidence of silent aspiration in elderly patients with community-acquired pneumonia. *Am. J. Respir. Crit. Care Med.*, **150**, 251-253.
- Kobayashi, H., Hoshino, M., Okayama, K., Sekizawa, K. & Sasaki, H. (1994) Swallowing and cough reflexes after on-



- set of stroke. *Chest*, **105**, 1623.
- Kobayashi, H., Nakagawa, T., Sekizawa, K., Arai, H. & Sasaki, H. (1996) Levodopa and swallowing reflex. *Lancet*, **348**, 1320-1321.
- Kobayashi, H., Sekizawa, K. & Sasaki, H. (1997) Aging effects on swallowing reflex. *Chest*, **111**, 1466.
- Kobayashi, S., Okada, K., Koide, H., Bokura, H. & Yamaguchi, S. (1997) Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke*, **28**, 1932-1939.
- Kubo, H., Nakayama, K., Ebihara, S. & Sasaki, H. (2005) Medical treatments and cares for geriatric syndrome: new strategies learned from frail elderly. *Tohoku J. Exp. Med.*, **205**, 205-214.
- Leclair, J.M., Freeman, J., Sullivan, B.F., Crowley, C.M. & Goldmann, D.A. (1987) Prevention of nosocomial respiratory syncytial virus infections through compliance with glove and gown isolation precautions. *N. Engl. J. Med.*, **317**, 329-334.
- Longstreth, W.T., Bernick, C., Monolio, T.A., Bryan, N., Jungreis, C.A. & Price, T.R. (1998) Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people. *Arch. Neurol.*, **55**, 1217-1225.
- Maki, D.G. (1978) Control of colonization and transmission of pathogenic bacteria in the hospital. *Ann. Intern. Med.*, **89**, 777-780.
- Marik, P.E. (2001) Aspiration pneumonitis and aspiration pneumonia. *N. Engl. J. Med.*, **344**, 665-671.
- Matsui, T., Yamaya, M., Ohru, T., Arai, H. & Sasaki, H. (2002) Sitting position to prevent aspiration in bed-bound patients. *Gerontology*, **48**, 194-195.
- Meguro, K., Yamaguchi, S., Doi, C., Nakamura, T., Sekizawa, K. & Sasaki, H. (1992) Prevention of respiratory infections in elderly bed-bound nursing home patients. *Tohoku J. Exp. Med.*, **167**, 135-142.
- Miller, A.J. (1982) Deglutition. *Physiol. Rev.*, **62**, 129-184.
- Muder, R.R. (1998) Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. *Am. J. Med.*, **105**, 319-330.
- Nakagawa, T., Ohru, T., Sekizawa, K. & Sasaki, H. (1995) Sputum substance P in aspiration pneumonia. *Lancet*, **345**, 1447.
- Nakagawa, T., Sekizawa, K., Arai, H., Kikuchi, R., Manabe, K. & Sasaki, H. (1997) High incidence of pneumonia in elderly patients with basal ganglia infarction. *Arch. Intern. Med.*, **157**, 321-324.
- Nakagawa, T., Wada, H., Sekizawa, K., Arai, H. & Sasaki, H. (1999) Amantadine and pneumonia. *Lancet*, **353**, 1157.
- Nakagawa, T., Sekizawa, K., Nakajoh, K., Tanji, H., Arai, H. & Sasaki, H. (2000) Silent cerebral infarction: a potential risk for pneumonia in the elderly. *J. Intern. Med.*, **247**, 255-259.
- Nakajoh, K., Nakagawa, T., Sekizawa, K., Matsui, T., Arai, H. & Sasaki, H. (2000) Relation between incidence of pneumonia and protective reflexes in post-stroke patients with oral or tube feeding. *J. Intern. Med.*, **247**, 39-42.
- Nakayama, K., Sekizawa, K. & Sasaki, H. (1998) ACE inhibitor and swallowing reflex. *Chest*, **113**, 1425.
- Nakayama, K., Monma, M., Fukushima, T., Ohru, T. & Sasaki, H. (2000) Tuberculin responses and risk of pneumonia in immobile elderly patients. *Thorax*, **55**, 867-869.
- Nakayama, K., Shinkawa, M., Ohru, T., Hirai, H. & Sasaki, H. (2002) Interferon-gamma responses to mycobacterial antigens in Heaf-positive children. *Lancet*, **360**, 1335.
- Nakazawa, H., Sekizawa, K., Ujiie, Y., Sasaki, H. & Takishima, T. (1993) Risk of aspiration pneumonia in the elderly. *Chest*, **103**, 1636-1637.
- Nichol, K.L., Wuorenma, J. & von Sternberg, T. (1998) Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch. Intern. Med.*, **158**, 1769-1776.
- Ohru, T., Takahashi, H., Ebihara, S., Matsui, T., Nakayama, K. & Sasaki, H. (2000) Influenza A virus infection and pulmonary microthromboembolism. *Tohoku J. Exp. Med.*, **192**, 81-86.
- Ohru, T., Kubo, H. & Sasaki, H. (2003) Care for the older people. *Intern. Med.*, **42**, 932-940.
- Pernow, B. (1983) Substance P. *Pharmacol. Rev.*, **35**, 85-141.
- Pierce, A.K. & Sanford, J.P. (1974) Aerobic gram-negative bacillary pneumonias. *Am. Rev. Respir. Dis.*, **110**, 647-658.
- Pinto, A., Yanai, M., Nakagawa, T., Sekizawa, K. & Sasaki, H. (1994) Swallowing reflex in the night. *Lancet*, **344**, 820-821.
- Pontoppidan, H. & Beecher, H.K. (1960) Progressive loss of protective reflexes in the airway with the advance of age. *JAMA*, **174**, 2209-2213.
- Sato, E., Ohru, T., Matsui, T., Arai, H. & Sasaki, H. (2001) Folate deficiency and risk of pneumonia in older people. *J. Am. Geriatr. Soc.*, **49**, 1739-1740.
- Sekizawa, K., Ujiie, Y., Itabashi, S., Sasaki, H. & Takishima, T. (1990) Lack of cough reflex in aspiration pneumonia. *Lancet*, **335**, 1228-1229.
- Sekizawa, K., Ebihara, T. & Sasaki, H. (1995) Role of substance P in cough during bronchoconstriction in awake guinea pigs. *Am. J. Respir. Crit. Care Med.*, **151**, 815-821.
- Sekizawa, K., Jia, Y.X., Ebihara, T., Hirose, Y., Hirayama, Y. & Sasaki, H. (1996) Role of substance P in cough. *Pulm. Pharmacol.*, **9**, 323-328.
- Sekizawa, K., Matsui, T., Nakagawa, T., Nakayama, K. & Sasaki, H. (1998) ACE inhibitors and pneumonia. *Lancet*, **352**, 1069.
- Sekizawa, K., Yanai, M., Yamaya, M., Arai, H. & Sasaki, H. (1999) Amantadine and pneumonia in elderly stroke patients. *Lancet*, **353**, 2156-2157.
- Sheth, N. & Diner, W.C. (1988) Swallowing problems in the elderly. *Dysphagia*, **2**, 209-215.
- Shore, S.A., Stimler-Gerard, N.P., Coats, S.R. & Drazen, J.M. (1988) Substance P-induced bronchoconstriction in guinea pig. Enhancement by inhibitors of neutral metalloendopeptidase and angiotensin-converting enzyme. *Am. Rev. Respir. Dis.*, **137**, 331-336.
- Sims, R.V., Steinmann, W.C., McConville, J.H., King, L.R., Zwick, W.C. & Schwartz, J.S. (1988) The clinical effectiveness of pneumococcal vaccine in the elderly. *Ann. Intern. Med.*, **108**, 653-657.
- Skidgel, R.A. & Erdos, E.G. (1987) Cleavage of peptide bonds by angiotensin I converting enzyme. *Agents Actions Suppl.*, **22**, 289-296.
- Teramoto, S. & Ouchi, Y. (1999) ACE inhibitors and prevention of aspiration pneumonia in the elderly hypertensives. *Lancet*, **353**, 843.
- Toews, G.B., Hansen, E.J. & Strieter, R.M. (1990) Pulmonary host defenses and oropharyngeal pathogens. *Am. J. Med.*, **88**, 20S-24S.
- Ujiie, Y., Sekizawa, K., Aikawa, T. & Sasaki, H. (1993) Evidence for substance P as an endogenous substance causing cough in guinea pigs. *Am. Rev. Respir. Dis.*, **148**, 1628-1632.
- U.S. Department of Health and Human Services (1997) Pre-

- vention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, **46**, RR-8.
- Wada, H., Nakajoh, K., Satoh-Nakagawa, T., Suzuki, T., Ohru, T., Arai, H. & Sasaki, H. (2001) Risk factors of Aspiration pneumonia in Alzheimer's disease patients. *Gerontology*, **47**, 271-276.
- Wakabayashi, K., Takahashi, H., Ohama, E. & Ikuta, F. (1989) Tyrosine hydroxylase- immunoreactive intrinsic neurons in Auerbach's and Meissner's plexuses of humans. *Neurosci. Lett.*, **96**, 259-263.
- Walker, A.E., Robins, M. & Weinfeld, F.D. (1981) Clinical findings: the National Survey of Stroke. *Stroke*, **12**, Suppl. 1, 113-137.
- Wang, H.D., Nakagawa, T., Sekizawa, K., Kamanaka, M. & Sasaki, H. (1998) Cough reflex in the night. *Chest*, **114**, 1496-1497.
- Xu, M., Moratalla, R., Gold, L.H., Hiroi, N., Koob, G.F., Graybiel, A.M. & Tonegawa, S. (1994) Dopamine D<sub>1</sub> receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. *Cell*, **79**, 729-742.
- Yamaya, M., Yanai, M., Ohru, T., Arai, H. & Sasaki, H. (2001a) Interventions to prevent pneumonia among older adults. *J. Am. Geriatr. Soc.*, **49**, 85-90.
- Yamaya, M., Yanai, M., Ohru, T., Arai, H., Sekizawa, K. & Sasaki, H. (2001b) Antithrombotic therapy for prevention of pneumonia. *J. Am. Geriatr. Soc.*, **49**, 687-688.
- Yamaya, M., Ohru, T., Kubo, H., Ebihara, S., Arai, H. & Sasaki, H. (2002) Prevention of respiratory infections in the elderly. *Geriatr. Gerontol. Internat.*, **2**, 115-121.
- Yoneyama, T., Yoshida, M., Matsui, T. & Sasaki, H. (1999) Oral care and pneumonia. *Lancet*, **354**, 515.
- Yoshino, A., Ebihara, T., Ebihara, S., Fuji, H. & Sasaki, H. (2001) Daily oral care and risk factors for pneumonia among elderly nursing home patients. *JAMA*, **286**, 2235-2236.
- Zafonte, R.D., Watanabe, T. & Mann, T.R. (1998) Amantadine: a potential treatment for the minimally conscious state. *Brain Injury*, **12**, 617-621.
- Zheng, S., Yanai, M., Matsui, T., Sekizawa, K. & Sasaki, H. (1997) Nocturnal cough in patients with sputum production. *Lancet*, **350**, 864-865.
- Zimmerman, R.K., Ruben, F.L. & Ahwesh, E.R. (1997) Influenza, influenza vaccine, and amantadine/rimantadine. *J. Fam. Practice*, **45**, 107-122.
-